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**Parent-Infant Interaction Dynamics and Links to
Brain Function in Infants at an Elevated Likelihood
for Autism Spectrum Disorder**

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Abstract

Delays in social communication and interaction represent core features of Autism Spectrum disorder (ASD). Increasing evidence shows that behavioural social communication precursors of ASD begin around the first birthday, though brain function measures have identified neural social attention differences earlier. Developmental antecedents of ASD are thought to affect parent-infant interactions (PII), while early brain function differences are hypothesised to amplify through atypical interactions with the child's caregiving environment, contributing to altered social development. To examine this, this thesis investigated PII trajectories and PII-brain function links in infants at an elevated and typical familial likelihood (EL and TL infants, respectively) for ASD participating in a prospective longitudinal study.

Chapter 2 reviewed and outlined the methods employed to examine PII and its association with brain function, involving an observational coding scheme and electroencephalography. *Chapter 3* was an observational study that sought to replicate previous findings investigating 8-14-month PII trajectories in EL and TL infants and their relation to 3-year ASD outcome prediction. *Chapter 4* further investigated whether 8-14-month PII changes are associated with 3-year dimensional outcomes. *Chapter 5* examined the relationship between infant neural social attention and specific PII qualities in EL and TL infants at 8 months. *Chapter 6* employed a data-driven approach integrating PII and brain features of social attention and explored what patterns of relationships predicted 3-year clinical classification.

This thesis provided novel evidence for early alterations in PII in EL infants with a later ASD diagnosis, it demonstrated PII's predictive value in terms of ASD outcome and socio-cognitive development and revealed early brain-PII relationships differentially expressed in EL and TL infants, linked to clinical outcome. The findings inform our

understanding of the developmental pathways of ASD and strengthen the evidence base to support the implementation of early pre-emptive interventions to optimise PII in infants with early ASD signs.

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List of Abbreviations

ABC	Adaptive Behaviour Composite
ADI-R	Autism Diagnostic Interview – Revised
AIC	Akaike information criterion
AOSI	Autism Observation Scale for Infants
ASD	Autism Spectrum Disorder
ADHD	Attention Deficit Hyperactivity Disorder
ADOS	Autism Diagnostic Observation Schedule
Atyp	Atypical
BAP	The Broader Autism Phenotype
BASIS	British Autism Study of Infant Siblings
BIC	Bayesian Information Criterion
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
DAWBA	Development and Well-being Assessment
DSM-5	Diagnostic and Statistical Manual of Mental Disorders - 5th edition
EEG	Electroencephalography
EFA	Exploratory Factor Analysis
EL	Elevated Likelihood
ELC	Early Learning Composite
ERP	Event-Related Potential
FDR	False Discovery Rate
FIML	Full Information Maximum Likelihood
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-Infrared Spectroscopy

iBASIS-VIPP	BASIS-Video Interaction for Promoting Positive Parenting
ICA	Independent Component Analysis
ICD-10	International Classification of Diseases – 10th edition
IS	Interactive Specialization
LCS	Latent Change Score
LMM	Linear Mixed Models
LRT	Likelihood Ratio Test
MACI	Manchester Assessment of Caregiver-Infant Interaction
MAR	Missing at Random
MCAR	Missing Completely at Random
MSEL	Mullen Scales of Early Learning
MRI	Magnetic Resonance Imaging
Nc	Negative central
PDI	Parent and Dyadic Interaction
PII	Parent-Infant Interaction
Q-CHAT	Quantitative CHecklist for Autism in Toddlers
RMSEA	Root Mean Square Error of Approximation
RRB	Restricted and Repetitive Behaviours
SCQ	Social Communication Questionnaire
SEM	Structural Equation Modelling
SRMR	Standardized Root Mean Square Residual
SRS	Social Responsiveness Scale
TL	Typical Likelihood
VABS	Vineland Adaptive Behaviour Scales

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Chapter 1

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Chapter 6

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Chapter 1. General Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition of great scientific interest with substantive research seeking to identify the factors and underlying mechanisms of its diagnosis. By investigating and linking aspects of brain function related to social attention and early caregiver-infant social interaction, this PhD work hopes to provide a stepping stone towards a better understanding of the development of ASD. An overview of the progress that has been made towards our understanding of ASD and the contribution of research looking at brain development and caregiver-infant social exchanges are provided in this chapter. The aims of this PhD work considering relevant theoretical frameworks and existing research are also discussed.

1.1 ASD Definition

The Diagnostic and Statistical Manual of Mental Disorders - 5th edition (DSM-5) by the American Psychiatric Association (APA, 2013) defines ASD as a neurodevelopmental condition, characterised by behavioural deficits in key areas of social communication and interaction, and restricted, repetitive behaviour patterns and interests. In DSM-5, social communication and interaction include deficits in areas of a) social-emotional reciprocity, b) nonverbal communication and c) developing, maintaining, and understanding relationships. Restricted, repetitive behaviours involve a) stereotyped or repetitive use of speech, objects or motor movements, b) sameness insistence, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behaviour, c) circumscribed interests atypical in intensity of focus, and d) sensory hyper- or hyposensitivity. To meet the criteria for an ASD diagnosis, persistent difficulties in the three areas of the former, and at least two areas of the latter domains are required. By introducing the term ‘spectrum’ in DSM-5, ASD encompasses four diagnostic categories

that were previously considered separate, though highly associated, pervasive developmental disorders (PDD) in the DSM-4 edition: autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS). The onset of ASD symptoms usually becomes apparent in early childhood, and an ASD diagnosis can be given following clinical behavioural assessment.

1.2 Prevalence

According to a recent systematic review, the current prevalence of ASD is approximately 1% globally (Zeidan et al., 2022). Since the earliest epidemiological data reported from surveys in the 1960s (Lotter, 1966), the global prevalence of ASD has seen an increase over the years, with estimates varying within and across sociodemographic groups (Elsabbagh, Divan, et al., 2012; Zeidan et al., 2022). While most studies have been conducted in the United States (US) and Europe, there is now more research on prevalence estimates from previously underrepresented regions, though with still considerable variability and smaller sample sizes, limiting statistical power (Chinawa et al., 2016). The factors contributing to the increase in prevalence are known to include a rise in public awareness and public health response, a broadening of diagnostic boundaries and increased diagnosis of milder forms of ASD and of females (King & Bearman, 2009; Loomes et al., 2017; Zeidan et al., 2022). To explain the variation in prevalence, many factors have been proposed, such as socioeconomic status, geography, migration or race/ethnicity, though no strong or consistent evidence exists to support these (Crafa & Warfa, 2015; Zeidan et al., 2022, for a review). Evidence shows that part of the variation in prevalence can be explained by health disparities. For instance, the differences that have been observed regarding prevalence in terms of race may be related

to an under-recognition of ASD symptomatology or access to services in minorities (Maenner et al., 2020).

Furthermore, ASD has been consistently shown to be more common in males than females, with the most common male-to-female ratio reported being approximately 4:1. Nevertheless, a lower ratio of 3:1 has been suggested in a systematic review and meta-analysis based on studies higher in methodological quality (Loomes et al., 2017), while some epidemiological studies report even smaller ratios (e.g. 2.5:1, Kim et al., 2011; 1.8:1, Mattila et al., 2011). One explanation for the sex differences in ASD prevalence could be attributed to the phenotypic expression of symptoms, which is likely to differ in females (Lai et al., 2011). Another possible reason may be that females adopt social behaviours that allow them to mask their ASD symptoms (Dean et al., 2017; Milner et al., 2019). On the other hand, the severity of ASD symptoms can be greater in females than males upon ASD diagnosis (Kirkovski et al., 2013), which indicates that a higher etiologic load may be required for females to show ASD behaviours, consistent with the female protective effect (Elsabbagh, 2020; Robinson et al., 2013).

1.3 Co-occurring Conditions

Autism Spectrum Disorder is frequently reported to co-occur with other conditions, with approximately 70% of autistic individuals having at least one co-occurring condition (Ameis & Szatmari, 2015) although challenges in their diagnosis exist in standard clinical practice (Lai et al., 2019). Co-occurrence could be the result of several factors, such as early life experiences related to being autistic (Fuld, 2018) or possible common underlying processes that transcend diagnostic boundaries (Stefanik et al., 2018). Frequent mental health co-occurring conditions include developmental coordination disorder, Attention Deficit Hyperactivity Disorder (ADHD), anxiety disorder, intellectual disability, feeding and eating disorder, disruptive behaviour, bipolar disorders,

schizophrenia disorder, Obsessive Compulsive Disorder (OCD), somatic symptom and related conditions, and sleep-wake disorders (Lai et al., 2019; Micai et al., 2023). In addition to mental health conditions, co-occurrence with medical conditions have also been found in ASD, with the most frequent being motor problems, obesity, elimination disorder, organic nutrition disorder, and gastrointestinal disorder (Micai et al., 2023).

Prevalence of these co-occurring conditions appears to differ by age group. For instance, ADHD, sleep-wake problems, somatic symptom and related disorders, and celiac disease have been found to be more prevalent in children and adolescents, while conditions such as depressive, bipolar, schizophrenia spectrum disorders, motor problems, gastrointestinal and depressive disorder, epilepsy, hearing disorder, and neurocutaneous disorder have been shown to be of higher prevalence with increased age and in autistic adults (Lai et al., 2019; Micai et al., 2023). Furthermore, prevalence rates vary considerably, possibly due to the heterogeneity of ASD, differences in study designs or even sociodemographic characteristic differences (e.g., socioeconomic status) (Havdahl & Bishop, 2019; Lai et al., 2019). Co-occurring conditions can contribute to ASD severity (Havdahl et al., 2016) and tend to persist over time (Simonoff et al., 2013) which can have implications on health, quality of life and psychological well-being.

1.4 Aetiologic Factors

Since the vastly disproved theory that prevailed around the 1950s and 1960s for a cold, rejecting parenting being the reason behind ASD (Bettelheim, 1967), researchers have made great efforts to delineate the etiologic factors of ASD. Twin studies were conducted, indicating that ASD has some genetic contribution, though the genes involved in the development of the condition were unknown. In turn, molecular genetic studies contributed to the identification of the genetic variants associated with the ASD phenotype. As a complex, heterogeneous disorder, ASD is hypothesised to be caused, not

only by genetic but also by environmental factors, or a combination of both. Yet, no single cause has been identified and evidence is still inconclusive. The following section provides a brief overview of the hypothesised factors contributing to ASD.

1.4.1 Genetic Heritability

1.4.1.1 Twin and Family Studies. A genetic influence in ASD could be inferred through twin studies. If the expression of a trait is influenced by genetic heritability, greater phenotypic similarity between relatives is expected to go in conjunction with increased genetic similarity. However, similarities shared between close relatives could also be due to shared experiences in the environment. Twin studies aimed to disentangle this by comparing monozygotic twins (MZ, identical twins) with dizygotic twins (DZ, fraternal). These pairs of relatives share the same environment but differ in their genetic resemblance. The former are hypothesised to have 100% genetic similarity compared to the latter who have a genetic similarity of around 50%. An estimate of heritability can be taken by comparing MZ and DZ twins, with a higher degree of difference in trait similarity between MZ than DZ twins indicating a greater genetic influence (Masini et al., 2020).

Early twin studies showed that heritability (or the proportion of ASD liability accounted for by genetic factors) was estimated to be approximately 90% (Bailey et al., 1995; Folstein & Rutter, 1977; Steffenburg et al., 1989). These studies suggested that ASD phenotypic concordance was higher for MZ (91% to 93%) than for DZ twins. Later large-scale population genetic studies painted a somewhat different picture and were contradictory, with some revealing that the ASD phenotypic variation was explained by genetic and shared environmental factors (Frazier, Thompson, et al., 2014; Hallmayer et al., 2011), and others suggesting an elevated genetic influence and smaller or no shared

environmental effects (Colvert et al., 2015; Sandin et al., 2014). The disparities in findings may have been due to methodological differences or sampling bias (Colvert et al., 2015). More recently, a meta-analysis involving 6,413 twin pairs showed considerable heritability (64-91%) and a high concordance between MZ twins (.98) compared to DZ twins (.53-.67, depending on prevalence rate; Tick et al., 2016). They also found that, with a reduction in prevalence rate, shared environmental contributions became significant (7-35%), suggesting that previously reported environmental effects may have been due to sampling ascertainment or statistical artefacts.

Family studies have also demonstrated that the susceptibility of ASD depends on the amount of relatedness and genome shared with an affected relative, with the relative likelihood of ASD diagnosis increasing with increased relatedness (Constantino et al., 2013; Grønberg et al., 2013; Hansen et al., 2019; S. Xie et al., 2019). For instance, a multi-national population-based cohort study examining the recurrence of ASD among siblings and cousins of diagnosed individuals found that siblings had an 8-fold increase in the odds of receiving an ASD diagnosis compared to a 2-fold increase for cousins (Hansen et al., 2019). In fact, later-born siblings of children diagnosed with ASD represent one of the most well-studied populations. Prospective research investigating ASD recurrence estimates in infants with an older autistic sibling identified that infants with at least one affected proband had a recurrence rate of 18.7%, a higher estimate compared to what had previously been found (Constantino et al., 2010; Ritvo et al., 1989).

However, later-born siblings of autistic individuals and other first-degree relatives (e.g., parents) who do have a diagnosis of ASD may themselves exhibit subclinical traits related to the condition, which is referred to as the Broader Autism Phenotype (BAP). For instance, research shows that, at 3 years, a proportion of non-ASD siblings of autistic individuals exhibit higher scores related to ASD severity, lower scores in verbal and non-verbal functioning, higher levels of developmental delay as measured through

standardised assessments, as well as higher parent-reported ASD symptoms and lower adaptive skills compared to controls (individuals with no relatives with ASD) (Charman et al., 2017; Messinger et al., 2013). These ASD-related behavioural characteristics appear to be more prevalent in males than females. Moreover, a percentage of parents of autistic probands ranging from 2.6% to 80% in different studies also display the BAP which seems to be more frequent in fathers than mothers (Rubenstein & Chawla, 2018). Social communication, pragmatic language difficulties, and rigid or aloof personality characteristics are some of the most consistently reported subclinical traits exhibited by parents (Ruparelia et al., 2017). In addition, the BAP expression is shown to be more consistently presented in parents or siblings of multiplex (families with multiple affected individuals) than simplex (families with a single affected individual) families (Frazier et al., 2015; Losh et al., 2008). The above studies focusing on the BAP of unaffected relatives emphasised that the heritability is not limited to ASD diagnostic borders. Overall, twin and family studies informed for a strong genetic component in the likelihood of ASD onset, which led to research looking further into the genetic variants responsible for ASD susceptibility.

1.4.1.2 Rare Variation. Knowledge of the genetic aetiology of ASD derives largely from research showing that de novo, rare, inherited variants contribute to ASD susceptibility. Rare variants are shared only with a low percentage of the population (0.5-5%), while an even smaller (< 1%) proportion is unique to the individual or is shared with the close family (Bourgeron, 2015). These variants are part of rare genetic syndromes which are found in around 10% of individuals with ASD (Devlin & Scherer, 2012), including, but not limited to Rett syndrome, Fragile X, neurofibromatosis, tuberous sclerosis and Williams-Beuren syndrome (Woodbury-Smith & Scherer, 2018). A single alteration in the genome has been hypothesised to be able to drive ASD susceptibility.

Research on whole genome rare variants involved copy number variants (CNVs), referring to variations in the number of copies of part of the DNA, including deletions and duplications (Bourgeron, 2015). Indeed, microarray analysis studies reveal that gene deletion or duplication is involved in ASD. For instance, compared to controls, individuals with ASD have been shown to carry an elevated load for de novo mutations, with an increase in de novo CNVs (Pinto et al., 2014). In particular, large or overlapping CNVs have a high mutational load for ASD subjects, while some subjects carry more than one deleterious CNV (Bourgeron, 2015; Pinto et al., 2010, 2014).

Furthermore, large-scale whole exome sequencing (WES) studies have identified de novo and inherited rare variants linked to ASD. One of the most recent and largest WES studies to date ($N = 35,584$, $n = 11,986$ with ASD) integrating de novo and case-control rare variation found 102 ASD-susceptibility genes as well as a 3.5 fold and a 1.2 fold increase in de novo protein-truncating variants (PTVs) and inherited PTVs, respectively (Satterstrom et al., 2020). Further, studies involving probands with ASD and their unaffected siblings show a greater amount of de novo mutations in the former than in the latter group (Krumm et al., 2014; O’Roak et al., 2014), while in families with both siblings with an ASD diagnosis, the degree of de novo mutations between them appears to be similar (Yuen et al., 2015). However, there are instances where mutations implicated in ASD seem to differ between affected siblings, who exhibit more variability in their clinical expression than siblings who share an ASD-related mutation (Yuen et al., 2015).

1.4.1.3 Common Variation. In addition to rare variation, emphasis has also been given to the role that common variation plays in ASD liability (Klei et al., 2012), in which, a great proportion of genetic variants an individual carries ($> 95\%$) are shared with 5% or more of the global population. Gaugler et al. (2014) investigated the genetic architecture of ASD, showing that accumulated common genetic variants explained a

large proportion of ASD liability (up to 50%), which was consistent with a polygenic risk of ASD. However, several genome-wide association studies (GWAS) for the identification of common variants have not been very fruitful, as they have not reached the genome-wide significance threshold (e.g. Anney et al., 2012). A recent GWAS case-control meta-analysis of 18,381 cases and 27,969 controls identified 5 risk loci (Grove et al., 2019). A meta-analysis of Grove et al.'s (2019) findings identified another candidate gene associated with ASD liability (Matoba et al., 2020). Individual common variants (single nucleotide polymorphisms, SNPs) show modest effects on ASD susceptibility (Anney et al., 2012). As a result, larger sample sizes might be necessary to increase the power to detect significant effects, such as those employed by GWASes for psychiatric disorders like schizophrenia (36,989 cases and 113,075 controls; Ripke et al., 2014).

An increasing focus in GWAS is the use of the polygenic risk score (PRS) approach, which is the weighted average of common gene risk variants found in an individual (Lewis & Vassos, 2020). Using this approach, studies have shown polygenic correlations between ASD and other conditions. Indicatively, associations have been observed between PRS for ASD and cognitive ability (Clarke et al., 2016), as well as between a higher genetic risk for ASD traits and schizophrenia in probands with childhood-onset schizophrenia than their unaffected siblings (Ahn et al., 2016). In another GWAS, PRS for ASD explained 0.11% of the phenotypic variance in OBD (Guo et al., 2017). These findings denoted that the co-occurring conditions observed in ASD could be explained, in part, by the implication of multiple risk genes of a small additive effect.

1.4.2 Environmental Factors

While genes evidently play a predominant role in ASD etiology, they do not entirely explain ASD. A substantial proportion of the variance of ASD liability can be explained by common (shared environment) or unique (stochastic) environmental effects

(41% based on Gaugler et al., 2014). Various prenatal, perinatal and postnatal environmental factors have been suggested to increase the susceptibility to ASD diagnosis.

Accumulating evidence shows that some of the prenatal factors implicated are related to maternal health during pregnancy, such as vulnerabilities linked to the immune system (Elsabbagh, 2020). Such factors include maternal autoimmune disease (S. Chen et al., 2016), autoimmune disease in family members (Wu et al., 2015), or maternal infection which could lead to inefficient immune activation (Bölte et al., 2019; H. Jiang et al., 2016). Factors related to nutrition, such as obesity and diabetes in mothers have also been postulated to increase ASD liability (Y.-M. Li et al., 2016; H. Wan et al., 2018), and maternal nutrition appears to interact with the immune system, both modulating gene expression processes and influencing prenatal brain development (Elsabbagh, 2020). Another factor concerns parental age, with evidence showing that advanced maternal and paternal age as well as an increased age gap between the parents increases the likelihood of ASD in the offspring (Sandin et al., 2016). In addition, the use of selective serotonin reuptake inhibitors (SSRIs) following a diagnosis of depression, assisted reproductive technology and maternal migration linked to stress or low levels of vitamin D have also been considered (Bölte et al., 2019). The last two environmental factors could lead to alterations in epigenetic mechanisms (Elsabbagh, 2020).

In addition, research has linked several perinatal and postnatal factors with the probability of an ASD diagnosis. Some perinatal factors include birth injury or trauma, caesarean delivery, umbilical cord complications, gestational age ≤ 36 weeks, and complications resulting from hypoxia, while some postnatal factors involve low birth weight, postpartum haemorrhage, male sex, and brain anomaly (Bölte et al., 2019; E. A. Curran et al., 2015; Wang et al., 2017).

Overall, the above evidence suggests that ASD does not have a single cause and multiple mechanisms are likely implicated. Although several lines of evidence propose an environment-ASD association, the causal factors linked to ASD liability have not been clarified yet.

1.5 Why is Early Development Important to Study?

Investigating aspects related to the development of neurodiverse (referring to people with diverse abilities and brain function, as part of normal variation in the population) individuals or those with an increased likelihood of neurodevelopmental conditions (conditions that affect brain development and function with an impact on behaviour and cognition) very early in life is paramount for several reasons. First, brain development is an ongoing process that begins in utero and continues postnatally until early adulthood. During early postnatal life, the brain develops at a remarkable pace. Within year one, the brain increases in volume and synaptic density quadruples, reaching greater levels than the adult brain over the first years, followed by a subsequent regression (Johnson & Haan, 2015). The basic structural and functional brain organisation is in place by the age of 2 (or earlier), followed by refinement and reconfiguration of the already formed major circuits and networks (Gilmore et al., 2018). This period of brain growth and specialisation is accompanied by and sets the stage for the development of significant cognitive abilities (e.g., memory) and behaviour (e.g., motor coordination) (Tierney & Nelson, 2009). Thus, brain development and maturation are characterised by complex processes that act hierarchically and in parallel, with more complex connections built upon earlier simpler ones in a bottom-up manner. Attempting to separately analyse these systems in the adult brain or after incidents of brain damage or diagnosis of neurodevelopmental conditions has proven to be difficult (Johnson & Haan, 2015). Therefore, focusing on early development is important as it is a period of brain growth

and change that constitutes the foundation for a range of behaviours and because it allows us to distinctly unravel hierarchical components of the infant brain, enabling a better understanding of the biological and neurocognitive processes linked to later behaviours.

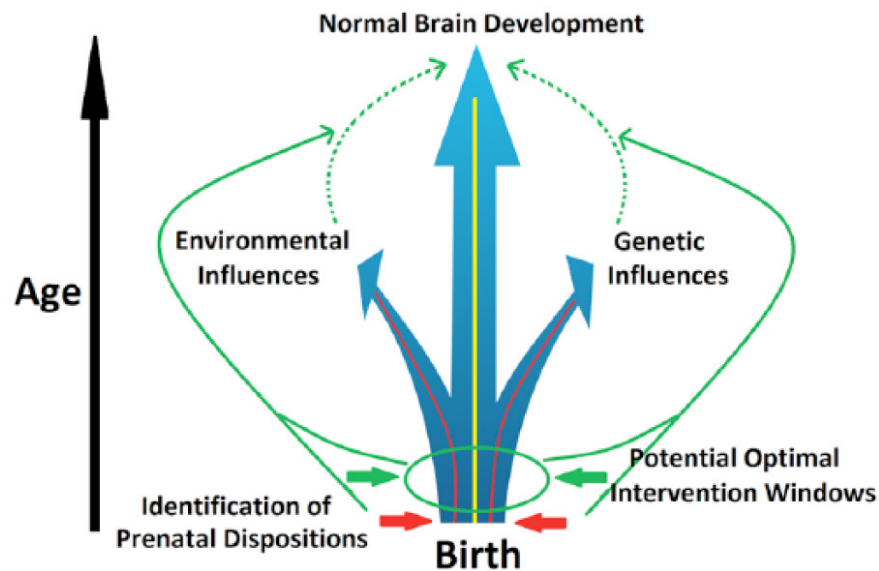
Furthermore, early development presents a window of opportunity and a point of vulnerability. The early years of life are a critical period of experience-dependent and experience-expectant increasing brain plasticity that is not indefinite (Andersen, 2003; Johnson & Haan, 2015). This means that early experiences can shape the structure and function of the developing brain and that appropriate early environmental input is necessary for neurotypical development. For instance, in the first months of life, infants can discriminate sounds from different languages, but as they grow older, this discrimination becomes specific to their native language (Kuhl, 2004). This is a result of brain specialisation to language infants are exposed to in their environment, a procedure of perceptual narrowing that happens in early life and is important for the development of subsequent language skills (Kuhl, 2004). This does not mean that infants are not able to learn sounds from different languages as they grow older. As the maturing brain becomes more specialised with experience across developmental time, future re-organisation or modification of already biased brain networks that took place in infancy becomes difficult (Tierney & Nelson, 2009). The importance of timing has also been evidenced in a study revealing that institutionalised children who received foster care intervention early (before 2 years) had better cognitive outcomes than those placed in foster care later (Nelson et al., 2007).

Considering these points, examining aspects of brain function and social experiences in the context of ASD emergence early in development is of substantial importance. As shown in later sections, later-born siblings of children with autism (considered to be at an Elevated Likelihood (EL) for ASD) and those with a subsequent diagnosis show early brain processing alterations before the appearance of overt

behavioural signs. These neural alterations might impact how these infants experience and respond to their environment in subtle ways that become clearer later in life, restricting opportunities for learning and leading to cascading effects on socio-cognitive functioning (E. J. H. Jones et al., 2014). Early compensatory or protective factors may also contribute to phenotypic characterisation later in life (Gliga et al., 2014). Consequently, the ASD characteristics shown at the time of diagnosis could be the result of neurodevelopmental atypicalities, compounded effects and adaptations within the child's environment stemming from several years of neurodiverse development (Gliga et al., 2014). Therefore, investigating aspects of development before diagnosis is critical to illuminate the neurocognitive, environmental and possible protective factors influencing later developmental outcomes and for informing early intervention efforts in a period of prodromal susceptibility for ASD constituting a window of opportunity due to maximal neuroplasticity (Klin et al., 2020) (**Figure 1.1**). The earlier the intervention takes place, the better the developmental outcomes (Daniolou et al., 2022).

Figure 1.1

Genetic and Environmental Risk Factors Affecting Brain Development and the Importance of Early Identification and Intervention



Note. Adapted from Gao et al. (2017). Genes and environment have an influencing role on the (re)organisation of brain functions across development. The characterisation of brain function capabilities early in development is important for understanding the developmental processes linked to phenotypic outcomes and for the early identification of possible prenatal dispositions. This can facilitate preventing intervention targets to rectify abnormal developmental routes in the first years of life, a critical developmental window representing the most modifiable stage of development (Gao et al., 2017).

1.6 Studying Infant Siblings

This PhD work employs a prospective infant sibling design to gain a greater understanding of how parent-infant free play interactions unfold over time and how they relate to infant brain function in the context of ASD. To better understand the developmental processes underlying ASD or ASD traits and the mediating factors of genotypic-phenotypic associations, many studies have employed the prospective design on infant siblings, whereby the development of infant siblings of autistic children is assessed prospectively from birth until the age where ASD is typically diagnosed. The infant sibling design was largely motivated by findings from research demonstrating that ASD recurrence increases with increased relatedness. As already mentioned, the incidence of ASD in infant siblings of autistic children is much higher than in more distant relatives or the general population (Constantino et al., 2013; Hansen et al., 2019; Ozonoff,

Young, et al., 2011; Risch et al., 2014; Zeidan et al., 2022). In addition, first-degree relatives of individuals with the condition can develop subclinical traits of ASD (Rubenstein & Chawla, 2018), suggesting that familial liability and common factors can affect the expression of behavioural characteristics. Moreover, studies reported a discontinuity in the timing of parent concerns (approximately 12 to 18 months) and the mean age of diagnosis (after 4 years of age) (Szatmari et al., 2016). Research employing a retrospective design was valuable for increasing our knowledge of the development of ASD, however, relying on parent recall, home videotapes or medical records had limitations, such as parent selective memory of symptoms or the inability to examine patterns of behaviour over developmental time (E. J. H. Jones et al., 2014; Szatmari et al., 2016).

Prospective studies of infant siblings have been able to observe patterns of development of infants at EL and those at Typical Likelihood (TL, infant siblings of neurotypically developing children) over several time points through a series of assessments. More specifically, in studies using the infant sibling design, EL infants are usually followed longitudinally from birth until 3 years of age, where they undergo clinical assessments by expert clinicians (Elsabbagh & Johnson, 2010). During this 3-year period, infants attend several lab visits where data are collected to track and evaluate patterns of characteristics through various measures, including parent interviews/questionnaires, standardised behavioural assessments, eye-tracking and neuroimaging experimental methods. This provides researchers with the opportunity to carefully examine the development of features of these infants retrospectively following clinical assessment and diagnostic classification at 3 years. Investigating aspects of infants who later do or do not meet the criteria for ASD diagnosis early in development using various measures has made the identification of early neural and behavioural signs prior to the appearance of full clinical symptoms possible. Furthermore, this design has

allowed the examination of distinct developmental trajectories of EL infants who later develop ASD as well as those with non-ASD outcomes at the neural and behavioural level, which can provide insights into the risk or protective/resilience factors of later developmental outcomes (Elsabbagh & Johnson, 2010; Newschaffer et al., 2012).

1.6.1 The Contribution of Infant Sibling Studies

The prospective studies of infant siblings of children with ASD have provided fundamental insights into the temporal onset of neurocognitive and behavioural markers of ASD. These studies have revealed that, within the first year, neural markers are more sensitive predictors of ASD than behavioural features (see following sections for details). Within the first year (around 6-8 months), infants who later develop ASD appear to be typical in a range of behavioural features (E. J. H. Jones et al., 2014), but atypicalities begin to become apparent around the first year of life and increase in severity over time (described in later sections) (Rogers, 2009). For instance, infants with emergent ASD begin to exhibit declining trajectories in social engagement and social communication across the second year of life (Ozonoff et al., 2014). At 14 months, behavioural markers evaluated from behavioural and developmental measures appear to have some predictive accuracy in determining a 3-year ASD outcome (Bussu et al., 2018), while an ASD diagnosis can be determined with high stability by 18-24 months, indicating that a diagnosis at this age has a high probability to be retained (Ozonoff et al., 2015; Szatmari et al., 2016).

In addition, infant sibling studies have provided important information on phenotypic expression, revealing the existence of high heterogeneity in developmental outcomes and behavioural characteristics predictive of ASD. For instance, studies using this design have shown that approximately 10-20% of EL infants who do not receive a later diagnosis may experience other developmental challenges (Charman et al., 2017;

Georgiades et al., 2013; Messinger et al., 2013), which may be a result of an interaction between protective and risk factors (Szatmari, 2018). Other studies have demonstrated that different combinations of behavioural characteristics are predictive of ASD outcome (Chawarska et al., 2014; Szatmari et al., 2016). Infant sibling studies have led to propositions that some symptoms driving variability in developmental outcomes may reflect genetic and environmental vulnerabilities, while others might be a result of compensatory processes that could have a protective effect or represent compounding effects from interactions between different risk factors and the environment (Gliga et al., 2014; Johnson, Gliga, et al., 2015).

Finally, infant sibling studies have led to understanding the value of using multiple measures and dimensional rather than categorical approaches to better capture the developmental processes leading to typical or atypical development. For instance, apart from the core behavioural features of ASD in the social domain, studies employing multiple behavioural and developmental measures have revealed that non-social atypicalities also appear in parallel or even before the emergence of core features, such as in early sensorimotor (Estes et al., 2015) or motor skills followed by social domain atypicalities (Bussu et al., 2018).

Overall, findings from infant sibling studies have played an important role in informing early interventions and clinicians regarding the various behavioural patterns and core emerging symptoms of the ASD phenotype (Szatmari et al., 2016). Findings from these studies providing evidence for the early behavioural symptoms of ASD are provided below.

1.7 Early Behavioural Markers of ASD

Symptoms of ASD manifest early in development (around/after the first year of life) and a clinical diagnosis is typically made by the age of 2 to 3 years on the basis of

behavioural characteristics (Zwaigenbaum et al., 2009). Behavioural symptoms can change children's attention and understanding of the environment, and can further decrease their opportunities for social learning (Jones et al., 2014). Indeed, parents of children later diagnosed with ASD have reported concerns regarding their infant's social behaviours expressed through reduced play, eye contact, affect and joint attention (Clifford & Dissanayake, 2008; Gillberg et al., 1990) as well as declining interest in faces and attention shifts to a person from a toy or object (M. A. Feldman et al., 2012). This has led to a range of behavioural studies focusing towards identifying early markers of ASD diagnosis by following a familial design.

Given the high heritability of ASD in close relatives, especially in later-born siblings of autistic children, researchers can track the behaviours of these siblings prospectively from infancy until the age of ASD diagnosis (Jones et al., 2014; Zwaigenbaum et al., 2013). A control group of infants at TL can also be followed at the same time for comparison. Using this design, research has identified a number of social and non-social behavioural features characteristic of ASD in infant siblings later diagnosed.

1.7.1 Social Behaviours

1.7.1.1 Social Communication Initiations. In neurotypical development, infants exhibit a range of communicative and emotional signals for social interaction (Trevarthen & Aitken, 2001). Before their first birthday, infants can gesture through pointing which is believed to serve direction of attention or information retrieval (E. Bates & Dick, 2002; Begus & Southgate, 2012). Around 8 to 9 months, infants can also initiate eye contact to share attention to objects or events with others (Mundy, 2018), referred to as initiation of joint attention or gaze alteration. In the context of ASD, behavioural studies with infants

at EL who later receive a diagnosis surprisingly indicate that within the first year of life, these infants show typical patterns in various social and communicative cues (Zwaigenbaum et al., 2005). For instance, a study using the still-face paradigm to investigate social gaze and joint attention in EL and TL infants revealed that EL siblings later diagnosed presented similarities with those not diagnosed and with TL controls in direct gaze, smiles and vocalisations toward their caregivers at 6 months of age (Rozga et al., 2011). Along the same lines, a study using eye-tracking and the still-face procedure showed that infants with a later ASD diagnosis ($n = 3$) displayed typical patterns of face scanning and affect at 6 months, and these measures were not associated with 24-month ASD symptoms (Young et al., 2009).

However, after the first year, delays are observable in social communication initiations in EL-ASD infants. For example, at 12 months, infants at EL with a later diagnosis (EL-ASD) were less likely to use gestures (e.g., pointing or showing) than EL infants without a subsequent ASD diagnosis (EL-no ASD) and those at TL (Rozga et al., 2011). Similarly, a lower inventory in gesture use was shown at 14 months in infants with early ASD signs diagnosed at 30 or 36 months compared to groups with no ASD outcome or those with a 30 or 36-month diagnosis showing no early signs (R. J. Landa et al., 2007). Other research identified that the 15-34-month rate of growth in child-initiated triadic communication (i.e., combination of gestures, vocalisations, gaze shifts) was associated with a 3-year ASD diagnosis and amount of social impairment (Yoder et al., 2009). Reductions in gesture use or in coordination of pointing and gaze after the first year in EL toddlers with a later ASD diagnosis were also reported by parents (M. A. Feldman et al., 2012; Mitchell et al., 2006; Zwaigenbaum et al., 2005).

Furthermore, a decrease in the rate of joint attention initiations at 14 and 15 months was evident in EL-ASD infants compared to groups with no ASD outcome (Cassel et al., 2007; R. J. Landa et al., 2007). Earlier at 12 months, EL-ASD infants did

not seem to differ from TL (Rozga et al., 2011) and non-ASD neurodiverse groups in this behaviour (Macari et al., 2012). However, more recently, Thorup et al. (2018) found that infants at EL at 10 months made fewer gaze alternations during a live interaction compared to the TL group of the same age, which was related to ASD symptoms in the social domain as well as to less pointing behaviour at 18 months. Similarly, Nyström et al. (2019) using a live eye-tracking paradigm indicated that EL-ASD siblings showed lower rates of gaze alteration than infants at TL and EL-no ASD at 10 months.

1.7.1.2 Response to Social Cues. Neurotypically developing infants exhibit a range of communicative signals for social interaction and show an interest in social stimuli (Trevvarthen & Aitken, 2001). Since birth, infants demonstrate a preferential orientation towards social cues, such as biological motion (Simion et al., 2008) and face-like stimuli, particularly when these stimuli include features such as eye-gaze (Farroni et al., 2005; Johnson, 2005) which is considered fundamental for the development of social skills (Baron-Cohen, 1995). For instance, infants have a strong tendency to track face-like configurations (Johnson et al., 1991), prefer to look at faces with direct than averted eye gaze (Farroni et al., 2002) and are sensitive to small changes in gaze direction during interactions with adults (Symons et al., 1998). Eye gaze develops from a basic gaze following in newborns (Farroni et al., 2004) to a more sophisticated response to referential communicative signals, where 6-month-old infants can follow gaze towards objects preceded by direct eye contact with a social partner (Senju & Csibra, 2008), which provides the basis for developing the ability to understand another person's perspective and to attribute mental states to others (Mundy & Newell, 2007). They respond to emotional cues such as crying (Geangu et al., 2010) and can imitate their mothers' vocalisations or actions (Masur & Olson, 2008).

It has been proposed that social and communication atypicalities observed in children with ASD derive from an early failure to spontaneously orientate to social cues in the environment, such as faces (Dawson et al., 1998; Gliga & Csibra, 2007). Chawarska et al. (2013) examined 6-month-old infants' attention to a social scene which was a video of a woman being involved in four different activities with objects. The study found that compared to infant siblings with no later ASD and typically developing infants, not only did those siblings who were subsequently diagnosed with ASD exhibit a decreased attention to the overall social scene, they also tended to look less at the woman and particularly her face. However, a study using a standardised table-top task found that EL-ASD and TL infants did not differ in gaze to faces, smiles and vocalisation rates at 6 months, but a decline in eye gaze and directed vocalisations was shown for the former group by 12 months, and in social smiling by 18 months (Ozonoff et al., 2010).

The disparity in the above findings may have been due to differences in the contexts used, meaning that infants' looking behaviour may be altered if a context is dynamic/complex or more static. In fact, this has been explored by Chawarska et al. (2012) and Shic et al. (2014), demonstrating that EL-ASD children's attention changes depending on condition, with 6-month infants (Shic et al., 2014) as well as 13- to 25-month-old toddlers (Chawarska et al., 2012) with ASD showing less attention to social (i.e. facial features/face speaking) relative to less social (i.e., toys or outer facial features) cues. Additionally, a longitudinal design may be more reliable for capturing early emerging social attention differences between these groups of infants. Longitudinal research using eye-tracking to explore orientation to the eyes during social videos between EL-ASD and TL infants from the age of 2 to 24 months revealed that at 2 months, the two groups did not differ in eye-fixation, suggesting that early developmental mechanisms biasing infants to spontaneously orient to social stimuli are present in this group (Jones & Klin, 2013). In fact, EL-ASD infants fixated more on the eyes, but eye-

fixation was gradually reduced from that age onwards for the EL-ASD infants, with significant differences in eye fixation between EL-ASD and TL infants at 12 months.

Another eye-tracking study using a face pop-out paradigm (a task involving a visual array of items including a face) demonstrated that infants with and without a later diagnosis were equally oriented to faces at 7 months, while at 14 months, the amount of time EL-ASD infants spent looking at faces was longer compared to TL infants (Elsabbagh, Gliga, et al., 2013). A later study looking at peak look durations at the face using the same paradigm showed similar results, with EL-ASD and EL-TD infants showing longer peak look durations to faces compared to those at TL at 15 months, and changes in peak look duration between 9 and 15 months were linked to effortful control (a characteristic of temperament defined as the ability to intentionally manage attention, behaviour and emotion) at 36 months (Hendry et al., 2018). Additionally, through a habituation paradigm, 6-month-old EL-ASD infants showed shorter peak look durations at faces versus objects that were delayed compared to those with no ASD outcome, predicting poorer social outcomes at 24 months. While habituation decreased (shorter peak looks) at 12 months for the latter group, this effect was not observed in the EL-ASD group (Jones et al., 2016). Longer habituation to faces was also observed in 18- to 30-month-old toddlers with ASD that was associated with poorer social and verbal skills (Webb et al., 2010).

The above results suggest that attention engagement and social information processing inefficiencies usually appear towards the end of the first year, they may affect later social skills and could be linked to ASD symptoms. It has been postulated that these findings may reflect emerging differences in endogenous control of attention that guide infants to orientation to social cues on a volitional basis (Colombo & Cheatham, 2006). An alternative theory posits that it is not motivation difficulties, but atypical social

processing interfering with cognitive control mechanisms affecting looking behaviour in late infancy (Hendry et al., 2018).

In addition to social orienting, research evidence suggests that infants with a later ASD diagnosis show differential responses to joint attention, an important skill for social communication and learning. Research exploring gaze following in EL and TL infants after the first year using different types of cues to elicit attention revealed a difficulty of EL infants to follow adult prompts relative to TL infants (Presmanes et al., 2007). Other studies used eye-tracking systems that can track infants' gaze direction when they observe a person performing eye-gaze shifts towards an object. For instance, studies examining gaze following in infants at EL and TL found that infants at 7, 13 and 15 months were able to follow gaze irrespective of ASD likelihood status (Bedford et al., 2012; Parsons et al., 2019), but after the first year, those later diagnosed with ASD showed decreased attention to the congruent object after gaze following. This result was explained as an inefficient engagement in joint attention in terms of understanding the communicative role of gaze following, rather than a difficulty in gaze following per se. Furthermore, Thorup and colleagues (2016) used eye-tracking during a social interaction comparing gaze following between a group of 10-month-old EL and TL infants. Two different conditions were used: gaze with head or gaze only of the experimenter directed towards objects. Results showed that TL infants were able to follow the adult's gaze in both conditions, while the EL group seemed to follow gaze more when it was accompanied by a head turn towards the object (Thorup et al., 2016). The above studies highlight that difficulties in emerging joint attention skills as reflected through eye gaze may be associated with later ASD. Thus, joint attention difficulties in EL-ASD infants do not seem to emerge before the first 7 months of life, a period where neural systems of joint attention are also developing for typically developing infants (Mundy, 2018).

Early imitation, an important skill for social learning also appears to be disrupted in ASD. Macari et al. (2012) found that infants at EL diagnosed at 24 months had poor imitation skills at 12 months compared to non-ASD groups, as measured by the toddler module of the Autism Diagnostic Observation Schedule (ADOS). Differences in imitation between EL-ASD and TL controls at 12 months were also observed in another prospective study (Zwaigenbaum et al., 2005). In addition, a further study revealed that relative to EL infants with no ASD outcomes, EL infants diagnosed at 36 months showed decreased imitation of sounds or words at 12, 18 and 24 months (M. A. Feldman et al., 2012). However, other research did not find differences between EL-ASD diagnosed at 3 years and EL-no ASD groups, though the former had delayed imitation skills compared to TL infants between 12 and 24 months (Young et al., 2011).

1.7.1.3 Language. Infants with a subsequent diagnosis of ASD also exhibit delays in language acquisition. In neurotypical development, language develops rapidly over the first years of life, with language comprehension preceding the development of language production. From an understanding of a few familiar words in the second half of the first year, receptive vocabulary increases dramatically towards the second year of life, reaching up to 321 words at 16 months (Fenson et al., 1994). In turn, expressive vocabulary develops from sounds, babbling and vocalisations in the first weeks or months to an accelerated production of words after the first year (Fenson et al., 1994; Jones et al., 2014).

Infant siblings at EL who later receive an ASD diagnosis differ from those with no ASD outcome in both receptive and expressive language after the first year of life (E. J. H. Jones et al., 2014; Zwaigenbaum et al., 2005). For example, a prospective study measuring infants' language and communication skills based on parent reports showed that EL-ASD infants diagnosed at 24 months had a lower understanding of phrases than

EL-no ASD and TL groups at 12 months, while they understood and produced fewer words than the other two groups at 18 months (Mitchell et al., 2006). Another study comparing TL with EL-ASD infants diagnosed at 36 months indicated that the latter group exhibited delays in their expressive and receptive language skills by 12 months (Ozonoff et al., 2010). Delays in early foundational language skills important for the development of language production have also been identified within the first year of life. For instance, EL infants with ASD symptoms at 24 months seemed to have lower expressive language scores (prelinguistic vocal behaviours) at 6 months relative to infants who did not develop ASD symptomatology (Paul et al., 2011a).

1.7.2 Non-Social Behaviours

1.7.2.1 Restricted, Repetitive Behaviours and Sensory Sensitivity. In neurotypical development, motor stereotypic behaviours appear to be common during the first year of life, after which period they follow a decline, followed by the development of neuromuscular pathways allowing the execution of goal-directed actions (Thelen, 1979). In the context of ASD, increasing evidence suggests that these behaviours follow atypical trajectories in infants with a later ASD diagnosis.

Based on retrospective parent reports, autistic children were observed to have increased symptomatology in repetitive behaviour by 10-12 months compared to typically developing children (Werner et al., 2005). Parent-reported infant repetitive behaviour through a prospective study of toddlers clinically assessed for ASD at 2 years also showed a higher degree of these behaviours in EL-ASD than TL and EL-no ASD groups at 12 months (Wolff et al., 2014). Another prospective study of EL and TL infant siblings implemented an object exploration task analysing typical (shaking, banging, mouthing, throwing) and atypical (spinning, rolling, rotating, unusual visual exploration)

object uses by infants at 12 months (Ozonoff et al., 2008). Results revealed that EL infants with 24- or 36-month ASD diagnosis showed more atypical uses of objects, particularly unusual visual object exploration than EL-no ASD and infants who developed neurotypically. In addition, Chawarska et al. (2014) found 18-month repetitive behaviour to be a significant predictor of 3-year ASD outcome. However, a study investigating several stereotypic movements and postures at 12 and 18 months through standardised assessments showed a high overlap between EL-ASD and non-ASD groups in these behaviours (Loh et al., 2007). Only one stereotypic movement (arm-waving) was more frequent in the EL-ASD group at both time points, while at 18 months, one posture (hands to ears) was more commonly observed in the EL-ASD and EL-no ASD groups relative to the TL group. Another study did not find differences in repetitive and stereotyped moves at 15 months between EL-ASD and TL infants, even though the former displayed these behaviours at a higher level (Damiano et al., 2013). This discrepancy in the findings could be due to the behaviours each study measured. For instance, it is likely that atypical behaviours measured by Ozonoff et al. (2008) may be more sensitive early predictors of ASD outcome.

Furthermore, some evidence points to early differences in sensory sensitivity (Canu et al., 2021 for a review), which is incorporated as a subtype of the restricted and repetitive behaviours domain in the DSM-5 criteria for ASD diagnosis. For instance, a study showed that parental concerns about EL-ASD infants' atypical sensory behaviour were evident from as early as 6 months and predicted ASD diagnosis at 3 years (Sacrey et al., 2015). Furthermore, (Zwaigenbaum et al., 2005) found that atypical sensory behaviours (use of play objects in a self-stimulatory, stereotyped manner) at 12 and not at 6 months were predictive of ASD at 2 years. Brian et al. (2008) found EL-ASD and EL-no ASD atypicalities in sensory behaviours (e.g., feeling textures, smelling of toys) compared to the TL group at 18 months. In Germani et al. (2014), parent-reported sensory

atypicalities were observed in response to auditory stimuli and awareness of sensory stimuli in the environment in 24-month-old EL infants diagnosed at 36 months, while Wolff et al. (2019) reported differences in all sensory domains (hyper-hyporesponsiveness, seeking, auditory, tactile, visual) between EL-ASD and infants with no ASD diagnosis at 12 months, becoming more prominent by 24 months. At both time points, most of the sensory domains were associated with restricted and repetitive behaviour. Overall, these research findings propose repetitive behaviour and its subdomain, sensory sensitivity, as early emerging ASD markers, mostly apparent by the first year of life.

1.7.3 Other Non-Social Behaviours

Although not included in the DSM-5 diagnostic criteria for ASD, other non-social behavioural features characteristic of ASD include executive functioning and motor development difficulties.

1.7.3.1 Executive Function. Executive function refers to higher-order cognitive processes that enable goal-driven behaviour, including working memory, inhibitory control and flexibility. These skills typically emerge along with prolonged changes and maturation of brain areas mediating these executive attention domains (Fiske & Holmboe, 2019). Aspects of executive function appear to be affected in EL-ASD siblings, as shown by studies examining non-social attention (Jones et al., 2014). For instance, Sacrey et al. (2013) measured attention when infants from 6 to 36 months were engaged in play with small toys. Attention engagement was measured as the duration of time spent looking at toy targets before reaching with the hand for them as well as after grasping the target. Infants at EL with a 36-month ASD diagnosis had a prolonged latency to disengage from the target compared to EL-no ASD and non-sibling controls at 12, 15, 18 and 24 months.

This “sticky attention” style is also present in typically developing infants but usually disappears by 12 months (Sacrey et al., 2012). Other studies examined attention-shifting in EL and TL siblings using the gap-overlap paradigm, measuring the latency to move the eyes to a peripheral stimulus on the screen after the disappearance of a central stimulus. Using this task, evidence showed that, at around 12-14 months, EL-ASD infants took longer to disengage their visual attention from the central stimulus than the other groups, while no attention disengagement differences were found at 6-7 months (Elsabbagh, Fernandes, et al., 2013; Zwaigenbaum et al., 2005). Using parent-report questionnaires, Zwaigenbaum et al. (2005) also found that EL infants diagnosed with ASD were reported by their parents as having longer fixations to specific objects in the environment at 12 months. Further, this study as well as further research showed that infant siblings with a later diagnosis had less inhibitory control as well as reduced effortful control and effortful emotion regulation after the first year (Clifford et al., 2013; Garon et al., 2009; Zwaigenbaum et al., 2005). This evidence suggests that disturbances in aspects of executive function may be involved in the developmental pathway of ASD.

1.7.3.2 Motor Skills. Several studies have indicated that motor delays are apparent in infants who later develop ASD. In neurotypical development, children gradually accomplish particular gross and fine motor milestones in different time windows during the first years of life, which are accompanied by the development of socio-cognitive functions (Jones et al., 2014). Standardised assessments of fine and gross motor skills have identified significant motor delays in infants with a subsequent ASD diagnosis, with mixed results on the timing of the emergence of early disruptions. Using the Mullen Scales of Early Learning (MSEL), Landa et al. (2012) found increasing delays from 18 to 30 (for gross motor skills) or 36 months (for fine motor skills) in these infants, but not at 6 months. Similarly, Landa & Garrett-Mayer (2006) observed fine and gross

motor delays at 14 months but not at 6 months in the EL-ASD group relative to unaffected infants. At 24 months, the EL-ASD group differed in these domains from unaffected siblings as well as from those with language delays. However, more recently, Estes et al. (2015) found delays in gross motor skills already at 6 months in EL-ASD infants, while both fine and gross motor skill delays in the EL-ASD group were evident at 24 months, differentiating them from EL-no ASD and TL groups. In addition, Iverson et al. (2019) indicated that fine motor skills at 6 months were predictive of a 36-month ASD diagnosis. Other research investigated a component of fine motor ability using the Peabody Developmental Motor Scales, which is a standardised observational measure. Results showed that visual-motor integration at 6 months was predictive of 24-36-month ASD diagnosis (LeBarton & Landa, 2019). Parent reports also indicated lower infant activity as early as 6 months in infants with a later diagnosis of ASD (Zwaigenbaum et al., 2005). Finally, a home-videotaped assessment of infant postural development during play and everyday activities revealed that infants at EL-ASD exhibited fewer posture initiations and had a smaller posture repertoire than EL-no ASD and TL groups between 6 and 12 months (Nickel et al., 2013). Taken together, despite the mixed results on the emergence of motor delays, these findings are suggestive of early motor delays as a characteristic of the ASD prodrome.

Overall, research indicates that infants at EL for ASD show typical patterns of behaviour within the first year, while social and non-social behaviours start to diverge toward the end of the first year of life, affecting infant socio-cognitive functioning and leading to an ASD diagnosis. These studies have been motivated by a number of theories of ASD that aim to provide an explanation of the possible behavioural and cognitive symptoms of ASD. These are described below.

1.8 Theories of ASD Development

1.8.1 Cognitive Theories

Throughout history, the field of ASD has seen the evolution of several sometimes clashing theoretical orientations that have guided researchers, clinicians and policy decisions. Starting from the 1980s, the increasing popularity of cognitive science in psychological disciplines opened the way for the development of different cognitive accounts of ASD. These theories have followed the perspective of the maturational framework. The maturation framework analyses development based on the ‘nature’ rather than ‘nurture’ viewpoint. This domain-specific framework posits that the neuroanatomical maturation of specific brain areas is set by genetic, biochemical, and/or neuroanatomical factors and gives rise to sensory, motor and cognitive functions. Only when an area has reached similar levels to those of adult functioning is considered mature, and this is a one-off, irreversible event (Johnson, 2011). Thus, when a new behavioural ability is achieved at a particular age, this is proposed to be due to the maturation of a new brain region, while an abnormality in any of the processes associated with the maturation of a brain region could eliminate or decrease its function. According to this theory, developmental conditions could result in a deficit located in a particular cortical region with a related cognitive deficit (Johnson, 2001).

Cognitive theories of ASD posited that the core symptoms of ASD could be explained by a ‘primary cognitive deficit’. Three of the most well-known cognitive theories that have been suggested to underpin the core features of ASD are weak theory of mind (ToM, Baron-Cohen, 1990), weak central coherence (Frith, 2003) or executive dysfunction (Ozonoff, Pennington, et al., 1991). The ToM approach postulated that the social difficulties observed in ASD resulted from an inability of autistic individuals to attribute mental states to others. One of the widely used paradigms to test this idea was

the false belief task (a task in which children must infer another person's knowledge based on their actions even if it is considered false information) developed by Wimmer & Perner (1983). In their seminal study, Baron-Cohen and colleagues (1985) found that, compared to children developing neurotypically and those with Down's syndrome, autistic children failed to impute mental states to others. These findings were later replicated using this or other tasks (e.g., the deceptive box, reading the mind in the eyes task, Baron-Cohen et al., 1997; Perner et al., 1989).

The executive dysfunction account emerged from observations that some autistic symptoms were similar to those seen in individuals with specific brain injury. Some of these symptoms were a need for sameness, difficulty switching attention, a tendency to perseverate and a lack of impulse control, which led to the conclusion that ASD could be explained as a deficit in executive function (Rajendran & Mitchell, 2007). Executive function deficits have been identified in individuals with prefrontal cortex damage and those with neurodevelopmental conditions, while research with autistic individuals has reported deficits in different executive function domains regardless of the existence of prefrontal lobe damage (Corbett et al., 2009; Elliott, 2003). Such domains included planning ability, cognitive flexibility, memory or inhibition (Corbett et al., 2009; Ozonoff & McEvoy, 1994; Prior & Hoffmann, 1990; Rumsey & Hamburger, 1988; Verté et al., 2006).

The weak central coherence theory principle was that neurotypically developing individuals process information by being able to derive a holistic meaning from parts of a situation (global coherence) and that ASD was characterised by an absence or difficulty for global coherence. In essence, it was thought that autistic individuals were able to process parts/details from a situation (local processing) and not the global whole, which explained their difficulty interpreting social situations or people's behaviours. This proposition has been supported by studies showing that autistic individuals outperformed

neurotypically developing individuals in local precedence tests (e.g., the block design test and the embedded figures test, Shah & Frith, 1983, 1993) and their performance was poor in tests examining global coherence. For instance, Happé (1996) found that children with autism are not susceptible to visual illusions, arguing that they do not process all the parts of an illusion in an integrative manner, rather they are processing them as separate components.

1.8.1.1 Challenges to Cognitive Theories of ASD. The above theories have been subject to criticism regarding their validity and universality in ASD. Studies testing the ToM deficit have shown associations with verbal skills, suggesting that performance in ToM tasks is affected to some extent by verbal ability (F. G. E. Happé, 1995; Sparrevohn & Howie, 1995). In addition, research has demonstrated that not all autistic individuals have a delay or deficit in ToM (Bowler, 1992; Ozonoff, Rogers, et al., 1991). Another argument has been that the ToM does not represent a sole impairment in autistic individuals. Indeed, children with ASD and patients with lesions in brain areas thought to be responsible for ToM skills (temporoparietal junction and orbitofrontal cortex) have also shown difficulties in social information processing aspects (e.g. eye gaze, facial expressions) (Stone & Gerrans, 2006). Last, the emergence of ToM has been thought to occur at around 3 to 5 years of age, however, evidence shows that markers predictive of ASD emerge after the first year of life.

The executive dysfunction theory has also been shown to be problematic. One problem with the theory is that findings revealing executive function as a deficit in ASD have been conflicting, as not all autistic individuals appear to have difficulties in all executive function domains such as cognitive flexibility, planning, inhibition or memory (Delli et al., 2017; Goldberg et al., 2005; F. Happé et al., 2006; Van Eylen et al., 2011). This might be explained by the high variability in executive function tasks employed,

though replication of previous findings hasn't been achieved even after using the same methodology or tasks (Rajendran & Mitchell, 2007). Furthermore, IQ or task demands may have played a role in executive function skills rather than ASD per se (Rajendran & Mitchell, 2007). Discriminant validity has also been another issue of this theory, with evidence indicating that executive function deficits are not unique to ASD. Although existing evidence shows that autistic children are differentiated from those with Tourette syndrome and ADHD in executive function skills, other studies have not been able to find differences between autistic and other neurodiverse groups (e.g., Nydén et al., 1999).

Inconsistencies have also been found in the weak central coherence theory. Again, evidence supporting this theory has not been consistent across studies (J. A. Brian & Bryson, 1996; Ropar & Mitchell, 1999, 2001). For instance, Ropar & Mitchell (1999) have found that autistic individuals and controls are equally susceptible to illusions. In addition, other research has demonstrated that weak central coherence (through testing lexical ambiguity resolution) is not observed in autistic individuals with language scores within the normal range but in those with comorbid conditions, such as language impairment (Norbury, 2005). This indicates that weak central coherence may not be a universal characteristic of the autistic population. Another limitation is that, over the years, different interpretations of the theory have been suggested and no clear conclusions have been reached (Rajendran & Mitchell, 2007).

A multiple-deficit account has also been proposed, incorporating the three theories described above and suggesting that ASD is explained by a combination of atypicalities in these three domains. However, while evidence for the multiple-deficit account has been shown at a group level, this profile does not seem to be universal at an individual level (Pellicano, 2010). Overall, evidence has put into question the validity and universality of these theories. Although they have significantly contributed to our understanding of ASD, they have failed to explain the variability characterising the ASD

phenotype and so far, findings highlight the challenge of attempting to isolate a particular brain area or skill as being responsible for ASD.

1.8.2 More Recent Models of ASD Development

The twenty-first century was characterised by a shift in theories from viewing ASD as a ‘static’, unitary construct to focusing on its conceptualisation as a developmental condition and on the possible processes and phenomena explaining ASD. Findings from prospective longitudinal studies of infant siblings, research on brain structure and function and brain-behaviour development in the first years of life propelled the development of new conceptual frameworks of ASD. However, concepts are still debated, including two lines of thought. One set of hypotheses, the social-first account, supports that ASD originates from differences specifically in the social domain by focusing on “social brain” mechanisms, and the other proposes a domain-general cause of ASD.

1.8.2.1 Social-First Accounts. In the adult brain, social information is perceived and processed through specialised interacting subcortical and cortical brain regions that make up the so-called ‘social brain network’ (Adolphs, 2009; Johnson, Senju, et al., 2015). Theory suggests that cortical specialisation in development derives from a subcortical route that initially biases the infant to orient to socially relevant stimuli (i.e., face detection). Over the course of development, subcortical structures provide input to cortical brain areas that eventually become part of the ‘social brain network’ (Johnson, Senju, et al., 2015). Therefore, social orienting transitions from an initial reflexive, subcortically mediated response to a more volitional response to social stimuli, controlled by cortical circuits. It has been suggested that any disruptions in the social brain network in sensitive periods could result in decreased responses to social cues, and subsequently

interfere with socially important developmental milestones (Johnson, 2000). This proposition was further reinforced by the aforementioned eye-tracking study by Jones and Klin (2013), demonstrating that eye fixations of infants with emerging ASD were at normative levels at 2 months but presented a subsequent decline. The authors postulated that the observed decline possibly reflected a derailment in the transition from subcortical to cortical, experience-dependent and reward-based circuits guiding attention to social visual stimuli (Klin et al., 2015; Shultz et al., 2018).

Another hypothesis aligned with the notion of social brain atypicality is reduced social motivation. According to this idea, social orienting is not sufficient if there is a lack of motivation for social interaction. Regions related to the social brain (orbitofrontal-striatal-amygdala circuitry) responsible for attributing social reward value to stimuli have been hypothesised to be disrupted in ASD, underlying autistic features and impacting the development of socio-cognitive skills (Chevallier et al., 2012). The notion argues that reduced social interest and initiation for social interaction in ASD occurs as autistic individuals find social stimuli less rewarding. Support for this theory has come from research showing differences between individuals with and without an ASD diagnosis in aspects related to social motivation such as social orienting (e.g., interest in faces, eye-contact), seeking and liking (interest in social engagement) and social maintaining (maintaining social bonds) (Chevallier et al., 2012). Of note, although simple orientation to a face (in an experimental context) could underlie social motivation, it does not necessarily provide strong evidence for it, as it does not require much effort from the infant (Gliga et al., 2014). In addition, support has come from studies revealing differences between EL and TL infants in look duration to social cues (e.g., faces), with EL infants later diagnosed with ASD looking less at social stimuli and showing decreases in social smiles than infants at TL (Chawarska et al., 2013; Ozonoff et al., 2010; Shic et al., 2014).

Despite the evidence in support of the social-first hypotheses, the wide range of early markers of ASD including non-social domains pose challenges to these theories and seem to be consistent with more domain-general, widespread effects. Therefore, it has been suggested that the focus should be on how the information from various stimuli is integrated across different brain areas (Elsabbagh & Johnson, 2016).

1.8.2.2 Domain-General Accounts. According to domain-general accounts, ASD characteristics are the product of compensatory processes from widespread and heterogeneous atypicalities (Vivanti & Messinger, 2021). In contrast to the social-first accounts centring the origin of ASD around the social domain, domain-general theories of ASD posit that early differences in social attention may reflect atypicalities observed more broadly across other non-social domains, such as attentional control and sensory processing. Executive control skills involve the ability to shift visual attention between people and objects in the environment, which appears to differ in infants at EL with a later ASD diagnosis and autistic children (Elsabbagh, Fernandes, et al., 2013; Landry & Bryson, 2004; Sacrey et al., 2013). Indeed, and as described in previous sections, atypical disengagement of attention is a characteristic of ASD. In addition, sensory processing is important for making sense of regularities in the environment and for producing appropriate motor responses. As mentioned earlier, evidence shows that sensory processing is also altered in ASD (e.g., J. Brian et al., 2008). Early atypical sensory processing has been thought to become compounded with the subsequent development of perceptual and cognitive aspects related to processing complex social stimuli in the environment (Gliga et al., 2014). Thus, social attention differences in ASD may result from an initially atypical sensory input.

Furthermore, it has been proposed that neurodiverse social attention in ASD is the end result of the infant's adaptive response to the external environment as a consequence

of suboptimal neural processing caused by different factors (i.e., genetic, sensory, environmental, etc.) or by their combination (Johnson et al., 2015). Signal to noise ratio dysregulation within the brain leading to a reduction in the fidelity of neural processing (expressed through delayed or anomalous specialisation of cortical regions and related microstructures) can have an impact on the brain regions requiring high temporal accuracy to respond to more variable, dynamic and less predictable information, such as attention to social stimuli (i.e., dynamic eye-gaze shifts) or social interactions (Johnson, 2017; Johnson, Jones & Gliga, 2015). Infants' synaptic processing limitations could lead to a more limited selection of information coming from the external environment as a way for the brain to adapt given its own processing capabilities. For instance, the narrowed focus of attention usually observed in ASD could reflect an adaptive brain response to constrain the intake of complex external information into more manageable attention to a certain stimulus. Therefore, it is likely that social symptoms of ASD do not originate from a localised dysfunction in the social brain, but rather from altered neural processing encompassing domain-general effects leading to sensorimotor and social orienting differences between neurotypically developing infants and infants who develop ASD (Elsabbagh & Johnson, 2016).

1.8.3 Theoretical Frameworks for This Thesis

The research reported in this thesis is based on two frameworks for understanding development: the domain-general framework 'Interactive Specialisation (IS)' and the 'transactional model' of development. Compared to other theoretical propositions, these frameworks offer a more dynamic and comprehensive approach to developmental change, in general, and to understanding ASD development, in particular. These frameworks are described in detail below.

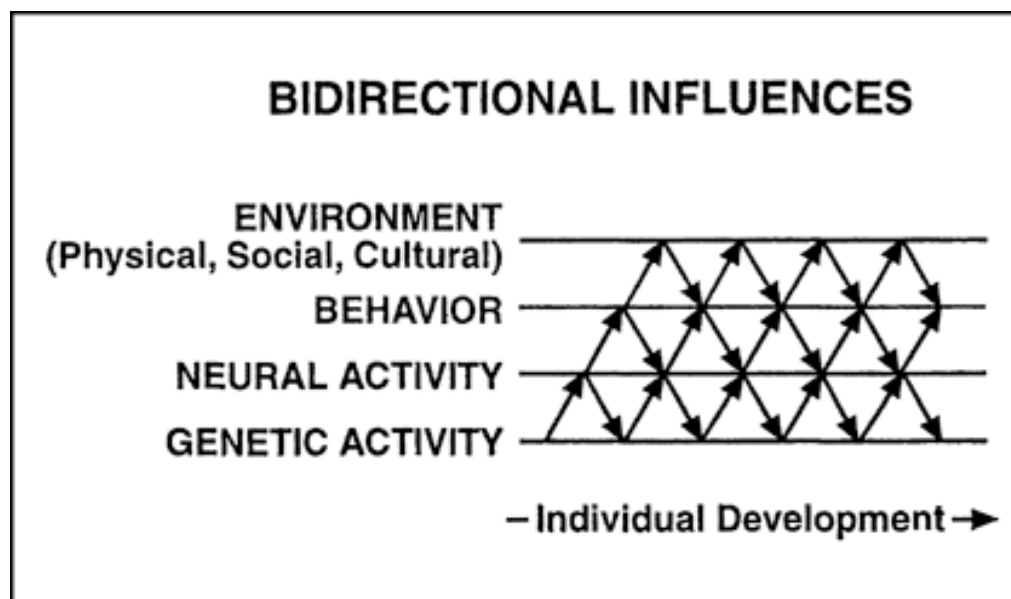
1.8.3.1 Interactive Specialization. The IS theory is a domain-general framework for understanding functional brain development, positing that postnatal brain development occurs through a process of activity-dependent dynamic brain organisation (Johnson, 2000, 2011). This theory lies within the broader framework of “neuroconstructivism” (Karmiloff-Smith, 2009). One fundamental idea of the IS is that competitive and interactive processes of brain regions take place when a new ability is acquired which drives a re-organisation in their response properties during development. Thus, some cortical regions initially have a broad range of functions and gradually become more fine-grained through activity-dependent interactions. This restricts their activity to a smaller number of conditions or inputs, such that they become more specialised across developmental time. A second fundamental idea is that postnatal brain development involves changes in connectivity between cortical regions that shape and influence intra-regional connectivity. The characteristics of responses of a cortical region are defined to some extent by its inter-regional interactions and the activity patterns of these regions. The acquirement of a new skill during early development, therefore, will be the result of activity changes in various networks of regions (Johnson, 2011).

The IS theory has several underlying assumptions. Firstly, it is in line with the “probabilistic epigenesis” model of development (**Figure 1.2**), which stresses that the development of behavioural traits derives from dynamic mutual/reciprocal influences between genes, neural activity, behaviour and the external environment, which contrasts the “predetermined epigenesis” for a one-way path from genes, to brain structure and then to brain function (Gottlieb, 2007). Secondly, as briefly discussed earlier, the IS theory emphasises the importance of interactive processes and brain networks. This assumption suggests that inter-regional connectivity drives cortical specialisation and it borrows principles from the adult functional neuroimaging literature that a cognitive task is supported by the interaction of a large number of specialised cortical networks (Johnson

et al., 2005). Extending this idea, the IS suggests that development and cognitive functions are dependent on interactions between regions and regional connectivity patterns. A third assumption focuses on brain development involving a self-organising and activity-dependent process, such that infants are driven to selective environmental stimuli that help their brains to further specialise (Johnson, 2000). A fourth and last assumption supports a dynamic mapping between cognitive functions and their underlying brain structures, such that a new ability is followed by a re-arrangement of inter-regional interactions and as a result, by changes in how cognitive functions are supported by brain structures and regions across development.

Figure 1.2

The Metatheoretical Model of Probabilistic Epigenesis by Gottlieb



Note. The model illustrates four levels of analysis that are bidirectionally affected across development: Genetic activity, neural activity, behaviour and the physical, social and cultural properties of the external environment. Adapted from Gottlieb (2007).

As described by Johnson (2011), the IS theory has several predictions, allowing it to formulate testable hypotheses. Some of these predictions are from the “Interactive”

part and some others from the “Specialisation” part. The latter part included the following hypotheses: Increased brain specialisation should be evident from neural responses that become selective to particular stimuli with age, whereas they were previously been elicited by other related stimuli; as part of neural specialisation, the brain will respond less to non-preferred stimuli, and thus, the degree of cortical tissue activation to a stimulus presentation will be reduced; it is expected that there will be a link between the extent of specialisation for a stimulus with the extent of localisation; after brain damage or sensory deprivation, brain plasticity will depend on the amount of existing functional specialisation, such that less specialised regions will be more plastic and vice versa. Regarding the interactive part, the hypotheses are as follows: behavioural changes during development will be expected to be coupled with changes in various cortical regions; specialisation will move from regions to networks over time that will be activated to a narrow set of stimuli; single cortical regions will become specialised through their connection with functional networks.

These hypotheses have been addressed and supported by several lines of research investigating face perception, social cognition, word learning, reading, executive function and resting state networks through functional connectivity analysis (e.g., Fair et al., 2007; Gathers et al., 2004; E. J. H. Jones et al., 2015; Lloyd-Fox et al., 2009; Luna et al., 2001; Schlaggar & McCandliss, 2007).

1.8.3.1.1 IS in the Context of Atypical Development. Following perspectives from the neuroconstructivist and probabilistic epigenesis approaches underlying development as a product of bidirectional influences between the individual and the environment, the IS theory proposes that developmental disorders do not emerge from localised neural defects in single regions, rather they result from diffuse deviations in widespread cortical structures (Johnson et al., 2002). In addition, contradicting traditional

deficit assumptions for a one-way path between a particular neural deficit to a behavioural abnormality, the IS approach suggests that, in developmental disorders, brain development follows an alternative developmental route with individuals varying in their cognitive and behavioural abilities. Therefore, different patterns of neural activation to a stimulus are expected across developmental time due to delayed or aberrant brain specialisation. For instance, it has been suggested that autistic children engage different brain mechanisms of processing eye gaze than typically developing children (e.g., same neural processing of social and non-social stimuli compared to typically developing children) and infants later diagnosed display an absence of differential sensitivity to eye gaze, indicative of a failure or delay in social brain network specialisation (Elsabbagh, Mercure, et al., 2012a; Johnson et al., 2005). In addition, individuals may show various profiles including typical or even superior competencies. For instance, infants with a later ASD diagnosis have been shown to exhibit enhanced visual search performance (Gliga et al., 2015).

Last, the IS framework maintains that, in neurodevelopmental conditions, sampling from the environment might differ. In ASD, it has been postulated that an abnormality or failure in the mechanisms biasing the infants to orient to social stimuli might be further amplified through interactions with the external environment, contributing to later social communication difficulties (Elsabbagh & Johnson, 2010). For instance, reduced social engagement in infants with an increased likelihood of ASD might lead to fewer parental responses towards the infant, which can, in turn, result in fewer infant social experiences. Subsequently, this can result in the emergence of symptoms affecting social functioning. Parental perceptions of infant atypical development might lead to fewer opportunities for environmental exploration from infants and thus, to increasing differences in the way the environment is sampled in atypically developing infants compared to those developing neurotypically (Karmiloff-Smith, 2009).

1.8.3.1.2 IS: Supporting Evidence and Challenges to the Framework. A great deal of evidence in support of the IS framework has come from neuroimaging research investigating domains of the social brain that are considered to be emerging as large-scale networks, increasingly becoming specialised to narrow stimulus categories with experience and age. Face perception has been a prominent domain of the social brain in explaining functional brain development through the IS. In addition, the IS framework has been applied to provide clarification around unresolved questions about the neural underpinnings of the specialisation of face-sensitive cortical areas, taking into account the importance of both intrinsic and extrinsic factors (Johnson, 2011). According to the IS view, developmental changes take place in both the specialisation and localization of neural responses to faces. This assumption has been supported by Functional Magnetic Resonance Imaging (fMRI) studies providing evidence for an increasing cortical specialisation in response to faces (Aylward et al., 2005; Gathers et al., 2004; Golarai et al., 2007). For instance, research investigating neural responses to faces and objects in children at different ages and adults showed that only older children (9-11- and not 5-8-year-olds) and adults showed fine-tuned face-preferential responses compared to objects (Gathers et al., 2004). A similar study investigating neural responses to faces and houses in 8-10- and 12-14-year-old children revealed that, in contrast to younger children, older children had an increased cortical activation to areas related to face processing (bilateral fusiform gyrus) when viewing faces compared to houses (Aylward et al., 2005), localized to the right hemisphere. In addition, evidence in support of the IS view has come from Event-Related Potential (ERP) studies, which have shown an increased cortical specialisation related to face processing with age, with changes in the magnitude and localisation of neural responses (de Haan et al., 2002). For instance, a study suggested that, similarly to adults, 12-month-old infants had differential neural responses between

inverted and upright human faces through the N290 face-sensitive ERP component, considered to be the precursor to the adult N170 component (de Haan et al., 2003; Halit et al., 2003), a pattern not observed in infants at younger age. Although younger infants could differentiate between the two stimuli through a different component (the P400), an N290 response was not observed until later, indicating that, as age increases, the N290 component becomes more sensitive and specialised to upright human faces (de Haan et al., 2003; Halit et al., 2003). These results provide evidence that both infant preferential orientation to the processing of faces and experience from the external environment drive gradual changes in the degree of specialisation and localization of cortical activity and responses resembling those of an adult.

Some of the challenges to the IS framework also need to be acknowledged. As described by Johnson (2011), the concentration in the degree of cortical region activation as a result of specialisation could be due to methodological artefacts. In particular, it has been suggested that the distributed neural activation observed in children relative to focal activation shown in adults could be due to activation maps including response errors (T. T. Brown et al., 2006). However, this explanation appears non-plausible, considering the convergence in results by various fMRI and ERP studies using different methodologies, age groups and analytical approaches, strengthening the reliability of the observed patterns in the data.

Another challenge is that some evidence supporting the IS theory could also be used to explain other theories (e.g. maturational or experience account). For instance, the IS view for an increased specialisation of a particular cortical region for faces with age is also consistent with the maturation framework (Joseph et al., 2011). Nevertheless, the IS view combines perspectives from different frameworks to explain that dynamic mechanisms are involved in development as opposed to a single process, encompassing different predictions, some of which are different to existing ideas (Johnson, 2011). One

differentiation to the maturational framework, for instance, is that the IS view supports that broadly defined cortical activation precedes more specialised brain activation to a specific stimulus shown with age, while the maturational account suggests cortical activation of a region can only be seen with specialisation in adulthood (Joseph et al., 2011).

1.8.3.2 The Transactional Model. To better understand the processes that drive variability in developmental outcomes, a model that considers both individual and contextual transactions is necessary. With this in mind, Sameroff and Chandler (1975) introduced the transactional model of development. This model proposes that developmental outcomes are driven by the ongoing dynamic interplay between the individual and their family or broader social environment (A. J. Sameroff, 1993). The model presents similarities with the probabilistic epigenesis model. Thus, the central idea of this model is that developmental outcomes are not only influenced by processes within the child following a linear trajectory, nor they are affected by the environmental context alone. Models focusing on one of these aspects can be misleading. In addition, models viewing the interactions between the child and the environment as constant over time are not appropriate. Instead, the emphasis should be placed on the dynamic, continuous and plastic child-context interrelationships.

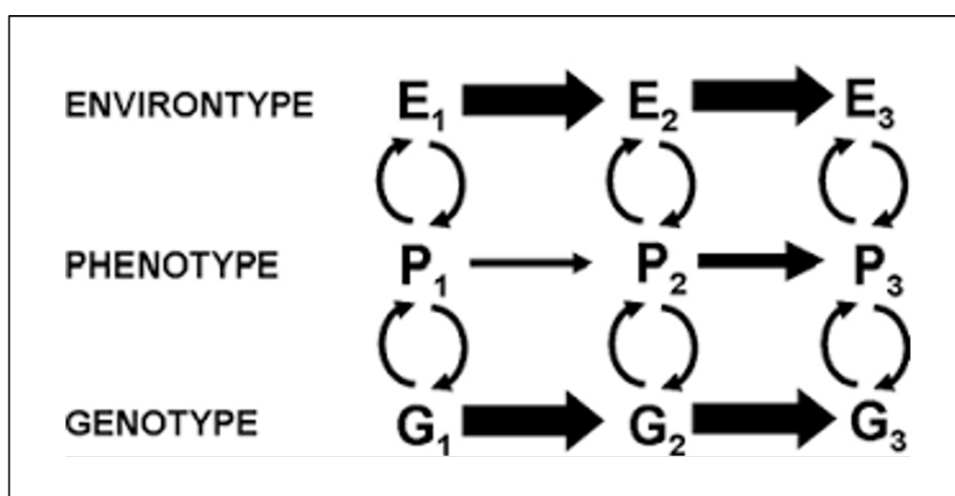
The transactional model has been greatly informed by Bell's study on the reinterpretation of the direction of effects in the development of socialisation (R. Q. Bell, 1968) and by Thomas's research on temperament (Thomas et al., 1963) that challenged leading accounts that parents were the sole drivers of children's outcomes. Bell noted that the child's attributes are not only driven by parental behaviours, but children can also affect parental responses, determining the landscape of social interactions. Similarly, Thomas et al. observed that children's temperamental behaviour affected parental

responses, which in turn was linked to children's development of adaptive behaviour. Extending these views for parent-child interactions, Sameroff and Chandler emphasised the role of continuing transactions between child and environment (i.e., caregivers, peers, school, etc.) for child development, through which both are changing/adapting to each other over time.

Sameroff (1989) depicted these views through a model (**Figure 1.3**) pointing out that the child's behaviour is a product of giving and taking between phenotype (the child), envirotype (social experiences) and genotype (biology). At any point in time, gene expression can change the phenotype, and this change can induce a different pattern of gene activation which can cause further alterations in the phenotype. Along the same lines, the envirotype provides experiences that regulate and are regulated by the responses of the child phenotype. The envirotype also consists of subsystems that transact with each other, such as parents and educators or other social agents (A. J. Sameroff, 2009).

Figure 1.3

Model of Transactional Development by Sameroff



Note. The phenotype influences and is influenced by the envirotype and the genotype over developmental time. Adapted from Sameroff (1989).

1.8.3.2.1 The Transactional Model in the Context of Atypical Development.

Intervention studies have led to recent propositions for seeing ASD emergence from a transactional perspective, considering the characteristics of both the individual and the individual's immediate or broader social environment (Green, 2022). The transactional model can be applied to research which aims to understand the underlying factors driving typical or atypical development. For this, the model suggests that it is necessary to examine the adaptive relationship between the individual and the individual's environment (A. J. Sameroff & Mackenzie, 2003). The transactional model can be used to study the causal processes leading to atypical trajectories by examining the bidirectional effects of multiple risk or protective factors (e.g., genetic, family, individual) (Fanti, 2011). By doing this, the model can also be valuable in informing prevention and intervention strategies to improve developmental outcomes (A. J. Sameroff & Mackenzie, 2003).

The transactional theory has been tested and supported by research in the context of ASD suggesting that pre-existing vulnerabilities or ASD-related symptoms can affect parental responses and behaviour towards the child, which can in turn amplify the child's ASD symptoms. For instance, studies have shown links between dyadic qualities of parent-child interactions (e.g., social reciprocity, mutuality) and later ASD outcome as well as differences in several qualitative aspects of parent-child interactions in infants with an ASD susceptibility compared to those with no genetic predisposition for ASD (Wan et al., 2019) (discussed in more detail in later sections). Other examples include research showing bidirectional influences between parent stress and behavioural problems or ASD symptomatology in autistic children (Rodriguez et al., 2019) as well as intervention trials focusing on changes in parent socio-communicative behaviours, revealing improvements in parent-child social interactions and ASD symptoms following

intervention (Green, Charman, Pickles, Wan, Elsabbagh, Slonims, Taylor, McNally, et al., 2015; Whitehouse et al., 2021).

1.8.3.2.2 The Transactional Model: Supporting Evidence and Challenges. A considerable amount of evidence from various domains across development has provided support for the transactional model of development implicitly or explicitly (A. J. Sameroff & Mackenzie, 2003). Examples include research on early mother-child attachment relationships, alluding to reciprocal processes by showing an association between infant irritability and caregiver responsiveness in building secure attachment (Crockenberg, 1981). Further support comes from but is not limited to research showing mutual influences between maternal stress and child temperament (Neece et al., 2012; Pesonen et al., 2008), children's social ability and maternal responsiveness (mothers of children displaying high social competence (cooperativeness, positive affect) being more contingent and positive compared to mothers of children showing anxious/withdrawn behaviours, LaFrenière & Dumas, 1992), or school readiness (through child task interest and completion persistence) and supportive parenting (Martin et al., 2013). Research on bidirectional influences extends to later ages, e.g., including, among others, studies on reciprocal effects of parental involvement in the home and child reading achievement or of the home learning environment and child language ability from early infancy/childhood to adolescence (Esposito, 2022; Sy et al., 2013). In addition to transactions between individual attributes/behaviours, transactional models have also been tested using different variables contributing to variation in the processes influencing transactions, such as the environmental (e.g., poverty) and biological (e.g., genetics) factors affecting parent behaviour, parent-child interactions, and children's developmental outcomes (Paschall & Mastergeorge, 2016). This evidence underlined the

mutually adaptive interchanges between parent-child behaviours, which sometimes were influenced under certain conditions (e.g., child genetic attributes).

However, the transactional model is not without its challenges. The model's core idea places an emphasis on the concurrent and ongoing reciprocity between different dynamic systems across development. To effectively operationalise the transactional model, various factors need to be considered across development, such as genetic, cognitive, familial, school, social, emotional, and others. Considering only a few of these factors may limit our understanding of development as proposed by the transactional model. On the other hand, taking into account the reciprocal effects of different factors and developmental change poses methodological challenges, and this has led to a large amount of research using static variables and investigating unidirectional relationships between ecological factors in relation to child developmental outcomes (Fanti, 2011; A. J. Sameroff & Mackenzie, 2003). Despite this challenge, more research has now shifted its focus towards the application of more advanced methodological approaches to disentangle bidirectional mechanisms, such as Structural Equation Modelling (SEM) techniques (Paschall & Mastergeorge, 2016).

1.9 Normative Brain Development

This section provides a brief overview of brain structure and function in neurotypical development, before discussing brain development in infants at EL for ASD. Understanding how the brain develops in neurotypical populations is an essential first step in order to gain greater insights into the underlying mechanisms facilitating the development of later behavioural outcomes. The knowledge of how the neurotypical brain develops can also help to better identify any alterations in brain development of infants with a raised likelihood for ASD.

1.9.1 Structural Brain Development

The first years of life are characterised by dramatic and rapid growth in brain structure and function. Infant brain volume increases from around 35% of adult brain volume in the first weeks after birth to about 100% in the first year and 15% in the second year (Gilmore et al., 2007; Knickmeyer et al., 2008). After birth, the trajectories of grey and white matter volume are somewhat different, as grey matter volume substantially increases in the first year, compared to a slower increase in white matter (Knickmeyer et al., 2008). In childhood, grey matter volume shows small increases while it decreases in adolescence, compared to white matter volume which shows a gradual increase through adulthood (Gilmore et al., 2018).

A significant growth in cortical thickness and surface area also takes place in the first two years of life (though at varying degrees depending on region), following a slower change at later ages through adolescence (Gilmore et al., 2018; Raznahan et al., 2011). Cortical thickness growth is greater than that of cortical surface area by the age of two, with the former reaching up to approximately 97% of that of adult values and the latter up to about 69% (Lyall et al., 2015). Imaging research suggests that cortical thickness increases in the first years of life and then follows a decline (Walhovd et al., 2017), while surface area continues to grow until late childhood (Raznahan et al., 2011). Increases in cortical folding (gyrification) with age are also apparent, more so in the first year (16.1%) than in the second year (6.6%) as measured by the gyrification index (the ratio between the cortical surface area and the surface area of the cerebral hull), with cortical gyrification development also being regionally heterogeneous (G. Li et al., 2014).

Developmental changes in the structural brain networks are also observed during postnatal life. White matter networks can be usually captured by measures such as diffusion magnetic resonance imaging (dMRI) or Diffusion Tensor Imaging (DTI). These methods have shown that a ‘rich club’ of highly connected cortical ‘hubs’ is present as

early as 30 weeks gestational age (Ball et al., 2014). This brain organisation has been suggested to provide the foundation for the development of subsequent structural networks (Ball et al., 2014). The structural brain networks appear to change in topology with age. In the first two years, node strength increases along with increased integration and a decrement in the clustering of brain structural networks as a result of network refinement, with major hubs appearing to be in place by the age of two (Hagmann et al., 2010). Between birth and late childhood, brain networks become more efficient and less susceptible to injury or random failure (Haartsen et al., 2016). Connections between brain regions develop from a localised topology to a more global and diffuse architecture as age increases (Vértes & Bullmore, 2015).

1.9.2 Functional Brain Development

The study of the development of the functional architecture of the brain has been possible through the use of non-invasive neuroimaging methods, such as fMRI, functional near-infrared spectroscopy (fNIRS) and electroencephalography (EEG). Brain function data are collected during resting-state (when infants are asleep, with eyes shut or looking at a fixation cross for older children) or upon performing a cognitive task.

Resting-state functional networks are present even before birth and become increasingly specialised during the first years of life (Haartsen et al., 2016; Vértes & Bullmore, 2015). Resting-state functional networks of the neonatal brain are comparable to the adult brain but they are less mature, while higher-order networks seem to be fragmented (Doria et al., 2010; Smyser & Neil, 2015). From birth, primary sensorimotor and auditory networks develop first, followed by the visual, attention and ‘default mode’ networks (Doria et al., 2010; Lin et al., 2008; Smyser & Neil, 2015). Finally, functional networks related to executive function begin to develop (Gao, Alcauter, Elton, et al., 2015). Over the first year, increases in the functional connections within the networks are

observed, while by the second year, decreases in diffuse inter-network connectivity are shown, possibly as a result of cortical specialisation of primary and higher-order functions (Gao, Alcauter, Smith, et al., 2015). In addition, the thalamus is a relay centre through which sensory information is transmitted to the cerebral cortex and is considered to be significant for the development of cortical circuits. Indeed, connectivity between the thalamus and the primary functional networks has been shown in the early postnatal years, while thalamocortical connectivity has been associated with cognitive skills, highlighting the importance of these connections in infancy (Alcauter et al., 2014).

With regard to task-related brain function, studies using functional neuroimaging have documented that brain functional responses to various stimuli, such as during the processing of spatiotemporal information, auditory or social processing, among others, emerge very early in infancy (Dehaene-Lambertz et al., 2002; Grossmann & Johnson, 2010; Wilcox et al., 2010), and that infant brain responses appear to be similar to those of adults (e.g., Allievi et al., 2016; Karen et al., 2008). Since difficulties in social cognition are a core behavioural characteristic of ASD, task-based brain function with a focus on normative social brain development will be discussed next.

1.9.2.1 Social Brain Development. Several studies have suggested that the specialisation of social brain areas in response to social stimuli comes in line early in development and is experience-dependent, which is consistent with the IS theory of brain development. Structures of the social brain are preferentially activated to social stimuli shortly after birth and gradually become more specialised and tuned with experience. For instance, research employing fNIRS revealed that newborns' brains (1-5 days old) showed a selective activation to dynamic social videos over the bilateral posterior temporal cortex and no activation to mechanical non-social videos (Farroni et al., 2013). The degree of cortical activation to the social stimulus was associated with infant age in

hours. Further, fNIRS research showed greater cortical activation to dynamic social stimuli than non-social stimuli localised in the posterior superior temporal sulcus (Lloyd-Fox et al., 2009), similar to the activation in response to social stimuli identified in adults (Pelphrey et al., 2005). Finally, developmental changes (6 and 12 months) in infant EEG oscillatory activity to dynamic social versus non-social stimuli appear to become stronger and more diffuse with age (E. J. H. Jones et al., 2015). This evidence agrees with propositions for an early, experience-dependent social brain specialisation and for age-related increases in the extent and strength of social brain activation.

1.9.2.1.1 Typical Development of Neural Correlates of Face and Gaze Processing. Our understanding of social brain development has also been largely informed by ERP studies examining the neural correlates of social information processing, such as the processing of faces and eye gaze. Event-related potentials allow the measurement of neural activity evoked directly after stimulus presentation and can provide insights about face and gaze perception at the neural level between different developmental populations. Evaluating how these neurophysiological correlates develop in neurotypical development can be very informative for understanding the neurodevelopmental processes of atypical social development in the context of ASD.

Faces and eye gaze provide key social information, and being able to detect and recognise faces and eye gaze direction is an important adaptive process that facilitates social communication and learning (Csibra & Gergely, 2006; Grossmann & Johnson, 2007). The early P1 and the later N290, P400 and Nc ERP components have been shown to be sensitive to tasks involving face perception in the first months of life. The early sensory P1 is a positive-going component occurring at around 100 ms after stimulus onset (over occipital electrodes) that is elicited in response to visual stimuli in all ages. It has shown to be sensitive to face encoding and different task requirements involving both

spatial and non-spatial visual tasks (de Haan et al., 2003; M. J. Taylor, 2002). The P1 appears to be faster and stronger in response to face compared to non-face stimuli, indicative of greater attention and faster processing of social information (Itier & Taylor, 2004; M. J. Taylor et al., 2001).

The negative-going N290 and the positive P400 components (over occipital electrodes) are believed to precede the adult N170 face-sensitive component which reflects the processing of facial features (de Haan et al., 2003). More specifically, the adult N170 is a negative-going component that has been found to be greater in amplitude and longer in latency for inverted than upright faces of humans (Bentin et al., 1996; de Haan et al., 2002; Itier & Taylor, 2002) or for normal compared to scrambled faces (George et al., 1996), but does not differ for animal faces or objects (de Haan et al., 2002; Rossion et al., 2000). The N290 component (peaking around 290 to 350 ms after stimulus onset) also shows greater amplitude to human- than non-human faces (Farroni et al., 2002; Halit et al., 2003) while the P400 (peaking around 300 to 600 ms after stimulus presentation) has a shorter latency to faces than objects (de Haan & Nelson, 1999). Similarly to the N170, the N290 component is sensitive to stimulus inversion (stronger amplitude for human faces but not monkey faces) at 12 months but does not appear to be influenced by it earlier, at 3 and 6 months (de Haan et al., 2002; Halit et al., 2003). Along the same lines, the P400 response to face inversion increases in specificity for human faces by 12 months, discriminating upright from inverted human faces than monkey faces (de Haan et al., 2002; Halit et al., 2003). Furthermore, within the first year, infants' brains show an enhanced P400 and N290 response differentiation to faces with eye gaze directed toward versus away from the infant (Elsabbagh, Mercure, et al., 2012a; Farroni et al., 2002). Although these components seem to be sensitive to face orientation and gaze direction, the adult N170 is not modulated by the direction of eye gaze (M. J. Taylor et al., 2001). This suggests that patterns of common cortical activation for face and gaze

processing may exist in early infancy and later segregate, becoming more specialised with age (Grossmann & Johnson, 2007).

The Nc is a negative deflection (over fronto-central electrodes) peaking around 500 ms after stimulus presentation modulated by face familiarity (i.e., greater/more negative amplitude for familiar than unfamiliar faces or objects, though the opposite effect is seen in older children for faces) and is believed to be an index of attention engagement to interesting or salient stimuli (de Haan et al., 2003; de Haan & Nelson, 1999; E. J. H. Jones et al., 2016). The Nc has also been linked to the processing of emotional information from faces (Nelson & De Haan, 1996). The component shows an increased response differentiation to fearful versus neutral faces with eye gaze directed towards objects after 6 months, while this differentiation is not observed at 3 months (Hoehl & Striano, 2010). These findings indicate an increased specialisation of parts of the social brain with age, resulting in neural activation patterns such as those usually observable in adults. This can have important implications for atypical development, particularly ASD, which may be characterised by disruptions or delays in social brain network specialisation affecting later social communication and interaction abilities.

1.10 Early Neural Markers of ASD

Several cross-sectional and longitudinal studies of infants at an EL for ASD for the identification of potential brain-based markers of ASD have revealed early alterations in both brain function and structure, emerging at the onset or within the first year of life, before the appearance of behavioural signs of ASD. This section provides a brief overview of these markers.

1.10.1 Brain Function

1.10.1.1 Task-Related Neural Markers. Electrophysiological studies have provided evidence of early brain function atypicalities in the processing of social stimuli in EL infants. For instance, EEG research using ERPs to investigate attentional engagement at 6 and 12 months identified differential neural processing of faces in EL-ASD than EL-no ASD infants at 6 months, with the former group showing faster P400 and smaller and shorter Nc responses to faces (E. J. H. Jones et al., 2016). Gui and colleagues also found a shorter Nc latency to faces in 8-month-old EL-ASD infants relative to TL and EL-no ASD groups, while the duration of microstates (scalp electromagnetic field topography) related to social attention (faces) played a role in ASD outcome prediction (Gui, Bussu, et al., 2021). In their further study, Gui et al. observed a reduced N290 latency ERP differentiation between face and non-face stimuli in EL-ASD infants relative to infants with no family history of ASD at 8 months (Gui, Meaburn, et al., 2021).

Similarly, other research used a data-driven approach to examine neural processing of both faces and eye gaze shifts using ERPs revealing a pattern of wide brain function alterations in EL-ASD infants at 8 months, suggesting that early social processing atypicalities are important candidate biomarkers of ASD diagnosis (Tye et al., 2020). In particular, compared to TL and EL-no ASD infants, the EL-ASD group exhibited a pattern of shorter N290 latencies to faces versus visual noise. In addition, longer latencies to dynamic eye gaze shifts directed toward versus away from the infant predicted ASD outcome at a group level in both the early sensory P1 and the higher-level subsequent P400 component, providing a high ASD classification accuracy. Along the same lines, another data-driven study reported a diffuse pattern of responses to eye gaze shifts involving the P1, P400 and N290 components, suggestive of greater attention to social stimuli that was diminished in EL-ASD compared to TL and EL-no ASD infants at 8 months (Bussu et al., 2020). Eye gaze sibling group differences have also been

reported in other studies, such as an absent P400 response differentiation to gaze shifts toward versus away from the infant in the EL-ASD group that was evident in TL and EL-no ASD groups at 6-10 months (Elsabbagh et al., 2012) or a slower P400 response to direct relative to averted eye gaze in EL relative to TL infants at around 10 months (Elsabbagh et al., 2009).

Additional research using EEG measures has also identified early atypicalities in infant neural responses to social attention, though results are mixed. van Noordt et al. (2022) investigated inter-trial coherence (phase consistency in oscillatory activity across trials, considered to be critical for brain functional organisation and information processing, Voytek & Knight, 2015) in the theta range in response to faces and visual noise and revealed that, between 6-10 months, infants at EL-ASD had a lower consistency in the theta frequency during face processing. Furthermore, EL-ASD atypical neural responses to faces were shown in research examining event-related intra-hemispheric gamma-band phase coherence during the first year, indicating that, by 12 months, EL-ASD infants had an atypical pattern of leftward-lateralisation compared to TL infants who showed a neurotypical rightward-lateralisation (Keehn et al., 2015). This study suggested that early alterations in the development of hemispheric specialisation for faces may be an important neural indicator of ASD diagnosis. However, Haartsen et al. (2022) explored EEG theta power and connectivity modulations to more naturalistic social (women singing nursery rhymes) and non-social (toys moving) videos and did not find any sibling group differences at 14 months or associations of these measures with behavioural outcomes in toddlerhood. The null results compared to other studies may be attributed to differences in stimuli, age or frequency bands used. Nevertheless, these results suggested no robust alterations in EL infants' neural responses to naturalistic social stimuli at this age, though further examination of the developmental change of these neural responses using multimodal techniques may help to further elucidate underlying mechanisms.

The neurophysiological measures of social attention have also shown an intervention effect by the first year in infants at EL for ASD. In a randomised clinical trial focusing on parent-targeted intervention to enhance social engagement, EL infants who received the intervention had a frontal EEG theta power to social and non-social videos between 6-12 months and a 12-month P400 ERP response to faces and objects that differed from the infants who did not receive the intervention. (E. J. H. Jones et al., 2017). In particular, the intervention group showed a greater increase in frontal EEG theta power than the no intervention group. Furthermore, it had a comparable P400 amplitude response to faces and objects, compared to stronger P400 responses to objects than faces shown by the group who did not receive the intervention. The intervention group's responses resembled those of age-matched neurotypical developing groups.

In addition to EEG studies, early social processing atypicalities in EL-ASD infants can be observed in neuroimaging research using fNIRS. For instance, Braukmann et al. (2018) found that as early as 5 months, infants at EL showed reduced activation to social dynamic visual presentations in the right posterior temporal cortex compared to TL controls. Accordingly, Lloyd-Fox et al. (2013) found an increased cortical selectivity and stronger neural responses to social stimuli (auditory and visual) in 4-6-month-old TL infants than in age-matched EL infants who exhibited a reduced neural response. Following up this sample at 36 months, Lloyd-Fox and colleagues identified a differentiation in EL infants with and without an ASD outcome according to brain response: 4 to 6-month-old infants later diagnosed with ASD showed decreased brain activation to socially relevant visual and auditory stimuli compared to non-social stimuli relative to TL controls and EL infants who did not receive an ASD diagnosis (Lloyd-Fox et al., 2017). Further fNIRS research has also distinguished EL and TL infants in hemodynamic responses to face identity and facial emotion at 7 months (Fox et al., 2013). The above findings provide support for the contention of a reduced depth of processing

and attention engagement to social stimuli that could result in alterations or delays in specialisation within the social brain network, with cascading effects on subsequent social learning.

1.10.1.2 Non-Task-Related Neural Markers. In addition to oscillatory rhythms in response to social stimuli, resting-state oscillatory activity disruptions captured by EEG measures, such as spectral power, are also suggested to be implicated in ASD as a potential neural marker of later diagnosis. Oscillatory activity contributes to neural synchrony of cortical networks that changes across development as a result of brain maturation. Therefore, any early perturbations in neural oscillations may have an effect on later developmental outcomes.

Infants at EL and TL for ASD have been differentiated in a range of frequency bands within the first year of life (Gabard-Durnam et al., 2015, 2019; Levin et al., 2017; Tierney et al., 2012). For instance, a study investigating the trajectories EEG power from 3 to 36 months in EL and TL infants showed that frontal EEG power most accurately differentiated EL from TL groups (delta and theta bands) and was the best discriminator of ASD diagnosis within the first year (Gabard-Durnam et al., 2019). In addition, trajectories of delta and gamma frequencies consistently differentiated the EL-ASD infants from the other groups, suggesting the developmental change in neural oscillations could be an index of ASD. Similarly, another study investigating 6-24-month changes in frontal EEG power across various frequency bands (delta, theta, alpha, beta and gamma) found lower levels of spectral power in EL relative to TL infants at 6 months (Tierney et al., 2012). Dynamic differences in spectral power between the groups from 6 to 24 months were also observed: group differences in alpha and gamma bands persisted by 24 months compared to delta, theta and beta bands, for which the effects disappeared. Group differences at 6 months have also been shown in frontal alpha asymmetry (difference

between the left and right hemisphere alpha band average), as well as subsequent divergent growth trajectories between EL and TL groups in alpha asymmetry from 6 to 18 months (Gabard-Durnam et al., 2015). Other research has revealed EL and TL group differences in frontal EEG power as early as 3 months (Levin et al., 2017), while early spectral power in the context of ASD susceptibility has been associated with subclinical traits, such as language ability (Huberty et al., 2023; Levin et al., 2017; Wilkinson et al., 2019, 2020). Overall, the above findings point to EEG power as a candidate neural marker of ASD diagnosis, present within the first year before the onset of overt behavioural signs of the condition.

1.10.1.3 Functional Connectivity. Some lines of evidence have suggested functional connectivity (referring to synchrony and interactions of brain regions) as a possible predictive biomarker of ASD diagnosis. For instance, research using fNIRS showed increased functional connectivity in the EL relative to the TL group from as early as 3 months, followed by decreased connectivity at 12 months (Keehn et al., 2013). These findings were viewed as an indication of an atypical developmental trajectory in network connectivity in infants with a family history of ASD. Indeed, Righi et al. (2014) found reduced functional connectivity (intrahemispheric linear coherence) in the gamma range by 12 months in EL-ASD infants compared to EL-no ASD and TL infants. However, another study using EEG to measure functional connectivity from a sample of 14-month EL and TL infants when viewing dynamic videos demonstrated that EL-ASD infants had increased connectivity in the alpha range, particularly in frontal and central brain areas (Orekhova et al., 2014). In addition, higher whole brain connectivity was linked to higher restricted and repetitive behaviours at 36 months. A subsequent study replicated this association (Haartsen et al., 2019). Nevertheless, functional connectivity differences between EL and TL infants have not been consistently observed within the first year. For

instance, Haartsen et al. (2019) did not replicate previous findings for an association between functional EEG connectivity and ASD diagnosis. In addition, no between-group differences were identified at 6 months in Righi et al.'s (2014) study, while Keehn et al. (2015) did not find 6-12-month differences in intrahemispheric coherence (despite the observed lateralisation effect in response to face processing mentioned earlier). These discrepancies likely reflect differences in tasks, age ranges, frequency bands employed or even differences in underlying mechanisms each method measures. Regardless of these contradictions, the above findings provide an indication that functional connectivity may play a role in the developmental pathways to ASD.

1.10.2 Brain Structure

In addition to brain function, infants at EL for ASD also show differences in brain structure before the appearance of behavioural precursors of ASD diagnosis. For instance, evidence for cerebral cortical volume increases in the first two years of life has been shown in EL-ASD infants (Dawson et al., 2023). A prospective neuroimaging study, Hazlett et al. (2017) revealed increases in the rate of cortical surface area from 6 to 12 months in EL-ASD infants compared to EL-no ASD and TL groups, particularly in the occipital lobe and to a lesser extent in the temporal and frontal lobes. These changes were followed by brain volume overgrowth in the second year of life. Another prospective study of infant siblings showed that infants with a subsequent ASD diagnosis had increased corpus callosum area and thickness relative to EL-no ASD and TL infants at 6 months and that these differences diminished by 24 months (Wolff et al., 2015). The study stressed the dynamic interchange of neurodevelopmental processes in infancy, and that any disruptions during these events could have cascading effects on later brain development. Furthermore, a longitudinal study found a faster growth in amygdala volume between 6 and 12 months in EL-ASD infants when compared to infants with

Fragile X syndrome, EL-no ASD and TL infants (Shen et al., 2022), while further research identified larger cerebellar and subcortical volumes in EL infants compared to TL infant siblings at 4-6 months, irrespective of ASD outcome (Pote et al., 2019). Atypicalities in brain morphology in EL infants within the first year have also been linked to repetitive behaviours at 2 and 3 years of age (Pote et al., 2019; Wolff et al., 2015).

Differences in fractional anisotropy (FA, a measure of the degree of fibre density and myelination) and extra-axial cerebrospinal fluid volumes have also been reported. For instance, Wolff et al. (2012) found that infants with a later ASD showed higher FA at 6 months followed by decrements in the rate of change by 24 months compared to infants with no ASD outcome. In addition, Shen et al. (2017) observed elevated levels of extra-axial cerebrospinal fluid volume from 6 to 24 months in EL-ASD infants relative to the no-ASD groups, with even higher volumes shown in those infants who had more severe ASD symptoms.

These findings provide evidence for early structural brain abnormalities that could be a contributing factor to ASD diagnosis, setting the stage for further disruptions in brain organisation and subsequent socio-cognitive skills at the behavioural level.

1.11 Why is Caregiving Important to Understanding in Interpreting Early Brain Differences in ASD?

The above studies underline the importance of recognising and understanding the intrinsic processes taking place in early development and how this may influence developmental outcomes. However, the context in which brain and behaviour development occur, and particularly, the early caregiving environment - and how it contributes to the way the infant experiences the world - cannot be viewed separately. This is because infant changes in brain function and behaviour during development do not happen in a vacuum; they are part of an iterative, dynamic process in which both the

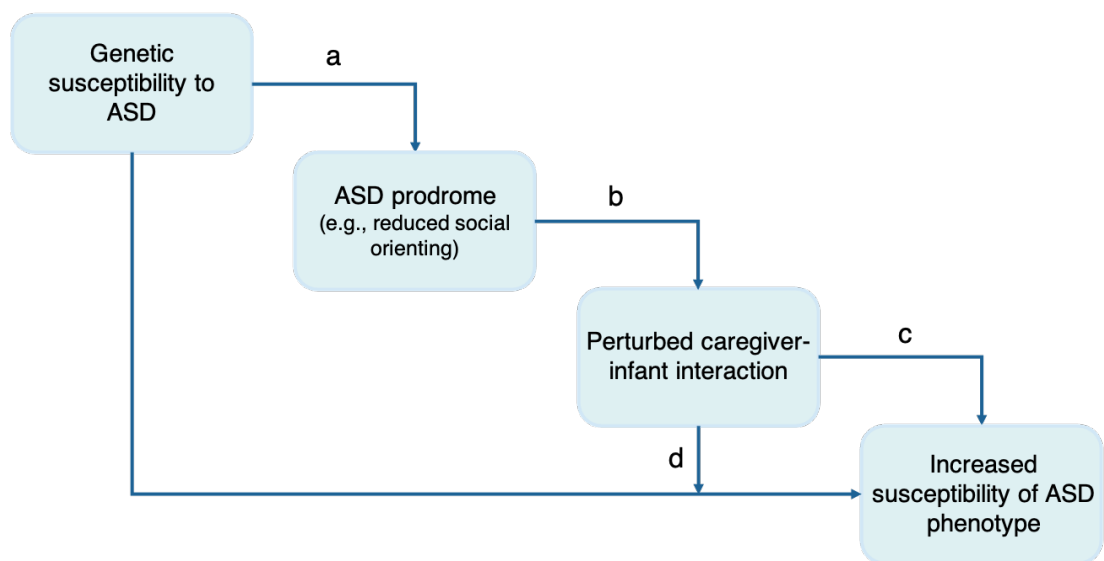
infant and caregiver are mutually affected. As described earlier, in the first year of life, the developing brain undergoes a considerable amount of growth and change. Genetic background and environment can influence the developing brain leading to a certain phenotypic outcome, and the quality of the experiences provided to the child is central, as it can affect brain mechanisms, possibly altering the course of development (Champagne & Curley, 2005). For instance, engaging with a social partner can enhance cortical specialisation and the fine-tuning of perceptual systems responsible for the processing of social stimuli (Dawson, 2008). Furthermore, research with normative and vulnerable populations (i.e., preterm infants, ASD likelihood, maternal depression) has shown clear links between the quality of parent-infant interaction (PII) and children's brain function, structure and connectivity, apparent very early and in some cases, lasting for months or decades (more details in following sections), highlighting the invaluable role that parents play on children's developmental outcomes (Ilyka et al., 2021 for a review).

More specifically, because ASD is characterised by atypicalities in the social domain (among others), its early expression could be influenced by the quality of caregiver-child relationships, in addition to other factors (i.e., genetic, brain, and so on). Indeed, there is evidence suggesting alterations in the quality of PII as well as a relationship between brain function and PII in infants at EL within the first year of life (see following sections). It has been hypothesised that the early caregiving environment can have a mediating effect (partially) on the links between ASD susceptibility and subsequent ASD phenotypic expression (**Figure 1.4**). Genetic predisposition for ASD affecting brain function may lead to reduced infant interest in the social world within the first year of life; this can disrupt the quality of early social interactions with caregivers (e.g., stimulating fewer caregiver responses or different caregiver interactions), which can, in turn, increase the susceptibility to social communication and interaction

atypicalities that characterise the ASD phenotype (Mandy & Lai, 2016). At this point, it is important to stress that early PII is neither necessary nor sufficient to lead to an ASD diagnosis. The quality of PII should be seen as a potential modifier of ASD predisposition (Mandy & Lai, 2016). Considering the above, exploring the relationships between infant brain mechanisms underlying social attention and early caregiver-infant interactions during a period of increasing brain plasticity in infants with a familial likelihood for ASD may provide important insights into the developmental processes leading to ASD outcome and can have significant implications for intervention.

Figure 1.4

Gene-Environment Interactions in the Development of Autism Spectrum Disorder



Note. Genetic susceptibility for ASD shapes infants' experience of the environment (pathway a). Early prodromal behavioural signs may affect caregiver-infant social interactions (pathway b). Alterations in caregiver-infant relationships can exacerbate social communication difficulties, increasing the probability of ASD diagnosis (pathway c). Caregiver-child interactions can act as a *modifier* of ASD predisposition (pathway d). Adapted from Mandy & Lai (2016).

1.12 Early Dynamic Parent-Infant Social Transactions

As discussed earlier, infancy and early life experiences are believed to have a huge impact on the course of later development. The infant brain is incredibly plastic and infants can learn from their environment with remarkable ease (Bornstein & Lamb, 2002). Social experiences in early life begin within the context of the family, as interaction with parents is a central aspect of infants' social environment. As the transactional model of development posits, a child's developmental trajectory is influenced by the continuous reciprocal interactions between the child and his/her parents (Sameroff, 2009) and any disruptions in the quality of parent-child interactions may have cascading effects on the child's socio-cognitive functioning later on in life (A. Sameroff, 2009). In the context of ASD and as depicted in **Figure 4**, ASD precursors can affect infants' social attention which can disrupt the quality of PII, contributing to an atypical developmental route. Empirical work in support of these hypotheses is presented below. An overview of research findings on the quality of PII in normative development is first discussed, followed by the presentation of empirical work examining PII aspects in relation to ASD susceptibility and outcome.

1.12.1 Caregiver-Infant Interaction in Neurotypical Development

1.12.1.1 Parent Behaviour. Parent interactive behaviour plays a significant role in determining the quality of PII and is central to enhancing infant development. The ways parents engage in interactions with their infants are important for infant attachment security and socio-emotional development (Ainsworth et al., 1978). Aspects of parent behaviour include many different dimensions broadly divided into positive and negative parenting (Taraban & Shaw, 2018). For instance, positive parenting involves behaviours such as contingent responses, warmth, scaffolding, sensitivity, positive reinforcement and

affect (Waller et al., 2015), whereas negative parenting includes behaviours that are harsh, inconsistent, intrusive or disengaged (Chang et al., 2003; Hall et al., 2015; Z. Jiang et al., 2023; Lovejoy et al., 2000).

Sensitive and responsive parent interaction has been a prominent focus in research examining the quality of caregiver-child relationships. Parent sensitivity and responsiveness broadly refer to the parent's capacity to respond appropriately and promptly to the infant's signals and behaviours with responses that are contingent, emotionally supportive and matched to the infant's developmental level (Ainsworth et al., 1991; Warren & Brady, 2007). A substantial body of research suggests that highly responsive and sensitive parenting promotes children's learning, attachment security, socio-emotional, cognitive and language development (Ainsworth et al., 1978; Edwards et al., 2010; Leerkes et al., 2009; Madigan et al., 2019; N. A. C. F. Rocha et al., 2020; Warren & Brady, 2007). Indeed, a study investigating 11-month infant development in relation to free play PII at 12 months found that infants who had better developmental outcomes in several areas (i.e., passive posture, active posture, manipulative, visual, hearing and language, speech and language, interactive social, cognition and global development) were those whose dyadic social interactions were characterised by high maternal sensitivity (Soares et al., 2018). Another study revealed that between 6 and 12 months, parent responsivity/sensitivity was associated with infant attentional skills reflected through perceptual sensitivity (Gartstein et al., 2008). Additional research findings from several studies show that maternal responsiveness and sensitivity have a positive effect on infant expressive and receptive language as well as word production (Rocha et al., 2020 for a review). On the other hand, higher mother intrusiveness and directive behaviour have been negatively associated with children's language and cognitive development (Rantalainen et al., 2022; Tamis-LeMonda et al., 2004), while

intrusive parent behaviour has been positively related to children's socio-emotional problems (Z. Jiang et al., 2023).

Parental interactive behaviours (i.e., sensitivity/responsiveness) appear to be relatively stable over time (Bigelow et al., 2010; Dallaire & Weinraub, 2005; Else-Quest et al., 2011; Hall et al., 2015; Holden & Miller, 1999). However, particular components of parent behaviours vary across time as parents adjust their behaviours to their child's developmental needs and abilities (Bornstein et al., 2008; Jahromi et al., 2004). For instance, Bornstein et al. (2008) found that the types of maternal responsiveness towards their infants during play changed between 10 and 21 months in accordance with infants' abilities, such that, earlier in life, mothers responded to their infants with descriptions and exploratory prompts. Later in toddlerhood, the use of mother imitations/expansions, questions and exploratory/play prompts increased. Similarly, van Huisstede et al. (2019) reported that the global index of sensitivity was relatively stable across the first year, while components of sensitivity fluctuated, showing increasing (e.g., vocal appropriateness), decreasing (e.g., touch, acknowledging) and stable (e.g., elaboration) trajectories.

Overall, findings demonstrate that highly sensitive and responsive parent interactive behaviours across infancy and early childhood can provide important benefits for children's developmental trajectories in a range of domains and that individual parent behaviours change over time, adjusting to their children's emergence of new competencies and behaviours.

1.12.1.2 Child Behaviour. For a long time, infants were considered passive receivers of environmental inputs, especially of their parent behaviours (Viaux-Savelon, 2016). Although parent responsiveness is fundamental for infant development, it does not operate independently of the child's behaviour. In fact, infants have an active role in

social interactions, they initiate social bids and develop expectations of their partner's interactive behaviour based on their own actions (Bigelow & Power, 2016).

From very early in development, infants show a selective orientation to social stimuli (Farroni et al., 2002) that is suggested to be modulated by subcortical brain pathways (Johnson, Senju, et al., 2015). Newborns have a selective preference for faces with gaze directed towards them while 4-month-old infants show enhanced neural responses to direct eye gaze (Farroni et al., 2002). They also show a preference for biological motion (Falck-Ytter et al., 2011) and they look more at faces with their eyes open than closed (Batki et al., 2000). As infants develop, attention to social stimuli such as faces becomes more robust, as infants at 6 months, and not at 3 months, detect and maintain gaze fixations to faces over objects (Di Giorgio et al., 2012). In addition, infant interactive competencies change from dyadic to triadic social interactions towards the end of the first year of life. Infants engage in episodes of shared attention by directing other's attention to events or objects through gestures (pointing, showing) and gaze (E. Bates & Dick, 2002; Carpenter et al., 1998; E. J. H. Jones et al., 2014) and make bids for social interaction through gaze, gestures and vocalisations (Clearfield et al., 2008). Research also shows that infants develop an awareness that they can affect parental behaviour and responses and have certain expectations about the progression of social interactions (Bigelow & Power, 2016). For instance, through the still-face paradigm (composed of an initial PII phase, followed by a still-face phase where the parent is unresponsive to the infant and a final phase of parent re-engagement of the infant in interaction), a study showed that maternal contingent responses during the initial interactive phase were predictive of infant social initiations in the subsequent still-face procedure (Bigelow & Power, 2016).

Together, these findings show that not only parents but also infants are active agents in social interactions, showing increasing social interest and understanding that

they can affect their social environment as contingent on prior social (or socioemotional) experiences from caregivers.

1.12.1.3 Unfolding the Dyadic “Dance” Between Parent and Infant. While individual behaviours are important for PII, it has been proposed that PII is more than the sum of its parts (the individual behaviours by parent and infant), meaning that the balance, mutual focus and give-and-take in parent-infant relationships as seen through a dyadic context are also of great significance (Kochanska et al., 2008; Moore et al., 2013). Parent-child relationships are reciprocal in nature. Aspects used in research such as turn-taking, co-regulation, reciprocity, shared affect, mutuality, rhythm or synchrony are all highly conceptually overlapping and closely related elements of dyadic PII.

Early in infancy, the caregiver is a key interaction partner determining most of the infant’s early experiences (Bornstein, 2019). Very shortly after birth, caregivers engage in interactions with their infants using eye gaze, “motherese” (high-pitched) vocalisations, positive expressions and affectionate touch (R. Feldman, 2007b). In addition, caregivers closely monitor their infants’ behaviours, adapting to their alert states (Apter et al., 2019; R. Feldman & Eidelman, 2007). Caregivers’ contingent responses can lead to an increase in infant alertness, thus, showing that the infant can notice a continuity between their and their caregiver’s behaviour towards them, significant for bonding and social learning (Apter et al., 2019; R. Feldman & Eidelman, 2007). Research has also provided support for a functional architecture in PII, where each partner is prepared to respond to the other’s particular behaviours in certain ways, which enhances infant social development (Murray et al., 2016). For instance, infant social expressiveness in the first 2 months postpartum has been associated with specific forms of parent responses to these social expressions (mirroring, marking with a smile) (Murray et al., 2016). Caregiver coordination to infant behaviour enhances infant engagement in social interactions early

on and is a precursor of parent-infant synchronous interactions. For instance, caregiver postpartum behaviour at 3 months has been a significant predictor of synchrony in the dyad (R. Feldman, 2007b). Towards the end of the first year, infants' capability to initiate social interactions develops (as described in the previous section) along with the development of more bidirectional interchanges between caregiver and infant, such as shared attention to objects and symbolic play (R. Feldman, 2007b).

Reciprocal PII have been shown to promote development in a range of domains (Leclère et al., 2014). For instance, synchrony in early PII has been associated with attachment security (Lundy, 2002). High interactional synchrony has also been related to better adjustment in preschool (Harrist et al., 1994), higher social competence (E. W. Lindsey et al., 2010), and has been linked with the development of empathy and self-regulation (R. Feldman, 2007a) as well as child compliance (Rocissano et al., 1987). On the other hand, lower mutual and synchronous interactions can have a negative effect on children's development. Research has shown that positive interactive synchrony and the amount of time it took dyads to repair breaks in synchrony were significant mediators in the relationship between preschool children's cumulative risk exposure and self-control ability, such that higher cumulative risk exposure was linked to less dyadic synchrony and longer latencies to repair ruptures, which in turn were associated with lower child self-control (Scholtes et al., 2021). Additional research shows that lower parent-child synchrony/mutuality is a significant contributor to child problem behaviour (Deater-Deckard et al., 2004; Im-Bolter et al., 2015) or cognitive skills (Kirsh et al., 1995).

Overall, both parent and child play an important role in shaping the dynamics of their relationships, building up social interchanges that are crucial for children's socio-emotional and cognitive development. Some of these important qualities of PII appear to be altered in the context of ASD early on before a clinical ASD diagnosis is made.

1.12.2 Caregiver-Infant Interaction in ASD

A substantial amount of research has employed a prospective infant sibling design to investigate the dynamics and trajectories of early PII between EL and TL infants. The aim was to gain a better understanding of how ASD unfolds, the role of PII qualities and how PII shapes later developmental trajectories in infants with an increased susceptibility to ASD diagnosis.

1.12.2.1 Parent Behaviour. Research has found EL and TL differences in parent interactive behaviour, though no parent aspects of interaction have contributed to ASD diagnosis as of yet (e.g., Baker et al., 2010; Campbell et al., 2015; Wan et al., 2013). Studies suggest that parents of EL infants tend to use more directive behaviour (more touch and verbal requests) to elicit infants' response and attention (Srinivasan & Bhat, 2020; Wan et al., 2012, 2013) and less sensitive responses compared to parents of TL infants (Wan et al., 2012, 2013). Although not using an infant sibling design, a recent study examined unstructured PII in a 9-14-month-old sample of infants exhibiting early ASD signs and found that low parent sensitive responsiveness predicted more severe autistic behaviour at 3 years (Loncarevic et al., 2022). Highly directive caregiver behaviour has predicted slower growth in parent-directed smiles from 9 to 18 months, whereas parental responsiveness has been related to greater growth in infant social smiling (Harker et al., 2016). Parents' directive behaviours in order to interact with their children have also been reported in PII studies with children with ASD and other disabilities (Blacher et al., 2013; Lemanek et al., 1993). However, it is not yet clear if directiveness was an independent characteristic of these parents, was due to a learned directive style from interacting with their older children with ASD or because they did not receive clear social-communicative stimuli from the infants. Parental stress could also be implicated in the observed pattern of parental behaviour (Bitsika & Sharpley, 2004).

Notably, Steiner et al. (2018) documented that although parents of both EL and TL 12-month infants equally synchronise their behaviours based on their child's focus, those of the former group exhibit more demanding behaviours irrespective of infant ASD outcome, suggesting that a directive parental way of interaction may exist in parents of EL infants regardless of the child's social-communicative capacities. However, using a within-family design, Doussard-Roosevelt et al. (2003) found that although mothers equally engaged both their children with and without ASD, they tended to use more physical and fewer social verbal approaches with the former than the latter. Indeed, parents' interactive style may reflect an adaptive response to infant behaviours; a study investigating the speech prosodic patterns of mothers of EL infants suggested that pitch and infant-directed speech (motherese) was more profound from 12 to 18 months in parents of EL infants compared to TL infants, whose parents seemed to be gradually moving away from this type of interaction (Quigley et al., 2016). Thus, it is likely that parents of EL infants tend to intensify their solicitations (hence infant-directed speech) as a more effective way to gain EL infants' attention.

While studies report early differences in the EL group in parent interactive behaviour, other evidence suggests no group differences in parent sensitive responsiveness (J. K. Baker et al., 2010; Campbell et al., 2015; Leezenbaum et al., 2014), warmth, scaffolding and directiveness at 11 months (Campbell et al., 2015) and other social behaviours such as eye-contact, positivity, vocalisation used separately or in combination at 6, 9 and 12 months (Schwichtenberg et al., 2019). In addition, maternal sensitive structuring at 18 months has been linked to expressive language growth in infants with later ASD outcome (J. K. Baker et al., 2010). Moreover, parents of EL-no ASD infants have shown to produce a higher rate of gestures compared to parents of EL-ASD- and TL-12-month-old infants in a study by Talbott et al. (2015). Maternal gesture

production was significantly associated with language at 18 months only for the EL-no ASD and TL groups.

1.12.2.2 Infant and Dyadic Behaviours. Regarding infant interactional behaviours, some early studies followed a retrospective design of home videos, suggesting that EL-ASD infant interactive behaviours were characterised by reduced eye contact and vocalisations (Maestro et al., 2005) by 6 months, a lack of response to name by the first year (Osterling et al., 2002) as well as deficits in imitation and joint attention between 9 and 12 months, showing only a slow rate of improvement at 15-18 months (Poon et al., 2012). Retrospective work of home videos is significant in that it shows high ecological validity. However, it has its limitations; videotaped events may depend on parents' memory and choice or may lack comparability due to varied settings. In contrast, studying EL and TL dyads prospectively was considered to be a way of overcoming these shortcomings (Szatmari et al., 2016).

Prospective work on PII has identified behavioural differences in some interactional aspects between EL dyads with a later ASD diagnosis and dyads of typically developing infants (Wan et al., 2019; Zwaigenbaum et al., 2013) during the first months of life, though results are mixed. For instance, an early microanalytic PII study by Yirmiya and colleagues (2006) showed that, at 4 months, infant-initiated free play lacked synchrony in EL dyads relative to TL dyads, suggesting that mothers of infants at EL possibly have difficulty or lack of experience in responding to their infants' initiations. Additionally, a study looking at global aspects of PII in 6 to 10-month-old infants indicated that infants at EL were less lively than TL infants at 6 months (Wan et al., 2012). Infants at EL-ASD and those at TL have also been shown to exhibit emotional expression differences at 6 months, with the former group showing a non-significant trend towards a lower rate of smiles during a face-to-face/still-face paradigm (Cassel et al., 2007). In

contrast, no group differences have been found between EL-ASD infants, EL-no ASD and TL infants in the rate of parent-directed social smiles, gaze and vocalisations at 6 months in another study (Rozga et al., 2011). However, the sample size used in this study was small, which could explain the lack of differences. More recently, research exploring global characteristics of unstructured PII in infants at EL compared to infants at TL at 5 and 10 months has found no differences in PII between the dyads. However, at 10 months, a significant effect was shown in infant initiations which showed a trend after controlling for parental education (Pijl et al., 2021). This study did not follow infants up to ASD outcome, therefore, it is not possible to know whether this effect was driven by EL-ASD infants.

Later, towards the end of the first year, group differences between EL and TL dyads are more apparent and become even more robust during the second year, with declining trajectories in EL infants with a later ASD diagnosis, predominantly in gestures. Evidence demonstrated that PII in EL-ASD infants at 11 months was low compared to interactions of infants at TL, with EL infants who later developed ASD initiating fewer gestures (e.g., giving or showing a toy), and having lower scores in the degree of reciprocity with the parent (Campbell et al., 2015). In addition, low infant reciprocity was a significant contributor to ASD symptom severity. The latter finding was similar to that by Choi et al. (2019), showing a low rate of gesture production and gesture-speech combinations at 12 months in EL-ASD compared to EL-no ASD infants, with the former finding predicting receptive language and ASD outcomes. Surprisingly, the same study also showed low gesture use for the TL siblings. Moreover, in a study by Talbott et al. (2015), lower gesture production was found in EL-ASD infants compared to EL-no ASD and TL infants, with links between infant gesture production at 12 months and language outcomes at 18 months shown for the EL-ASD group. More generally, during the second year, delays in gestures have been consistently found in EL-ASD infants (Parladé &

Iverson, 2015; Winder et al., 2013) with infants at EL making fewer non-verbal gestural requests at 14 months (Yirmiya et al., 2006), showing lower use of gesture-vocalisation combinations as well as a slower decrease of non-word vocalisations by 18 months than TL infants (Leezenbaum et al., 2014; Parladé & Iverson, 2015).

Furthermore, studies have identified group differences in other social behaviours at the end of the first year of life during play-based interactions. Infants at EL with a subsequent diagnosis have shown to be less responsive to their mothers' bids at 12 months, which has been linked to a higher ASD symptomatology at 3 years (Kellerman et al., 2020). This finding agrees with previous research demonstrating that at 12 months, EL-ASD infants exhibit less frequent joint attention and requesting behaviours than TL and EL-no ASD siblings (Rozga et al., 2011). Similarly, following up on their previous study (see Wan et al., 2012), Wan et al. (2013) showed that, not at 6, but at 12 months, EL infants' positivity, dyadic mutuality, attentiveness and dyadic engagement intensity scores were lower relative to the TL and EL-no ASD groups, with the former three predicting three-year ASD outcome. More recently, employing a sample of infants displaying early ASD signs (though not infant siblings) at 9-14 months, Loncarevic et al. (2022) found that lower parent-infant mutuality and higher infant negative affect were associated with 3-year child autism behaviours. In a further study including this infant sample, Loncarevic et al. (2023) found that infant attentiveness to parent and negative affect within PII at 9-14 months were significant mediators in the links between parent characteristics (aloofness, psychological stress) and infant autistic behaviours.

All in all, the above findings on parent, infant and dyadic aspects of social interaction indicate that PII is altered in infants with an increased susceptibility to ASD. In particular, infants with an eventual ASD diagnosis or other developmental atypicalities show a divergence in PII becoming more pronounced towards/after the end of the first year of life. Uniquely PII aspects are affected, such as mutuality/reciprocity, infant

attentiveness or preverbal communication, while social interaction alterations in parent behaviours are evident but have not yet shown to be reliable predictors of later ASD outcome.

1.13 Linking Brain Function and PII

As previously discussed, in the first months/years of life, the infant brain undergoes a considerable amount of growth and change and early experiences can contribute towards further refinement and re-organisation of brain circuits (e.g., functional networks supporting social processing). Specifically, it was discussed that the caregiving environment is an integral part of infants' early experiences, thus, PII can be crucial for brain differentiation and re-organisation (Champagne & Curley, 2005). The previous section provided evidence for the important contribution of the quality of the early caregiving environment on child development at the behavioural level. This section will further discuss research evidence showing links between qualities of PII and brain function and structure early in neurotypical development and in the context of ASD.

This is of particular importance in the context of ASD for several reasons. Research has demonstrated that pronounced differences in PII between EL and TL infants begin in the first year, with interactions between EL-ASD infants and their caregivers after the first year showing an increasingly atypical trajectory. On the other hand, behavioural signs within the first year are not yet reliable predictors of subsequent ASD and any evidence is far from conclusive. As previously mentioned, brain differences within the first year appear before the emergence of early behavioural signs (e.g., Elsabbagh et al., 2012). Therefore, linking brain function measures and qualities of PII can possibly help to identify whether or which of these interactions have an effect on children's developmental routes and will provide a better view of early emerging behavioural atypicalities before the presence of overt clinical symptoms.

1.13.1 Brain Function and PII Links in Neurotypical Development

Research on brain-PII relationships in neurotypical development is ample. Studies have used different neural measures, including task-evoked experiments using EEG/ERPs, connectivity and brain volume with MRI and have identified links with different PII measures (Ilyka et al., 2021). Regarding parent behaviour, several studies have reported brain associations with parent sensitivity, positive affect and intrusiveness. For instance, a preliminary study indicated that maternal sensitivity at 6 months was associated with hippocampal volume and functional connectivity between the hippocampus and areas related to emotion regulation, cognitive flexibility, social communication and memory (Rifkin-Graboi et al., 2015). Conversely, another study found that maternal sensitivity at 6 months was not linked to overall volume, but lateralised aspects of amygdala and hippocampal microstructure at 4.5 and 6 years (Lee et al., 2019). Further research showed that high parent sensitivity was linked to greater Nc amplitudes in response to positive facial expressions in infants at 7 months (Taylor-Colls & Pasco Fearon, 2015). Interestingly, associations between sensitive parenting and brain development have been found even earlier. Using MRI, Sethna et al. (2017) revealed that as early as 3 months, infants from both sexes show smaller subcortical grey matter volumes (including the caudate, putamen, globus pallidus and thalamus) with lower maternal sensitivity. Additional findings showed that high parent responsiveness and positive emotional tone in interactions were associated with increased frontal-posterior connectivity in the gamma and alpha range, respectively, in infants between 6-11 months. Similarly, infants whose parents exhibited high positive affect and were less physically stimulating showed developmental increases in frontal resting EEG power (alpha and theta) between 5 and 10 months, and between 10 and 24 months (Bernier et al., 2016). In turn, maternal intrusive/directive interactive behaviour was linked to infant

neural response differentiation to emotional utterances (Huffmeijer et al., 2020; Zhao et al., 2019). The above findings indicate that variations in parenting behaviours are likely to play an important role in infant brain development and socio-cognitive functioning.

Concerning infant interactional behaviours, several studies have revealed brain-infant behaviour associations, such as a relationship between infant attachment and brain activity and morphology (Cortes Hidalgo et al., 2019; Leblanc et al., 2017; Moutsiana et al., 2014; K. Quevedo et al., 2017). For instance, a longitudinal study prospectively examining 15-month-old infant attachment to the mother in relation to whole-brain grey matter volume and thickness at 10-11 years reported that higher infant attachment security was linked to increased grey matter volumes in the social brain network in childhood (Leblanc et al., 2017). Other research has identified brain association with particular aspects of infant social interaction, such as joint attention. Eggebrecht et al. (2017) found that joint attention initiation was correlated with brain resting state functional connectivity (i.e., visual-dorsal attention networks and visual-posterior cingulate default mode networks) at 12 and 24 months. Further research has demonstrated relationships between infant brain asymmetry and emotional availability: 14-month infant higher left frontal EEG activation was linked to greater child involvement during PII at 50 months in a study by Licata et al. (2015). These findings highlight that infant capacity to engage in social interactions is influenced by and develops along with the maturation of brain regions important for social functioning.

In addition to individual parent and infant behaviours, dyadic behaviours, which represent a critical aspect of effective social interactions, have also played a role in infant brain development. For example, Perone and Gartstein (2019) showed that lower frontal-posterior theta connectivity was associated with higher parent-infant reciprocity at 6-11 months, suggesting a greater stability in brain activity and development leveraged by the quality of PII early on, which can support cognitive development. Brain-dyadic

interactions have also been shown at a later age. Romeo et al. (2018) revealed a positive association between adult-child conversational turns in the home environment and child Broca's area (left inferior frontal) activation during language processing at 4-6 years, which significantly mediated the relationship between the number of conversational turns and children's verbal skills. The study emphasised the importance of child linguistic experience on neural processing of language.

1.13.2 Brain Function and PII Links in Relation to ASD Susceptibility and Diagnosis

While there is considerable research on early brain-PII associations in neurotypical development, studies investigating how early social interactions are related to infant brain function in the context of ASD predisposition or diagnosis are limited. This is striking considering propositions for atypicalities in social brain development and in PII patterns in infants with a family history of ASD. Investigating their links in the context of ASD could help elucidate the underlying developmental processes of the condition.

A few studies have attempted to fill this gap in literature. Elsabbagh et al. (2015) examined the relationships between unstructured PII involving infant, parent and dyadic interaction aspects and ERP (P100 and P400) responses to eye gaze shifts directed toward versus away from the infant in a group of 7-month-old infants at EL and TL for ASD. The variables included had previously differentiated EL from TL infants (Elsabbagh et al., 2012; M. W. Wan et al., 2013) while the ERP components selected are associated with social information processing (as described in previous sections). Results showed that infants at EL who exhibited more positive affect in the interaction displayed faster latencies (reflected through the P400) to faces with gaze directed toward versus away from the infant. Supplementary analysis revealed that this effect was driven by EL-no ASD infants. Concerning parent interactive behaviour, significant associations were only

found in the TL group: higher scores on parent sensitive responsiveness were associated with greater ERP (P100 latency) response differentiation to dynamic eye gaze shifts. A relationship between dyadic mutuality and P400 latency difference was also observed but was excluded from the analysis due to collinearity issues. These findings indicate that TL and EL infants may employ different neural pathways to processing social information which likely affect their PII patterns.

Moreover, another study investigated how parental language input associates with brain oscillations and language development in EL and TL infants (Romeo et al., 2022). The findings revealed a significant positive association between 18-month parent language input (number of words, lexical diversity and grammatical complexity) and 24-month expressive language skills, with stronger effects for the EL infants, and particularly those who later received an ASD diagnosis. These associations were explained by frontal and temporal gamma power at 24 months in EL-ASD infants, such that higher parent quality input was linked to lower baseline frontal and temporal gamma power at 24 months, which in turn was associated with higher expressive language skills. These findings possibly indicate EL infants' differential susceptibility to their language environment affecting their neural functioning in ways that promote language development. Furthermore, although not in a PII context, a further study examined EL and TL infant neural responses to face expressions (positive affect) at 9 months and their association to later infant joint attention skills at 15 months (assessed through a semi-structured interaction with an examiner), a valuable component of PII. Greater and more prolonged neural processing of small smile versus neutral faces was linked to higher initiation of joint attention, but was not moderated by ASD likelihood group. Perhaps, examining these associations using a more 'naturalistic', PII context, may have been able to capture possible EL infant atypicalities in social attention more accurately, revealing significant associations.

Overall, these findings illustrate that links between PII and brain function in the context of ASD likelihood and diagnosis are yet to be clearly defined. Although limited, the above studies provide an indication of the value of examining these links in ASD further in order to gain a more fine-grained insight into the developmental pathways of ASD.

1.14 A Note on the Dimensional and Categorical Approaches to Studying ASD

There is a fundamental question of whether ASD is best represented as a dimensional or a categorical framework. In DSM-5, ASD is represented as a categorical construct with clear diagnostic criteria assessing the presence or absence of ASD. Consequently, considerable research has focused on examining group differences between autistic and non-autistic individuals rather than investigating broader ASD-related traits. In fact, some studies have provided evidence for the validity of the categorical structure of ASD (Frazier et al., 2010, 2023). On the other hand, increasing evidence points to the dimensionality of ASD, suggesting that ASD traits are quantitative in nature and continuously distributed in the general population (Constantino, 2011).

While the categorical framework is valuable for clarifying diagnostic decisions and understanding the core ASD symptoms, it overlooks the heterogeneity in the severity of phenotypic expression in this condition (Lord et al., 2020). Furthermore, there is evidence for sub-clinical ASD traits and the BAP in the general population, as well as ASD overlapping with other conditions (Ameis & Szatmari, 2015; Sucksmith et al., 2011), which cannot be explained by viewing ASD as a discrete category. Therefore, although the categorical approach is beneficial for a better understanding of ASD development, the dimensional approach can offer a more nuanced view and deeper research insights into the condition. The dimensional approach can provide a clearer view of individual differences and of the possible factors associated not only with ASD

diagnosis but also with comorbid conditions and sub-clinical traits that may impact daily functioning, which is fundamental for developing early targeted interventions.

This thesis combines the strengths of both approaches. It first seeks to investigate PII and brain function aspects through sibling group comparisons and in relation to ASD diagnosis and extends this by incorporating dimensional outcomes and methods that take into account individual variability (details in following sections). Using both approaches as complementary can lead to a more comprehensive understanding of ASD development.

1.15 Unresolved Questions

The aforementioned literature offers some insights into the effects of early social experiences on brain development as well as into the nature of PII and the emergence of ASD. However, robust PII alterations in EL-ASD infants (relative to those at TL) are not shown until after the first year, while findings on PII differences in EL infants or PII's predictive validity of ASD diagnosis within the first year lack consistency. This is possibly due to the small sample sizes used, cross-sectional studies examining PII at distinct time points and due to the heterogeneity in PII variables employed (discussed in more detail in **Chapter 3**). Therefore, replication of previous findings on early PII using a longitudinal design and larger sample sizes is necessary (and is the focus of **Chapter 3**) to increase the consistency in findings in terms of the PII aspects that best differentiate EL from TL infants and those that relate to later ASD diagnosis. Considering that early interaction qualities are important for children's long-term socio-cognitive functioning and developmental outcome, investigating this further can provide a clearer view of how behavioural atypicalities unfold early, prior to the appearance of full clinical symptoms of ASD and will enable a better understanding of the potential role of PII in ASD emergence.

Another issue that naturally follows from this point is the consideration of ASD heterogeneity. Autism Spectrum disorder is a highly heterogeneous condition in symptomatology and outcome (Varcin & Jeste, 2017). This issue cannot be ignored when investigating EL infants' developmental trajectories. As previously reviewed, not all infants at EL for ASD go on to receive an ASD diagnosis at 3 years, while, in most cases, they are differentiated from EL-ASD infants in the qualities of social interactions. In addition, if qualitative aspects of PII are predictors of later ASD outcome, they may also be related to ASD-related traits usually present in first-degree relatives of individuals with ASD (Pisula & Ziegart-Sadowska, 2015). Taking a dimensional approach to studying ASD development (rather than focusing solely on ASD outcome) could enhance our understanding of the developmental trajectories of ASD (Visser et al., 2017) and PIIs' contribution. Yet, only a handful of studies have looked into how social interactive trajectories between parents and EL infants are linked to later developmental dimensions other than ASD diagnosis, such as language skills, adaptive behaviour or ASD-related traits. **Chapter 4** aims to add to the existing literature and to extend **Chapter 3**'s study by addressing this issue.

Another concern is that the empirical evidence on the interplay between PII and brain function in ASD symptomatology and outcome is scarce. Investigating these links early in development is of particular importance due to the apparently experience-dependent nature of brain development (Kolb et al., 2012). The IS theory proposes that possible alterations in the social brain network could result in decreased infant responses to social cues (Johnson et al., 2005). This could in turn affect infants' social interactions within their environment (e.g., caregiver-infant relationships), further amplifying the alterations of these brain mechanisms and subsequently interfering with socially important developmental milestones (Elsabbagh & Johnson, 2010). Indeed, early brain function alterations in EL-ASD infants are seen within the first year, while behavioural

symptoms and robust PII differences become more apparent later, after the first year of life. It is likely that brain function measures, particularly those measuring social attention (i.e., ERP responses to eye gaze/faces), a key feature of ASD, might be capturing early subtle atypicalities that appear later in behaviour. These early atypicalities could affect the quality of PII and subsequently, long-term social functioning. Preliminary research suggests this, showing EL and TL group differences in brain-PII relationships (Elsabbagh et al., 2012), though more evidence is needed to better understand the dynamics of these associations early in development. This is important for illuminating the developmental pathways linked to ASD diagnosis, which may enable earlier detection and improved access to early intervention. To this end, **Chapters 5 and 6** will take a theory- and a data-driven approach, respectively, to examine how several qualitative aspects of PII associate with different measures of brain function (ERP measures to socially relevant stimuli).

In sum, the experimental studies of this thesis will aim to address the following questions:

1. Are previous findings on PII differences in infants at EL for ASD replicable?
 - a) What are the trajectories of PII in infants with a subsequent ASD outcome compared to EL-no ASD and TL infants?
 - b) What aspects of PII are similar or different between these groups over time?
2. How do early PII trajectories that differentiate EL from TL infants contribute to developmental outcomes other than ASD diagnosis?
3. How and what features of PII relate to measures of infant brain function within the first year?
 - a) Are any patterns of relationships similar or different between the groups?
 - b) How are these associations linked to ASD outcome?

Thus, the evidence from the studies of this thesis will contribute to our understanding of the early developmental trajectories of social interaction and their links to brain function (neural social attention) in early ASD emergence.

1.16 Overview of the Present Work

As discussed, the present thesis takes a developmental approach to prospectively investigate early PII trajectories in the context of ASD susceptibility and developmental outcome (including ASD and non-ASD), as well as early brain-PII associations. Examining these can offer important new information on the developmental pathways contributing to ASD symptomatology and diagnosis. It can provide a greater understanding of the contribution of PII qualities in infant developmental routes, which can have important implications for intervention. It will also help to better explain the heterogeneity of the condition by adding to the understanding of which behavioural and brain patterns are unique to infants who develop ASD and which ones are shared or independent for infants who are equally susceptible but do not receive a subsequent diagnosis (Jones et al., 2014). This is also important for a clearer picture of the areas that can be affected by the condition expressed through ASD-related characteristics. Last, examining the behavioural (through PII) and brain processes linked to later developmental outcomes could indicate which of/whether these processes could serve as protective factors, enabling infants to access important social experiences and modifying their trajectories towards neurotypical or distinct outcomes.

Chapter 2 discusses the methodology employed in the series of studies of this thesis. In particular, it provides information about PII observational measures and details of the specific PII measure used in this thesis. In addition, it provides information on brain function measures and elaborates on the particular neural measure applied in some of the studies of this thesis to investigate PII-brain function links.

Chapter 3 examines the trajectories of parent, infant and dyadic social interactions at 8 and 14 months in infants at EL (EL-ASD, EL-no ASD) and TL and whether/which PII aspects are significant predictors of 3-year ASD diagnosis. This research tests the replicability of previous PII findings and the PIIs' contribution to the developmental trajectories of infants with an increased ASD predisposition.

Chapter 4 is an extension of Chapter 3. Using an SEM method, it takes a dimensional approach to investigate whether developmental change (8-14 months) in PII aspects that have differentiated EL from TL infants predicts developmental outcomes (ASD-related traits, language, social communication, maladaptive behaviour) at 36 months. It further explores whether these predictive associations differ in EL-ASD, EL-no ASD and TL infants, testing the possible protective effects of PII trajectories on developmental outcomes.

Chapter 5 aims to bring PII and neural measures of social attention together using SEM. Following the hypothesis that EL infants' brain processing capabilities may affect their interactions with the social environment, the chapter examines whether 8-month-old infant brain responses to social and non-social stimuli are associated with infant behavioural attentiveness to the parent during PII and whether this affects parental responses towards the infant in EL and TL infants.

Chapter 6 builds on the study from Chapter 5. It aims to gain a greater insight into the PII-brain function associations by being driven by the data, considering individual variability. To this aim, it brings together several PII and brain features related to visual attention to undertake a novel, unsupervised data-driven approach to identify emerging PII and brain patterns in the data. Then, it seeks to examine whether/how these brain-PII patterns relate to clinical outcomes.

Finally, **Chapter 7** discusses the contribution of this work to our understanding of the possible developmental pathways of ASD and the role of PII in infants'

development. In addition, the limitations of the aforementioned studies are acknowledged. Future directions and implications of this work are also highlighted.

Chapter 2. General Methods

This chapter describes the methods conducted throughout this thesis for the investigation of PII and neural social information processing in infants at EL for ASD. First, it briefly describes the study design and provides an overview of observational measures of PII in infancy and the context of ASD emergence. It discusses their advantages and disadvantages and further provides details of the observational tool used across all the studies of this thesis, explaining the rationale for choosing this measure. Further, it gives an overview of EEG in infancy. It provides details on ERPs and discusses considerations when using EEG with developmental populations. It also describes the EEG data collection and analysis procedure for this thesis and provides the rationale for using particular ERP components.

2.1 Study Design

The current thesis used a secondary data analysis, multi-method approach (incorporating brain and PII measures) and a longitudinal observational design to investigate patterns of PII and their association with brain function measures in infants with and without and EL for ASD. The data utilised for the present work were sourced from the BASIS network, a UK collaborative network for the study of infants at EL for ASD (BASIS: www.basisnetwork.org). Almost all the data had already been collected by other researchers and were subsequently accessed by the researcher for secondary data analysis to address the research questions of this thesis. Part of the PII data collection was completed by the researcher (details in following sections), while the EEG data had already been processed

2.1.1 Participants

A prospective infant sibling design was necessary in order to investigate the patterns of PII over time, their links to brain function measures between EL and TL infants, and how these were associated with three-year diagnostic classification (ASD diagnosis, non-ASD diagnosis, neurotypical development) and dimensional outcome. Therefore, the current study included two prospective cohorts: A cohort of infants at EL and TL who were recruited in the initial Phase of the BASIS, Phase 1, and another independent prospective cohort included in a subsequent phase, Phase 2 ($N = 247$ in total, **Table 2.1** provides the sample size and methods used in each Phase and study). These infants had been followed over several time points through lab visits (visit 1: 8 months, visit 2: 14 months, visit 3: 24 months, visit 4: 36 months and visit 5: 4-7 years) where they underwent a series of assessments by expert clinicians to track their developmental trajectories. Data from children included in this thesis were used from assessments undertaken when infants were around 8 months, 14 months and 3 years. These time points were selected as 1) they are critical for infant neurodevelopment, 2) due to existing research showing sibling group differences in brain function and PII during this time, 3) clinical diagnosis of ASD following assessment was available at 3 years, and 4) both PII and brain function data were available at 8 and 14 months, while data from other time points could not be used due to time constraints and/or limited availability.

Table 2.1*Sample and Methods in Each Phase and Study*

The BASIS Sample	
Phase 1 <i>N</i> = 104 (TL: 50, EL = 54)	Phase 2 <i>N</i> = 143 (TL: 27, EL = 116)
Sample and methods included in each study of the thesis	
Study 1: Examining parent-infant interaction trajectories in infants with and without an elevated likelihood for autism – a replication study	Only the Phase 2 sample included because the study replicated included the sample from Phase 1. Final sample included: 140 infants (EL: 113, TL: 27). Main methods: Linear mixed models and logistic regressions
Study 2: Parent-infant interaction changes predict developmental outcomes in infants with and without an elevated likelihood for ASD – a latent change score modelling approach	Included both Phase 1 and 2 samples. Final sample included: 243 infants (EL: 166, TL: 77). Main method: Latent change score models
Study 3: Neural correlates of social attention are linked to parent-infant interaction in 8-month-old infants at elevated likelihood for ASD	Included both Phase 1 and 2 samples. Final sample included: 240 infants (EL: 165, TL: 75). Main method: Mediation through structural equation modelling
Study 4: Parent-infant interaction in infants at elevated likelihood of autism: exploring infant brain function correlates using a data-driven approach	Included both Phase 1 and 2 samples. Final sample included: 240 infants (EL: 165, TL: 75). Main method: Linked independent component analysis

2.1.2 Confirmation of ASD Likelihood Status

For the infants at EL, confirmation of EL status was based on information taken from the Development and Well-being Assessment (DAWBA; Goodman, Ford, Richards, Gatward & Meltzer, 2000) and the parent-report Social Communication

Questionnaire (SCQ; Rutter, Bailey & Lord, 2003), reviewed by experienced research clinicians (TC and GP) in order to verify local clinical diagnosis. Infants in the TL group were recruited separately from a volunteer database at the Birkbeck Centre for Brain and Cognitive Development. The criteria for their inclusion were full-term birth (37-42 weeks), normal birthweight and no ASD within first-degree relatives (information obtained through parent interview). The older siblings of infants at TL were screened for the likelihood of ASD symptomatology using the SCQ, with all of them scoring below the instrument threshold for ASD (<15).

2.1.3 Assessment Measures

Upon enrolment, the infants had not been diagnosed with a developmental disorder or another medical condition. The infants included in this study attended a series of cognitive, behavioural and interactive lab assessments at every time point. At the 8- and 14-month lab visits, the infants were also administered experimental tasks, such as EEG and eye-tracking. Parents completed questionnaires and interviews related to their infants' behaviour and development at each time point. Testing of the infants was undertaken by researchers from the BASIS team who worked at Birkbeck (for the 8- and 14-month assessments) and King's College London (for the 36-month assessments). Assessments evaluated infant cognitive capacity and motor development using the Mullen Scales of Early Learning (MSEL, Mullen, 1995), daily adaptive behaviour using the Vineland Adaptive Behaviour Scales – second edition (VABS-II, Sparrow et al., 2005) parent report and early ASD symptomatology using the Autism Observation Scale for Infants (AOSI; Bryson et al., 2008) observational measure. A detailed description of these measures is provided in **Chapter 3** of this thesis. Details of the PII and brain measures' procedures of data collection, setting and task are provided later in this chapter.

2.1.4 Characterisation of Atypical Outcome

At 36 months, children underwent a battery of clinical assessments by an independent team to establish whether they had developed ASD. Following this, and based on available information from all visits, experienced clinical researchers (GP, TC, CC), as well as members of the testing team, determined possible ASD outcome according to DSM-5 (American Psychiatric Association, 2013) and no ASD outcome (typical developmental outcome or other pervasive developmental disorders). Specifically, ASD diagnosis was estimated based on, among other measures, 36-month results from the following assessments: The ‘Autism Diagnostic Observation Schedule- Generic (ADOS-G) – Second Edition’ (Lord et al., 2012), a semi-structured observational assessment for the evaluation of symptoms of ASD, focusing on the child’s social behaviour through activities triggering social interaction, communication, play, language and Restricted and Repetitive Behaviours (RRB); the Autism Diagnostic Interview – Revised (ADI-R), a semi-structured interview assessing ASD symptoms that was conducted with parents; the Social Responsiveness Scale (SRS, Constantino & Gruber, 2012), a questionnaire that continuously measures ASD symptom severity with regards to social ability completed by parents (alongside the VABS and SCQ); the Quantitative Checklist for Autism in Toddlers (Q-CHAT) parent report questionnaire assessing behaviours related to ASD based on the International Classification of Diseases – 10th edition (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) domains, such as social communication and language, joint attention, pretend play, repetitive and sensory behaviours. These measures are described in detail in **Chapter 3**. Results from clinical assessments showed that a proportion of infants at EL met the criteria for an ASD diagnosis, a proportion was categorised as typically developing, while another proportion was categorised as showing symptoms of atypical development, based on scores that were above the autism spectrum threshold on the ADOS-G and/or the ADI-

R, and/or low scores (more than 1.5 standard deviations below average) on the MSEL Early Learning Composite, Visual Reception, Receptive Language or Expressive Language subscales. Details of the percentages of infant clinical outcome categorisation can be found in the experimental chapters.

2.1.5 Data analysis

Advanced quantitative methods were used for data analysis considering the research aims of each study of this thesis. Specific statistical analysis methods included linear mixed models and logistic regressions (**Chapter 3**), SEM approaches such as Latent Change Score (LCS) models, (**Chapter 4**), mediation and multigroup analysis (**Chapter 5**), as well as Linked Independent Component Analysis (Linked ICA, **Chapter 6**). These statistical methods allowed the investigation of aspects of infant development at different time points, provided the flexibility to include different variables taking into account individual variability and were able to account for missing data and violations of the normality assumption. In addition, through the SEM methods and Linked ICA, it was possible to investigate a series of relationships between different variables simultaneously, examine the developmental changes of variables of interest and how these differed between sibling groups. These techniques are discussed in the corresponding chapters of this thesis.

2.2 Measuring Behaviour

2.2.1 Using Observational Tools to Evaluate PII

As mentioned in **Chapter 1**, it is widely acknowledged that the quality of PII is a significant predictor of children's language, social, emotional and cognitive development (Harrista et al., 2000; Rocha et al., 2020). This is further reinforced by epigenetic

evidence suggesting that early environmental experiences as well as parental intrinsic factors (i.e. maternal stress) can have long-term effects on the infant brain (Bick & Nelson, 2016; Champagne, 2008). Even though the attachment theory highlighted maternal sensitivity as a crucial construct for the development of secure parent-child relationships, the infant as well as the dyad as a whole are equally important. The quality of parent-infant interaction is a reciprocal process that depends on the active participation of both partners, with parent and infant equally contributing to the interaction (Moore et al., 2013). Given the significance of these early caregiver-infant exchanges, early observation of PII has been considered one of the most objective and effective ways of assessing its quality and detecting possible relational disruptions, how these develop and whether they are further retained or remediated.

Observations appear to be the gold standard for the assessment of PII. This increasing interest in observational methods also largely derives from family systems theories emphasising the interrelatedness of individuals and their reciprocal relationships in the family environment, and the need to grasp and unfold the nature of these complex interactional systems in a scientific way (Kerig, 2000; Kerr & Bowen, 1988).

Direct observations offer significant advantages in comparison to other tools, such as parent report measures. To begin with, the evaluations of observations can be undertaken in a consistent and reliable way by a certified examiner/researcher, compared to parent reports that could be less accurate and biased, possibly capturing caregiver expectations or perceptions about their or their child's behaviour (Ozonoff, Iosif, et al., 2011; Sachse & Suchodoletz, 2008). Methodologically, although parent reports can be useful for assessing particular family-related aspects (e.g., members' opinions of their role within the family), observational measures can provide a more comprehensive view of the complexity of family functioning by encapsulating, among others, different interactional patterns, nonverbal behaviour, affective expression or rates of behaviour

(Lindahl, 2001). In addition, a strength of observations compared to other assessment measures is that they can evaluate behaviour directly and can be conducted in different settings (e.g., at home or in the lab).

Moreover, the Early Head Start programmes stress the importance of observations of PII, acknowledging that parent-child relationships should be an integral part of child assessment (Early Head Start National Resource Center, 2013). Direct observations are important for both clinicians and researchers as they can be used for designing appropriate interventions and assessing treatment outcomes, as well as for investigating research hypotheses about the processes involved in PII. For instance, observations of PII are proven to have a high clinical utility as they can inform clinicians of PII aspects that warrant further consideration in vulnerable populations (Borrego Jr. et al., 2004; M. W. Wan et al., 2019a). Importantly, observations have shown to be sensitive to changes in PII qualities following intervention. For instance, interventions have shown an enhancement in PII and child development assessed through observation, with evidence revealing positive effects on responsive parent behaviours, social communication, interaction, language and autism severity in young autistic children (Casenhiser et al., 2013; Green et al., 2010; Oono et al., 2013; Siller et al., 2013). Furthermore, pre-emptive intervention has shown treatment effect (up to 24 months following intervention end), with a reduction in symptom severity in infants at EL for ASD and an improvement in PII qualities (Green et al., 2017).

Observational measures are not without their limitations. One limitation compared to parent reports is that observations can be considered costly and time-consuming or labouring (Gardner, 2000). In addition, they can introduce some bias (expectations of PII by the observer) and are subject to errors. However, steps can be taken to reduce these possibilities, such as by receiving training and by assessing PIIs blind to participant information (Aspland & Gardner, 2003). A further limitation concerns

the participants' self-consciousness that they are being observed. This can introduce a positive bias, as caregivers might try to behave in a more socially desirable way (Aspland & Gardner, 2003). Participant familiarisation with the observational procedures and environment as well as having the same observer or fewer observers across visits might help reduce this bias. Nevertheless, research suggests that caregiver behaviour changes as a result of observation probably do not seem to be so substantial to affect the validity of the information gathered from the observation (Gardner, 1997).

2.2.2 Evaluating Psychometric Properties

Assessment of PII using comprehensive, valid and reliable observational tools is crucial for the effectiveness of interventions and for identifying patterns of interaction that may impact later infant development (Ruble et al., 2008). Therefore, examining an observational measure's psychometric properties is important for its selection. Of note, determining the type of validity and reliability of an observational measure depends on the target population being assessed as well as the reason for its use.

Several kinds of evaluation of an instrument's validity and reliability exist and have been used across studies. Reliability determines the extent of measurement error of an instrument. Inter-rater reliability and inter-rater agreement are very important aspects of assessing the quality of a measurement. Although they are usually used interchangeably, they have been suggested to represent different notions of reliability assessment (Kottner et al., 2011). Inter-rater (observer) reliability is termed as the extent to which objects or subjects of measurement can be differentiated in the rating procedure (Kottner et al., 2011). The most commonly used type of reliability assessment is inter-rater agreement, referring to the extent of agreement between two (or more) observers on a particular behaviour. Methods to examine inter-rater agreement usually include intra-class correlations, percentages or kappa calculations, depending on the type of question

and data generated by the instrument (Aspland & Gardner, 2003). Intra-rater reliability is another assessment of rater consistency, which refers to scores derived from the same person at different time points. Other components of reliability have also been considered important, such as internal consistency and test-retest reliability (Aspland & Gardner, 2003; Gridley et al., 2019). Internal consistency is defined as the extent of interrelationship within the domains of the measure and is appropriate to use with measures that record in frequency counts or with Likert-type scales. Test-retest reliability tests the stability of a measure across time. In turn, examples of a measure's validity include but are not limited to, *content validity* (the extent to which a measure reflects the underlying construct it is supposed to measure), *convergent/divergent validity* (whether a measure correlates/does not correlate with another measure evaluating a similar/unrelated construct), *discriminant validity* (whether constructs of a measure are dissimilar between relevant populations), *concurrent validity* (the extent to which different measures assessing the same behaviour are associated), *predictive validity* (whether a measure's construct is predictive of a future construct) or *cross-cultural validity* (the degree to which a measure's original scores reflect the scores of the measure when is translated or culturally adapted) (Aspland & Gardner, 2003; Lotzin et al., 2015). Systematic reviews assessing the psychometric quality and reliability of observational measures focusing on early PII, PII used in randomised controlled trials of parenting programme research or PII designed for use with clinical populations documented that an adequate level of evidence for validity in the observational tools was not strong in many cases, while inter-rater reliability was used more frequently (Cañas et al., 2020; Gridley et al., 2019; Lotzin et al., 2015). Thus, the need for further strengthening and refinement of the psychometric properties of observational measures has been suggested.

2.2.3 Conceptualisation of PII Coding Systems

Observational tools have a long-standing tradition in the field of parenting research and various observational coding schemes have been developed for studies investigating the quality of PII (Lotzin et al., 2015). These schemes commonly use either a microanalytic or a global/macro-level approach to code PII. Microanalytic coding schemes involve the assessment of specific PII constructs capturing moment-by-moment behaviours, analysing them in short segments of time (i.e. analysing each video frame or coding in time units) through interval coding or recording every occurring behaviour (Mesman, 2010; Morawska et al., 2015; Rosenberg et al., 1986). In contrast, global coding takes into account the overall context and qualitative aspects of the interaction using broader domains, such as maternal sensitivity or infant interest (Kerig, 2000; Morawska et al., 2015; Rosenberg et al., 1986). A meso-analytic approach also exists that involves a combination of global and microanalytic scales to code PCI, though this method is rarely used (Lotzin et al., 2015). For instance, the Meso-Analytic Behavioural Rating System for Family Interactions (MeBRF, Mahoney et al., 2000) focuses on coding each behaviour in each minute of the interaction and its codes can be analysed individually while also providing a summary of behaviour assessments over time.

Both microanalytic and macroanalytic coding approaches are complementary but offer unique information about parent-child relationships (Bohr et al., 2018; Bornstein et al., 2011; Mesman, 2010). Although few studies to date have utilised both approaches, research using a combination of microanalytic and macroanalytic schemes reveals mixed findings on their convergence (Bardack et al., 2017; Bassett et al., 2006; Berk & Spuhl, 1995; Hodges et al., 2007; Kochanska & Aksan, 2004; Mesman, 2010; Morawska et al., 2015). Both approaches have strengths and weaknesses, and the choice of one over the other depends on the study's rationale and research question of interest. However, global rating schemes tend to be favoured more, since they are less labour-intensive and require

fewer costs. Importantly, it is because they can capture interaction styles characteristic of the individual (i.e., the caregiver) and are evaluative of the sum of PII, accurately providing a global picture of complex aspects of PII, while microanalytic coding schemes are only descriptive, providing details of specific parent, infant or dyadic behavioural cues (Bornstein et al., 2011). Considering this, microanalytic approaches appear to be better suited to address questions related to quantity than the quality of PII. On the other hand, microanalytic approaches can capture specific behaviours or their relations compared to global rating approaches. In addition, coding using microanalysis of behaviour can be learned and applied more easily than using global rating scales. Another advantage of microanalytic approaches is that, since they are explicit, they are less prone to judgment and inferences by the observer, compared to global rating approaches that require some level of inference or interpretation when coding. Nevertheless, microanalytic approaches are situation-specific (they are variable depending on context), and thus, difficult to generalise and provide continuing, core patterns of interaction across settings (Bornstein et al., 2011). In turn, macroanalytic approaches tend to be more consistent in PII patterns across contexts, offering opportunities for generalisability (Gardner, 2000). Therefore, they may also be able to capture possible behavioural differences across contexts (Morawska et al., 2015). It has also been suggested that they may be sensitive to subtle behavioural changes during PII. For instance, an observer using a global coding approach may be able to identify cues in parent behaviour indicative of negativity, which a microanalytic coding system may not detect (Morawska et al., 2015).

2.2.4 Observational Coding Schemes Used in Infancy

A multitude of observational measures have been developed for the assessment of PII. Many PII rating schemes are global (e.g., the Nursing Child Assessment Feeding Scales (NCAFS, Sumner & Spietz, 1994), the Nursing Child Assessment Teaching Scales

(NCATS, Oxford & Findlay, 2012), the Emotional Availability Scales (EAS, Biringen et al., 2014), the Child–Adult Relationship Experimental Index (CARE-Index, Crittenden, 2006), the Global Rating Scales of Mother–Infant Interaction (GRS, Murray et al., 1996), and others), while microanalytic rating scales (e.g., Monadic Phases (Tronick et al., 1980), Belsky (unnamed) dichotomous scale (Belsky et al., 1984), the Greenspan-Lieberman Observational Scale-Revised (GLOS-R, Greenspan & Lieberman, (1989), and others) also exist. In addition, there is heterogeneity in the constructs used between observational tools, ranging from particular aspects (e.g., object attend, social attend, object play; Monadic Phases) to more broadly defined constructs (e.g. caregiver sensitivity, intrusiveness, infant social involvement; the Coding Interactive Behaviour (CIB) global scheme). Many measures also use a large number of items for the evaluation of caregiver, infant and dyadic behaviours. Indicative examples are the Monadic Phases and the NCAFS/NCATS containing more than 70 domains, or schemes like the Functional Emotional Assessment Scale (FEAS, Greenspan et al. (2001)), a global rating scheme that includes between 27-47 domains for assessing interactional qualities. However, not all measures examine parent, infant and dyadic behaviours, with some focusing only on caregiver-infant aspects (e.g., NCAFS, NCATS, FEAS, Monadic Phases), others on caregiver-dyadic domains (e.g., Belsky scale) and others solely on dyadic interactional aspects (e.g., the Revised Relational Coding System (RCS, Fogel et al., 2003).

Furthermore, of the different constructs, caregiver sensitivity as well as its elements, such as responsiveness, appears to be the most commonly used construct, recurrent throughout many measures. The construct of sensitivity was first defined in the context of attachment theory and was introduced by Mary Ainsworth during careful, continuing observations of PII in her seminal research, referred to as the Baltimore study (Ainsworth et al., 1978). Since then, many observational measures have incorporated this

construct, including the EAS, CIB, NCAFS, NCATS and the CARE-Index, among others. However, the definition of the construct has not been used uniformly across measures. Although sensitivity in different measures may conceptually relate to the original construct by Ainsworth, many researchers have used their own definitions or operationalisations for its description. This has resulted in measures evaluating different aspects of sensitivity than the broader concept, therefore this scale cannot be used interchangeably across measures, which has implications for research and clinical practice (Bohr et al., 2018). For instance, the EAS global scheme captures caregiver sensitivity holistically, while the NCAFS/NCATS scales assess caregiver's sensitivity to infant cues on a dichotomous scale (observed/not observed). This is very different to a more global scale including both the frequency and intensity of behaviours.

Regarding validity and reliability, many the tools have demonstrated evidence for internal structure validity (e.g., internal consistency, inter-rater reliability), whereas not all of them have provided evidence for test-retest validity, sensitivity to change, convergent/divergent or criterion (concurrent/predictive) validity based on studies with credible quality (see Lotzin et al., 2015 for a review). For instance, research has not demonstrated a strong association between the NCATS and another observational measure, showing low evidence for concurrent validity (Byrne & Keefe, 2003), while evidence for test-retest reliability in the EAS is mixed (Endendijk et al., 2019). Furthermore, coding schemes range from those that have been designed for both clinical and research use (e.g., the Parent–Child Early Relational Assessment (PCERA, Clark, 1999) global scale, Belsky, GRS, and others) to those designed only for one of the two (e.g., the Assessment of Mother–Infant Sensitivity (AMIS, Price, 1983) global scale or the Monadic Phases scale). Thus, some have shown evidence for discriminant validity, differentiating between high and low-risk populations. For example, the CARE-Index has differentiated irritable and non-irritable infants in the context of maternal depression

during PII (Ayissi & Hubin-Gayte, 2006). In addition, the PCERA has shown differences in PII (in maternal subscales in particular) between dyads of substance abuse mothers and non-clinical dyads (Siqueland et al., 2014). Overall, tools vary in terms of the level of approach, constructs used, number of items, validity evidence or purpose.

2.2.5 Observational Coding Schemes Used in ASD

Several observational measures have been employed in research investigating PII aspects in infants at EL for ASD or those with emergent ASD (before 3 years of age). Some of these observational tools are presented in **Table 2.2**. Again, the large heterogeneity of the observational measures used across these studies is prominent. However, this is not surprising, considering each study has different research aims and focus. It can be observed that some of the schemes used include many different items, and items are characterised by a lack of uniformity. However, some commonalities are also observed across measures in the item/constructs used. For instance, the evaluation of caregiver responsiveness, sensitivity or intrusiveness/directive behaviour and infant affective behaviours are observed in more than one measure. Furthermore, there are observational schemes focusing only on caregiver (e.g., the Maternal Behavior Rating Scale (MBRS)) or infant behaviours (e.g., the Early Social Communication Scales (ESCS)), and others assessing both caregiver-infant (e.g., Scales developed by the National Institute of Child Health and Human Development (NICHD)) or caregiver-infant-dyadic behaviours (e.g., the Manchester Assessment of Caregiver-Infant Interaction (MACI), Parent-infant/toddler coding of interaction (PInTCI), the Communication Play Protocol (CPP)). The measures used in these studies also vary in duration of observation for coding. For example, the PInTCI aims to code PII observation lasting for at least 5 minutes, while in other measures, such as the ESCS, 15-25 minutes are required.

Most of the measures presented in **Table 2.2** have been validated. Inter-rater reliability is consistently reported and discriminant validity has also been achieved (e.g., NICHD, MBRS, PInTCI), evident in the studies included in the Table. Other examples of validity include predictive validity and sensitivity to change (e.g., the Erickson scales, Jokihaka et al. 2022; Stams et al., 2001), stability over time and good internal consistency (e.g., the MACI, Wan et al., 2013).

Moreover, as can be seen in **Table 2.2**, different levels of assessment of PII have been used across studies. Some studies have chosen to evaluate PII through microanalytic/frequency coding (e.g., Rozga et al., 2011) or through a global rating approach (e.g., Pijl et al., 2021), while others have incorporated both approaches (e.g., Campbell et al., 2015). The most commonly used measure across these studies appears to be the MACI global rating scheme. In addition, some of these studies have used observational measures of PII in relation to brain function measures (Elsabbagh, Bruno, Wan, Charman, Johnson, Green, & Team, 2015), in the context of intervention (Green et al., 2017) or to examine play behaviour (Campbell et al., 2018).

Table 2.2

Observational Measures of Parent-Infant Interaction Used in Studies with Infants at an Elevated Likelihood or Emerging ASD

Measure	Scoring	Studies	Scales
Scales developed by the (NICHD) Early Child Care Research Network (ECCRN) (NICHD Early Child Care Research Network, 1999)	4-point/7-point rating global scales	Baker et al. (2010) Campbell et al. (2015, 2018) Ding et al. (2021)	<i>4-point rating scales up to 24 months</i> Caregiver: sensitivity to nondistress, intrusiveness, detachment, stimulation of cognitive development, positive regard for the child, negative regard for the child, and flatness of affect. Infant: positive mood, negative mood, activity level, sustained attention, sociability to others (at 6 months only), engagement with the mother (at 15 and 24 months). Composites are available for maternal sensitivity (sum of sensitivity to nondistress, intrusiveness (reverse scored), and positive regard) and child positive engagement (the sum of child engagement and positive mood). <i>7-point rating scales at 36 months</i> Caregiver: supportive presence (sensitivity to nondistress), respect for the child's autonomy (lack of intrusiveness), stimulation of cognitive development, hostility (negative regard), confidence. Infant: enthusiasm, negativity, persistence, and affection for mother. Composites available for the maternal sensitivity (sum of supportive presence, hostility (reverse scored), and respect for autonomy and child positive engagement (sum of child affection to mother and negativity (reverse scored))).
Frequency coding (unnamed)	Frequency coding	Campbell et al. (2015)	Caregiver: scaffold play, initiate/direct play, and praise. Infant: shared positive affect, give toy, showing and giving toys, and pointing to request/share interest with the parent, socially-directed vocalizations.

MBRS (G. Mahoney et al., 1986)	5-point rating global scale	Harker et al. (2016)	Caregiver: responsiveness (responsivity, sensitivity, effectiveness), affect (acceptance, enjoyment, expressiveness, inventiveness, warmth), achievement orientation (achievement, praise), and directiveness (directiveness, pace).
ESCS (Mundy et al., 2003)	Frequency coding	Rozga et al. (2011)	Infant: joint attention (Initiating joint attention, responding to joint attention), behavioural requests (initiating behavioural requests, responding to behavioural requests), social interaction (initiating social interaction, responding to social interaction, language).
Monadic Phases (Tronick et al., 1980)	Dichotomous scale, 1-s time sampling	Yirmiya et al. (2006)	Caregiver: avert, social attend, social elicit, object attend, play, object play, talk (34 items in total) Infant: protest, avert, social attend, social play, object attend, object play, talk, pick-me-up, greet, positive away (50 items in total)
PInTCI (Pijl et al., 2016)	7-point global rating scale	Pijl et al. (2021)	Caregiver: sensitive responsiveness, negative control, scaffolding, positive affect, negative affect. Infant: attentiveness, initiations, sharing of affect, positive affect, negative affect Dyad: reciprocity.
CPP (Adamson et al., 2001, 2004, 2012)	Different data capture procedures exist for use with the CPP (e.g. event-based coding, 7-point Likert scale: the Joint Engagement Rating Inventory (JERI))	Suma et al. (2016)	Parent-infant: Social interacting (sharing music, taking turns), requesting (assistance gaining toys from a high shelf, help playing with complicated toys) commenting (sharing pictures, discussing objects in a container), and narrating (originally used, past and future) Engagement state codes: unengaged, object, supported joint, coordinated joint, symbol infused supported joint, symbol-infused coordinated joint, other (onlooking, person, symbol only, person-symbol, and object-symbol).

			17 rating items: joint engagement (total, supported, coordinated, symbol-infused), child (initiation of communication, responsiveness to communication, expressive language level and use, quality of behaviour patterns, child affective communication), parent (scaffolding, symbol highlighting, following child's focus, affective communication), shared topic (elaboration, sustainability, scope, fluency and connectedness of conversation).
Erickson scales (Erickson et al., 1985)	7-point rating scale	Oosterling et al. (2010)	Caregiver: supportive presence, lack of respect for autonomy (intrusiveness), hostility, clarity of instruction, sensitivity and timing of instruction, confidence. These scales can be combined to create a composite termed 'sensitivity'. Infant scales developed by Erickson: persistence, enthusiasm for the tasks, anger/negativity, compliance, reliance on mother for help and encouragement, affection for mother, avoidance of mother, and general quality of experience for the child.
MACI (M. W. Wan, 2022)	7-point global rating scale	Del Rosario et al. (2023) Elsabbagh, Bruno, Wan, Charman, Johnson, Green, & The BASIS Team (2015) Green et al. (2015, 2017) Loncarevic et al. (2022, 2023)	Caregiver: sensitive responsiveness, nondirectiveness Infant: attentiveness, positive affect, negative affect, liveliness Dyad: mutuality, engagement intensity

Wan et al. (2012,
2013) Whitehouse et
al. (2019, 2021)

2.2.6 The Manchester Assessment of Caregiver-Infant Interaction

The MACI (updated version 2.2) was used to assess PII qualities across all the studies of this thesis. The MACI is a global rating scheme for the evaluation of the quality of key aspects of interaction between the primary caregiver and the infant through observation of videotaped unstructured play (MACI; Wan et al., 2012, 2013). In theory, it converges with the transactional model of development which emphasizes gene-environment transactions and the importance of PII in children's developmental trajectories. The measure focuses on infancy and is a modified version of other existing measures that have already been validated (details below). It was developed to summarise important features of parent, infant and dyadic aspects of interaction, and while it was initially utilised for research in infants at EL for ASD, it is based on a normative developmental model and is intended for use with various samples, including clinical or non-clinical, at-risk and vulnerable infants or caregivers. In addition, the measure was developed to globally assess key qualities of PII for the purposes of research in a relatively brief and quick way, based on empirical evidence and not solely on theoretical assumptions, enabling the measurement of PII over developmental time across infancy (M. W. Wan, 2022).

Interactions are evaluated by rating 8 items on a 7-point scale, one being the lowest and seven the highest. Items consider behavioural and affective aspects of interaction: parental behaviour (caregiver sensitive responsiveness and caregiver nondirectiveness), infant behaviour (infant attentiveness to caregiver, infant positive affect, infant negative affect and infant liveliness) as well as the dynamics of the interaction between the dyad (mutuality and engagement intensity). The particular aspects of interaction are believed to echo to some extent the infant's early social experiences within the caregiving environment, and can have important implications for children's social, cognitive and emotional development. The scales are mostly

conceptually broad and consider both the quality and quantity of the interaction. Importantly, each scale is not to be understood as a standalone construct where a particular skill or capacity is measured. Rather, MACI focuses on the interactive dynamic in which parent-infant behaviours are bidirectionally affected within the dyadic context. **Table 2.3** provides a detailed description of each item.

Table 2.3*Brief Description of the MACI Constructs and Scores*

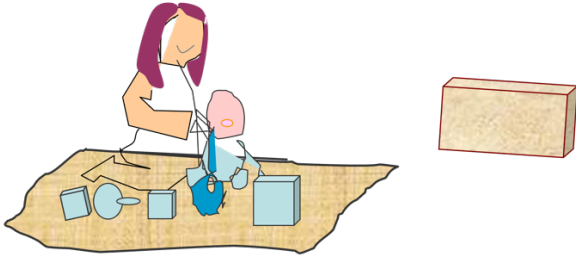
Item	Description	Extreme scores
<i>Caregiver</i>		
Sensitive responsiveness	The extent to which the caregiver responds promptly and in a congruent and effective way to infant behaviour (including lack of behaviour), interests and affective state.	1 = Minimal sensitive response. Very few responses are seen that are inappropriate and inadequate. 7 = Consistent sensitive responses throughout the interaction that are atuned to the infant's age and developmental level.
Nondirectiveness	The extent to which the caregiver's behaviour is aligned with the infant's needs, autonomy and experience. In contrast, directive behaviours include the caregiver's tendency to interact in a particular way and to control infant's expression and interests.	1 = Highly directive. Infant's autonomy is restricted. 7 = Highly non-directive. The interaction is infant-focused. High acceptance of infant's experience.
<i>Infant</i>		
Attentiveness to parent	The amount to which the infant voluntarily directs attention towards the caregiver through eye contact, shared interest, vocalisations and attention to an object or activity initiated by the caregiver.	1 = Minimal or no attentiveness. There is no eye contact and the infant is avoidant. 7 = Highly attentive. High and consistent orientation to the caregiver.
Positive affect	The amount and degree of infant's positive emotional state expressed through smiles, vocalisations, bodily/facial expressions and overall enthusiasm.	1 = No positivity. No positive affect observed, despite infant's cooperativeness. 7 = Substantial positivity. A high predisposition to positive affect.
Negative affect	The amount and degree of infant's negative emotional state expressed through vocalisations, facial/bodily expressions, including avoidance and distress.	1 = No negativity. No negative affect observed, despite infant's unresponsiveness to the caregiver.

		7 = Substantial negativity. High tendency to negative affect.
Liveliness	The overall amount and degree of infant's voluntary physical activity, regardless of whether it is expressed through the interaction or not. The infant's developmental level is taken into consideration.	1 = Unlively. Long periods of little or no activity. 7 = Extremely lively. High infant activity dominates the interaction, even though there may be brief periods of little activity too.
<i>Dyad</i>		
Mutuality	The amount and degree of jointness between caregiver and infant through shared attention, acceptance of caregiver involvement, body coordination, smoothness and interactivity.	1 = Non-mutual. Almost no mutuality. The interaction seems to be stilted and the infant generally distant. 7 = Consistently mutual. There is evidence of high and almost consistent mutual behaviour.
Intensity of engagement	The incident where engagement with the caregiver is most intense, revealed through shared attention and affect. This scale focuses on the quality rather than the quantity of engagement.	1 = Almost no intensity. There is no mutual focus, or there may be a very brief example that is considered ambiguous. 7 = Very high intensity which is prolonged and reaches a peak of excitement.

2.2.6.1 Procedure. In the PII assessment, unstructured play between infants and their parents is video recorded in a laboratory setting or at home after a period of familiarisation. The dyad is sat on a mat with a small set of selected toys and is instructed to engage in free play with their infants as they would normally do at home, with or without the use of toys as they prefer. The video clips are evaluated for 6 minutes from the moment the researcher leaves the room, blind to all participant information (**Table 2.4** provides the details of the coding procedure).

Table 2.4

Coding Procedure for Each Clip and Play Interaction Set-Up

Steps of Coding	
1. Narrative	Six-minute observation of unstructured interaction accompanied by the creation of a descriptive narrative. The goal is to obtain an overview of the interactive patterns.
2. Initial rating	Focusing on a few areas of interaction at a time and making provisional ratings and supporting notes. The goal is to accurately describe what has been observed to support the rating, which also helps with subsequent inter-rater agreement checks.
3. Checks	Re-reviewing of the video at least once in order for coding to be completed. The goal is to re-evaluate areas that may need more attention (i.e. initial evaluation may have focused more on the infant and less on the caregiver), check any provisional notes and add/modify existing notes.
Play set-up	
1. Caregiver and infant (shown below) sat on floor mat (not required to stay on mat for the whole duration of the interaction) with selected toys in front.	
2. Any box for the toys and other potentially occluding objects needs to be out of the way.	
	

Note. Adapted from the MACI coding manual (version 2.3), Wan et al. (2022).

2.2.6.2 The Development of the MACI. As mentioned, the measure was developed out of the need to acquire more ‘qualitative’ characteristics of social interactions between infants and their primary caregivers as opposed to molecular aspects. Therefore, with a focus on capturing key PII domains and making the rating procedure less time-consuming, the development of the MACI capitalised from previous work, carefully selecting and adapting/modifying (through extensive piloting work and precise operationalisation) already validated scales to suit a wide age range in infancy, an unstructured PII and longitudinal assessment of PII. Most of the MACI scales were taken from parts of the GRS validated measure, which is used to evaluate PII in at-risk populations (e.g. postnatal depression) (Murray et al., 1996). In turn, the aspects of parent sensitive responsiveness and dyadic mutuality were based on the *Coding of Attachment-Related Parenting in Autism* (CARP-A, Blazey et al., 2008) which is a modified and validated version for autism of the original CARP, which is centred around affect and mutuality in older children (Matias, 2006).

2.2.6.3 Reliability and Validity. The measure has demonstrated excellent psychometric properties and inter-rater reliability, independent of infant gender, developmental level, maternal age and socioeconomic status (M. W. Wan et al., 2012, 2013, 2017a). It has been used in several studies, including studies with children displaying early symptoms of ASD (Loncarevic et al., 2022) and infants at EL for ASD (Del Rosario et al., 2023; M. W. Wan et al., 2012, 2013) with evidence for predictive validity (M. W. Wan et al., 2013). It is also sensitive to intervention effects (Green, Charman, Pickles, Wan, Elsabbagh, Slonims, Taylor, McNally, et al., 2015; Green et al., 2017; Whitehouse et al., 2021). Even though the MACI has previously differentiated infants at EL from those at TL (Del Rosario et al., 2023; M. W. Wan et al., 2012, 2013)

it is designed as a research tool and not as a screening tool. The MACI scales have also been linked with brain data in several studies, including fMRI (Abel et al., 2018; Elmadih et al., 2016; Wan et al., 2014), fNIRS (Zhao et al., 2019) and EEG (Elsabbagh, Bruno, Wan, Charman, Johnson, Green, & Team, 2015). Evidence for the reliability (and validity) of the coding using the MACI for the research of this thesis is offered in the following experimental chapters.

2.2.6.4 Training and Reliability. The MACI includes a coding manual that is not freely distributed. To ensure the validity and reliability of the measure, a certain amount of training is required, and the manual can only be used by certified coders or by those in training. An important aspect the measure takes into account is that of test-retest reliability and involves blind-coding of a sub-sample of videos by an independent, certified coder, rather than relying only on training reliability. The researcher is a fully-trained, certified and reliable coder of the MACI scheme.

2.2.6.5 The Rationale for Using the MACI. The selection of the MACI as the measure of PII for this thesis was made for several reasons. Firstly, this thesis aimed to examine the interaction quality of PIIs in a prospective sample of infants at EL for ASD, their relationship to subsequent developmental outcome and their links to brain function measures. As mentioned, the MACI was initially used for researching infants at EL for ASD, it has been utilised in several studies including this population (differentiating EL from TL infants) and has shown an association with measures of brain function. Therefore, in addition to the fact that the MACI aligns with one of the theoretical propositions that this thesis is based on (i.e., transactional model), its choice also allowed the empirical work in this thesis to build on existing evidence and examine the

consistency and reliability of previous findings on PII and PII-brain associations in the context of ASD susceptibility.

Secondly, it was important to select a measure that was relatively brief, less time-consuming and captured key features characterising the general quality of PII with robust evidence for reliability and validity. A systematic analysis of various observational measures of PII indicated that only a limited number of measures were brief, such as microanalytic tools, or those focusing on a particular construct and have been designed for hospital use or screening (Lotzin et al., 2015). A global rating scheme such as the MACI was considered ideal, as opposed to other measures that are time-consuming (i.e. microanalytic measures) and tend to encompass a large number of scales of increased complexity. In addition, although brief microanalytic measures exist, global rating scales can evaluate the context and the parent-infant behaviours holistically (e.g., can pick up subtle cues indicative of directive behaviour) that might be missed by microanalytic tools. Using a measure that could capture subtle cues in early interactive behaviour of caregiver-infant dyads in ASD susceptibility, before the appearance of robust child ASD characteristics was essential for the series of studies conducted in this thesis. It can provide important information on early ASD indicators and possible alterations in PII qualities, which can inform intervention targets. Global rating schemes have also shown to be more sensitive in measuring behaviour in the context of play than microanalytic measures (Morawska et al., 2015). Another advantage of the MACI is that the key features that assesses involve parent, infant and dyadic qualities. All these MACI domains have differentiated EL and TL infants in previous studies and have been sensitive to intervention effects, thus, further investigation of these qualities was of particular importance in this thesis. Last, and as mentioned above, the MACI has provided evidence for internal consistency, reliability and validity, which was an essential requirement for its selection.

2.2.7 PII Data Collection Procedure for This Thesis

As the sample used in this thesis was part of the BASIS (see **Chapter 3** for details on the participants (Phases 1 and 2), video-taped recordings of PII with the parent-infant dyads considered in this thesis had already been undertaken. Thus, the clips were available for coding. A proportion of the clips had already been coded by independent researchers (all the clips from Phase 1; 56 clips from Phase 2, 8 and 14 months combined) for other research purposes, achieving high inter-rater reliability (details in later chapters) while a considerable proportion were digitised ($n = 46$) and coded by the researcher for the purposes of the research of this thesis (99 clips in the 8-month PII assessment and 106 clips in the 14-month PII assessment), blind to all participant information. Inter-rater agreement was tested by independent blind coding of a proportion of the clips. Any disagreements in coding were resolved by the raters re-reviewing the clips. Recoding of the clips was also undertaken in the case of low inter-rater reliability in any of the PII items. Details on the inter-rater reliability are discussed in the following experimental chapters.

2.3 Measuring Neural Activity

2.3.1 Using EEG in Infancy

Electroencephalography is one of the most traditional brain imaging methods and has been a very useful technique in developmental research. It is a non-invasive and painless technique recording the ongoing brain electrical activity from the surface of the scalp using electrodes. This method allows the measurement of neural activity directly and can capture the dynamics of cognitive processes at the time of fast-occurring cognitive events (Cohen, 2014). It offers an easy recording of brain activity and allows

some movement flexibility, thus, it does not pose demands that other neuroimaging techniques pose, such as MRI which is highly sensitive to head motion affecting the quality of the signal. As such, it is extensively used to record the brain activity of neonates, infants and older children. A great advantage of EEG is that it is suited to a wide age range, allowing the examination of brain activity longitudinally, which is fundamental for the study of neurodevelopment. In addition, EEG permits the investigation of aspects that cannot be captured by behavioural measures (e.g., neural responses to the presentation of several stimuli), as it does not necessarily require a behavioural or verbal response (DeBoer et al., 2007). Another significant advantage of EEG is its excellent temporal resolution, as patterns of neural activity can be recorded within milliseconds after stimulus administration. This has allowed researchers to examine, among others, emotion processing (W. Xie et al., 2019), working memory (M. A. Bell, 2012), recognition memory (de Haan, 2013), habituation (Katus et al., 2023), acoustic change detection (Musacchia et al., 2015) or brain function differences in atypical development, as shown in Chapter 1.

Infants limited verbal and attentional abilities and behavioural repertoire mean that the task design of EEG studies needs to be adjusted. Therefore, compared to adult studies, the complexity of the stimuli and the length of trials is reduced in infancy (DeBoer et al., 2007). Experimental tasks have been developed or adapted to suit the infant population, such as resting state paradigms, where neural activity is recorded with no need for task completion (during sleep, with eyes closed or looking at a fixation cross, or when sitting on parent's lap). For instance, some studies have examined infant resting EEG through a passive auditory oddball procedure separated by a 3-minute block (resting EEG data collection) during which no stimulus was presented and the child was quietly playing on parent's lap (Benasich et al., 2008; Gou et al., 2011). Other examples include paradigms that involve looking at a woman singing nursery rhymes or at toys moving (E.

J. H. Jones et al., 2015). Another advantage is that the EEG technique is much less expensive than others, such as fMRI.

Moreover, a distinctive characteristic of the EEG signal is its multidimensionality. EEG data consist of several dimensions, such as time, space, frequency, power, and phase (the timing of neural activity) (Cohen, 2014). This dimensionality offers the advantage and ability to examine hypotheses embedded in psychology and neurophysiology and to investigate links with recordings from non-human populations, enhancing the translational potential of findings.

Despite the many advantages offered by EEG, it is not without its limitations. First, although EEG has excellent temporal resolution compared to other tools (e.g., MRI), it lacks precision in terms of spatial resolution. Greater neural responses to a stimulus can be found in electrodes related to that particular stimulus (e.g., greater ERP responses to a visual stimulus evoked over occipital than frontal regions), but the neural source of electrical activity generated at the scalp is difficult to identify, as the skull can distort the underlying brain activity and because of the complexity of brain geometry (de Haan & Johnson, 2005).

Another limitation is that the EEG signal might be contaminated with artefacts that might not reflect brain activity. Such artefacts are eye blinks and lateral eye movements, or movement related to heart rate and myogenic activity (EMG). This is particularly challenging with developmental populations, as it is difficult for infants to stay still or keep their eyes fixated on the screen for a long time. Detection and cleaning of the data from these types of artefacts can be done during EEG processing, while keeping the infants on their parents' laps can also help reduce movement. Furthermore, combining EEG tasks with behavioural tasks can be a challenge. Although recording behaviour during or immediately after ERP recording can provide significant insights into brain-behaviour associations, it can lead to increases in the length of time required for

testing, and coupled with the fact that EEG necessitates a highly constrained testing environment (limited movement), this cannot always be feasible.

Dynamic developmental changes in EEG and ERP morphology take place during infancy and can be related to a combination of factors, such as myelination, synaptic density, skull thickness, total brain volume or the amount of neural generators involved in the response (de Haan, 2013; Haartsen et al., 2016) and not necessarily to changes in the experimental task. Therefore, dissociating the processes underlying change can be very challenging.

An important methodological shortcoming in EEG data collection and analysis is the signal-to-noise ratio (SNR) generated by artefacts mentioned above as well as general background noise (e.g., electrical equipment in the surrounding environment). The neural activity generated in the brain is very small compared to noise that is unrelated to the experimental task, and consequently, the resulting recorded signal is a combination of noise and genuine brain responses. One solution to this issue is to increase the number of trials because, in this way, consistent neural activity can be identified compared to random noise. However, although this might be efficient with adults, it can be challenging for infants where EEG data collection is undertaken in a short period. Placing the participants in different conditions in a random order and making a comparison is also problematic as it can introduce confounds (de Haan, 2013). Recording with high density electrode nets has been suggested as an alternative, which allows the swift placement of a large number of electrodes (> 64) on the scalp surface. This technique allows the use of the average reference, providing a high-quality EEG signal and an unbiased estimation of noise (DeBoer et al., 2007). Another advantage of high density EEG is that it can better capture the topography of brain activity as it can provide better scalp coverage, differentiating activity deriving from superficial cortical and subcortical activity and can be used in source localisation (DeBoer et al., 2007). This can also help overcome the issue

of ambiguity of the source of the electrical activity which could be deriving from different cortical or subcortical structures. Last, taking the issue of SNR into account during the experimental design procedure can help minimise this possibility.

2.3.2 The Neural Origins of EEG

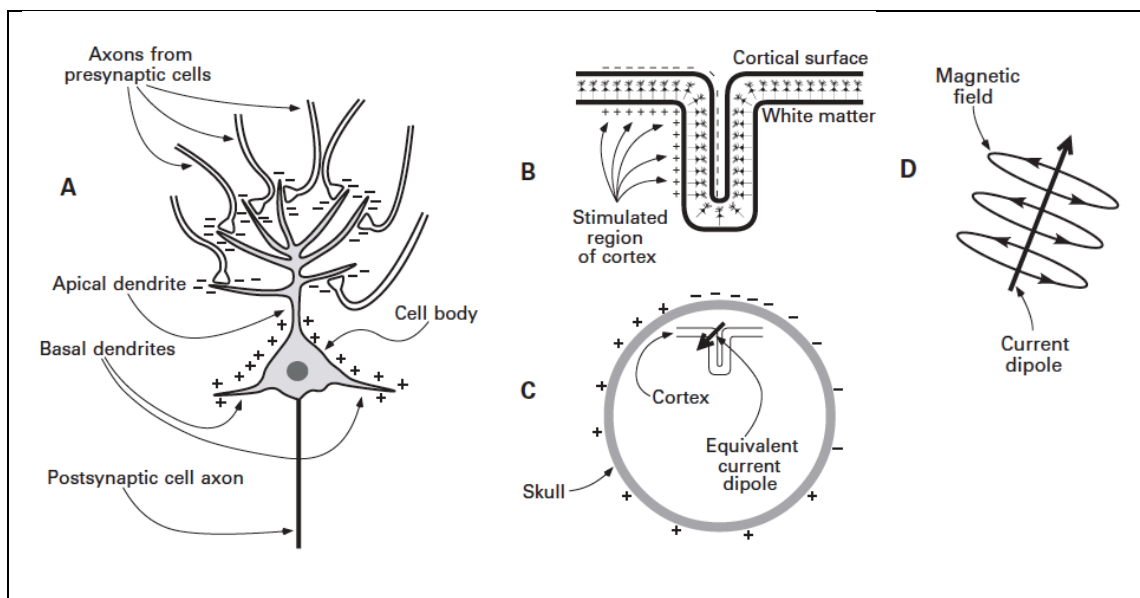
Excitatory or inhibitory postsynaptic potentials that occur simultaneously and in summation by tens of thousands of neurons of similar orientation give rise to the EEG (and ERP) signal recorded on the scalp. The postsynaptic potentials through which the signal is generated result from the binding of neurotransmitters to the receptors of postsynaptic neurons (Luck, 2014). The main neurons responsible for the generation of the signal are believed to be cortical pyramidal cells which are aligned in parallel, perpendicular to the cortical surface. Current flowing along the cortical pyramidal cell, creating net negativity in the area of the apical dendrites and net positivity in the area of the cell body and basal dendrites produce a small dipole (a pair of opposite electrical charges separated by a small distance) (Luck, 2014). In order for the resulting voltage (microvolts, μV) to be measurable at the scalp, the dipoles from a large number of synchronised neurons must be similarly oriented. If their orientations differ the dipoles will cancel out and will not be measurable. Another type of voltage that can be generated in the brain is action potentials, but these, in most cases, are not detectable by electrodes as they are shorter in duration compared to postsynaptic potentials, they tend to cancel out and thus the signal generated is not strong (Luck, 2014; Tatum IV, 2021). **Figure 2.1** depicts the ERP generation.

Of note, the EEG waveform produced from recording brain electrical activity reflects the difference in voltage between two areas, the desired area of the scalp where the electrode is placed and a reference electrode which is positioned somewhere on the head (Pizzagalli, 2007). Thus, the recorded microvolts can be considered relative values.

This means that the resulting waveform/microvolt values can change as they can be determined by large by the analytical methods chosen (e.g., filtering, reference selection, baseline correction). In addition, microvolt values may also differ by subject (e.g., due to variations in skull shape and thickness, although not so problematic for infants who do not have much hair and a thick skull). Nevertheless, since these aspects can equally influence all conditions and trials, the resulting waveform can still be meaningful and valid to interpret (Cohen, 2014).

Figure 2.1

Generation of the ERP Signal



Note. Pyramidal cell during neurotransmission. **A** The picture shows an excitatory neurotransmitter being released from the presynaptic terminals in the apical dendrite, which leads to positive ions flowing into this region of the postsynaptic neuron. This creates a net negative voltage outside the apical dendrite (indicated with the “-” symbol). Voltage then flows through the neuron and exits in the cell body and basal dendrites area (indicated with the “+” symbol). This flow of current forms a small dipole. **B** Folded sheet of cortex that contains many pyramidal cells. The stimulation of a region of this sheet causes the summation of the dipoles of the individual neurons. **C** The summated dipoles can be approximated by a single equivalent current dipole (arrow). The arrowhead indicates the positive end of the dipole. The position and

orientation of the dipole determine the distribution of positive and negative voltages recorded at the head surface. **D** A current dipole with a magnetic field traveling around it. Picture and description adapted from Luck (2014).

2.3.3 *ERPs*

Electroencephalography offers the opportunity to explore different aspects of the neural signal, such as by using ERPs, connectivity or spectral power approaches. Thus, the EEG signal can be measured in different ways, depending on the aim of research. This thesis focuses on the ERP approach by exploring neural responses to social attention and links to PII in **Chapters 5 and 6**.

As mentioned in the previous chapter, ERPs represent changes in neural activity in response to a particular stimulus or condition. Therefore, they are considered to be ‘time-locked’ to a distinct event/stimulus (de Haan, 2013). Event-related potential data are collected from several trials across subjects and are averaged together, producing a grand average ERP waveform, which consists of a voltage value at a specific time point (Luck, 2014). Depending on the type of stimulus, certain components (ERP deflections) are produced defined by their amplitude and latency. More specifically, they are named by their polarity (positive-going or negative-going peaks) and temporal profile (e.g., N170) of information processing or order of appearance (e.g., N1, N2) within the waveform. The recording of ERPs takes place at multiple regions on the scalp and different components display maximal responses over specific brain areas.

The ERP technique has offered important insights into aspects of cognitive development. Different components have been used to gain insights into the facets of sensory, motor and cognitive processes underpinning behaviour (Luck & Kappenman, 2013). A great advantage of the ERP technique is that, by averaging, random noise (not related to the stimulus) is reduced, and thus, the resulting waveform reflects the brain response to that stimulus. In addition, ERPs have excellent temporal accuracy as they

require limited processing of data and temporal filtering, compared to other approaches, such as time-frequency decomposition that includes temporal smoothing (Cohen, 2014). Furthermore, ERPs are simple and can be computed fast, requiring few assumptions for analysis. For example, they can be used to test differences in neural processing between two conditions. Due to their simplicity, they can be quickly visually inspected for data quality for each individual. Last, there is abundant literature on ERP findings and theories have been developed based on these findings, which one can build on to explain new results and generate new and testable hypotheses (Cohen, 2014).

An important limitation of the ERP component is that its functional significance is not clear (Luck, 2014). It is difficult to clarify what the signal means, meaning that the biophysical events leading to an ERP response generation as well as how they affect information processing can be difficult to understand (Luck, 2014). Measuring individual components can be difficult. For instance, peaks or troughs could be the sum of different sources, and thus, not represent a singular process (Otten & Rugg, 2005). Although a certain amount of inference is necessary, careful design of the experiment and experimental conditions, as well as careful hypothesis formulation whilst acknowledging the limitations are necessary steps when making functional interpretations. Another limitation is that, through the use of grand averages, the variability across subjects is hidden, therefore, they may not be an accurate representation of the individual results. Nevertheless, the grand average can offer the advantage of being able to observe similar patterns in the results, which cannot be done by looking only at single-subject ERP waveforms. Finally, interpreting null results in ERPs can be difficult, as ERPs only reflect part of the information presented in EEG data. This means that there are various dynamics of EEG data that are not reflected in the ERP (Cohen, 2014).

2.3.4 Considerations for Research With Developmental Populations

Although EEG is a non-invasive method, working with developmental populations can be challenging when collecting EEG data. The task and duration of the experiment as well as the electrodes can pose limitations during EEG application for infants and toddlers as they may not tolerate them. A strategy usually followed by researchers is to have the infant sit on parent's lap during EEG recording, distracting the infant with toys or bubbles to enhance their attention to the screen, or even providing snacks (although this may introduce artefacts). This may help with young infants but becomes more challenging as age increases and children become more active. Indeed, it has been shown that EEG attrition rates are higher in toddlers than in infants (Cuevas et al., 2012; Morasch & Bell, 2011). Quick and unobtrusive application of the electrodes, using engaging stimuli and having short testing sessions can be very helpful for reducing attrition rates and improving the EEG signal quality (de Haan & Johnson, 2005).

Another important consideration is that the ERP components can vary over developmental time. Firstly, the adult ERP components are different to those of young children and infants. Furthermore, due to reduced synaptic efficiency, ERPs across the first 2 years of life are characterised by smaller amplitudes compared to adult ERP responses that have better-defined peak activity (DeBoer et al., 2007). Since the way that the neural activity is distributed across the scalp changes with development, it can be suggested that the neural source of electrical activity giving rise to the ERP components also changes throughout development. Another important point is that the strength of ERP response may vary depending on the demand of the task. Specifically, if a task is easy for a participant and requires less effort, it may also require less cortical activation, which could lead to smaller amplitudes (DeBoer et al., 2007). Moreover, while the passive viewing paradigms are very useful for developmental populations, it is important to bear in mind that it is not easy to understand whether the participant is paying attention to the

screen for the whole duration of the task. Using video to record and monitor infants' attention to the screen can be helpful, especially for tasks involving visual stimuli.

In addition, depending on the hypothesis of interest, a key aspect of ERP measurements is the selection of a task that is clear and meaningful, as it can affect the recorded ERP components. The stimulus size and probability as well as the speed of stimulus presentation are some aspects of the task that can greatly influence the ERP measurements and should be taken into consideration (de Haan & Johnson, 2005). It is also important to use an appropriate control stimulus to decrease the likelihood of any unexpected effects in the ERP results (de Haan & Johnson, 2005).

Last, this thesis includes neurodiverse populations who are at EL for developing ASD. Special considerations in methodology are required in research involving neurodiverse populations (Webb et al., 2015). Researchers should be aware that caregivers may have a neurodevelopmental condition themselves or subclinical traits of ASD and make appropriate provisions to ensure the benefits of their participation in the study. In addition, since infants may vary in their cognitive or physical skills, the researchers should also ensure that testing protocols are adapted to individual variations in ability.

2.3.5 EEG Data Collection Procedure for This Thesis

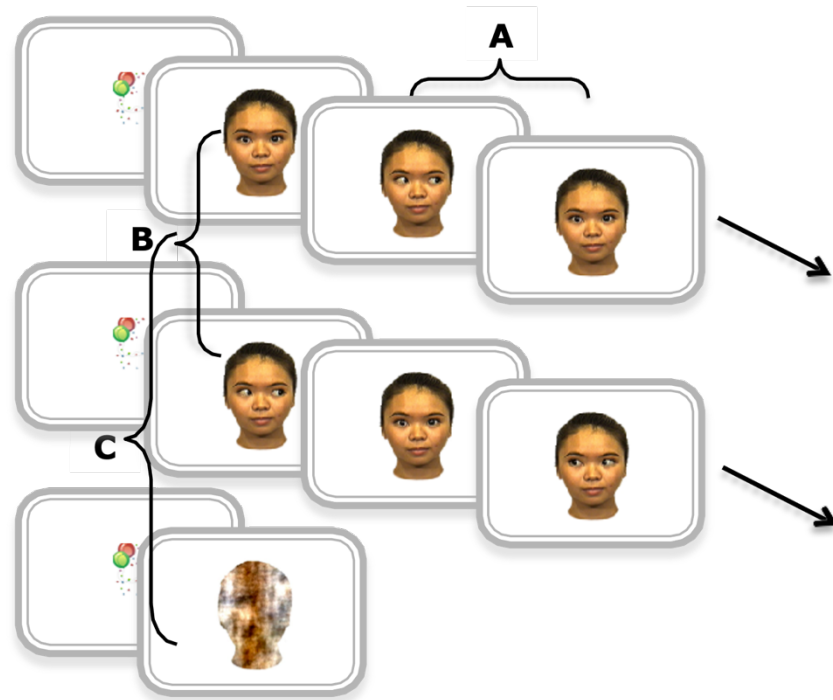
As mentioned earlier, the EEG data used in the studies of this thesis had already been collected, processed and analysed as part of the BASIS project. The following sections provide a description of the EEG data collection, processing and analysis procedure which followed the same protocol as Elsabbagh et al. (2012).

2.3.5.1 Task. Infants sat on their parents' laps in front of a 40 x 29 cm computer screen that was 60 cm away from them, and a video camera recorded infants' fixation on

the screen during stimulus presentation. At the beginning of each trial block, a static colourful fixation stimulus preceded the appearance of an image of one of four colourful female faces with gaze directed either toward or away from the infant. In addition to faces, “visual noise” stimuli appeared in one third of all blocks, created from the female face stimulus by randomizing the phase spectra while keeping the amplitude and colour spectra constant (Halit et al., 2004). The faces were shown at the centre of the screen with the eyes positioned at the place of the fixation stimuli to ensure infants’ concentration on the location of the eyes. In following trials of the same block, the face displayed on the screen remained and alternated direction of gaze towards and away from the infant 3 to 6 times. Thus, the task evaluated responses to social and non-social stimuli (static faces with direct gaze, static faces with averted gaze, gaze shifts toward the infant, gaze shifts away from the infant and visual noise) and was designed to assess three contrasts: faces (static face vs. visual noise stimuli), static gaze (faces with direct vs. averted gaze), and dynamic gaze shifts (toward vs. away from the infant). **Figure 2.2** depicts the different trial groupings analogous to each contrast. In the face-noise contrast, the trial types consisted of all of the valid first trials at the beginning of each presentation block (after the presentation of the fixation stimulus), which were faces (irrespective of gaze direction) or noise stimuli. In the second static gaze contrast, all the first face trials within each block were separated into those with direct gaze and those with averted gaze. In the last contrast (dynamic gaze shifts), any such following trials were compared after appearance of the initial face within each block. The faces spanned 21 x 14 degrees of visual angle. The fixation stimuli spanned roughly 1.6 x 1.6 degrees and were presented for 800 to 1,200 ms. The duration of each trial was 800 ms, succeeded by a 500 ms interval of no stimulus presentation.

Figure 2.2

Experimental Stimuli



Note. **A** Eye gaze shifts directed toward versus away from the infant, **B** Face with direct versus averted gaze, **C** Face versus visual noise (Adapted from Elsabbagh et al., 2012).

2.3.5.2 Electrophysiological Data Acquisition, Pre-Processing and Analysis.

For the EEG recording, electrical activity from the surface of the scalp was captured simultaneously through different electrodes placed on the scalp. A Hydrocel Sensor Net was placed on infants' head while they were sitting on their parents' laps in front of the computer screen. It consisted of an array of 128 silver-silver chloride electrodes and a reference electrode. Brain activity was measured during trial presentation which included 50 trials, presented continuously when the infants paid attention to the screen. The electrode used as a reference was located at the vertex (Cz in the conventional 10/20 system). EGI NetAmps 200 was used (gain = 1,000).

EEG data pre-processing was conducted by M. Elsabbagh (for the data collected at Phase 1) and C. Tye (for the data collected at Phase 2, see Chapter 3 for details on

participant recruitment at each phase). The signal was digitized at a sampling rate of 500Hz and a band-pass filter between 0.1-1000Hz was applied. Beyond the EEG data filters used for recording, filtering was not conducted at the analysis stage, as this can cause distortions to the signal. EGI Netstation software 4 (for Phase 1) and 5 (for Phase 2) was used for offline data storage and analysis. In the trials used, infants were focusing their gaze on the centre of the screen throughout the 800 ms segment after stimulus presentation using the concurrent video recording. Artifacts such as infant gaze shifts, head movement and blinking during or 100 ms before stimulus presentation were excluded through video coding. Following from this, data were corrected to the -200ms baseline. Segments with significant artifacts were removed through automated artifact rejection. In particular, for each segment, the channels removed due to bad signal recording were those with EEG signal $>400 \mu\text{V}$. Data with the signal reaching amplitudes $>400 \mu\text{V}$ for 1,000 ms were removed for constituting eye-blinks, while data for 160 samples were removed for constituting eye movements. Channels in which more than 75% of the data were counted as artifacts were considered bad. Subsequently, experienced EEG researchers (M. Elsabbagh and C. Tye) examined each trial visually for manual rejection of EEG data that contained artifacts. The interpolation of missing data from 12 or fewer channels was undertaken or the whole trial was rejected. Next, data were re-referenced to the average. Re-referencing plays an important role in EEG signal processing due to the arbitrariness of the chosen reference point, as no site can assure a constant value during EEG recording.

Stimulus-locked epochs (-200 to 800 ms peri-stimulus window for the face with direct gaze condition, -200 ms to 795 ms for the face with averted gaze and noise) were averaged within each presentation block. Averages were calculated for each participant based on a minimum of 10 trials per stimulus. There was no difference in the valid trials used for each outcome group. Additionally, occipito-temporal montages from Elsabbagh

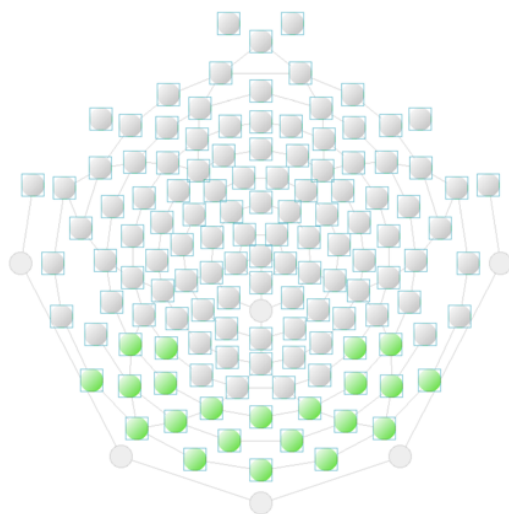
et al. (2012) were used and were confirmed through visual examination of the grand average for each condition across the three contrasts (**Figure 2.3**). The P100, P400, and N290 components were averaged for each stimulus across occipito-temporal channels and the Nc component across frontal channels, quantified by their amplitude and latency and were used in subsequent analysis for the studies of this thesis. The particular channels were selected, as visual inspection of the grand average separately for each condition and based on previous literature (Jones et al., 2016; Elsabbagh et al., 2012) clearly revealed these components in overlapping occipitotemporal channels (for the P1, N290, P400) and frontal channels (for the Nc).

Peak (the most positive point of deflection) amplitude and latency of the averaged P1 (temporal windows: static face and face vs. noise contrast (100-219), gaze shift (100-199)), N290 (temporal windows: 200-319 for all conditions) and P400 (temporal windows: static face/face vs. noise contrast (320-540), gaze shift (320-520)) components for each stimulus/contrast were used in subsequent analyses, as it has consistently been shown to be modulated in face processing tasks in the first year of life (Tye et al., 2020; Elsabbagh et al., 2012). For consistency with previous research (Gui et al., 2021; Jones et al., 2016; Webb et al., 2011), in the averaged Nc component, mean amplitude and peak latency (the most negative point of deflection) between 300 and 800 ms after stimulus onset were used across left and right frontal regions (Gui 2019; Jones et al., 2016).

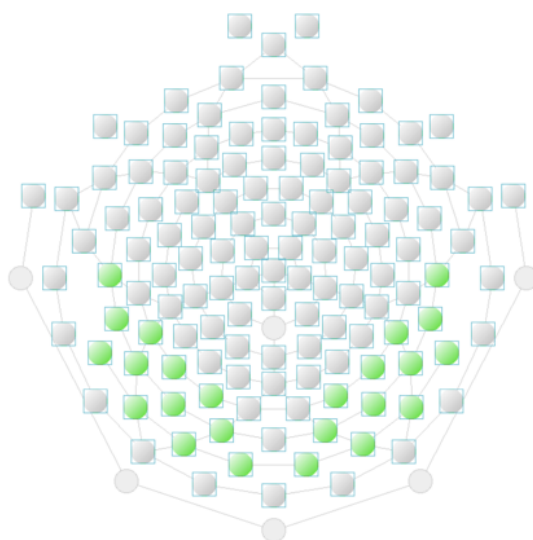
Figure 2.3

Selected Channel Montages

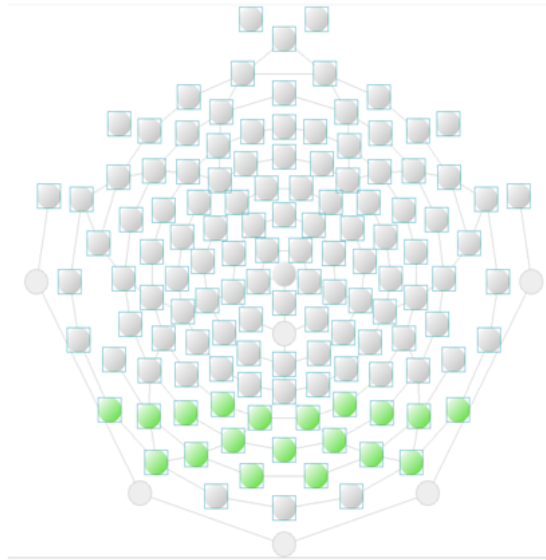
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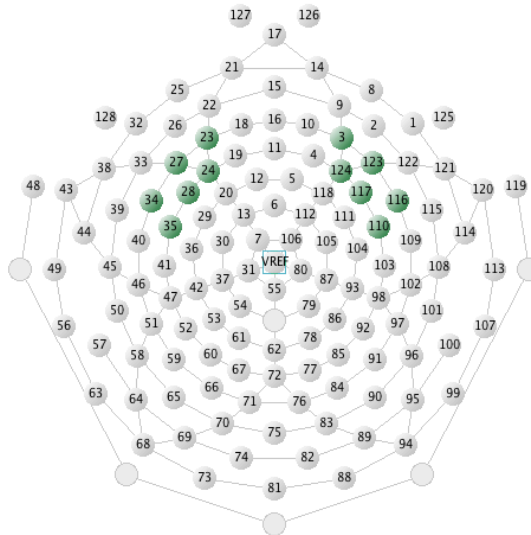
B



C



D



Note. **A** Static gaze contrast montage, **B** Dynamic gaze contrast, **C** Face/noise contrast, adapted from Elsabbagh et al. (2012); **D** Left and right frontal electrodes for the Nc component examining responses to social stimuli, adapted from .

2.3.6 The Rationale for ERP Component Selection

The P1, N290, P400 and Nc components were selected as they have been shown to be consistently modulated in tasks related to the perception of faces within the first year of life (discussed in detail in **Chapter 1**). In particular, the Nc component has been hypothesised to reflect attention engagement to interesting or salient stimuli, while the other components have been linked to the processing of structural and semantic aspects

of faces. As discussed in **Chapter 1**, these components have differentiated EL from TL infants in several studies, with infants receiving a subsequent ASD diagnosis exhibiting altered brain responses to faces versus non-faces and a reduced differentiation to dynamic eye gaze shifts. This is of particular importance considering that social engagement, and particularly, attention to faces are important aspects of social development to which EL-ASD infants present a decline (W. Jones & Klin, 2013). These atypicalities have been suggested to amplify over time, restricting opportunities for social learning (leading to social communication differences characterising the ASD phenotype) and could affect caregiver-infant social interactions. Indeed, research has shown links between some of these components and PII measures within the first year in EL and TL infants (Elsabbagh, Bruno, Wan, Charman, Johnson, Green, & The BASIS Team, 2015), emphasising the bidirectional nature of the individual and their social environment, which is an important notion of the IS theory and the transactional model, although the evidence on these associations is still emerging. These reasons motivated the use of the P1, N290, P400 and Nc components and to associate them with aspects of caregiver-infant social interactions in the context of ASD susceptibility, which could provide important information on the developmental pathways to ASD development.

2.4 Conclusion

Overall, the chapter provided an overview of the methods that will be conducted in this thesis. It began by discussing observational measures of PII in infancy and the context of ASD emergence. It described the MACI coding scheme, explaining the rationale for choosing this measure. Further, it provided an overview of EEG in infancy with details on ERPs. It described the EEG data collection and analysis procedure for this thesis and provided the rationale for using particular ERP components. The following four chapters describe the empirical studies undertaken in this thesis, with **Chapters 3**

and **4** examining PII in ASD emergence using the MACI observational coding scheme, and **Chapters 5 and 6** investigating brain function-PII relationships using both the MACI and the EEG (ERPs) measures.

Chapter 3. Examining Parent-Infant Interaction Trajectories in Infants with and Without an Elevated Likelihood for Autism – A Replication Study

3.1 Introduction

Social experiences in early life begin within the family environment, as infant interactions with their parents are a central aspect of infants' social development. In the context of the emergence of ASD, early precursors of ASD are hypothesised to bidirectionally affect the quality of infant and parent interactive behaviour (Dawson, 2008). Indeed, several studies have employed an infant sibling design to demarcate the quality of PII between infants at EL and those at TL of ASD, as the former are at an increased ASD likelihood (approximately 18.7%) compared to neurotypically developing infants (Ozonoff et al., 2011), and they have been distinguished from the latter at a group level in several behaviours (Jones et al., 2014; Zwaigenbaum et al., 2005). These infant sibling studies reveal altered PII in the second half of the first year, reporting EL and TL group differences predominantly in pre-verbal communication interactive behaviours (Wan et al., 2019 for a review). These differences have motivated parent-mediated interventions, which have shown some efficacy in supporting early social communication development in infants with a family history of autism (Green et al., 2017; Whitehouse et al., 2021).

The transactional model of development posits that a child's developmental trajectory is influenced by the continuous reciprocal interactions between the child and his/her parents and that any disruptions in the quality of PII may have cascading consequences on the child's socio-cognitive functioning later on in life (A. Sameroff, 2009). This is supported by empirical work demonstrating that the quality of PII can have an effect on infants' social-communicative outcomes (NICHD, 2000). For instance, more

synchronous PII (i.e. emotional and behavioural matching) has been associated with more positive child social and cognitive outcomes (see Leclère et al., 2014 for a review). Additionally, PII qualities have been shown to play a significant mediating role in the relationship between parental characteristics (i.e., psychological distress/alooofness) and child autistic behaviours (Loncarevic et al., 2023). As such, early differences in the quality of social interactions between infants at EL and their caregivers may have an effect on these infants' later developmental outcomes.

3.1.1 PII Dynamics

Wan et al. (2012, 2013) conducted one of the earliest studies to prospectively evaluate both parent and infant qualities of PII in infants at EL, as well as follow them up to three-year ASD outcome. This work identified EL and TL infant differences in PII from around 7 months of age, with the EL group being less lively, while their parents were less sensitively responsive and nondirective than those at TL. Lower sensitive responding and higher directiveness remained at 14 months while differences in dyadic engagement intensity emerged. However, it was specifically EL infants' positivity, dyadic mutuality and infant attentiveness to parent that were lower relative to infants at TL at 14 months and were significant predictors of 3-year ASD outcome.

Since then, several studies have also reported parent-infant interactive differences in the context of emerging ASD. In the latter half of the first year, infants at EL with a subsequent ASD diagnosis (EL-ASD) were found to show fewer gestures and fewer gesture-speech combinations (EL: $n = 55$, Choi et al., 2019), to initiate fewer gestures (i.e. giving or showing a toy) (EL: $n = 35$, Campbell et al., 2015), and to be less responsive to their mother's bids (EL: $n = 104$, Kellerman et al, 2020) relative to no-ASD EL infants. A further study that did not follow infants up to ASD outcome also found that EL infants show fewer infant initiations at 10 months than TL controls (EL: $n = 101$, Pijl et al., 2021).

Such communication differences in gesture and vocalisations persisted at 18 months in EL-ASD infants (EL *ns* ranging between 12-50, Leezenbaum et al., 2014; Paradé & Iverson, 2015; Winder et al., 2013). These differences in social communication behaviour during naturalistic interaction could have cascading effects on social learning and subsequent development.

Evidence for differences in parental behaviour is more limited. Addressing this question is important because parent-mediated interventions are designed to work through parent behaviour in supporting development. Consistent with the parental directiveness reported in Wan et al. (2012), two studies found that parents of EL infants compared with parents of TL infants tended to use more touch and verbal requests to elicit infants' response and attention from 9 to 15 months (EL: $n = 16$, Srinivasan & Bhat, 2020) and highly directive parental behaviour predicted slower growth in infants' parent-directed smiles from 9 to 18 months (EL: $n = 30$, Harker et al., 2016). These studies did not follow EL infants up to ASD outcome. Directiveness may also be adaptive to infant behaviours; for example, parents of infants at EL intensify their prosodic expressions (infant-directed speech) from 12 to 18 months compared to parents of TL infants (Quigley et al., 2016). Nevertheless, other studies, mostly with smaller samples, suggest no EL and TL group differences in parent directiveness or other social behaviours and no associations between parent behaviour and later ASD outcome (Campbell et al., 2015; Del Rosario et al., 2023; Leezenbaum et al., 2014; Schwichtenberg et al., 2019).

3.1.2 Aims of the Study

Although studies have made a great effort in delineating PII in infants at EL, progress in our understanding of the role of PII in the EL context has been hampered by the small sample sizes and/or the heterogeneity of PII variables. Intensive resources required to recruit and conduct PII measures with EL and TL samples, and sample

attrition when conducting longitudinal sibling studies, mean that EL-ASD subsamples are typically very small, and likely underpowered to capture PII differences, especially in parental or dyadic behaviour, which may be more subtle than infant interactive differences. The present study represents the largest PII study to date of EL infants ($n = 113$) at 8 and 14 months following up to 3-year ASD outcome, utilising the same methodology as Wan et al. (2013) provides an opportunity for replication. Examining the replicability of previous effects including a larger independent sample was one of the main goals of the study and represents a core principle of open science, important for the improvement of the reliability of research findings (Nosek et al., 2022). Consistent with Wan et al.'s (2013) findings, it was expected that there would be differences between EL and TL infants in PII qualities in parent domains (sensitive responsiveness and nondirectiveness) and infant liveliness at 8 months. It was also predicted that PII differences would increase between 8 and 14 months with more areas of interaction affected at 14 months (both parent domains, infant attentiveness to parent, infant positive affect, dyadic mutuality and engagement intensity). Finally, it was expected that differences between the EL and TL groups (particularly in infant positive affect, infant attentiveness and dyadic mutuality) at 14 months would relate to later ASD. Overall, owing to the transactional model, it was anticipated that the qualitative aspects of PII between the groups would predictably have some effect on the infants' developmental trajectories, expressed through later clinical outcome.

3.2 Methods

3.2.1 Participants

3.2.1.1 Participant Recruitment and Confirmation of ASD Likelihood Status.

Participant recruitment, ethical approval (UK National Health Service National Research Ethics Service London reference number: 06/MRE/02/73) and parental informed consent was made available for this study through the BASIS. Two independent samples of participants were recruited from BASIS in 2 different phases (Phase 1 and Phase 2, total $N = 247$). This study included a total of 143 participants who took part in Phase 2, consisting of 116 infants (64 male; 52 female) with an older sibling with a community clinical diagnosis of ASD (hereby infants at EL) and 27 infants (14 male; 13 female) with at least one older sibling at TL. For the infants at EL, confirmation of EL status was based on information taken from the Development and Well-being Assessment (DAWBA; Goodman, Ford, Richards, Gatward & Meltzer, 2000) and the parent-report Social Communication Questionnaire (SCQ; Rutter, Bailey & Lord, 2003), reviewed by experienced research clinicians (TC and GP) in order to verify local clinical diagnosis. Infants in the TL group were recruited separately from a volunteer database at the Birkbeck Centre for Brain and Cognitive Development. The criteria for their inclusion were full-term birth (37-42 weeks), except one infant who was born prior to 37 weeks, normal birthweight and no ASD within first-degree relatives (information obtained through parent interview). The older siblings of infants at TL were screened for the likelihood of ASD symptomatology using the SCQ, with all of them scoring below the instrument threshold for ASD (<15).

3.2.1.2 Participants in the Current Study. Of the 143 children participated in Phase 2, three were excluded from this study because they were absent from the 36-month assessment. The final sample consisted of 140 participants (113 at EL, 27 at TL), as they took part in the 36-month visit and provided data for one or both time points. At 8 months, 16 participants had missing data due to technical issues with the videotapes or because

data were not collected (no clip/clips not digitised: $n = 10$; technical issues: $n = 6$). Therefore, 124 infants provided data for the 8-month visit. Regarding the 14-month visit, 10 participants had missing data (no clip: $n = 6$; technical issues (no sound/too brief): $n = 4$). Therefore, 130 participants had available data at 14 months. However, these participants were not excluded because the statistical method for data analysis used in the study can handle missing data and unbalanced designs well (see analyses section below for details).

3.2.2 Measures

3.2.2.1 Parent-Infant Interaction Measure. The MACI (version 2.2) global rating scheme was applied to evaluate aspects of interaction between the primary caregiver and the infant (Wan et al., 2017). As shown in **Chapter 2**, the MACI comprises 8 7-point scales that evaluate caregiver, infant and dyadic aspects of interaction through observation of videotaped unstructured play. The scales consider parental behaviour (caregiver sensitive responsiveness and caregiver nondirectiveness), infant behaviour (infant attentiveness to caregiver, infant positive affect, infant negative affect and infant liveliness) as well as the dynamics of the interaction between the dyad (mutuality and engagement intensity). Additionally, this measure has demonstrated excellent psychometric characteristics and inter-rater reliability, independent of infant gender, developmental level, maternal age and socioeconomic status (Wan et al., 2012; 2013; 2017). The MACI has previously differentiated infants at EL from those at TL (Wan et al., 2012; 2013), but it is designed to be used only for research purposes and not as a screening tool. It has also shown to be sensitive to the effects of intervention in children showing early signs of ASD (Whitehouse et al., 2019).

In terms of the inter-rater reliability procedure, 10% of PII clips at each time point were independently blind-coded and further tested for inter-rater agreement through single measures intraclass correlations using a two-way mixed effects model based on absolute agreement definition. Possible discrepancies in the ratings were resolved by re-reviewing the clips and by mutual agreement. The results revealed reasonable to high agreement in all the PII items across both time points ($rs \geq 0.62, ps < .001$). The intraclass correlations in the PII items at 8 and 14 months are shown in detail in **Table A3.1**.

3.2.2.1.1 Procedure. The PII assessment took place at both the 8- and 14-month visit. Six-minute unstructured play between infants and their parents was video recorded in a laboratory setting after a period of familiarisation. The parent sat on a play mat with a small set of selected toys and was instructed to play with their infant as they would normally do at home, with or without the use of toys as they preferred. The video clips were coded blind to all participant information.

3.2.2.2 Assessment Measures. Upon enrolment, the infants had not been diagnosed with a developmental disorder or another medical condition. The infants attended a series of cognitive, behavioural and interactive lab assessments when they were about 8, 14 and 36 months old, including experimental tasks, such as EEG and eye-tracking at 8 and 14 months. Parents completed questionnaires and interviews related to their infants' behaviour and development at each time point. Testing of the infants was undertaken by researchers from the BASIS team.

3.2.2.2.1 Developmental Level. The Mullen Scales of Early Learning (Mullen, 1995), a standardised assessment of overall cognitive capacity and motor development was administered by an experimenter at each visit. The assessment involves a number of

tasks appropriate for the child's developmental level. Scoring during the tasks required the establishment of a basal and a ceiling criterion: Testing initially involved the basal level, where the child scored at least one in three consecutive items, followed by the ceiling level, for which scores of zero in three consecutive items were required. The MSEL consists of five domains measuring expressive and receptive language, visual reception as well as gross and fine motor abilities administered to children from birth to 68 months old (Mean = 50, $SD = 10$). The expressive language scale is a 28-item scale measuring the child's capacity to use language productively focusing on speaking, language formation and verbal conceptualisation. The receptive language scale is a 33-item scale, assessing the processing of linguistic input, including auditory comprehension/memory/sequencing. The 33-item visual reception scale assesses visual discrimination/memory/organisation/sequencing/spatial awareness abilities. The fine motor scale contains 30 items measuring motor planning and control, writing readiness and unilateral/bilateral manipulation. Last, the gross motor scale, administered until 33 months, assesses central motor control, supine, prone, sitting and upright mobility. The score of these areas (apart from gross motor skills) was combined to produce an Early Learning Composite (ELC) standard score (mean = 100, $SD = 15$), which was used in the current study. A higher MSEL score indicates greater developmental skill.

3.2.2.2.2 Adaptive Functioning. The Vineland Adaptive Behaviour Scales – second edition (Sparrow et al., 2005) is a parent-report measure of daily adaptive behaviour administered at each visit. The VABS can be administered in different formats. At 8 and 14 months, a semi-structured parent-report questionnaire was used, while at 36 months, parent semi-structured interviews were completed. The VABS has been widely used to characterise different profiles of those with early difficulties in adaptive functioning as well as in infants at an EL for ASD (Bussu et al., 2019; Estes et al., 2015).

It can be administered from birth to 90 years of age, incorporating four main domains, each including different sub-domains: communication (sub-domains: receptive, expressive, written), daily living skills (sub-domains: personal, domestic, community), socialisation (sub-domains: interpersonal relationships, play and leisure time, coping skills) and motor skills (sub-domains: fine and gross). It also includes an optional maladaptive behaviour index (sub-domains: internalising, externalising, other). Raw scores of the sub-domains are added to form the four main domains' standard scores (mean = 100, $SD = 15$). The four main domains can then be combined to yield an Adaptive Behaviour Composite score (ABC) (mean = 100, $SD = 15$), a standardised measure of general adaptive behaviour. Lower scores indicate greater difficulties in adaptive behaviour. The ABC was used in this study for participant background characterisation.

3.2.2.2.3 Atypical Behaviour. In addition, the Autism Observation Scale for Infants (Bryson et al., 2008), a 19-item observational measure of early ASD symptoms was administered at the 8- and 14-month visits. The AOSI consists of a standard number of semi-structured tasks led by an examiner while the infant sits on the parent's lap. Assessment of early ASD signs includes particular behaviours (eye contact, atypical motor and sensory behaviour, response to name, imitation, reciprocity, differential response to facial emotion, tracking and attentional disengagement and social-communicative behaviours). Target behaviours are rated on a scale from 0 (typical behaviour) to 2 or 3 (atypical behaviour) and scores are summed to yield an overall score.

3.2.2.2.4 Assessment of ASD Outcome at 3 Years. At 36 months, children underwent a battery of clinical assessments by an independent team to establish whether they had developed ASD. Following this, and based on available information from all visits, experienced clinical researchers (GP, TC, CC), as well as members of the testing

team, determined possible ASD outcome according to DSM-5 (American Psychiatric Association, 2013) and no ASD outcome (typical developmental outcome or other pervasive developmental disorders). The assessments described below did not include blindness to ASD likelihood status and were undertaken by expert clinical researchers, or under their supervision.

3.2.2.2.5 *The Autism Diagnostic Observation Schedule.* Autism Spectrum Disorder diagnosis was estimated based on, among other measures, 24- and 36-month results from assessments using the ADOS-G – II (Lord, Rutter, et al., 2012). ADOS is a semi-structured observational assessment for the evaluation of symptoms of ASD, focusing on the child’s social behaviour through activities triggering social interaction, communication, play, language and RRB. ADOS-2 total scores were calculated using the ADOS-G raw item scores. One hundred and sixteen children were administered Module 2 while 20 were administered Module 1. Calibrated Severity Scores for Social Affect, and RRB were used (Gotham, et al., 2009) as standardised measures of ASD severity that considered differences in module applied, age and verbal ability.

3.2.2.2.6 *The Autism Diagnostic Interview – Revised (ADI-R).* The ADI-R (Rutter, Le Couteur, et al., 2003) a widely used semi-structured interview concerning assessment of ASD symptoms conducted with infants’ parents, was completed. The ADI-R takes approximately 60 to 90 minutes to complete and is composed of 93 items coded based on current and past behaviours, focusing on three domains (aggregated totals of specific items based on the ICD-10 and DSM-IV criteria): Reciprocal Social Interactions (Social), Communication and Restricted and Repetitive Behaviours (RRB). The items comprising the three domains are age-specific. In addition, a diagnostic algorithm is available, consisting of Most Abnormal 4–5/Ever codes in which fulfilment or exceeding

of cut-off scores means that the child meets the criteria of an ASD diagnosis. Separate cut-offs and totals for verbal and non-verbal children are offered in the Communication domain. A Current Behaviour algorithm is also available that focuses on current functioning and is usually applied in treatment and educational planning. In the sample of this study, estimation of standard algorithm scores was undertaken for the three domains of the ADI-R.

3.2.2.2.7 The Social Responsiveness Scale. The SRS (Constantino & Gruber, 2012) pre-school form (ages 2.5 to 4.5), a 65-item rating questionnaire that continuously measures ASD symptom severity with regards to social ability was completed by parents and was also included (alongside the VABS and SCQ) to assess ASD outcome. The SRS quantitative measure has been extensively used with clinical and population-based samples (Constantino & Gruber, 2005; Frazier, Ratliff, et al., 2014). Each item is scored on a 4-point Likert Scale, ranging from 1 (not true), 2 (sometimes true), 3 (often true), to 4 (almost always true). The SRS scale takes approximately 15 to 20 minutes to complete. In addition to a total score measuring the severity of ASD social impairment, scores from five sub-scales are generated: Social awareness (AWR), social cognition (COG), social communication (COMM), social motivation (MOT) and restricted interests and repetitive behaviour (RRB). Each of these domains' raw scores are aggregated with their total converted into the SRS-2 Total T-score. In addition, the instrument includes two sub-scales corresponding to DSM-5 criteria: Social communication and interaction (SCI) and RRB. For the SCI score, raw scores from the AWR, COG, COMM and MOT domains are combined, converting the total into the SCI T-score. T-scores from each domain are sex- and age-specific with a mean of 50 and a standard deviation of 10 points. Scores range from zero to 195, with higher scores indicating greater severity of social impairment

(< 59 indicates no social impairment, 66 - 75 indicates moderate and > 76 severe social impairment).

3.2.2.2.8 The Quantitative CHAT for Autism in Toddlers. Parents were asked to complete the Q-CHAT, a 25-item parent-report questionnaire at the 14-, 24- and 36-month visits. The Q-CHAT is designed to assess behaviours related to ASD based on ICD-10 and DSM-IV domains such as social communication and language, joint attention, pretend play, repetitive and sensory behaviours. Each Q-CHAT item is scored on a 5-point scale (0-4), focusing on the dimensionality of ASD-related traits, with higher scores indicating greater ASD traits. A total Q-CHAT score can be calculated by the aggregation of each item score. The measure has shown cross-cultural validity (Ruta et al., 2019), good test-retest reliability, internal consistency and can differentiate young children with an ASD diagnosis from an unselected control sample (Allison et al., 2008).

Among the remaining 113 infants at EL, 17 (15%) met the criteria for an ASD diagnosis, 64 (56.6%) were categorised as typically developing, and 32 (28.3%) were categorised as showing symptoms of atypical development, based on scores that were above the autism spectrum threshold on the ADOS-G and/or the ADI-R, and/or low scores (more than 1.5 standard deviations below average) on the MSEL Early Learning Composite, Visual Reception, Receptive Language or Expressive Language subscales.

3.2.3 Analyses

3.2.3.1 Internal Characteristics and Stability of the MACI Scheme. Initially, to examine the internal characteristics between the MACI scales at each time point (8 and 14 months) as well as their stability between the 8 and 14-month time points for each scale, correlations by ASD likelihood group (infants at TL, infants at EL) within the

MACI items at 8 and 14 months as well as between the time points were conducted, based on the available interaction data at both time points ($N = 114$). These associations were conducted by group to investigate possible similarities or differences in the patterns of relationships for the EL and TL infants. Correlations between the MACI items, age and AOSI were also conducted, consistent with Wan et al. (2013) analytic procedure. All the PII variables across both time points were inspected for distribution normality, linearity and extreme cases through Shapiro-Wilk tests, histograms and Q-Q plots. In addition, the variables were standardised and screened for outliers. Liveliness and negative affect had non-normally distributed scores, therefore, a Van der Waerden transformation was applied which is a test used for ordinal data transforming ranks into normal scores based on the standard normal distribution.

3.2.3.2 Testing differences in PII based on ASD Outcome Status. Linear mixed effects models¹ were performed to examine differences in PII by 3-year ASD outcome status (developmental groups: EL-ASD, EL-no ASD, TL) across 8 and 14 months of age. Linear mixed effects models were chosen because this method is flexible and more advantageous relative to more traditional methods, such as the Analysis of Variance (ANOVA). Firstly, it overcomes the issue of independence in repeated measures, taking into account variability among subjects and items concurrently at baseline and across time (V. A. Brown, 2021; A. Field et al., 2012). This allowed the investigation of group and

¹ Given that the PII data were ordinal, analysis using cumulative link mixed models was also considered and performed, providing the same results as linear mixed effects models analysis. However, the latter was preferred due to ease of interpretation compared to the former, for consistency and comparability with the study replicated, and considering evidence suggesting that data with roughly distributed scores and more than 5 categories can provide less biased parameter estimates when treated as continuous than scores with less than 5 categories (Rhemtulla et al., 2012).

age interactions in PII. Secondly, it accommodates missing data in longitudinal designs, such that when a data point is missing, parameter estimation can be achieved with the data that are available (A. Field et al., 2012; Krueger & Tian, 2004). Last, it can allow the inclusion of both continuous and categorical predictors, and it can be extended to include categorical outcome variables through the use of ‘*generalised* linear mixed effects models’ (V. A. Brown, 2021).

Each PII item was included in a separate model as the dependent variable. Subject was included as a random intercept to account for individual variability at the baseline. Fixed effects of developmental group, age (to adjust for variability in age, the actual age in months was included: 6-11 and 11-18 months), their interaction as well as the effect of gender were tested by comparing the fit of a series of successive models against a null model with the Likelihood Ratio Test (LRT). Given that a portion of the participants ($n = 28$) had received parent-targeted intervention at 14 months (Green, Charman, Pickles, Wan, Elsabbagh, Slonims, Taylor, McNally, et al., 2015), supplementary analysis was run including ‘intervention’ as a further categorical predictor/control variable (those undergone intervention compared to the rest of the sample) in the models that showed group and age or group by age effects in PII. To adjust for multiple comparisons in the main analysis, False Discovery Rate (FDR) correction was applied, which controls for the proportion of incorrect rejection of null hypotheses (Benjamini & Hochberg, 1995). The ‘lmer’ function within the ‘lme4’ package in R was used (Bates et al., 2014).

The PII data from infants who did not receive a subsequent diagnosis of ASD but did not develop neurotypically (EL-Atyp group) were analysed descriptively to maintain the consistency with Wan and colleagues’ study, in which descriptive analysis was chosen for this sample due to sample size limitations. Wan et al. found similar PII scores between the EL-Atyp and TL infants, whereby more ‘social’ interactions were observed compared to the EL-ASD group, speculating that positive social interactions might shift social

development towards a neurotypical trajectory. Therefore, it was of interest to examine whether the same pattern would be observed in this study.

3.2.3.3 Testing PII as a Predictor of ASD Outcome. Consistent with Wan et al. (2013), further analysis was performed to further elucidate whether the PII aspects were significant predictors of 36-month ASD outcome. Thus, the PII items in which a developmental group or a developmental group by age effect was shown (adjusting for age and gender) were tested in relation to ASD outcome (no ASD outcome/ASD outcome groups) using binomial logistic regression² separately at 8 and 14 months. Given that PII variables correlate with each other both statistically and conceptually, each PII item was analysed in a separate regression model, adjusting for age and AOSI to control for the variance this accounted for in ASD outcome. In each regression model, a hierarchical design was employed: the PII item was entered first, age was added second and AOSI last. In addition to the main analysis, as a supplemental analysis, following the analytical procedure by Wan et al. (2013), binomial logistic regressions were performed again including MSEL as a further covariate to explore the variance it accounted for in ASD outcome in addition to the other covariates in the model. Data were screened for influential cases, linearity of the logit and multicollinearity. The statistical package IBM SPSS version 27 was used for this analysis.

3.3 Results

² Generalised linear mixed effects models analysis was also performed which resulted in convergence issues. Therefore, binomial logistic regression was chosen as the best approach which also enabled consistency and comparability with the study replicated.

3.3.1 Participant Demographic Characteristics

Infant demographic characteristics for both time points are presented in detail in **Table 3.1** (refer to **Table A3.2** for the demographic and clinical characteristics by clinical outcome group at 36 months). At both time points, no group differences were found in infant age. Infant gender differed, with males being over-represented in the EL-ASD group $\chi^2(2) = 8.67, p = .01$. In addition, at both time points, there were significant group differences in AOSI: at 8 months, a Games-Howell post hoc test (chosen due to unequal variances) found that the significant differences were due to lower AOSI scores in the TL compared to the EL-no ASD ($p < .001$) and EL-ASD ($p = .002$) groups. At 14 months, a Scheffe post hoc test found that the differences were due to higher AOSI scores in the EL-ASD from the TL ($p = .001$) and EL-no ASD ($p = .008$) groups. There was also a significant group effect in MSEL and VABS at 14 months, where scores were lower in the EL-ASD compared with the TL ($p = .001$) and EL-no ASD ($p = .02$) groups for the MSEL, and higher in the TL compared with the EL-ASD group ($p = .008$) in the VABS, as confirmed by Scheffe post hoc tests. For the MSEL and VABS at 8 months, the TL group showed borderline higher scores than the other groups ($ps < .1$).

Table 3.1*Demographic Characteristics by ASD Outcome Status at 8 and 14 months*

	8 months					14 months				
	Group mean (<i>SD</i>)					Group mean (<i>SD</i>)				
	TL	EL-no	EL-ASD	F / χ^2	η^2	TL	EL-no	EL-ASD	F / χ^2	η^2
	<i>N</i> = 27	ASD <i>N</i> = 96	<i>N</i> = 17			<i>N</i> = 27	ASD <i>N</i> = 96	<i>N</i> = 17		
Age in months	8.89 (0.89)	8.67 (0.83)	8.59 (0.80)	0.91	0.01	15.11 (0.89)	14.92 (0.95)	14.88 (0.99)	0.50	0.01
Sex M/F	14/13	48/48	15/2	8.67*	0.25 ^c	-	-	-	-	-
MSEL ELC^a	112.48 (13.36)	107.54 (15.13)	101.82 (16.70)	2.68 ⁺	0.04	102.56 (14.43)	95.95 (14.13)	85.53 (12.81)	7.68* *	0.10
VABS ABC^b	98.69 (10.72)	94.62 (11.73)	90.65 (14.57)	2.42 ⁺	0.04	101.37 (11.68)	97.26 (12.13)	89.63 (8.63)	5.07* *	0.07
AOSI Total Score^c	5.26 (3.13)	8.74 (4.62)	10.24 (4.76)	12.81* * ^d	0.11	4.07 (3.52)	5.86 (4.40) (5.23)	9.47 (5.23)	8.07* *	0.11

^a Missing MSEL values for two EL-no ASD infants at 14 months.^b Missing VABS values for one TL sibling and two EL-no ASD infants at 8 months, three EL-no ASD and one EL-ASD infant at 14 months.^c Missing AOSI values for one EL-no ASD infant at 14 months.

^d Welch's F ratio is reported because homogeneity of variance was not met.

^e Cramer's *V* statistic was used as a measure of effect size.

Abbreviations: AOSI: Autism Observation Scale for Infants; ASD: Autism Spectrum Disorder; EL: Elevated Likelihood; F: F statistic; MSEL ELC: Mullen Scales of Early Learning Early Learning Composite; TL: Typical Likelihood; VABS: Vineland Adaptive Behaviour Scales; χ^2 : Chi-square statistic; η^2 : Eta-squared, measure of effect size.

⁺p < 0.1; *p < 0.05; **p < 0.01.

3.3.2 Internal Characteristics and Stability of the PII Items

The results of the internal characteristics and stability of the PII items are provided in the appendix (section 3.6.1).

3.3.3 Group and Time Effects of Parent-Infant Interaction at 8 and 14 Months

The results of the model selection process using LRTs are provided in the appendix (section 3.6.2). After selecting the best-fitting model, linear mixed effects models were used to examine PII differences between EL-ASD, EL-no ASD and TL infants at 8 and 14 months with age as a covariate. The results partially replicated those of Wan et al. (2012). Regarding the parent MACI scales, a significant effect of developmental group (Sensitive responsiveness: $F(2, 129.38) = 5.72, p = .004, \eta^2 = 0.08$; Nondirectiveness: $F(2, 132.03) = 10.80, p < .001, \eta^2 = 0.14$) and age (Sensitive responsiveness: $F(1, 136.64) = 34.75, p < .001, \eta^2 = 0.20$; Nondirectiveness: $F(1, 140.73) = 7.06, p = .008, \eta^2 = 0.05$) was found. This meant that ratings in these PII variables increased from 8 to 14 months, and FDR-adjusted post hoc comparisons revealed that TL ratings in parent sensitive responsiveness were higher compared to EL-no ASD ($p = .02$) and EL-ASD group ($p = .004$). However, no sensitive responsiveness differences between EL groups were found ($p = .07$). On the other hand, while the TL group similarly received the highest nondirectiveness ratings (vs. EL-no ASD: $p = .001$; vs. EL-ASD group: $p < .0001$), some of the significant result is also attributable to the higher nondirectiveness of the EL-no ASD group than the EL-ASD group ($p = .02$).

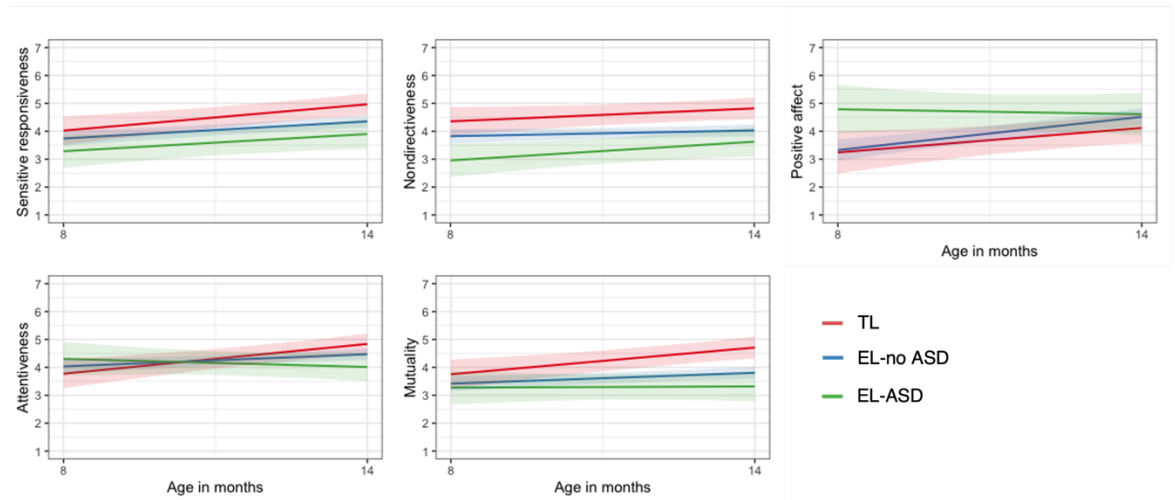
Concerning the infant MACI scales, ratings increased with age while ASD likelihood group differences emerged. In particular, there was a significant effect of age ($F(1, 132.24) = 5.94, p = .02, \eta^2 = 0.04$), as well as a marginally significant effect of developmental group ($F(2, 156.72) = 2.95, p = .06, \eta^2 = 0.04$) on attentiveness, with the highest ratings shown in the TL group and the lowest in the EL-ASD group based on FDR

correction for multiple comparisons. Importantly, the age by developmental group interaction was significant ($F(2, 133.81) = 4.19, p = .02, \eta^2 = 0.06$), showing increasing attentiveness ratings for the TL group and decreasing scores for the EL-ASD group from 8 to 14 months. In addition, there was a significant effect of group ($F(2, 158.41) = 3.93, p = .02, \eta^2 = 0.05$) and age ($F(1, 136.24) = 6.90, p = .009, \eta^2 = 0.05$) on positivity. Pairwise comparisons using FDR showed higher positive affect scores in the EL groups compared to the TL group but the results were non-significant. The groups did not differ: TL and EL-ASD ($p = .09$), TL and EL-no ASD ($p = .31$), EL-no ASD and EL-ASD groups ($p = .13$). Furthermore, there was a significant effect of age ($F(1, 149.27) = 95.65, p < .001, \eta^2 = 0.39$) on liveliness.

In the dyadic scales, a significant effect of developmental group ($F(2, 128.08) = 8.71, p < .001, \eta^2 = 0.12$) and age ($F(1, 139.89) = 13.77, p < .001, \eta^2 = 0.09$) on mutuality was found. False Discovery Rate-adjusted post hoc comparisons indicated higher dyadic mutuality in the TL group compared to EL-no ASD ($p < .001$) and EL-ASD groups ($p < .001$), while EL-no ASD and EL-ASD groups did not differ ($p = .17$). Last, only a significant effect of age $F(1, 152.47) = 23.29, p < .001, \eta^2 = 0.13$ on engagement intensity was shown. **Table 3.2** provides detailed statistics of the linear mixed-effects model analyses. **Figure 3.1** provides a depiction of the significant effects.

Figure 3.1

Predicted Values of the Significant MACI Scales by Age and Group (TL, EL-ASD, EL-no ASD)



Note. This Figure illustrates the PII scales that differed significantly by group across 7-11 (8 months) and 13-18 (14 months). Compared to the other scales, infant attentiveness showed an age by group interaction. The scores on the Y axis range from 1 to 7 equating to minimal to high parent sensitive responsiveness, nondirectiveness, infant positive affect, attentiveness and dyad mutuality, respectively.

The EL-Atyp group that was explored descriptively (**Table A3.5**) showed high AOSI scores at both time points that were comparable to the EL-ASD group. Mean scores of the EL-Atyp group in the interactional aspects that showed group effects at 8 and 14 months were higher compared to the EL-ASD group and closer to EL siblings who developed typically (EL-TD) except for attentiveness scores that were similar and scores on positivity that were higher in the EL-ASD group at 8 months. Mean ratings of the EL-Atyp group in all the variables increased at 14 months.

In the supplementary analysis including ‘intervention’ as a further covariate, the results remained the same, except for dyadic mutuality, where ‘intervention’ emerged as a significant predictor in the model ($B = -0.72, p = .003$). However, the effect of age and developmental group on mutuality remained significant.

Table 3.2

Results of The Linear Mixed Model (LMM) Analyses Testing for Differences in PII Between the TL and EL Groups Controlling for Infant Age

<i>Sensitive responsiveness</i>	Estimate	SE	df	t	p	95 % CI
(Intercept)	3.31	0.30	241.12	11.18	<0.001	[2.73, 3.89]
Age in months	0.11	0.02	136.64	5.89	<0.001	[0.08, 0.15]
Group (EL-no ASD)	-0.51	0.21	128.75	-2.49	<0.001	[-0.91, -0.11]
Group (EL-ASD)	-0.96	0.29	129.39	-3.28	<0.001	[-1.53, -0.39]
<i>Non-directiveness</i>	Estimate	SE	df	t	p	95 % CI
(Intercept)	4.05	0.30	242.47	13.71	<0.001	[3.47, 4.63]
Age in months	0.05	0.02	142.02	2.67	<0.001	[0.01, 0.09]
Group (EL-no ASD)	-0.71	0.20	134.28	-3.53	<0.001	[-1.10, -0.31]
Group (EL-ASD)	-1.30	0.29	134.95	-4.54	<0.001	[-1.86, -0.73]
<i>Attentiveness</i>	Estimate	SE	df	t	p	95 % CI
(Intercept)	2.35	0.62	160.18	3.82	<0.001	[1.15, 3.55]
Age in months	0.18	0.05	137.63	3.66	<0.001	[0.08, 0.27]
Group (EL-no ASD)	1.10	0.69	161.97	1.59	0.11	[-0.25, 2.45]
Group (EL-ASD)	2.34	0.97	153.75	2.42	0.02	[0.45, 4.23]
Age : Group (EL-no ASD)	-0.10	0.05	138.82	-1.91	0.06	[-0.21, 0.00]
Age : Group (EL-ASD)	-0.23	0.08	131.14	-2.86	0.004	[-0.38, -0.07]
<i>Liveliness</i>	Estimate	SE	df	t	p	95 % CI
(Intercept)	2.17	0.32	173.03	6.83	<0.001	[1.55, 2.80]
Age in months	0.25	0.03	149.27	9.78	<0.001	[0.20, 0.30]
<i>Positivity</i>	Estimate	SE	df	t	p	95 % CI
(Intercept)	2.07	0.89	160.21	2.34	0.02	[0.35, 3.81]
Age in months	0.15	0.07	138.00	2.09	0.04	[0.00, 0.28]
Group (EL-no ASD)	-0.34	1.00	161.89	-0.34	0.74	[-2.29, 1.60]
Group (EL-ASD)	2.95	1.40	156.11	2.11	0.04	[0.22, 5.67]
Age : Group (EL-no ASD)	0.05	0.08	139.41	0.67	0.51	[-0.10, 0.21]
Age : Group (EL-ASD)	-0.18	0.11	135.40	-1.53	0.13	[-0.40, 0.05]
<i>Mutuality</i>	Estimate	SE	df	t	p	95 % CI
(Intercept)	3.49	0.31	235.66	11.35	<0.001	[2.89, 4.09]
Age in months	0.08	0.02	139.89	3.71	<0.001	[0.04, 0.12]
Group (EL-no ASD)	-0.73	0.20	127.42	-3.61	<0.001	[-1.13, -0.34]

Group (EL-ASD)	-1.07	0.29	128.09	-3.72	<0.001	[-1.64, -0.51]
<i>Engagement intensity</i>	Estimate	SE	df	t	p	95 % CI
(Intercept)	3.15	0.26	174.88	12.22	<0.001	[2.64, 3.65]
Age in months	0.10	0.02	152.47	4.83	<0.001	[0.06, 0.14]

Note. ‘:’ indicates group by age interactions; Untransformed values for liveliness are reported as results using both transformed and untransformed values were similar

Abbreviations: CI: confidence interval.

3.3.4 PII and AOSI in Relation to ASD Outcome

A series of logistic regressions were performed separately at 8 and 14 months to examine whether the PII items that differentiated the developmental groups in the earlier analyses predicted ASD outcome, controlling for the effect of age and AOSI. Examining assumptions revealed no significant correlations among the explanatory variables (each PII item was not correlated with age and AOSI separately at 8 and 14 months), with Variance Inflation Factor (VIF) values of approximately 1 and tolerance values ranging from 0.8 to 0.9 (VIF values less than 0.1 and tolerance values greater than 10 would indicate an issue, Menard, 2002; Myers, 1990). In addition, all the interactions between the predictors and their log of themselves had significance values greater than .05, indicating that the assumption of linearity of the logit had been met for the PII variables, age and AOSI at 8 and 14 months. Last, no influential cases on the model were found (all values < 1 based on Cook’s distance).

Again, the results from this study partially replicated those of Wan et al. (2012). Firstly, in contrast to Wan et al.’s (2012) null findings at 6 months, at 8 months, parent nondirectiveness and infant positive affect were found to be significant predictors of 3-year ASD outcome irrespective of the addition of age and AOSI (Nondirectiveness: $p = .02$; Positive affect: $p = .001$; **models 2 & 4, Block 3 in Table 3.3**). The logistic regression models were statistically significant (Nondirectiveness: $\chi^2(3) = 9.033$, $p = .03$; Positive affect: $\chi^2(3) = 15.410$, $p = .001$). The former explained 13% and the latter 22%

(Nagelkerke R^2) of the variance in 3-year ASD outcome. Nondirectiveness emerged as a negative significant predictor in the model, with increasing nondirectiveness being associated with a reduction in the likelihood of receiving an ASD outcome, having an odds ratio of 0.54 (95% CI [0.33, 0.89]) and correctly classifying 87.1% of the cases. Positive affect was a positive significant predictor, with increasing positivity being associated with an increased probability of ASD diagnosis, with an odds ratio of 1.90 (95% CI [1.30, 2.78]) and correctly classifying 87.9% of cases.

At 14 months, and consistent with Wan et al.'s (2012) findings at 12 months, infant attentiveness and dyadic mutuality were significant predictors of ASD outcome ($p = .02$; **models 8 & 10, Block 1 in Table 3.3**). Both interaction domains were negative significant predictors in the model, with increasing attentiveness and mutuality being associated with a decrease in the probability of ASD outcome. However, and in contrast to Wan et al.'s (2012) results, these domains became marginally significant with the addition of AOSI (Attentiveness: $p = .06$; Mutuality: $p = .09$). AOSI emerged as a significant predictor of ASD outcome (AOSI in the attentiveness model: $p = .008$; AOSI in the mutuality model: $p = .01$; **models 8 & 10, Block 3 in Table 3.3**). The logistic regression models were statistically significant (Model 8, Block 3: $\chi^2(3) = 14.241$, $p = .003$; Model 10, Block 3: $\chi^2(3) = 13.458$, $p = .004$). The former explained 20% (Nagelkerke R^2) of the variance in ASD classification, having an odds ratio of 0.57 (95% CI [0.31, 1.02]). The latter explained 19% (Nagelkerke R^2) of the variance with an odds ratio of 0.66 (95% CI [0.41, 1.06]). Both models correctly classified 88.5% of the cases. In addition, borderline significant effects were found in the parent scales, whereas positive affect was found to be a non-significant predictor of ASD outcome, which contrasts with the results by Wan et al (2012). Full results including regression coefficients at 8 and 14 months are shown in **Table 3.3**.

The analysis was re-run including MSEL as a further predictor in the model to examine the variance infant developmental level accounted for in ASD prediction, over and above PII, age and atypical behaviour. At 8 months, there was no essential change in the results, with nondirectiveness and positive affect remaining significant predictors in the model. At 14 months, including MSEL led to a further drop in effect size for the otherwise marginally non-significant infant attentiveness and dyadic mutuality predictors (Attentiveness: $B = -0.39, p = .20$; Mutuality: $B = -0.26, p = .32$). Furthermore, including intervention as a further covariate (in addition to age and AOSI) at 14 months did not change the results of the main logistic regression analyses.

Table 3.3

Logistic Regression Models Showing the 8- and 14-Month Contribution of Each PII Item separately and Together with Age and AOSI in ASD Outcome Prediction

Model	Predictor	<i>B</i> (<i>SE</i>)	Wald (<i>p</i> value)	95% CI for odds ratio			Nagelkerke <i>R</i> ²
<i>8 months</i>				Odds			
				Lower	ratio	Upper	
1	Constant	-0.54 (0.84)	0.42 (0.52)	-	0.58	-	0.04
	Sensitive responsiveness	-0.38 (0.23)	2.63 (0.11)	0.44	0.69	1.08	
2	Constant	0.42 (0.83)	0.26 (0.61)	-	1.53	-	0.12
Block 1	Nondirectiveness	-0.66 (0.25)	7.28 (0.007)**	0.32	0.52	0.83	
	Constant	-0.69 (3.38)	0.04 (0.84)	-	0.50	-	0.13
Block 3	Nondirectiveness	-0.62 (0.25)	5.91 (0.02)*	0.33	0.54	0.89	
	Age	0.06 (0.38)	0.02 (0.88)	0.51	1.06	2.23	
	AOSI	0.05 (0.06)	0.73 (0.39)	0.94	1.05	1.18	
3	Constant	2.73 (1.02)	7.19 (0.007)	-	0.07	-	0.01
	Attentiveness	0.20 (0.23)	0.73 (0.39)	0.78	1.22	1.91	
4	Constant	-4.28 (0.90)	22.77 (<0.001)	-	0.01	-	0.16
Block 1	Positive affect	0.58 (0.19)	9.64 (0.002)**	1.24	1.78	2.56	
	Constant	5.51 (3.67)	2.26 (0.13)	-	0.004	-	0.22

		10.82					
Block 3	Positive affect	0.64 (0.20)	(0.001)**	1.30	1.90	2.78	
	Age	0.02 (0.38)	0.002(0.97)	0.47	0.98	2.08	
	AOSI	0.13 (0.06)	3.90 (0.05) ⁺	1.00	1.13	1.28	
5	Constant	-1.31 (0.81)	2.62 (0.11)	-	0.27	-	0.09
	Mutuality	-0.17 (0.23)	0.58 (0.45)	0.54	0.84	1.32	
Model	Predictor	<i>B</i> (<i>SE</i>)	Wald (<i>p</i> value)	95% CI for odds ratio		Nagelkerke <i>R</i> ²	
14 months				Odds			
				Lower	radio	Upper	
6	Constant	-0.03 (1)	0.001 (0.97)	-	0.97	-	0.06
	Sensitive responsiveness	-0.47 (0.24)	3.90 (0.05) ⁺	0.39	0.62	1	
7	Constant	-0.16 (0.99)	0.03 (0.87)	-	0.85	-	0.06
	Nondirectiveness	-0.48 (0.26)	3.49 (0.06) ⁺	0.37	0.62	1.02	
8	Constant	0.79 (1.18)	0.45 (0.50)	-	2.20	-	0.09
Block 1	Attentiveness	-0.66 (0.28)	5.40 (0.02)*	0.30	0.52	0.90	
	Constant	5.62 (5.81)	0.93 (0.33)	-	275.62	-	0.20
Block 3	Attentiveness	-0.57 (0.30)	3.63 (0.06) ⁺	0.31	0.57	1.02	
	Age	-0.43 (0.39)	1.19 (0.26)	0.30	0.65	1.41	
	AOSI	0.15 (0.06)	6.95 (0.008)**	1.04	1.17	1.31	
9	Constant	-1.83 (0.80)	5.23 (0.02)	-	0.16	-	0.002

	Positive affect	-0.06 (0.17)	0.11 (0.74)	0.69	0.95	1.31	
10	Constant	0.03 (0.86)	0.001 (0.98)	-	1.03	-	0.09
Block 1	Mutuality	-0.56 (0.24)	5.38 (0.02)*	0.35	0.57	0.92	
	Constant	4.56 (5.76)	0.63 (0.43)	-	95.78	-	0.19
Block 3	Mutuality	-0.42 (0.25)	2.96 (0.09) ⁺	0.41	0.66	1.06	
	Age	-0.42 (0.40)	1.11 (0.29)	0.30	0.66	1.43	
	AOSI	0.15 (0.06)	6.66 (0.01)*	1.04	1.16	1.30	

Note. Each variable was entered in the model hierarchically: the PII item was entered first (Block 1), Age was added second (PII item and age; Block 2) and AOSI last (PII, Age and AOSI; Block 3). Blocks 1 and 3 are shown in the significant PII predictors to demonstrate the variance each PII item accounted for in ASD outcome separately and in addition to both age and AOSI.

Abbreviations: AOSI: Autism Observation Scale for Infants; CI: confidence interval.

⁺ $p < 0.1$; * $p < 0.05$; ** $p < 0.01$.

3.4 Discussion

Examining early patterns of PII in relation to ASD susceptibility and diagnosis is significant for a greater understanding of how ASD develops. Previous findings by Wan et al. revealed EL and TL group differences at 6-10 and 12-15 months in parent sensitive responsiveness and nondirectiveness, in infant liveliness at 6 months, as well as in infant attentiveness, positive affect, dyadic mutuality and engagement intensity at 12-15 months. Ratings were lower for infants at EL (especially for EL-ASD infants) than infants at TL, and 12-15-month interaction was predictive of 3-year ASD outcome (in dyad mutuality, infant positive affect and attentiveness). The aim of the current study was to replicate previous findings on PII in ASD development by Wan and colleagues (2013) using a larger independent cohort from the BASIS in order to investigate the consistency and predictive value of PII aspects in relation to ASD likelihood at 8 and 14 months as well as to ASD outcome at 36 months.

The study results partially replicated previous findings. In agreement with Wan and colleagues, parent sensitive responsiveness (appropriate, prompt and infant-centred responses) and nondirectiveness (acceptance of infant experience as opposed to caregiver-directed activities) differed between the groups at 8 and 14 months. Group differences in dyadic mutuality (dyad sharedness and reciprocity in play) also emerged. Infants at TL had higher scores in these domains compared to both EL groups. Particularly for nondirectiveness, the EL-ASD group had significantly lower scores, indicating more directive parent behaviours in relation to the other two groups. Furthermore, changes in attentiveness to parent were observed in the groups across 8 and 14 months compared to Wan and colleagues who found differences only at 14 months; initially, the TL group had lower scores compared to the other groups, which increased from 8 to 14 months. Conversely, attentiveness in the EL-ASD group followed an alternative trajectory, with ratings decreasing across time, while the EL-no ASD group's

scores remained relatively stable across 8 and 14 months. Interestingly, and in contrast to previous findings, infants at EL with a later ASD diagnosis had higher scores on positive affect compared to the other groups, but group differences did not survive correction for multiple comparisons. In addition, unlike previous findings, infant liveliness and dyadic engagement intensity did not show a group effect. Regarding ASD outcome prediction, although results from the previous study revealed that interaction differences at 12 months were predictive of 3-year ASD outcome classification, the current study found earlier predictive effects, demonstrating that high infant positive affect and low parent nondirectiveness predicted ASD outcome at 8 months, irrespective of early behavioural atypicality and developmental level. At 14 months, and consistent with Wan et al.'s findings, lower infant attentiveness and mutuality predicted ASD outcome but showed a trend after controlling for infant behavioural atypicality. However, infant positive affect did not emerge as a significant predictor, which is what was previously found. Overall, the present results provide evidence for an effect of the quality of PII in infant developmental outcomes which may have implications for the timing and focus of parent-mediated interventions.

3.4.1 Evaluating Group and Time Effects of Parent-Infant Interaction at 8 and 14 Months

In addition to previous reports by Wan and colleagues (2013), the differences observed between the groups in parental behaviour during the interactions have also been observed in other studies. For instance, studies have reported that parents of infants at EL for ASD tend to use more directive behaviours when interacting with their infants than parents of infants at TL (Harker et al., 2016; Srinivasan & Bhat, 2020; Steiner et al., 2018; M. W. Wan et al., 2019a). However, there is also evidence suggesting similarities in parent responsiveness, structuring or directiveness towards EL and TL infants (Baker et

al., 2010; Campbell et al., 2015), which could be attributed to differences in sample size or methods used. In view of the present findings, what could have driven the identified differences between the groups in parent behaviour? A range of factors may be impacting parent behaviour; one possibility is that, regardless of infant behaviour, parent responses reflect a pattern of behavioural responses learned from interactions with their older siblings who have an ASD diagnosis. Parent sensitive responsiveness was not associated with later ASD outcome, which may indicate that parent behaviour is not explained by infant early emerging ASD atypicalities. Nevertheless, the results showed that parent directiveness at 8 months was higher in the EL-ASD group compared to the other groups, predicting later ASD. Higher AOSI scores in infants at EL were also related to higher parent directiveness. This is consistent with the interpretation that parent behaviours may be adaptive, such that they may notice subtle differences in their infants' responses and behaviour, leading to more directive behaviours in order to engage their infants in social interactions. Other research has shown that parents of infants at EL intensify their prosodic expressions from 12 to 18 months compared to parents of infants at TL, possibly as a way of eliciting infants' attention (Quigley et al., 2016).

Furthermore, it cannot be ruled out that parent stress or ASD-related traits, usually shown in first-degree relatives of individuals with ASD (Pisula & Ziegart-Sadowska, 2015, for a review), could have also played a role in their interactive behaviour. Although a recent study did not find a relationship between parent distress or BAP characteristics and 3-year autism behaviours (Loncarevic et al., 2022), there is other evidence highlighting links between parent stress and lower responsiveness to the child (Flykt et al., 2010; Shin et al., 2008), as well as parents' BAP traits and child language, socio-emotional and communication skills or severity of ASD behaviours (Bishop et al., 2006; Loncarevic et al., 2021).

Differences in mutuality observed between the groups have also been found in other studies (in addition to the one replicated), predictive of ASD severity (Campbell et al., 2015; Loncarevic et al., 2022). Equally to parental aspects of interaction, no change was observed in mutuality within the first year, which was lower in the EL groups compared to the TL group (**Table A3.8**). These results show that not only parental but also dyadic domains of interaction, which are fundamental for later child socio-cognitive development (Shultz et al., 2018), are affected in infants at EL for ASD. Interestingly, at 14 months, those infants who underwent intervention also had lower scores in dyadic mutuality. This was not surprising, as there are likely to be differences in infants enrolled in the intervention per se compared to the rest of the sample. Of note, in Green et al.'s (2015) randomised controlled trial findings, parent-mediated intervention effects at the 14-month endpoint were observed for other variables (infant attentiveness and parent nondirectiveness) but not for mutuality.

Regarding infant behaviours, a divergence in infant attentiveness is observed from 8 months, which was not observed in the previous 7-month sample (Wan et al., 2013). Changes in attentiveness between the groups, becoming more pronounced with time and predicting ASD outcome at 36 months also agree with research evidence for lower joint attention behaviours or responses of EL-ASD infants to caregivers' invitations than TL infants around the first year, linked to higher ASD symptoms at 3 years (Kellerman et al., 2020; Rozga et al., 2011). This study's finding adds to the existing literature by showing changes in attentiveness to parent from as early as 8 months and strengthens already existing evidence for possible emerging infant atypicalities affecting early social behavioural attention in PII with an impact on later developmental outcome.

3.4.2 Evaluating the PII and AOSI Contribution to ASD Outcome

This is the first prospective study to delineate parental interactive behaviour (nondirectiveness) in EL infants within the first year, particularly at 8 months, as a predictor of 3-year ASD outcome. This effect was independent of infant atypical behaviour and developmental level, even though the groups differed in AOSI at 8 months, highlighting the predictive value of unstructured PII compared to standardised assessments early in development. This means that possible disruptions in free play caregiver-infant interaction linked to ASD outcome signify that PII may be able to capture early emerging behavioural atypicalities more accurately than standardised measures, through which they may not be observable at such an early age. Again, these findings are consistent with the interpretation that parents may adopt an active interaction style based on their expectations of infant play and their infant's social capacities, leading to more directive behaviours to engage their infants in social interactions. Further, infant attentiveness and mutuality at 14, and not at 8 months, were significant predictors of ASD outcome but became non-significant with the addition of the AOSI and MSEL. However, attentiveness and mutuality had larger effect sizes and explained almost half of the variance in ASD outcome. Although not consistent with the study replicated, the shared variance identified was not surprising, considering that these measures involve elements of social interactions. Further, it is shown in previous research that infants at EL and those receiving a clinical diagnosis of ASD display more pronounced social-communication difficulties and developmental delays over time (Loncarevic et al., 2021; Ozonoff et al., 2010; Zwaigenbaum et al., 2005). Thus, this finding reveals a change (decrement) in parent-infant mutuality and infant behavioural attention with age, suggesting that differences are more pervasive with development in infants with a subsequent ASD diagnosis.

Moreover, the findings on positive affect revealed that infants at EL with a later ASD diagnosis displayed high positivity during the interactions at 8 months predicting 3-year ASD outcome. This contradicts Wan and colleagues' findings for lower positive affect at 12-15 months predicting of 3-year ASD outcome. One possible explanation of the disparity in findings could be due to coding scheme differences, as Wan et al.'s study used an earlier version of the MACI that incorporated positive and negative affect into a single variable named 'positive affect' (with lower (< 4) ratings indicating more negative affect and higher (> 4) ratings more positive affect), while this study used an updated version that separated affect into two variables, namely 'positive' and 'negative' affect. The positive affect scale used in the current study did not incorporate elements of negativity. Interestingly, in this study, even though no significant differences were shown in the negative affect scale between the groups, EL-ASD infants had higher scores on this scale compared to the other two groups at both time points. Therefore, this could suggest that Wan and colleagues' findings on positive affect as a predictor of ASD outcome derived more from negative affect, rather than less positivity.

Another possibility is that the difference in the findings possibly reflects changes in infant affect at different ages, where differences in positive affect between ASD versus no ASD outcome groups are seen at around 8 and 12 months but not at 6 or 14 months. Therefore, it could be that initially high positivity can be seen at 8 months, while more negative affect is seen at around the first year, differentiating the groups (as shown by Wan et al.) and linked to ASD outcome classification at 36 months. Given that the positive affect scales used between the studies were slightly different, of interest was to delineate whether the positive affect scale from the previous study would be comparable to the one used here. If this was true, it could possibly mean that the different results shown in positive affect between the studies could be attributed to age effects. To examine the comparability of the scales, correlations were performed between the old 'positive

affect' scale and the new 'positive' and 'negative' affect scales with a sub-sample of infants from this study whose interactions had been coded using both the old and the new coding schemes. If the scales were highly associated, it would indicate that they are similar, and thus, the findings from both studies would possibly be attributed to positive affect differences or changes shown at 8 and 12 months in EL-ASD infants. If not, the results could possibly be explained by differences in the coding scheme used. The results revealed that the old and new positive affect scales were not highly correlated. Thus, the disparity in the findings is more likely to be related to coding scheme differences.

Despite this discrepancy, it is likely that the high positivity observed in the EL-ASD group relative to the other groups predicting ASD outcome reflects a temperamental characteristic. This group also showed high negative affect in addition to high positive affect, but no differences emerged in negativity between the groups. In particular, the effect of positivity might be related to surgency (referring to infant engagement/approaching behaviours, positive affective display and activity level). Some empirical work has shown that infants at EL-for ASD exhibit high levels of surgency, while a reduction in positive affect begins to become apparent after the first year (del Rosario et al., 2014; Garon et al., 2009; Ozonoff et al., 2010; Zwaigenbaum et al., 2005). Indeed, positivity for the other groups increased while it seemed to slightly attenuate in the EL-ASD group at 14 months (**Table A3.8**). In addition, similarly to infants in this study, infants with higher symptoms of ADHD later in development seem to show high levels of positive affect within the first year of life (Frick et al., 2019), which has been linked to low maternal caregiving in girls (N. V. Miller et al., 2019). Considering that ADHD and ASD in some cases share the same symptoms and appear to overlap (Rommelse et al., 2010), it is also possible that the result shown in the current study may reflect ADHD-related traits.

It is also very likely that high positive affect might reflect developmental delays in EL-ASD infants' social play such that they are inclined toward more dyadic styles of play (without toys) or simpler toy play, which elicit moments of positive arousal (e.g. laughter in Peekaboo), while triadic styles of play (with toys) may involve deeper attention on toys and more sophisticated joint attention social skills (e.g. in book sharing). Indeed, MSEL scores in this group were lower than the other groups. A retrospective (unblinded) re-observation of the PIIs in the EL-ASD subgroup found that, while dyadic interactions were not necessarily more common in the EL-ASD group, some of the parents showed a strong tendency to repeatedly try and elicit some kind of positive infant response (e.g. by quickly showing and hiding a toy), sometimes in the context of infant wanting to explore the wider environment (moving away from the parent). In other words, infant positivity in this subgroup did not seem to reflect enduring high-quality interaction but rather may reflect the parents' choice of directive interactive attempts (which aligns with our finding that parent directiveness predicted 3-year ASD outcome) which 'successfully' elicited instances of strong positivity (e.g., brief laughter, enthusiastic vocalisation). However, a future blinded study would be needed to confirm this interactive style in an EL-ASD group.

All in all, as the transactional model proposes, pre-existing ASD susceptibilities compounding the quality of early PII can decrease infant opportunities to learn from their social environment. Considering that potential early brain function alterations in social attention have also been observed in infants at EL-ASD within the first year (Elsabbagh et al., 2012; Tye et al., 2020), this can have cascading effects on infant social functioning. The study's findings support this transactional approach: low scores in parent, infant and dyadic interactional aspects were observed at both time points; parent directiveness and infant positive affect predicted later ASD outcome at 8 months, with attentiveness decreasing over time and mutuality being affected, both at 14 months (along with AOSI

and MSEL) predicting ASD outcome at 36 months. Therefore, PII differences at 8 and 14 months combined with increasing infant atypical behaviours and developmental delays may have an influencing role on later ASD classification. On the other hand, and in agreement with Wan et al. (2013), higher quality of social interactions with parents could possibly contribute towards an alternative developmental trajectory; descriptive analysis in the EL-Atyp group showed that this group generally had higher PII ratings than the EL-ASD group. Some of these ratings were more similar to siblings who were categorised as typically developing, thus, indicating that infants at EL who have more positive social interaction experiences and are more socially engaged may not follow a developmental route leading to ASD diagnosis. However, even though ratings in this group were higher compared to the EL-ASD group, interactional behaviours such as infant attentiveness and mutuality at 8 months as well as positive affect and nondirectiveness at 14 months were not as different as the EL-ASD group. This also highlights the complexity and heterogeneity of the condition.

Overall, these findings suggest that interventions aiming to improve the quality of PII in infancy would be valuable in optimising infant social communication outcomes. In particular, pre-emptive interventions (e.g., the BASIS-Video Interaction for Promoting Positive Parenting (iBASIS-VIPP)) that aim to support parents to follow a child's attentional focus have shown positive subsequent effects on social communication development (Green et al., 2017 (intervention delivered between 9 and 14 months of age; Watson et al., 2017 (intervention delivered at 1 year of age); Whitehouse et al., 2021 (intervention delivered in infants aged 9 to 14 months). The present study suggests that beginning such interventions in even earlier development may be beneficial (Grzadzinski et al., 2021). Future longitudinal studies that can map longitudinal outcomes that include child psychological well-being (e.g., anxiety and depression) will be critical to address this question.

3.4.3 A Note on the Internal Characteristics and 8- to 14-Month Stability of the PII Items

Considering the MACI items' psychometric characteristics, low to moderate stability was observed in the EL group across time in the parental aspects of interaction and dyadic mutuality. No stability was shown in the TL group, which could possibly be explained by sample size differences (23 TL and 91 EL infants). Internal consistency was also observed, particularly in the parental and dyadic scales and, to a lesser extent, in the infant scales. Given that infant interactive behaviour can be logically affected by developmental changes and parent behaviour is expected to stay relatively stable over time (Bigelow et al., 2010; M. W. Wan et al., 2017b), these results were unsurprising.

Of note, correlations between a few areas, such as between sensitive responsiveness and attentiveness, mutuality and nondirectiveness or positivity and negativity seemed to decouple at 14 months, particularly in the TL group, whereas they remained relatively stable in the EL group. This could be a developmental phenomenon; the qualities of PII are dynamic and can change as infant behavioural repertoire changes with development. The opposite was observed in the EL group, where there was stability in these interactional qualities, which could underlie a delay in the PII changes normally taking place across infant development. Interestingly, Wan et al. (2012, 2013) observed a somewhat differential pattern of relations, where correlations remained relatively stable in both groups from 6 to 12 months, but seemed to couple in a few areas, mostly in the TL group. This coupling of associations which contrasts with the current study's results could be explained by the fact that the sample in that study was slightly younger than this study's sample. Although in a different direction, this pattern of relations in the interactional qualities in the TL group is again a possible indication of the dynamic changes in PII expected to be seen over time, compared to the EL group where alterations

in PII patterns might be more stable/delayed across time. This emphasises the bidirectional nature of PII, likely indicating that the parent and child's qualities of the interaction depend more closely on how both interact towards one another over time.

Moreover, regarding positive and negative affect correlations, while they seem to be closely intertwined earlier in infancy, they become segregated later as infants' affective states are likely to change quickly and more flexibly across development. This provides evidence for validity in separating the affect scale in the updated version of the MACI.

3.4.4 Limitations and Future Directions

The study offers important new insights into the role of PII in infants who are at a higher likelihood of developing ASD, however, some limitations need to be acknowledged. First, although the EL sample was one the largest to date, the TL group was small. However, many of this group's PII ratings were similar to those by Wan et al. (2013) which employed a larger TL sample, or those by Whitehouse et al.'s (2019) baseline ratings. In addition, since EL and TL differences in PII were already much better established (Wan et al., 2019), the focus was on coding PII in a large EL group. Nevertheless, future research should endeavour to include even larger sample sizes due to the low percentage of infants with a family history of ASD receiving a later diagnosis (Ozonoff, Young, et al., 2011). One explanation of the borderline significant effects observed in the PII variables with the addition of the covariates could possibly be attributed to the sample size differences between the ASD likelihood groups. A larger sample size would possibly be more powered to maintain these effects.

Second, while examining PII at 8 and 14 months provided valuable information on the early PII dynamics in ASD, using two time points was quite restrictive as it was not possible to observe non-linear effects, if any. Investigating PII over several time points across development would add to these findings, possibly offering a clearer view

and insight into how social interactions between parents and infants unfold, how or whether they change and how they are associated with different clinical outcomes.

Third, the MACI global coding scheme offers significant insights into the overall quality of PII in key interactional aspects to delineate parent-infant interactions, a microanalytic measure examining specific aspects of parent-infant relationships (i.e., which patterns of attentiveness trigger which parental responses, or which of the positive or negative affect behaviours are spontaneous or in response to caregiver behaviour) would help make better sense of the processes associated with later ASD.

Another limitation is that parental stress or BAP were not measured but may have played a part in the quality of interactions with infants, taking into account previous literature. Future longitudinal study designs should examine the mediating effects of these variables to help understand whether the observed effects represent an affirmative parenting style or not, and to interpret the results with greater confidence.

In addition, investigating the progression of PII in association with other dimensions over developmental time, such as ASD- or ADHD-related traits or measures of developmental level related to social communication will be an important addition to the existing findings. The findings of the current study suggest that the effects shown on positivity might reflect temperamental patterns linked to ADHD traits. Measures of ASD-related behaviour and developmental level seem to have an effect on ASD outcome (in addition to PII) at 14 months but not earlier, which may be a manifestation of increasing difficulties becoming apparent over time. Taking a dimensional approach to studying longitudinal patterns of PII in infants who are at EL for ASD can immensely contribute to understanding the developmental pathways to ASD and the influencing role of PII.

Last, it is important to stress that causal inferences of the effect of early PII on ASD diagnosis cannot be drawn. Designs measuring PII at several time points with larger samples are needed to investigate the possible influence of parent-child relationships on

long-term outcomes. Further, potential causal effects could be inferred by intervention studies aiming to alter these particular aspects of PII to optimise later developmental trajectories.

3.5 Conclusion

This study replicates and strengthens previous findings for emerging differences in parent sensitive responsiveness, parent nondirectiveness, infant attentiveness and mutuality, especially among infants with a 3-year ASD diagnosis. It also replicates previous reports for infant attentiveness and mutuality at 14 months as predictors of ASD outcome. Furthermore, the study extends previous findings showing positive affect at 8 months as a predictor of ASD outcome. Importantly, it is the first to show that parent nondirectiveness within the first year predicts later ASD outcome and suggests a divergence in infant attentiveness from 8 months. These robust longitudinal analyses of one of the largest samples to date examining PII and its relation to subsequent ASD contribute to a greater understanding of parent-infant social experiences in the first year of life in infants with a raised likelihood of ASD. Further empirical work should examine whether these changes in PII reflect an adaptive parenting style. The findings from this study add to an increasing amount of research that can help in the design of early parent-mediated interventions.

3.6 Appendix

3.6.1 Internal Characteristics and Stability of the PII Items

At both 8 and 14 months, most MACI scales were significantly intercorrelated, especially in the parent and dyadic scales in both EL and TL groups, with low, moderate and high correlations observed (**Table A3.3**). Patterns of correlation in the parent and dyadic scales remained stable from 8 to 14 months, except for the correlations between the dyadic scales in the TL group which were only evident at 14 months. Infant liveliness was unrelated to most other MACI scales for both groups at both time points. In the EL group, infant attentiveness was correlated with sensitive responsiveness, positive affect and the dyadic scales at 8 months, and to both parent and dyadic scales at 14 months, with correlations increasing with time for the parent scales and dyadic mutuality. Somewhat differently, in the TL group, attentiveness was correlated with sensitive responsiveness, negative affect (negatively) and mutuality at 8 months, but correlation remained only with the mutuality scale at 14 months. In addition, in the TL group, positive affect was related to negative affect (negatively) and engagement intensity at 8 months, with a correlation remaining only with the latter scale at 14 months. Negative affect was also correlated with engagement intensity at 14 months. In the EL group, in addition to attentiveness, positive affect at 8 months was correlated with sensitive responsiveness and the dyadic scales, while at 14 months, it was correlated with sensitive responsiveness, liveliness and engagement intensity. In turn, in negative affect, low and negative associations were shown with nondirectiveness, liveliness and mutuality at 8 months, and only with sensitive responsiveness at 14 months.

In addition, in the TL group at 8 months, age and AOSI were significantly correlated with sensitive responsiveness (Age: $r = .42, p = .04$; AOSI: $r = .45, p = .03$). Age was also related to liveliness ($r = .62, p = .001$). In the EL group, age was

significantly correlated with some of the interaction items (Sensitive responsiveness: $r = .21, p = .04$; Nondirectiveness: $r = .21, p = .04$; Liveliness: $r = .35, p < .001$). The AOSI was significantly and negatively correlated with nondirectiveness ($r = -.24, p = .02$), attentiveness ($r = -.24, p = .02$), liveliness ($r = -.34, p < .001$) and positive affect ($r = -.21, p = .04$). None of the interaction items was correlated with age and AOSI in either of the groups at 14 months.

Furthermore, in the correlations between time points in the EL and TL groups, controlling for infant age and considering the data available across time for each group (TL: $N = 23$; EL: $N = 91$) moderate to low stability was shown for the parent scales and dyadic mutuality in the infants at EL only (**Table A3.4**).

3.6.2 Model Selection

Given that liveliness and negative affect were non-normally distributed, LRTs were conducted using both their transformed and untransformed values and yielded very similar results, therefore, their untransformed values are reported (but see **Table A3.6** for LRT results with liveliness and negative affect transformed for comparison).

Initially, LRTs for the selection of the model with the best fit were conducted. LRTs for sensitive responsiveness, nondirectiveness and dyadic mutuality indicated that only the addition of age (Sensitive responsiveness: Akaike information criterion (AIC) = 793.33, Bayesian Information Criterion (BIC) = 807.48, deviance = 785.33, $\chi^2(1) = 32.83, p < .001$; Nondirectiveness: AIC = 803.34, BIC = 817.49, deviance = 795.34, $\chi^2(1) = 8.04, p = .004$; Mutuality: AIC = 813.50, BIC = 827.65, deviance = 805.50, $\chi^2(1) = 14.46, p < .001$) and developmental group as fixed effects provided a better fit for the data (Sensitive responsiveness: AIC = 786.09, BIC = 807.32, deviance = 774.09, $\chi^2(2) = 11.24, p = .003$; Nondirectiveness: AIC = 787.05, BIC = 808.27, deviance = 775.05, $\chi^2(2) = 20.29, p < .001$; Mutuality: AIC = 800.83, BIC = 822.05, deviance = 788.83, $\chi^2(2) =$

16.67, $p < .001$) compared to the null. Furthermore, for infant attentiveness and positive affect, the AIC and the deviance significantly decreased with the addition of age (Attentiveness: AIC = 798.13, BIC = 812.27, deviance = 790.13, $\chi^2(1) = 13.57$, $p < .001$; Positive affect: AIC = 970.74, BIC = 984.83, deviance = 962.74, $\chi^2(1) = 23.40$, $p < .001$), while the interaction between age and developmental group (Attentiveness: AIC = 796.17, BIC = 824.47, deviance = 780.17, $\chi^2(2) = 8.33$, $p = .02$; Positive affect: AIC = 967.33, BIC = 995.50, deviance = 951.33, $\chi^2(4) = 11.42$, $p = .02$) further improved model fit. In addition, for liveliness and dyadic engagement intensity, only the inclusion of age led to a significant improvement in the fit of the model (Liveliness: AIC = 888.18, BIC = 902.33, deviance = 880.18, $\chi^2(1) = 76.57$, $p < .001$; Engagement intensity: AIC = 776.78, BIC = 790.93, deviance = 768.78, $\chi^2(1) = 22.74$, $p < .001$) compared to the model without it. Last, for negative affect, none of the variables (fixed effects) added led to an improvement in model fit compared to the null model, therefore, no further analysis was conducted on this scale. For all the details on the model selection process, refer to **Table A3.7**.

Table A3.1*Intra-Class Correlation Coefficients (ICC) Between Coders for the MACI Items*

		Inter-rater reliability ICC at 8 months (10%)	Inter-rater reliability ICC at 14 months (10%)
<i>Infant</i>	Attentiveness	0.82	0.73
	Liveliness	0.64	0.62
	Positive affect	0.70	0.71
	Negative affect	0.81	0.71
	Sensitive		
<i>Parent</i>	Responsiveness	0.88	0.67
	Non-directiveness	0.68	0.67
<i>Dyad</i>	Mutuality	0.75	0.70
	Engagement		
	intensity	0.78	0.75

Note. Values ≥ 0.60 indicate good to excellent ICC. MACI: Manchester Assessment of Caregiver-Infant Interaction.

Table A3.2*Sample Demographic and Clinical Characteristics by Clinical Outcome Group at 36 Months*

	Total	TL	EL-no ASD	EL-ASD	F/H	Group comparisons
Participants, <i>N</i>	140	27	96	17		
	Mean (SD)					
Age	38.79 (1.61)	38.72 (1.62)	38.84 (1.60)	38.56 (1.71)	0.23	-
MSEL ELC	105.59 (24.47)	119.48 (15.27)	105.43 (23.42)	84.81 (28.21)	17.25*** ^a	TL>EL-noASD/EL-ASD; EL-noASD>EL-ASD
VABS ABC	97.00 (13.42)	106.52 (6.0)	97.77 (11.42)	76.33 (12.44)	40.72*** ^a	TL>EL-noASD/EL-ASD; EL-noASD>EL-ASD
ADOS-2 Social Affect Total Score^b	3.49 (3.81)	3.88 (3.03)	3.28 (3.15)	6.50 (6.11)	5.76 ^{+a}	TL<EL-ASD; EL-noASD<EL-ASD
ADOS-2 RRB Total Score^b	1.26 (1.44)	0.80 (0.91)	1.21 (1.42)	2.31 (1.74)	10.48*** ^a	TL<EL-ASD; EL-noASD<EL-ASD
ADOS-2 CSS^b	2.37 (2.15)	1.96 (1.59)	2.23 (1.93)	3.88 (3.40)	3.57 ^a	-
ADI-R Social	3.00 (4.47)	0.96 (1.49)	2.00 (2.55)	12.13 (5.76)	41.87*** ^a	TL<EL-ASD; EL-noASD<EL-ASD
ADI-R Communication	3.27 (4.47)	0.48 (1.05)	2.62 (3.29)	11.50 (4.69)	48.64*** ^a	TL<EL-noASD/EL-ASD; EL-noASD<EL-ASD
ADI-R Behaviours/Repetitive Interests	1.18 (2.24)	0.08 (0.28)	0.73 (1.49)	5.63 (2.55)	48.08*** ^a	TL/EL-noASD<EL-ASD

SRS Total Score	32.70 (25.41)	19.79 (9.50)	30.75 (22.87)	62.31 (32.22)	20.00** ^a	TL<EL-ASD; EL- noASD<EL-ASD

^a The Kruskal-Wallis test was used for variables with non-normally distributed scores based on histograms, Q-Q plots and Shapiro-Wilk tests. Differences between groups have been adjusted by the Bonferroni correction for multiple comparisons.

^b ADOS-G item scores were used for the calculation of ADOS-2 total scores.

Abbreviations: ADI-R: Autism Diagnostic Interview-revised; ADOS: Autism Diagnostic Observation Schedule; ASD: Autism spectrum disorder; Atyp: Infant siblings with atypical development but no ASD; CSS: ADOS-2 Calibrated Severity Scale; EL: Elevated likelihood; H: Kruskal-Wallis test; MSEL ELC: Mullen Scales of Early Learning Early Learning Composite; min-max: minimum-maximum values; RRB: Restricted and Repetitive Behaviours; SRS: Social Responsiveness Scale; TL: Typically developing infants; VABS: Vineland Adaptive Behaviour Scales.

⁺p < 0.1. *p < 0.05. **p < 0.001.

Table A3.3

Correlations Within the MACI Global Aspects of PII in the TL and EL Groups at 8 and 14 Months^a

	1	2	3	4	5	6	7	8
<i>8 months</i>								
<i>Infants at TL</i>								
1. Sensitive responsiveness		.79**	.44*	.02	.11	-.12	.80**	.18
2. Nondirectiveness	.74**		.33	.07	-.08	-.04	.60**	.09
3. Attentiveness	.22*	.10		.06	.40	-.44*	.68**	.24
4. Liveliness	.21*	.37**	.12		-.02	-.16	-.15	.08
5. Positive affect	.24*	.06	.47**	.18		-.55**	.24	.53**
6. Negative affect	-.19	-.23*	-.13	-.29**	-.07		-.26	-.22
7. Mutuality	.77**	.53**	.58**	.16	.39**	-.31**		.04
8. Engagement intensity	.38**	.14	.58**	.05	.63**	-.15	.62**	
<i>Infants at EL</i>								
	1	2	3	4	5	6	7	8
<i>14 months</i>								
<i>Infants at TL</i>								
1. Sensitive responsiveness		.81**	.23	-.25	.14	-.35	.50**	.22
2. Nondirectiveness	.74**		.20	-.26	.004	-.17	.33	-.02
3. Attentiveness	.57**	.46**		-.27	.08	-.26	.86**	.16
4. Liveliness	-.03	.009	-.21*		.33	.19	-.41*	-.08
5. Positive affect	.22*	.15	.10	.39**		-.19	.18	.54**
6. Negative affect	-.26*	-.19	-.15	.13	-.05		-.40	-.57**
7. Mutuality	.64**	.50**	.82**	-.24*	.16	-.19		.41*
8. Engagement intensity	.37**	.23*	.51**	.02	.42**	-.13	.61**	
<i>Infants at EL</i>								

^a Adjusting for infant age and MSEL at each time point yielded very similar results. However, at 8 months, in the TL group, the correlation of attentiveness with positive affect became significant ($r = .61$, $p = 0.003$), and with sensitive responsiveness marginally non-significant ($p = 0.06$). In the EL group, the correlation of liveliness with sensitive responsiveness became non-significant ($p = 0.12$), and with positivity significant but remained low ($r = .23$, $p = 0.03$).

Abbreviations: EL: Elevated likelihood; TL: Typical likelihood.

* $p < 0.05$; ** $p < 0.01$.

Table A3.4

Partial Correlations in The MACI Global Aspects of PII Between 8 and 14 Months for Infants at TL and EL, Controlling for Infant Age

	SR	ND	Att	Liv	Pos	Neg	Mut	Eng
TL	-.18	.04	.24	.02	-.01	.04	.20	-.05
EL	.40**	.32**	.07	.09	.10	.11	.22*	.05

Abbreviations: Att: infant attentiveness; EL: Elevated Likelihood; Eng: dyadic engagement intensity; Liv: infant liveliness; Mut: dyadic mutuality; ND: parent nondirectiveness; Neg: infant negative affect; Pos: infant positive affect; SR: parent sensitive responsiveness; TL: Typical Likelihood.

* $p < 0.05$; ** $p < 0.01$.

Table A3.5

Clinical Outcome Group Means on the AOSI and Parent-Infant Interaction Items at 8 and 14 Months

	TL	EL-TD	EL-Atyp	EL-ASD
<i>8 months</i>	Mean (SD)			
AOSI Total Score	5.26 (3.13)	8.39 (4.62)	9.44 (4.62)	10.24 (4.76)
Sensitive responsiveness	4.21 (1.41)	3.91 (1.14)	3.67 (1.18)	3.38 (1.26)
Nondirectiveness	4.46 (0.88)	3.91 (1.23)	3.78 (1.31)	3.06 (1.24)
Attentiveness	3.96 (1.12)	4.04 (1.13)	4.11 (1.42)	4.31 (1.25)
Positive affect	3.29 (1.30)	3.28 (1.61)	3.67 (1.47)	4.81 (1.83)
Mutuality	3.92 (1.32)	3.51 (1.12)	3.33 (1.18)	3.31 (1.25)
<i>14 months</i>	TL	EL-TD	EL-Atyp	EL-ASD
AOSI Total Score	4.07 (3.52)	4.97 (4.11)	7.71 (4.48)	9.47 (5.23)
Sensitive responsiveness	5.12 (0.82)	4.45 (1.14)	4.31 (1.23)	3.93 (1.10)
Nondirectiveness	4.88 (0.99)	4.08 (1.14)	3.86 (1.25)	3.60 (0.83)
Attentiveness	5.04 (1.04)	4.60 (1.06)	4.45 (1.24)	3.93 (0.80)
Positive affect	4.38 (1.65)	4.79 (1.71)	4.66 (1.65)	4.50 (1.95)
Mutuality	4.88 (0.82)	3.90 (1.18)	3.72 (1.39)	3.27 (0.96)

Abbreviations: AOSI: Autism Observation Scale for Infants; ASD: Autism spectrum disorder; Atyp: Infant siblings with atypical development but no ASD; EL: Elevated likelihood; SD: Standard Deviation; TD: Infant siblings with typical development; TL: Typically developing infants.

Table A3.6

Likelihood Ratio Tests (LRTs) Comparing Increasingly Complex Models Using the Transformed Infant Liveliness and Negative Affect Values

Models	parameters	AIC	BIC	LogLik	deviance	X²	X²df	p
<i>Infant liveliness</i>								
Null	3	655.81	666.42	-324.90	649.81	-	-	-
Model 1								
+ Age	4	585.73	599.88	-288.87	577.73	72.08	1	<0.001
Model 2								
+ Group	6	589.29	610.51	-288.64	577.29	0.44	2	0.80
Model 4								
+ Age *								
Group	8	586.34	614.64	-285.17	570.34	7.39	4	0.12
Model 5								
+ Sex	5	587.65	605.34	-288.83	577.65	0.08	1	0.78
Models	parameters	AIC	BIC	LogLik	deviance	X²	X²df	p
<i>Infant negative affect</i>								
Null	3	635.8	646.36	-314.9	629.8	-	-	-
Model 1								
+ Age	4	637.7	651.79	-314.85	629.7	0.10	1	0.76
Model 2								
+ Group	5	635.54	653.15	-312.77	625.54	4.26	2	0.12
Model 4								
+ Age *								
Group	8	639.9	668.07	-311.95	623.9	5.90	5	0.32
Model 5								
+ Sex	8	639.9	668.07	-311.95	623.9	5.90	5	0.32

Note. “*” indicates reciprocal interactions including the lower order terms.

Abbreviations. AIC: Akaike Information Criteria; BIC: Bayesian Information Criteria; LogLik: Logarithmic Likelihood; X²: Chi-square statistic; Group: ASD likelihood group (EL-ASD, EL-no ASD, TL).

Table A3.7*Comparison of Increasingly Complex Models for Each PII Item with the Likelihood Ratio Test (LRT)*

Models	parameters	AIC	BIC	LogLik	deviance	X²	X²df	p
<i>Sensitive responsiveness</i>								
Null	3	824.16	834.77	-409.08	818.16	-	-	-
Model 1 + Age	4	793.33	807.48	-392.66	785.33	32.83	1	<0.001***
Model 2 + Group	6	786.09	807.32	-387.05	774.09	11.24	2	0.003**
Model 4 + Age * Group	8	788.79	817.09	-386.40	772.79	1.30	2	0.52
Model 5 + Sex	7	785.99	810.76	-386.00	771.99	3.00	1	0.15
Models	parameters	AIC	BIC	LogLik	deviance	X²	X²df	p
<i>Non-directiveness</i>								
Null	3	809.38	819.99	-401.69	803.38	-	-	-
Model 1 + Age	4	803.34	817.49	-397.67	795.34	8.04	1	0.004**
Model 2 + Group	6	787.05	808.27	-387.52	775.05	20.29	2	<0.001***
Model 4 + Age * Group	8	789.02	817.32	-386.51	773.02	2.03	2	0.36
Model 5 + Sex	7	787.19	811.95	-386.59	773.19	1.86	1	0.17

Models	parameters	AIC	BIC	LogLik	deviance	X²	X²df	p
<i>Infant attentiveness</i>								
Null	3	809.69	820.31	-401.85	803.69	-	-	-
Model 1								
+ Age	4	798.13	812.27	-395.06	790.13	13.57	1	<0.001***
Model 2								
+ Group	6	800.50	821.72	-394.25	788.5	1.62	2	0.44
Model 4								
+ Age * Group	8	796.17	824.47	-390.08	780.17	8.33	2	0.02*
Model 5								
+ Sex	9	798.15	829.98	-390.07	780.15	0.02	1	0.88
Models	parameters	AIC	BIC	LogLik	deviance	X²	X²df	p
<i>Infant liveliness</i>								
Null	3	962.75	973.36	-478.37	956.75	-	-	-
Model 1								
+ Age	4	888.18	902.33	-440.09	880.18	76.57	1	<0.001***
Model 2								
+ Group	6	891.57	912.8	-439.79	879.57	0.61	2	0.74
Model 4								
+ Age * Group	8	887.72	916.02	-435.86	871.72	8.46	4	0.08+
Model 5								
+ Sex	5	890.12	907.81	-440.06	880.12	0.06	1	0.81
Models	parameters	AIC	BIC	LogLik	deviance	X²	X²df	p
<i>Infant positive affect</i>								

Null	3	992.14	1002.71	-493.07	986.14	-	-	-
Model 1								
+ Age	4	970.74	984.83	-481.37	962.74	23.40	1	<0.001***
Model 2								
+ Group	6	968.89	990.02	-478.44	956.89	5.86	2	0.05+
Model 4								
+ Age * Group	8	967.33	995.50	-475.66	951.33	11.42	4	0.02*
Model 5								
+ Sex	9	967.11	998.80	-474.56	949.11	2.22	1	0.14
Models	parameters	AIC	BIC	LogLik	deviance	X²	X²df	p
<i>Infant negative affect</i>								
Null	3	951.78	962.34	-472.89	945.78	-	-	-
Model 1								
+ Age	4	953.71	967.79	-472.85	945.71	0.07	1	0.79
Model 2								
+ Group	5	951.35	968.96	-470.68	941.35	4.42	2	0.11
Model 4								
+ Age * Group	8	955.66	983.84	-469.83	939.66	6.11	5	0.30
Model 5								
+ Sex	4	953.72	967.8	-472.86	945.72	0.06	1	0.81
Models	parameters	AIC	BIC	LogLik	deviance	X²	X²df	p
<i>Dyadic mutuality</i>								
Null	3	825.96	836.57	-409.98	819.96	-	-	-

Model 1								
+ Age	4	813.50	827.65	-402.75	805.50	14.46	1	<0.001***
Model 2								
+ Group	6	800.83	822.05	-394.41	788.83	16.67	2	<0.001***
Model 4								
+ Age * Group	8	800.03	828.32	-392.01	784.03	4.80	2	0.09 ⁺
Model 5								
+ Sex	7	802.44	827.2	-394.22	788.44	0.39	1	0.53
Models	parameters	AIC	BIC	LogLik	deviance	X ²	X ² df	p
<i>Dyadic engagement intensity</i>								
Null	3	797.51	808.13	-395.76	791.51	-	-	-
Model 1								
+ Age	4	776.78	790.93	-384.39	768.78	22.74	1	<0.001***
Model 2								
+ Group	6	778.91	800.13	-383.45	766.91	1.87	2	0.39
Model 4								
+ Age * Group	8	778.23	806.53	-381.12	762.23	6.55	4	0.16
Model 5								
+ Sex	5	777.36	795.04	-383.68	767.36	1.42	1	0.23

Note. ‘*’ indicates reciprocal interactions including the lower order terms.

AIC: Akaike Information Criteria; BIC: Bayesian Information Criteria; LogLik: Logarithmic Likelihood X²: Chi-square statistic;

Group: ASD likelihood group (EL-ASD, EL-no ASD, TL).

Table A3.8*Sibling Group Means on the PII Items at 8 and 14 Months*

	8 months $N = 124$			14 months $N = 130$		
	Sibling group mean (SD)					
<i>Parent scales</i>	TL	EL-no ASD	EL-ASD	TL	EL-no ASD	EL-ASD
Sensitive						
responsiveness	4.21 (1.41)	3.83 (1.15)	3.38 (1.26)	5.12 (0.82)	4.40 (1.17)	3.93 (1.10)
<i>n</i>	24	84	16	26	89	15
Nondirectiveness	4.46 (0.88)	3.87 (1.25)	3.06 (1.24)	4.88 (0.99)	4.01 (1.17)	3.60 (0.82)
<i>n</i>	24	84	16	26	89	15
<i>Infant scales</i>						
Attentiveness	3.96 (1.12)	4.06 (1.23)	4.31 (1.25)	5.04 (1.04)	4.55 (1.12)	3.93 (0.80)
<i>n</i>	24	84	16	26	89	15
Liveliness	4.58 (1.74)	4.48 (1.53)	3.75 (1.39)	6.12 (1.03)	5.80 (5.80)	6.27 (1.03)
<i>n</i>	24	84	16	26	89	15
Positive affect	3.29 (1.30)	3.40 (1.57)	4.81 (1.83)	4.38 (1.65)	4.74 (1.68)	4.50 (1.95)
<i>n</i>	24	84	16	26	86	14
Negative affect	2.37 (1.56)	2.33 (1.61)	3.25 (1.84)	2.27 (1.25)	2.60 (1.67)	2.93 (1.59)
<i>n</i>	24	84	16	26	86	14
<i>Dyadic scales</i>						
Mutuality	3.92 (1.32)	3.45 (1.13)	3.31 (1.25)	4.88 (0.82)	3.84 (1.24)	3.27 (0.96)
<i>n</i>	24	84	16	26	89	15
Engagement intensity	4.04 (0.81)	3.88 (1.18)	4.63 (1.26)	4.85 (0.78)	4.66 (1.11)	4.40 (1.24)
<i>n</i>	24	84	16	26	89	15

Abbreviations. ASD: Autism Spectrum Disorder; EL: Elevated likelihood; TL: Typical likelihood.

Chapter 4. Parent-Infant Interaction Changes Predict Developmental Outcomes in Infants With and Without an Elevated Likelihood for ASD: A Latent Change Score Modelling Approach

4.1 Introduction

The crucial role that parent-child interactions play in the child's development is widely recognised. Empirical evidence demonstrates that the quality of interaction between infants and their parents influences the child's development in a range of areas, such as adaptive behaviour, social communication, language, cognitive and motor development (NICHD Early Child Care Research Network, 1999; Rocha et al., 2019 for a review). These studies support theoretical propositions for the importance of reciprocal parent-child interactions on children's development (Sameroff, 2009). They are further strengthened by research highlighting that early infant social experiences with caregivers are associated with infant brain function and structure (Ilyka et al., 2021) and that these experiences can also drive resilience in early susceptibility for atypical development, possibly altering developmental trajectories (Elsabbagh, 2020; Fenning & Baker, 2012).

Difficulties in social communication and interaction represent core features of ASD (R. J. Landa et al., 2007; Szatmari et al., 2016). Early precursors of ASD tap into these characteristics in infants at EL, who seem to differ from TL infants in attention, language and communication (Johnson, Gliga, et al., 2015; E. J. H. Jones et al., 2014). Other behaviours involve emerging difficulties in adaptive functioning in those with a later ASD diagnosis (Bussu et al., 2019; R. J. Landa et al., 2012), such as internalising and externalising behaviours (Ding et al., 2021). Infants with a later ASD diagnosis show a deterioration in their language and adaptive skills over time (Bussu et al., 2019; Lord, Luyster, et al., 2012; Visser et al., 2017) and trajectories of persistent ASD symptoms seem to co-occur with ADHD traits in some children (Visser et al., 2017). As already

discussed in previous chapters, emerging delays in infant social communication development may alter the interactional quality with their parents, further affecting infant brain networks related to social behaviour, and thus, increasing pre-existing susceptibility to atypical development. On the other hand, an ameliorated interactional environment may contribute towards better developmental outcomes, as shown in parent-targeted intervention studies with infants at EL as well as those with an existing ASD condition (Drew et al., 2002; Green, Charman, Pickles, Wan, Elsabbagh, Slonims, Taylor, McNally, et al., 2015). Thus, tracking patterns of early developmental change in PII quality in relation to different developmental dimensions may allow us to gain a clearer understanding of how interactional qualities drive variability in language, social communication and adaptive behaviour.

The previous chapter replicated already existing evidence for PII differences between infants with and without an EL for ASD, with PII from as early as 8 months predicting ASD outcome, thus, highlighting the predictive validity of the quality of parent-infant social interactions in ASD outcome. However, in addition to ASD prediction, it is essential to examine the interactive processes related to different ASD-related dimensions. Nevertheless, there is limited research investigating the relationship between PII aspects and emerging behavioural symptoms other than ASD outcome in infants at EL for ASD. Even more limited is the investigation of how early changes in interactional patterns relate to developmental dimensions. Further, several existing studies that have examined PII in relation to dimensional outcome have used microanalytic coding schemes (Northrup & Iverson, 2015; Salo et al., 2018; Talbott & Tager-Flusberg, 2015), though a global rating PII measure might be more sensitive in assessing behaviour during play (Morawska et al., 2015).

This study aimed to add to the existing literature by investigating how developmental change in global PII characteristics that differentiated infants with and

without an EL for ASD in the previous study related to dimensional outcomes in an expanded cohort including EL and TL infants. Firstly, examining PII change by employing flexible analytical approaches (e.g., LCS modelling) can offer an enhanced understanding of how PII unfolds early on and to what degree individual differences in PII change contribute to later development, which can be obscured by looking at single time points. Secondly, if qualitative aspects of PII predict a later ASD diagnosis, it is also likely that they will be related to other sub-clinical ASD traits usually present in first-degree relatives of individuals with ASD (Pisula & Ziegart-Sadowska, 2015). Thirdly, ASD is characterised by substantial heterogeneity in symptomatology and clinical outcome, presenting, in many cases, comorbidity with other developmental conditions, such as ADHD (Rommelse et al., 2010). Research has underscored how the use of non-ASD features, such as language, cognition and ADHD-related symptoms can contribute towards a greater understanding of the developmental trajectories of ASD (Visser et al., 2017).

Investigating early PII change in relation to different dimensions can provide a much clearer view of the possible factors contributing specifically to ASD, the BAP, and those that are shared (or not) with other conditions, such as ADHD. It can also provide significant insights into how developmental changes in PII contribute to infant developmental trajectories. Understanding these is not only important for identifying the developmental pathways to ASD traits, but also for informing parent-targeted interventions already underway. It is also important for supporting developmental populations who may not develop ASD but may exhibit delays in several other domains of functioning, such as social responsiveness, receptive/expressive language or internalising/externalising behaviours (M. Miller et al., 2015).

The following sections provide a brief overview of the existing research around PII (with a focus on the PII aspects that differentiated EL from TL infants in the previous chapter)

in relation to infant socio-cognitive outcomes in both ASD and neurotypical development.

4.1.1 PII in Relation to Neurotypical Development

4.1.1.1 Social-Communication and Language. In neurotypical development, both the parent and infant, as well as dyadic aspects of interaction have been shown to be important contributors to children's developmental trajectories. In particular, from the infant perspective, joint attention ability and temperament, which can influence the input infants receive or the way they respond to their environment, have been shown to be predictive of later socio-cognitive outcomes (Carpenter et al., 1998; M. Morales et al., 2000; Mundy & Gomes, 1998; Van Hecke et al., 2007). For instance, Morales et al. (2000) examining gaze following, temperament and language acquisition in infants at 6 and 12 months revealed that individual differences in attention engagement were related to language development, and that attention duration and positive affectivity were correlated with receptive language. However, no association between duration of orienting and language development has been observed in other research (Pérez-Pereira et al., 2016). In addition, 12-month responding and 18-month initiating shared attention was linked to 24-month infant language ability, even after controlling for cognition (Mundy et al., 2007). Further, 4-month infant positivity during interactions was a significant predictor of verbal IQ in early childhood (Sheinkopf et al., 2017), while parent-reported positive affect in infants at 10 months was related to expressive language in those infants at 14 months (Laake & Bridgett, 2014). This association appears to run both ways, as 13-month-olds with higher language production ability have been shown to display higher positive emotional expression at 15 months (Kubicek & Emde, 2012). Overall, this literature highlights that greater infant joint attention and positive affect may

create more opportunities for social interactions which can facilitate subsequent language and social development.

Furthermore, several studies investigating parental behaviours reveal a positive association between parental sensitivity or responsiveness and infant social and cognitive development (Rocha et al., 2019 for a review). A study using a prospective longitudinal design examined aspects of maternal responsiveness through parent-infant play at 9 and 13 months and their relationship to parent-reported infant language milestone achievement from 9 to 21 months (Tamis-LeMonda et al., 2001). Findings showed that maternal responsiveness predicted infant expressive language milestones at both time points, and that particular responses were linked to particular language milestones at specific time points, suggestive of a parent adaptive response to infant developmental level. Similarly, another study found that maternal attunement to infant emotional expressions at 9 months was predictive of infant language milestones in the first and second year (Nicely et al., 1999). Other research has found positive correlations between maternal sensitivity and infant development of social ability towards the end of the first year (Soares et al., 2018) and that, not the frequency, but the types of parental contingent responses (i.e. mirroring and positive marking), predicted infant development of social expressions (Murray et al., 2016).

Dyadic processes in PII have also been shown to be significant for infant socialisation and cognition (Provenzi et al., 2018). For instance, evidence shows that dyads that were highly synchronous during interactions at 18 months exhibited greater language and communication skills at 36 months (E. W. Lindsey et al., 2009), while maternal attunement of infant affect at 9 months was linked to second-year verbal IQ in the child (R. Feldman & Greenbaum, 1997).

4.1.1.2 Emotional and Behavioural Difficulties. Parent-infant interactions have also been considered to play an important part in children's internalising and externalising behaviours. Internalising behaviours are related to withdrawal, such as anxiety, somatisation or depression (Achenbach, 1966; Achenbach & Edelbrock, 1978), while externalising behaviours are externally-directed behaviours related to aggression or hyperactivity (Achenbach, 1991). Child joint attention and affect have been shown to be significant contributors to these behaviours (Eisenberg et al., 2009; Moore et al., 2001; S. Morales et al., 2022; Mundy & Sigman, 2015; Van Hecke et al., 2007). Previous work indicated that 12-month-old infants who initiated more often or consistently responded to episodes of joint attention during interactions with an adult had lower externalising scores at 30 months of age (Van Hecke et al., 2007). In addition, infants who displayed more positive affect at 6 months during a still-face interaction were considered by their caregivers as having lower externalising behaviours at 18 months, while those with an absence of negative affect had lower internalizing behaviours (Moore et al., 2001).

Furthermore, parent sensitive responsiveness has been suggested to limit the likelihood of children developing internalising or externalising problems (Bradley & Corwyn, 2007; Kok et al., 2013), while supportive parenting has also been linked to lower behavioural problems later in adolescence (Parker & Benson, 2004). On the other hand, higher parent directiveness or negativity appears to increase the possibility of children developing internalising or externalising problems (Graziano et al., 2010; Morris et al., 2002; Rubin et al., 2003), though there is some research showing a negative correlation between parent intrusiveness and children internalising problems (Steenhoff et al., 2021). This finding was interpreted as a possible adaptive child response to parent intrusiveness rather than having a negative effect, increasing internalising behaviour.

In addition, research concerning the synchrony or mutuality in interactions consistently highlights that this aspect of PII also contributes towards better self-control

and fewer behavioural problems (R. Feldman et al., 1999; Harrist & Waugh, 2002; Im-Bolter et al., 2015; E. W. Lindsey et al., 2009; Scholtes et al., 2021). For example, dyadic reciprocity and shared positive affect in 18-month-old infants have been considered to be important in the prediction of self-control at 36 months (E. W. Lindsey et al., 2009), an aspect related to the development of externalising behaviours (Calkins & Perry, 2016; Gerstein et al., 2011). Further, longitudinal research on synchrony at the neural level has shown that stronger dyadic neural synchronisation predicts lower internalising behaviour problems during the preschool years (Quiñones-Camacho et al., 2022).

Taken together, the aforementioned findings provide evidence for the impact of parental, child and dyadic interactional aspects on children's developmental outcomes, suggesting that higher infant attentiveness or positive affect, parent responsiveness and dyadic synchrony during interactions could act as a protective factor, decreasing maladaptive behaviour and facilitating greater social exchanges, enhancing children's language and social abilities later in development.

4.1.2 PII in relation to Dimensional Outcomes in Infants at EL for ASD

Research exploring interactional qualities between parent-infant dyads shows delays in the development of social communication and language skills in infants at EL for ASD, becoming more apparent towards the first year. Some examples include parent-directed smiles, vocalisations, attentiveness or positive affect (Wan et al., 2019, for a review). At the same time, parental and dyadic interactional qualities involve lower parent sensitive responsiveness, dyadic synchrony and mutuality as well as higher parent directiveness in EL compared to TL populations (Srinivasan & Bhat, 2020; M. W. Wan et al., 2012, 2013; Yirmiya et al., 2006). Yet, limited empirical work has examined the aforementioned interactional qualities in infancy and their links to later dimensional outcome in the context of ASD susceptibility.

4.1.2.1 Social Communication and Language. Previous studies examining children's interactional qualities, such as attentiveness and affect in relation to social communication and language dimensions have mostly involved individuals with a formal diagnosis of ASD. This research shows that early joint attention skills or temperament in these individuals are associated with their concurrent or later language or social abilities (Charman et al., 2003; Dawson et al., 2004; Kasari & Sigman, 1997; Schwartz et al., 2009; Siller & Sigman, 2008). For example, Siller and Sigman (2008) demonstrated that autistic children who responded more to joint attention initiations developed language skills at a faster rate than those who exhibited fewer responses. However, research investigating global characteristics of unstructured PII in relation to later social communication outcomes in the context of ASD likelihood has received less attention. A recent study by Del Rosario et al. (2023) attempted to fill this gap in literature by looking at the relationship between PII characteristics at 6 months using the MACI global rating scheme and developmental outcomes at 12 and 24 months. Results showed that in the TL group, dyadic engagement intensity was linked to higher 12-month expressive language scores and better social functioning at 24 months. In turn, infants at EL were less attentive to their parent, which was linked to higher 24-month autistic symptoms related to communication. The authors suggested that PII differentially affects the developmental outcomes of EL and TL infants, though findings were considered preliminary. Another study employed the still-face paradigm during face-to-face PII in a sample of infants at EL and TL and interestingly found that at 6 months, EL infants who were later diagnosed displayed a normative pattern of face scanning and affect, with face scanning (gaze to the mouth) being associated with higher expressive language and socialisation on the MSEL and VABS at 24 months across groups (Young et al., 2009). It was suggested that gazing

not only at the eyes but also at the mouth of the caregiver could facilitate language development, possibly serving as a protective factor.

Other empirical work has focused on infant vocal characteristics or gesture production during PII. A study investigating EL and TL infant vocal production through lab-based free PII at 6, 9 and 12 months showed that infants at EL produced fewer consonant types, canonical syllables and vocalisations reminiscent of speech compared to infants at TL, with consonant production at 6 months being associated with expressive language at 12 months (Paul et al., 2011b). These differences were not interpreted as a lower developmental level, but rather as slowed progress in vocal development as a result of emerging social atypicality that could reduce EL infants' opportunities to engage in sound exchanges with their caregivers in order to develop their communication and language skills. Further research on gesture production showed that EL-ASD infants produced fewer gestures than those at TL and that infant gesture use at 12 months was related to later language ability (Choi et al., 2019; Talbott et al., 2015).

Regarding parental interactional behaviours, Baker et al. (2010) showed that maternal sensitivity, particularly sensitive structuring at 18 months, was a significant predictor of infant change in expressive language in EL infants with subsequent ASD at 2 to 3 years of age, highlighting the importance of parenting in emergent ASD. Similarly, another study found positive links between caregiver responsiveness (verbal labelling) to infants' points or shows at 13 months and 18-month word production in both EL and TL groups, though these types of gestures were reduced in the former group (Leezenbaum et al., 2014). Of interest was also that caregivers of TL infants increased their responses to their infant non-word vocalisations across time compared to caregivers of EL infants who did not show this pattern, possibly reflecting EL infants' communication and language delays affecting parental input towards the infants. However, other research suggested that caregivers' responses to infant gesture use were similar across EL and TL groups and

did not relate to later infant language ability (Choi et al., 2019). This discrepancy could be due to coding scheme differences between studies in the parental responsiveness scale. More recent research using microanalysis of PII in EL-ASD and TL dyads at 6, 9 and 12 months suggested that, overall, more responsiveness at 12 months was linked to higher receptive and expressive language scores at 3 years of age (Kellerman et al., 2020).

Considering mutual engagement during PII, no relationship has been observed between 5-month synchrony and 14-month language/non-verbal communication in infants at EL and TL (Yirmiya et al., 2006). However, results from a study examining vocal coordination in parent-infant dyads at EL and TL revealed that 9-month infant vocal interruptions during caregivers' speech significantly predicted language delay in toddlerhood (Northrup & Iverson, 2015). More recent research compared synchrony in interactions in children with an ASD diagnosis and neurotypically developing peers, showing that across the whole sample, non-verbal synchrony positively predicted social communication skills, though autistic children had less synchronous interactions compared to neurotypically developing children (Zampella et al., 2020). These studies underscored the importance of investigating bi-directional behaviours in children's social development.

4.1.2.2 Emotional and Behavioural Difficulties. Research investigating infant behavioural characteristics within the context of PII and how they contribute to the prediction of subsequent internalising and externalising behaviours in infants considered to be at EL for ASD has been scarce. Several studies already demonstrate that individuals with ASD as well as those involving infants at EL with or without a later ASD diagnosis show temperament profiles characterised by high negative affectivity, low positive affect and attention control, and these profiles in autistic individuals have been related to internalising and externalising behaviours (Adamek et al., 2011; Chetcuti et al., 2021;

Clifford et al., 2013; Garon et al., 2009; Pijl et al., 2019). In addition, it is thought that social function difficulties, such as difficulties interpreting social cues or understanding social expectations are factors contributing to internalising and externalising behaviours (Klin & Volkmar, 2000; Volker et al., 2010).

As discussed in the previous chapter, infant affect and attentiveness during social interactions with parents differ between EL and TL infants and have been shown to be significant predictors of ASD outcome. Since behavioural or mental health issues tend to be maintained over developmental time (Bosquet & Egeland, 2006; Campbell et al., 2006), it is fundamental to detect the factors contributing to variability in mental health outcomes early on, and investigations of early caregiver-infant interactions could play an important part in identifying these, considering transactional model of development. Although limited, one study examined lab-based free play interactions and relations to subsequent internalising and externalising behaviours in EL and TL infants, showing that EL-ASD infants had higher scores on internalising and externalising behaviours than TL infants, while child negative engagement (i.e. crying, distressed vocalisations, anger, etc.) was related to greater externalising problems (Ding et al., 2021). A more recent study found that different temperament dimensions at 6, 12 and 18 months in infants at EL for ASD predicted internalising and externalising problems at the age of 5, though this study was based on parent-reports (Sacrey et al., 2022).

The aspect of mutuality in PII in infants at EL for ASD and its relation to internalising and externalising behaviours also remains largely unexplored. Nonetheless, some research evidence comes from studies of autistic children or other risk populations. For instance, a study examining interpersonal behaviours in 3- to 6-year-old children with ASD and their caregivers found that their internalising behaviours were negatively associated with complementary child dominance (complementarity refers to dominant behaviours followed by compliant responses), while there was no evidence for

associations between dyadic flexibility (mutual adaptive behaviours) and internalising or externalising problems (Rozenblatt-Perkal & Zaidman-Zait, 2020). In another study on co-regulation of emotions during PII, it was shown that an increase in dyadic flexibility (measured through engagement state dispersion and duration) and positive mutual engagement contributed to less internalising and externalising behaviours in children with ASD, underscoring the possible protective effects of these interactive processes on children's behaviour (Valentovich et al., 2018). In addition, other research observed lower dyadic synchrony in clinic-refereed non-autistic children between 6 and 10 years who exhibited higher internalising and externalising behaviours compared to a non-clinic referred group (Im-Bolter et al., 2015).

Notwithstanding the gap in literature in the context of PII in ASD likelihood, some research has focused on parent interactional behaviour as a predictor of later internalising and externalising problems in infants at EL. For instance, through PII in 8-30-month-old EL and TL infants, Ding et al. (2021) found that parent negative engagement (expressed through angry, hostile, irritable, negative vocalizations) was associated with both internalising and externalising behaviours in the child and significantly predicted higher scores on the former. Another study surprisingly indicated that higher maternal sensitivity was associated with higher problematic behaviours in 18-month-old EL infants with a subsequent ASD diagnosis, while the opposite association was observed for infants with no emergent ASD (Baker et al., 2010). One likely explanation for this finding was that greater parents' efforts to engage their infants in interactions may negatively affect infant behaviours temporarily, but may have a positive effect over time, though, a longitudinal design would be needed to confirm this. In addition, while evaluating synchrony in PII between EL and TL infants at 12 months, Steiner et al. (2018) revealed that parent non-synchronous, demanding behaviours were higher in EL than TL siblings and were linked to infant negative emotionality irrespective of ASD outcome. Other

research involving children with ASD using parent reports revealed that supportive and disengaged parenting was related to fewer internalising and higher externalising behaviours, respectively (McRae et al., 2018). Similarly, positive parenting was associated with fewer behavioural problems and vice versa in autistic children with a decreased severity of ASD symptoms (Lindsey et al., 2020).

Overall, although previous studies provide essential insights into how aspects of PII relate to different developmental outcomes, more research is needed to better understand these relationships. Much of the aforementioned literature appears to be largely dominated by cross-sectional data (looking at scores at different time points) or has looked at PII domains in relation to changes in a developmental dimension. Although informative, it restricts our understanding of the temporal dynamics of PII and its links to child development, while research looking at global PII aspects and dimensional outcome relationships in EL and TL infants is limited. Nevertheless, the above findings highlight that investigating early PII change in the context of ASD likelihood in relation to later infant behaviour represents a promising area to further our knowledge of the development of the condition, the role the early social environment plays in later child behaviour and how we can best deliver early parent-targeted interventions to optimise mental health, regardless of diagnostic classification.

4.1.3 Aims of the Study

Investigating developmental change in early PII is fruitful, as it can capture the developmental dynamics of PII quality over a time period characterised by substantial changes in infant socio-cognitive development alongside changes in patterns of parent-infant social interactions. Cross-sectional aggregation of data may obscure this picture, as this approach cannot distinguish developmental changes, it can be affected by cohort effects (e.g., different populations) and cannot evaluate individual differences in change

(Kievit et al., 2018). Furthermore, modelling PII change in relation to different developmental dimensions is important, considering the substantial variability in developmental outcomes, extending across different domains and the importance of early PII in children's developmental trajectories.

Based on the above, the current study aimed to investigate PII changes from 8 to 14 months and their contribution to social communication and maladaptive behaviour dimensions at 3 years of age in a prospective cohort of EL and TL infants. Using a LCS modelling approach including a larger prospective cohort of infants, the study aimed to extend the previous chapter's findings to investigate changes across 8 and 14 months in interactional domains that differentiated EL and TL infants (parent sensitive responsiveness and nondirectiveness, infant attentiveness and positive affect, dyadic mutuality), and sought to identify whether these predicted different socio-cognitive outcomes (ASD traits, adaptive behaviour and language skills) at 36 months. Of note, although no group differences were found on positive affect after correction for multiple comparisons in the previous chapter, given that it showed an effect and significantly predicted diagnostic outcome as well as taking into account literature underscoring the contribution of temperament in dimensional outcome prediction, it was included in the study.

Firstly, considering the findings from the previous chapter, an average increase was expected in all PII ratings from 8 to 14 months. However, it was also likely that a relative stability in average change would be seen for the parent and dyadic scales, given that this is a larger sample size and based on research showing that parent behaviour tends to remain stable over time, whereas infant interactive behaviour changes with development (Bigelow et al., 2010; M. W. Wan et al., 2017b). Secondly, PII change between 8 and 14 months would differ between TL and EL infants only in attentiveness, as the previous study identified group-by-time interactions only for this scale. Thirdly, it

was hypothesised that PII change would predict all the dimensional outcomes of interest, based on literature underscoring the importance of PII for children's developmental outcomes. It was also expected that the TL group would exhibit higher scores on social communication and language and lower on maladaptive behaviour compared to the EL group.

4.2 Methods

4.2.1 Participants

Ethical approval was made available from the UK National Health Service National Research Ethics Service London (REC reference numbers: 06/MRE02/73, 08/H0718/76). Informed consent was given by one or both parents to participate in the study. Details of the process of verification of ASD likelihood status in the older sibling are described in the previous chapter (**section 3.2.1.1**) for Phase 2 and are the same for Phase 1. To briefly recapitulate, the DAWBA and the SCQ measures were used by expert clinicians for proband ASD diagnosis confirmation. For Phase 1, most of the older siblings (hereafter, probands) of EL infants met criteria for ASD ($n = 44$) in the DAWBA and the SCQ. A small number of probands ($n = 4$) scored below instrument cut-off on the SCQ but were included after meeting threshold on the DAWBA and expert judgement. Two probands had available data for only 1 of the 2 assessment measures. Only parent-confirmed local clinical ASD diagnosis was available for 4 probands. No exclusions were made after the examination of parent-reported medical history for significant medical conditions in probands and family members of EL infants. Regarding the TL infants, results from the SCQ indicated that none of the older siblings scored above instrument cut-off for ASD (>15).

The participants included in this study comprised two independent samples that were recruited from the BASIS network in two phases ($N = 247$). In particular, Phase 1 consisted of 54 infants at EL (21 male) and 50 infants at TL (21 male), and Phase 2 of 116 infants at EL (64 male) and 27 infants at TL (14 male). Across phases, 239 children took part in the 36-month visit. Four EL children were absent from the 36-month visit and therefore were excluded from the analyses. Four TL controls dropped out but were included based on assessments in previous visits. At 8 months, 216 infants provided PII data (no clip or technical issues: $n = 21$; tapes not digitised: $n = 6$) while at 14 months, 221 data were available (no clip or technical issues: $n = 22$). No data exclusions were made, as missing data were handled within the chosen analytical method (see the results section). The remaining sample comprised 243 infants (EL = 166; TL = 77).

4.2.2 Measures

4.2.2.1 PII Measure. The MACI (version 1 for Phase 1 data and version 2.2 for Phase 2 data) global rating scheme was used to evaluate aspects of interaction between the primary caregiver and the infant (M. W. Wan et al., 2017b). **Chapter 2** describes the MACI scheme in detail. Of the 8 7-point scales, the scales that were used for the current study were: Parent sensitive responsiveness, parent nondirectiveness, infant attentiveness, infant affect and dyadic mutuality. These domains were selected as they differentiated EL from TL infants in the previous chapter and have been shown to play an important role in children's development. In order to examine 'infant affect' in the combined Phase 1 and 2 sample, some adjustments were necessary, since the 'affect' scale differed between phases due to different MACI versions used (details below). Regarding the procedure, unstructured laboratory-based PII evaluation took place at 8 and 14 months. The parent and infant sat on a play mat with a small selection of toys and the parent was instructed

to play with their infant as they would normally do at home. Coding of the video clips was undertaken blind to all participant information.

4.2.2.1.1 Inter-Rater Reliability. Independent rating of a portion of the PII video clips blind to all participant information was undertaken at 8 and 14 months. Single measures intraclass correlation (two-way mixed effects model using an absolute agreement definition) was used. When necessary, both raters re-reviewed the video clips in areas that were disagreements until a common agreement in the ratings was reached. Agreement was reasonable to high, ranging from $r = 0.58$ to $r = 0.88$ ($p < .001$; refer to **Table A4.1** in the Appendix for further details).

4.2.2.2 Assessment Measures. Measures of assessment of developmental level, adaptive functioning, early ASD signs, severity of ASD and 36-month ASD outcome echo those described in **Chapter 3** for the Phase 2 sample. A brief description of these measures is provided below.

4.2.2.2.1 Receptive and Expressive Language. The MSEL standardised measure (Mullen, 1995) was used at each visit to evaluate infant cognitive functioning in five key domains: Gross and fine motor, visual reception, and receptive and expressive language (Mean = 50, $SD = 10$). Of these domains, T-scores (converted from raw scores) of the expressive and receptive language variables were used for the univariate and bivariate analyses at 8, 14 and 36-month assessments. In particular, the expressive language scale consists of 28 items and evaluates the ability to use language productively, specifically, speaking, language formation and verbal conceptualization. The receptive language scale includes 33 items and assesses the processing of linguistic input, focusing on auditory comprehension, auditory memory and auditory sequencing skills. To decrease the number

of variables in the model, both the expressive and receptive scales were averaged, producing a single variable named ‘language’ to include in the analyses. A higher score in the language domain would indicate greater language ability.

4.2.2.2.2 Adaptive Functioning. The VABS-II, a semi-structured parent-report measure (questionnaire at 8 and 14 months and parent semi-structured interview at 36 months) of adaptive behaviour was used, which evaluates everyday personal and social abilities in four main domains, such as communication, daily living skills, socialisation and motor skills, as well as a maladaptive behaviour index (optional). Each of these domains consists of sub-domains. For this study, standard scores from the internalising and externalising behaviour sub-domains of the maladaptive behaviour index were used as 36-month outcome variables in the univariate LSC models examining PII latent change and prediction of dimensional outcomes.

In addition, from the main domains, the socialisation and communication domains were used for this study. The communication domain measures receptive, expressive and written communication abilities, while the socialisation domain evaluates play, leisure time, interpersonal relationships and coping skills. Standard scores from the socialisation and communication domains were averaged into a single variable named ‘social communication’. The ‘social communication’ variable was included in the LCS models as outcome variable based on the 36-month assessment. It was also used to examine concurrent associations with the PII variables and cross-domain couplings based on the 8- and 14-month assessments.

4.2.2.2.3 Early ASD Signs. The AOSI, a 19-item semi-structured observational measure of early ASD symptoms was administered at 8 and 14 months.

4.2.2.2.4 ASD Severity. The SRS-2 65-item questionnaire (pre-school form) completed by parents at 36 months was used to assess ASD likelihood and severity of ASD symptoms in the social domain (Constantino & Gruber, 2012). Each item includes ratings from 1 (not true) to 4 (almost always true) and the instrument takes 15-20 minutes to complete. It comprises 5 treatment sub-scales corresponding to 2 DSM-5 compatible domains: Social Communication and Interaction and Restricted Interests and Repetitive Behaviour. Each sub-scale produces raw scores that are converted into T-scores based on age and sex. The scores of all items are summed up to produce a Total score (max 195). Higher scores indicate higher ASD symptomatology. In addition, the SCQ parent-report screening instrument was used to evaluate putative ASD symptoms (Rutter, Bailey, et al., 2003). The SCQ consists of 40 yes or no items. It is based on the ADI-R and contains two forms, the Current and Lifetime forms. The instrument yields a Total score for the evaluation of the degree of ASD, with higher scores representing more social communication deficit. In this study, Total scores from the SRS and the SCQ were used in the univariate models examining PII latent change and prediction of ASD traits at 36 months.

4.2.2.2.5 Assessment of ASD Outcome at 36 Months. Details of the assessment procedure are provided in section 4.6.1. Of the 166 EL infants participated in both phases, 34 (20%) met criteria for ASD diagnosis (EL-ASD) based on ICD-10 criteria (Phase 1) and DSM-5 (Phase 2), 88 (53%) were identified as typically developing (EL-TD) and 44 (27%) were classified as having other developmental concerns (EL-Aty), scoring above the ASD threshold on the ADOS-G and ADI-R as well as scoring below -1.5 standard deviations on the MSEL ELC score.

4.2.3 Analyses

4.2.3.1 Latent Change Score Modelling. Latent Change Score models (McArdle & Hamagami, 2001; McArdle & Nesselroade, 1994) were used to analyse latent change within the PII aspects of interest from 8 to 14 months and dimensional outcome prediction in childhood. Latent Change Score models were also used to test the interdependent relationships and influences between the PII variables and the developmental measures of interest at 8 to 14 months (see later sections). Latent change Score Models are a category of Structural Equation Models that can model dynamic developmental processes as well as longitudinal bidirectional influences between two constructs. This technique was chosen because it offered robustness and flexibility to test the hypotheses of interest. First, LSC models allowed the modelling of change and cross-domain couplings with only 2 time points. Second, they enabled the investigation of time-dependent change in PII and developmental measures, and PII in relation to socio-cognitive outcomes, including different independent and outcome variables, where possible. Third, compared to more traditional methods, LCS models allowed the possibility to use different indicator variables represented by a latent factor, thus, removing measurement error (Kievit et al., 2018). Fourth, LCS models could deal with the violation of the normality assumption and could accommodate missing data without excluding participants with any incomplete cases, increasing statistical power and reducing bias (Kievit et al., 2018).

Model fit was assessed through the use of absolute goodness of fit indices, such as the Chi-square (χ^2) statistic, the comparative fit index (CFI), the root mean square error of approximation (RMSEA), and the standardized root mean square residual (SRMR). The use of cut-off criteria to assess model fit is under controversy (Marsh et al., 2004), though some general rules of thumb exist and the following values were used to indicate acceptable fit: Chi-square p-value > 0.05, CFI > 0.95 or > 0.90 (for acceptable fit),

RMSEA < 0.06 or < 0.07 (or less conservatively, < 0.08) and SRMR < 0.08 (Hu & Bentler, 1999; Schermelleh-Engel et al., 2003; Steiger, 2007). The analyses were conducted in R (version 4.2.2) using the lavaan package (Rosseel, 2012).

4.2.3.2 Adjustments of the ‘Positive Affect’ Scale for Inclusion in the LCS

Model. As mentioned above, the secondary analysis used a combined sample of infants from Phase 1 and 2. Phase 1 PII data were coded using an older version of the MACI while Phase 2 data were coded using an updated version which included an additional ‘infant negative affect’ scale. This scale was previously incorporated into a single infant ‘positive affect’ scale in the older MACI version. In order to be able to use the combined sample to explore trajectories of positive affect and prediction of dimensional outcomes using an LCS model, the following procedure was employed: 1) a sub-sample ($N = 53$) of infants from the BASIS that had been coded using both the old and new version of the MACI was used, in which negative affect was reverse-scored and was then averaged with positive affect (updated MACI scales), which provided an overall mean of positive and negative affect; 2) linear regression was performed with ‘mean positive and negative affect’ as the predictor variable and ‘affect’ (the old MACI scale) as the dependent variable. Data were screened for linearity, homoscedasticity and normality. A visual inspection of these assumptions with histograms, P-P plots and scatterplots indicated that the assumption of linearity and homoscedasticity was met. Data of the ‘affect’ variable were non-normally distributed, therefore, linear regression with bootstrapped confidence intervals was performed. A high positive association between these variables would justify using the mean positive and negative affect variable from Phase 2 and combining it with ‘affect’ from Phase 1, creating a single variable across phases.

The above procedure was performed because further coding of Phase 1 data to separate affect into positive and negative was not possible due to time constraints. In

addition, using a large sample for running an LCS model can increase statistical power and lead to more robust inferences (Kievit et al., 2018). Therefore, combining phase 1 and 2 data for positive affect was highly beneficial.

4.2.3.3 Main analysis: Examining PII Change and Prediction of 36-Month Socio-Cognitive Outcomes. The first analysis involved the use of a series of univariate LCS models modelling change in the PII variables between 8 and 14 months (EL and TL sample combined) in which an effect by ASD likelihood status was found in the previous chapter (parent sensitive responsiveness, parent nondirectiveness, infant attentiveness, infant positive affect and dyadic mutuality), and how latent change in these interactional aspects predicted socio-cognitive outcomes at 3 years: social communication as well as internalising and externalising behaviours through the VABS scales, ASD traits through the SRS and the SCQ and language ability through the MSEL.

As a first step, a visual inspection of the outcome variables with histograms, Q-Q plots and Shapiro-Wilk tests (**Table A4.2**) was performed, showing that some of these data were non-normally distributed. Visual inspection of the PII data showed that they approximated a normal distribution, but Shapiro-Wilk tests indicated non-normality. However, variable transformation was not performed for the following reasons: 1) transforming the data would have implications for the interpretation of the results, 2) it can be problematic, as the transformed data cannot mimic the original data and transformation may not necessarily lead to a more normal distribution (Feng et al., 2014; Grayson, 2004). Instead, where necessary, Maximum Likelihood estimation with robust standard errors was performed. Next, Pearson correlation coefficients³ were conducted

³ Given that the purpose of the correlations was only to identify and create latent factors and did not constitute the main analysis, correction for multiple correlations was not performed.

between the PII variables to examine their associations for the possibility to create a PII latent factor for inclusion in the LCS model. This led to the creation of a latent construct named “Parent and Dyadic Interaction (PDI)” with parent sensitive responsiveness, parent nondirectiveness and dyadic mutuality as indicators representing this latent factor due to high intercorrelations between them (**section 4.3.4**). Infant attentiveness and affect were not constrained to load into a latent factor due to their low intercorrelations (**section 4.3.4**). Therefore, three LCS models were performed, each with the following PII variables:

1. A multiple indicator LCS model with parent sensitive responsiveness, parent nondirectiveness and dyadic mutuality items regressed on a latent factor, namely ‘PDI’ (after ensuring measurement invariance over time; details in following sections).
2. A univariate LCS model with infant attentiveness as a single indicator variable.
3. A univariate LCS model with infant affect as a single indicator variable.

To investigate whether biological sex needed to be included in the models as a possible confound, t-tests were conducted to examine differences between each of the variables of the LCS models and sex. Due to limited differences, sex effects were not investigated further. In addition, ASD likelihood group (TL-EL) was included as a predictor of PII latent change and all dimensional outcomes, since it was expected for sibling groups to explain some variability in PII change and 3-year outcomes. In the PDI LCS model, the loading of the first indicator was fixed to one for identification purposes. Residual covariance of the error terms for each indicator with itself was allowed across

the two time points (Kievit et al., 2018). With the above three models, it was possible to examine mean PII changes from 8 to 14 months, individual variability in change, PII change proportional to PII scores at 8 months, and whether PII change predicted 36-month dimensional outcomes. In all the models, the autoregressive parameter between PII at 8 and 14 months was fixed to unity, implying that the age intervals were equidistant across individuals (Kievit et al., 2018). More details on this are provided in the appendix in the section “**4.6.2 Examination of Age Intervals in the LCS Models**”. Phase was not included as a covariate, as controlling for differences in age (**section 4.6.2**) also accounted for the different phases of participant recruitment. A portion of the participants ($n = 28$) had received parent-targeted intervention at 14 months, though ‘intervention’ was not controlled for in the current analysis. This is because it constituted a much smaller proportion of the sample here compared to the replication study (**Chapter 3**) and because in the PII replication study, the associations between PII and ‘intervention’ were minimal (an association was found only with mutuality). Last, as no correction for multiple comparisons was applied, a more conservative p-value threshold ($p < .01$) was used instead whilst evaluating the significance of the associations.

4.2.3.3.1 Secondary Analysis 1: Examining Bivariate Associations Between PII and Language/Social Communication Dimensions at 8 and 14 Months. Assuming that PII change significantly predicted 3-year dimensional outcomes, supplementary analyses were conducted to examine how the relationship between the particular PII and dimensional outcomes unfolded at prior time points (between 8 and 14 months). Given that only social communication and language dimensions had been measured at 8 and 14 months, bivariate associations could only be examined using these variables. Therefore, two separate bivariate LCS models were performed, where possible, which allowed the examination of whether the rate of change in PII was a function of the starting point in

social communication or language and vice versa (cross-domain couplings). It also allowed testing of the covariances between these domains at baseline as well as correlated change, representing the extent to which PII and social communication or language changes were mutually affected, after considering the coupling pathways (Kievit et al., 2018).

The bivariate models were conducted with and without the inclusion of ASD likelihood group as the predictor and social communication/language dimensions at 36 months as the outcome variables. The models without these variables were retained and presented here to aid with model parsimony, and because their inclusion did not make a difference to the results in the bivariate models (**Figures A4.1 and A4.2** in the appendix). In addition, the same patterns of associations as in the univariate models were found in the paths including these variables.

4.2.3.3.2 Secondary Analysis 2: Testing the Protective Value of PII.

Supplementary analyses were also conducted to examine the possible protective effects of PII trajectories on developmental outcomes. In particular, multi-group analysis was run to investigate whether the results from the univariate analyses were similar or different between three clinical outcome groups (EL-ASD, EL-no ASD, TL). The aim was to explore whether infants at EL who achieved ‘better than expected outcomes’ (Szatmari, 2018), meaning the infants who did not develop ASD despite having some genetic predisposition for it, would show similar patterns of associations between PII change and dimensional outcomes with the TL group with no susceptibility for atypical outcome or the group who received a subsequent ASD diagnosis. If a positive association between PII change and social communication and language, and if a negative association between PII change and ASD traits or maladaptive behaviour at 36 months was observed in this group, this would suggest that the specific PII aspects could possibly serve as

protective factors against genetic/familial susceptibility for ASD diagnosis. Given that no correction for multiple comparisons was undertaken, a more conservative p-value threshold ($p < 0.01$) was used instead whilst evaluating these associations.

An important prerequisite for multi-group analysis in the multiple indicator LCS model was to initially establish measurement invariance in the PDI construct across groups and time.

4.2.3.4 Measurement Invariance Testing. Prior to the main analysis and to secondary analysis 2, measurement invariance analysis was conducted to evaluate whether the factor structure of the ‘PDI’ construct was invariant across time (ages 8 and 14) and group (EL-ASD, EL-no ASD, TL). This is a necessary step to establish that the construct measured has the same attributes under different conditions, which is a prerequisite for drawing scientific inference (Beaujean, 2014). Initially, the fit of a simple confirmatory factor analysis (CFA) model was necessary for each time point and group separately to ensure that the hypothesised model fitted well across time in the whole sample as well as in each group at each time point (Gana & Broc, 2019). However, a three-item CFA model is always saturated (0 degrees of freedom) indicating a perfect fit. Therefore, the fit statistics of the CFA models were not reported, and the focus was to specify a series of models to test for measurement invariance at different levels in a hierarchical manner. In each model, specific parameters were tested to examine whether they were equivalent across time for the whole sample.

For the groups, measurement invariance was tested: 1) across the groups at each time point separately, and 2) over time within each group. The following levels of measurement invariance were tested: a) configural invariance, testing for factor structure equivalence. In this configural model, no equality constraints were placed; b) weak or metric invariance, testing for the equality of the factor loadings by placing equality

constraints on the factor loadings; c) strong or scalar invariance, testing for the equivalence of factor loadings and items' intercepts, placing equality constraints on factor loadings and intercepts. At this level, the latent factor mean of the first time point/group was fixed to zero and was freely estimated in the other time point/groups; d) strict invariance, testing for the equivalence of residual variances, placing equality constraints on factor loadings, intercepts and residual variances. However, achievement of the 'strict' invariance level is not a requisite to imply measurement invariance (Mackinnon et al., 2022; Putnick & Bornstein, 2016).

To test measurement invariance across the time points in the whole sample, residual correlations within the same items between time points were specified, as, considering that the repeated measures were taken on the same individuals, some dependence between the residuals of each PII item was expected over time. In addition, the factor at the first time point was standardized and equality of loadings and intercepts in one of the items (randomly chosen) were assumed in order to set the scale of the latent factors. To test measurement invariance between groups at each time point, the latent factors' scale was set by fixing the factor loading of the first indicator of each latent factor (time 1 and 2) to one, respectively (Beaujean, 2014).

Firstly, measurement invariance was assessed through the use of absolute goodness of fit indices. In addition, alternative fit indices for nested model comparisons were also used: change in comparative fit index (ΔCFI), change in root mean squared error of approximation ($\Delta RMSEA$), change in standardized root mean square residual ($\Delta SRMR$) and Chi-square difference tests ($\Delta \chi^2$), though keeping in mind that chi-square tests are sensitive to sample size and violation of normality and can lead to model rejection even with negligible discrepancies (Bollen, 1989). The cut-off criteria used based on $N \leq 300$ and unequal sample sizes were: $CFI \leq .995$, $RMSEA \geq .010$, $SRMR \geq .025$ for testing

loading invariance, and $CFI \geq .005$, $RMSEA \geq .010$, $SRMR \geq -.005$ for testing intercept or residual invariance (F. F. Chen, 2007).

Inspection of the modification indices and partial invariance would be tested in case the models indicated unacceptable fit, where necessary. Although there is a debate around the use of partial invariance testing (Steinmetz, 2013; Widaman & Reise, 1997), it is generally deemed justifiable (Putnick & Bornstein, 2016).

4.2.3.5 Missing Data Evaluation. Missing data analysis was performed across phase 1 and 2 separately at 8 and 14 months in order to investigate whether data used in this study were missing at random (MAR), completely at random (MCAR), or neither (see section 4.6.3 for details of the procedure).

4.3 Results

4.3.1 Participant Demographic Characteristics

Demographic characteristics for the three infant sibling groups at 8 and 14 months are shown in **Table 4.1** (refer to **Table A4.3** for the demographic and clinical characteristics by clinical outcome group at 36 months). The groups did not differ in age, but differences emerged in biological sex based on clinical outcome, with more males in the EL-ASD group. A significant group effect was found in the MSEL, VABS and AOSI domains at both time points. At 8 months, the TL group differed from the EL-ASD group in MSEL ($p = .003$), with the former having higher scores than the latter. Differences were also evident between the EL-no ASD and EL-ASD groups ($p = .04$). At 14 months, TL had higher MSEL scores than both the EL-no ASD ($p = .004$) and EL-ASD ($p < .001$) groups. Significant differences at 14 months persisted between the EL-no ASD and EL-ASD groups ($p = .002$). In VABS, 8-month differences were found between the TL and

EL-no ASD ($p = .002$) and EL-ASD group ($p < .001$) due to higher scores in the TL group. At 14 months, these differences remained (TL > EL-ASD: $p < .001$; TL > EL no ASD: $p = .02$). In AOSI at 8 months, TL infants had lower scores than both EL-no ASD ($p = .002$) and EL-ASD infants ($p < .001$). A similar pattern was observed at 14 months (TL < EL-no ASD: $p = .003$, TL < EL-ASD, $p = .001$), and EL-no ASD infants had lower AOSI scores than those at EL-ASD ($p = .03$). **Table A4.4** provides the mean scores of the variables used in the study.

Table 4.1

Demographic Characteristics of the Overall Sample as well as by EL Likelihood Group (TL, EL-no ASD, EL-ASD)

	Mean (<i>SD</i>)				<i>F</i> / χ^2	η^2
	Total	TL	EL-no ASD	EL-ASD		
	<i>N</i> = 243	<i>n</i> = 77	<i>n</i> = 132	<i>n</i> = 34		
<i>8 months</i>						
Age (months)	8.12 (1.22)	7.91 (1.34)	8.26 (1.14)	8.06 (1.17)	2.05	0.06
Sex M/F	119/124	35/42	58/74	26/8	12.19**a	0.22 ^b
	104.17	107.25	104.13	97.12		
MSEL ELC ^c	(14.97)	(12.59)	(15.10)	(17.44)	5.48**	0.04
	95.68	100.73	94.16	90.32		
VABS ABC ^c	(13.43)	(12.76)	(12.88)	(13.80)	9.48**	0.08
				10.53		
AOSI Total	8.28 (4.79)	6.47 (3.86)	8.77 (4.75)	(5.57)	10.72**	0.08
<i>14 months</i>						
	14.46	14.35		14.41		
Age (months)	(1.32)	(1.32)	14.54 (1.30)	(1.40)	0.55	0.005
	98.39	104.81	97.62	87.35		
MSEL ELC ^d	(16.03)	(15.26)	(14.86)	(15.67)	15.93**	0.12
	96.70	101.04	96.35	88.55		
VABS ABC ^e	(12.28)	(9.94)	(12.63)	(11.37)	13.08**	0.1
AOSI Total ^{f,g}	5.12 (4.45)	3.49 (3.36)	5.35 (4.46)	7.82 (5.09)	12.55***h	0.1

Note. Hochberg's GT2 test was used where homogeneity of variance was met (noted with superscript if otherwise) but sample sizes were unequal.

^aFisher's exact test was used due to low expected cell count.

^bCramer's V statistic was used as a measure of effect size.

^cTwo missing values in the TL group and three missing values in the EL-no ASD group.

^dThree missing values in the TL group and three missing values in the EL-no ASD group.

^eFive missing values in the TL group, six missing values in the EL-no ASD group and one missing value in the EL-ASD group.

^fTwo missing values in the TL and EL-no ASD group.

^gGames-Howell post-hoc test was used where homogeneity of variance was not met and due to unequal sample sizes.

^hWelch's F ratio is reported because homogeneity of variance was not met.

Abbreviations. AOSI: Autism Observation Scale for Infants; ASD: Autism Spectrum Disorder; EL: Elevated Likelihood; MSEL ELC: Mullen Scales of Early Learning Early Learning Composite; TL: Typical Likelihood; VABS ABC: Vineland Adaptive Behaviour Scales Adaptive Behaviour Composite.

⁺ $p < 0.1$; * $p < 0.05$; ** $p < 0.01$.

4.3.2 Missing Data Analysis

Missing data were considered as MAR. Thus, missing data were handled using Full Information Maximum Likelihood (FIML) (see section 4.6.3 for further details).

4.3.3 Evaluation of Measurement Invariance

4.3.3.1 Longitudinal Measurement Invariance Across the Whole Sample.

Table A4.5 shows the results of the longitudinal measurement invariance for the PDI factor across the whole sample. Initially, running the configural model resulted in a negative variance estimate for the 'sensitive responsiveness' variable. The variance was manually fixed to zero. The models testing for configural, metric, scalar and strict invariance provided a negligible change in fit indices and an acceptable standalone fit

except for RMSEA's standalone fit which was unacceptable for configural and metric invariance (> 0.08). However, since most of the alternative and absolute goodness of fit indices were acceptable and considering that RMSEA can be affected by sample size, the models were not rejected (F. Chen et al., 2008). Therefore, strict measurement invariance was concluded.

4.3.3.2 Multigroup Measurement Invariance. The procedure of multigroup measurement invariance testing is provided in detail in the appendix (section 4.6.4). Overall, measurement invariance (at least partial strong measurement invariance) was not achieved across all the steps of the multigroup measurement invariance testing.

4.3.4 PII Change and Association with 36-Month Dimensional Outcome Prediction

Table 4.2 reports the Pearson correlation coefficients within the PII items of interest at 8 and 14 months. As expected, the PII scales were intercorrelated. Infant affect correlated moderately to weakly with the other PII items. Infant attentiveness was particularly highly correlated with dyadic mutuality at both time points and parent sensitive responsiveness at 14 months and showed a low to moderate correlation with the other PII domains. Dyadic mutuality correlated highly with all the PII variables except for a moderate correlation with 14-month affect. Moderate to strong correlations were consistently observed between parent sensitive responsiveness, parent nondirectiveness and dyadic mutuality across 8 and 14 months, which justified the decision to be considered as indicator variables regressed on the latent "PDI" factor. Given that no strong correlations were observed in infant attentiveness/affect with the other PII domains, these scales were considered separately for analysis.

Table 4.2*Correlations Within the MACI Global Aspects at 8 and 14 Months*

	1	2	3	4	5
	<i>14 months</i>				
1. Sensitive responsiveness		.69**	.63**	.41**	.77**
2. Nondirectiveness	.73**		.45**	.23	.54**
3. Attentiveness	.40**	.19**		.27**	.85**
4. Affect	.34**	0.23**	.45**		.34**
5. Dyadic Mutuality	.78**	.52**	.71**	.50**	
	<i>8 months</i>				

* $p < 0.05$; ** $p < 0.01$.

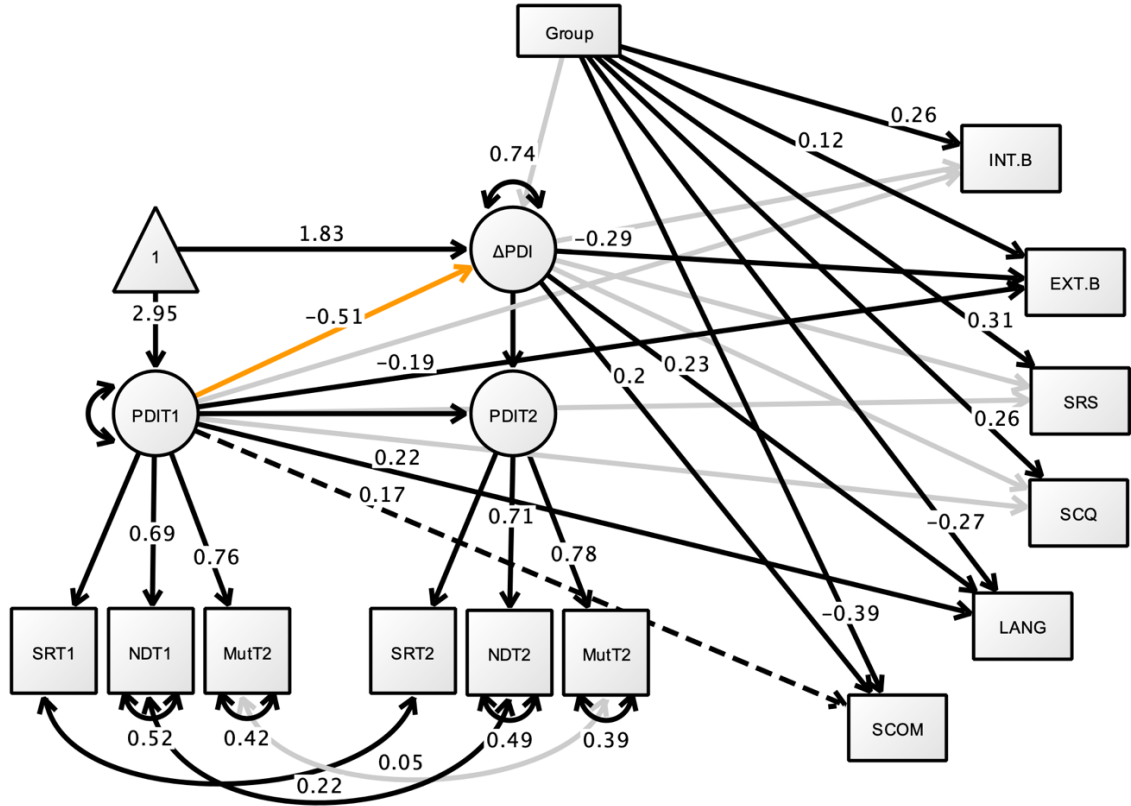
4.3.4.1 Parent-Dyadic Interaction. The parameter estimates of the multiple indicator univariate LCS model of PDI excluding the outcome and control variables are shown in **Table A4.11** of the Appendix. The multiple indicator univariate LCS model of the PDI latent factor predicting dimensional outcomes fitted the data well: $\chi^2(43) = 86.575, p < .001$, CFI = 0.973, RMSEA = 0.069, 90% CI [0.046, 0.091], SRMR = 0.064. Inspection of the key parameters revealed that average scores in PDI significantly increased from 8 to 14 months (Est = 1.91, $SE = 0.31$, $z = 8.95$). There were significant individual differences in the rate of change of PDI from 8 to 14 months (Est = 0.74, $SE = 0.12$, $z = 12.19$). A negative self-feedback parameter (the degree of change proportional to the starting point, orange arrow in **Figure 4.1**) indicated that the rate of change depended on the starting point, suggesting that parent-infant dyads who initially had high scores in PDI showed a decline in PDI over time (Est = -0.51, $SE = 0.06$, $z = -9.10$).

In addition, greater change (increase) in PDI was a significant predictor of lower externalising behaviour (Est = -0.29, $SE = 0.15$, $z = -3.46$), higher language (Est = 0.23, $SE = 0.64$, $z = 3.04$) and social communication scores (Est = 0.20, $SE = 0.59$, $z = 2.89$).

Similarly, higher scores in parent-dyad interaction at 8 months significantly predicted lower externalising behaviour (Est = -0.19, SE = 0.15, $z = -2.49$) and higher language skills (Est = 0.22, SE = 0.69, $z = 3.11$). The ASD likelihood group did not significantly predict PDI change but was a significant predictor of all the dimensional outcome variables at 36 months (Internalising behaviour: Est = 0.26, SE = 0.31, $z = 4.73$; Externalising behaviour: Est = 0.12, SE = 0.33, $z = 2.0$; SRS: Est = 0.31, SE = 2.30, $z = 6.70$; SCQ: Est = 0.26, SE = 0.62, $z = 5.56$; Language: Est = -0.27, SE = 1.38, $z = -5.07$; Social communication: Est = -0.39 SE = 1.32, $z = -7.92$). A schematic of the model is shown in **Figure 4.1**. **Table A4.12** provides detailed statistics of the model.

Figure 4.1

Multiple Indicator Univariate Latent Change Score Model for PDI with Dimensional Outcomes



Note. The covariances of the dimensional outcomes are omitted for visual clarity. For all parameters, see **Table A4.12**. Δ PDI: The latent variable representing the change in parent-dyadic interaction qualities between 8 and 14 months; PDIT1: Parent-dyadic interaction assessed at 8 months; PDIT2: Parent-dyadic interaction assessed at 14 months. Mut: Mutuality; ND: Nondirectiveness; SR: Sensitive responsiveness; EXT.B: Externalising behaviour; INT.B: Internalising behaviour; LANG: Language; SCOM: Social communication; SCQ: Social communication questionnaire; SRS: Social responsiveness scale. Black arrows with no values indicate relationships where parameters are fixed. Black and orange arrows indicate significant relationships. Dashed arrows indicate marginal relationships. Grey arrows indicate nonsignificant relationships. Circles indicate latent variables and squares indicator/observed variables. The triangle indicates the intercept of the PDIT1 and Δ PDI latent factors. Standardised estimates are reported.

4.3.4.2 Infant Attentiveness. The parameter estimates of the univariate LCS model of attentiveness excluding the outcome and control variables are shown in **Table A4.13** of the Appendix. The single indicator univariate LCS model of infant attentiveness predicting dimensional outcomes fitted the data well: $\chi^2(7) = 16.301, p = .02$, CFI = 0.989, RMSEA = 0.076, 90% CI [0.022, 0.127], SRMR = 0.050. Inspection of the key parameters revealed that average scores in attentiveness significantly increased from 8 to 14 months (Est = 2.56, SE = 0.30, $z = 13.48$). There were significant individual differences in the rate of change of attentiveness across time (Est = 0.56, SE = 0.11, $z = 12.07$). A negative self-feedback parameter (orange arrow in **Figure 4.2**) indicated that the rate of change depended on the starting point, suggesting that infants who initially had high scores in attentiveness to parent showed a smaller increase in attentiveness over time (Est = -0.65, SE = 0.07, $z = -11.49$).

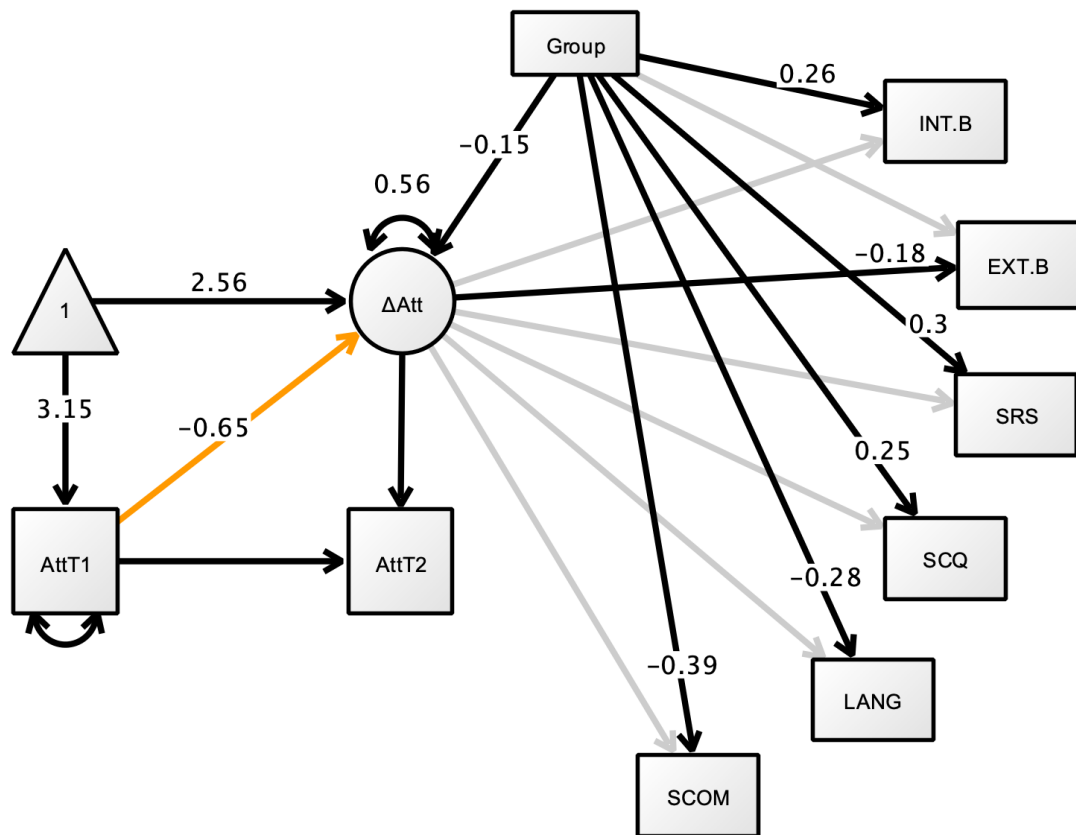
Furthermore, a greater increase in infant attentiveness was associated with lower externalising behaviour (Est = -0.18, SE = 0.10, $z = -2.84$). The ASD likelihood group significantly predicted change in attentiveness (Est = -0.15, SE = 0.17, $z = -2.99$) and was a significant predictor of all the dimensional outcome variables at 36 months, excluding

externalising behaviour (Internalising behaviour: $Est = 0.26$, $SE = 0.32$, $z = 4.58$; SRS: $Est = 0.30$, $SE = 2.32$, $z = 6.43$; SCQ: $Est = 0.25$, $SE = 0.62$, $z = 5.35$; Language: $Est = -0.28$, $SE = 1.44$, $z = -5.06$; Social communication: $Est = -0.39$, $SE = 1.38$, $z = -7.52$). A schematic of the model is shown in **Figure 4.2**. **Table A4.14** provides detailed statistics of the model.

4.3.4.2.1 Supplementary Analysis of the Attentiveness Model. The fact that the ASD likelihood group did not predict externalizing behaviour in this model but there was a predictive relationship between attentiveness change and ASD likelihood group as well as externalizing behaviour suggested potential mediation effects of attentiveness change. Thus, mediation analysis was conducted within the existing model to examine the indirect effect of attentiveness change in the relationship between ASD likelihood group and externalizing behaviour. Since the mediation was testing a targeted hypothesis, the p -value threshold used here was $p < 0.05$. The results revealed that there was a marginally nonsignificant direct effect between ASD likelihood group and externalizing behaviour ($\beta = 0.11$, $SE = 0.34$, $z = 1.75$, $p = 0.08$), showing a trend towards higher externalising behaviour in the EL than the TL group. However, there was a significant positive indirect effect between these variables through 8-14-month change in infant attentiveness to the caregiver ($\beta = 0.03$, $SE = 0.07$, $z = 2.10$, $p = 0.04$), meaning that a change in infant attentiveness had an influencing role in group's externalising behaviour level at 3 years.

Figure 4.2

Univariate Latent Change Score Model for Infant Attentiveness with Dimensional Outcomes



Note. The covariances of the dimensional outcomes are omitted for visual clarity. For all parameters, see **Table A4.14**. ΔAtt : The latent variable representing the change in infant attentiveness between 8 and 14 months. AttT1 : Infant attentiveness assessed at 8 months. AttT2 : Infant attentiveness assessed at 14 months. EXT.B : Externalising behaviour; INT.B : Internalising behaviour; LANG : Language; SCOM : Social communication; SCQ : Social communication questionnaire; SRS : Social responsiveness scale. Black arrows with no values indicate relationships where parameters are fixed. Black and orange arrows indicate significant relationships. Grey arrows indicate nonsignificant relationships. The circle indicates a latent variable and squares indicator/observed variables. The triangle indicates the intercept of the AttT1 observed variable and ΔAtt latent factor. Standardised estimates are reported.

4.3.4.3 Infant Affect. The linear regression investigating the predictive relationship between ‘mean positive and negative affect’ (updated MACI version) and

‘affect’ (old MACI version) showed a significant predictive relationship between the two variables ($\beta = 0.646, p < .001$). The regression was statistically significant ($R^2 = 0.42, F(1, 47) = 33.61, p < .001$). This justified using the mean positive and negative affect variable from Phase 2 and combining it with ‘affect’ from Phase 1, creating a single ‘affect’ variable across phases.

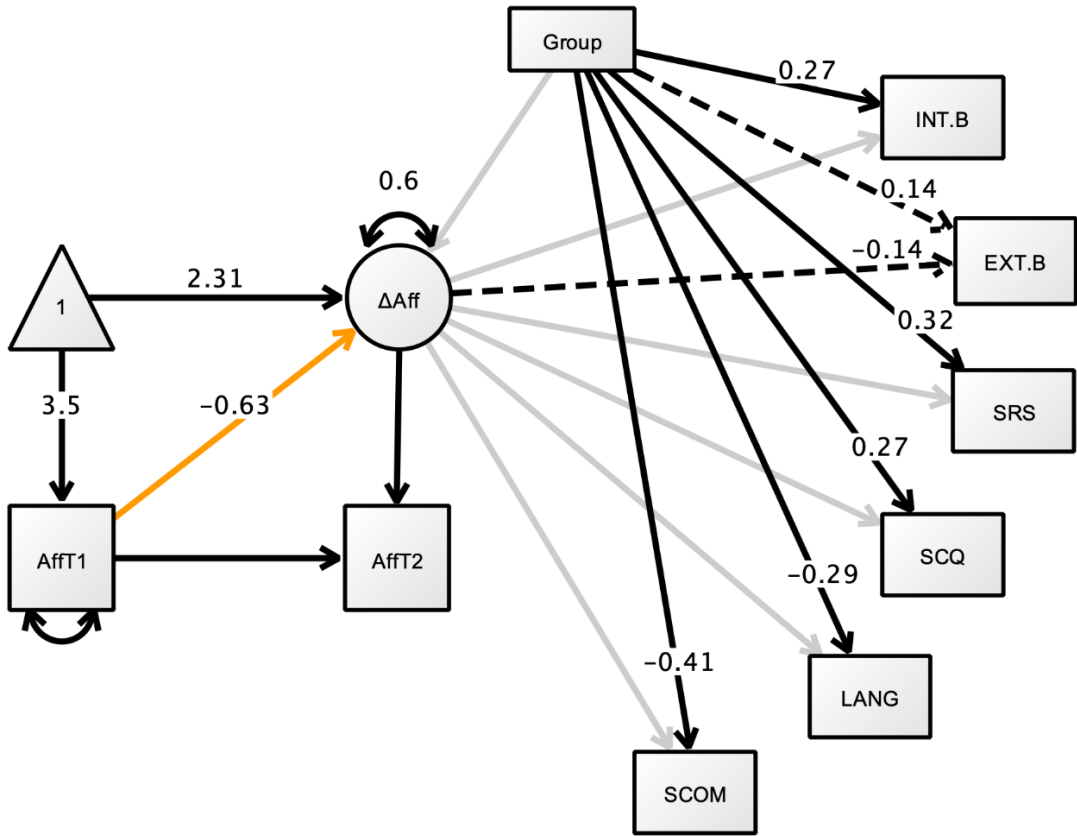
The parameter estimates of the univariate LCS model of infant affect excluding the outcome and control variables is shown in **Table A4.15** of the Appendix. The single indicator univariate LCS model of infant affect predicting dimensional outcomes fitted the data well: $\chi^2(7) = 16.385, p = .02, CFI = 0.989, RMSEA = 0.074, 90\% CI [0.026, 0.122], SRMR = 0.035$. Inspection of the key parameters revealed that average scores in infant affect significantly increased from 8 to 14 months (Est = 2.31, $SE = 0.30, z = 11.83$). There were significant individual differences in the rate of change of infant affect across time (Est = 0.60, $SE = 0.12, z = 11.93$). A negative self-feedback (orange arrow in **Figure 4.3**) parameter indicated that the rate of change depended on the starting point, suggesting that infants who initially had high scores in affect showed a decline over time (Est = -0.68, $SE = 0.07, z = -11.27$).

Furthermore, change in infant affect was a marginally nonsignificant predictor of externalising behaviour (Est = -0.14, $SE = 0.11, z = -2.0$). The ASD likelihood group significantly predicted dimensional outcomes on internalising behaviour (Est = 0.27, $SE = 0.31, z = 5.02$), ASD-related traits (SRS: Est = 0.32, $SE = 2.33, z = 6.82$; SCQ: Est = 0.27, $SE = 0.62, z = 5.78$), language (Est = -0.29, $SE = 1.39, z = -5.49$) and social communication (Est = -0.41, $SE = 1.35, z = -8.10$), but did not predict change in affect. This meant that the EL group had higher scores in internalising behaviour and socially related ASD symptoms, but lower scores in language and social communication than the TL group. The effect on externalising behaviour was marginally nonsignificant (Est =

0.14, $SE = 0.34$, $z = 2.26$). A schematic of the model is shown in **Figure 4.3**. **Table A4.16** provides detailed statistics of the model.

Figure 4.3

Univariate Latent Change Score Model for Infant Affect with Dimensional Outcomes



Note. The covariances of the dimensional outcomes are omitted for visual clarity. For all parameters, see **Table A4.16**. Δ Aff: The latent variable representing the change in infant affect between 8 and 14 months. AffT1: Infant affect assessed at 8 months. AffT2: Infant affect assessed at 14 months. EXT.B: Externalising behaviour; INT.B: Internalising behaviour; LANG: Language; SCOM: Social communication; SCQ: Social communication questionnaire; SRS: Social responsiveness scale. Black arrows with no values indicate relationships where parameters are fixed. Black and orange arrows indicate significant relationships. Grey arrows indicate nonsignificant relationships. Dashed arrows indicate marginal relationships. The circle indicates a latent variable and squares indicator/observed variables. The triangle indicates the

intercept of the AffT1 observed variable and ΔAff latent factor. Standardised estimates are reported.

4.3.4.3.1 Supplementary Analyses Separating Positive and Negative Affect.

Considering that the infant affect variable incorporated both positive and negative affect, supplementary analyses were conducted to examine whether the marginal effect of infant affect change on externalising behaviour was driven by infant high positivity or lower negativity. Thus, three separate univariate LCS models were run: Model 1 investigated the effect of positive affect change and Model 2 the effect of negative affect change on externalising behaviour. For these analyses, a smaller sample size was employed (Phase 2 sample only, $N = 143$). This is because, in this sample, PII had been coded using the updated MACI version which included a positive and a negative affect scale, compared to the Phase 1 sample where PII had been assessed with the old MACI version which incorporated positive and negative affect into a single ‘positive’ affect scale. Model 3 included the Phase 1 sample only ($N = 104$) and examined the effect of the single ‘positive’ affect scale (old MACI scale) on externalising behaviour. These models were identical to the main mean affect univariate LCS model (same pathways, dimensional outcome variables and ASD likelihood group as predictor included).

The results from Model 1 showed that change in positive affect was not a significant predictor of externalising behaviour ($\text{Est} = 0.005$, $SE = 0.10$, $z = 0.06$). However, Model 2 results revealed that infant negative affect scores increased from 8 to 14 months ($\text{Est} = 1.04$, $SE = 0.36$, $z = 6.37$). Negative affect change was a significant predictor of externalising behaviour ($\text{Est} = 0.24$, $SE = 0.10$, $z = 2.77$), such that high infant negative affect change from 8 to 14 months was associated with higher scores on externalising behaviour at 3 years of age. Similarly to Model 1, Model 3 results showed that ‘positive’ affect change was a nonsignificant predictor of externalising behaviour ($\text{Est} = -0.12$, $SE = 0.19$, $z = -1.09$). Overall, these results suggest that negative affect had

a larger impact on the main model, which explains the marginal association between affect and externalising behaviour shown.

4.3.5 Bivariate Associations Between PDI and Language/Social Communication Dimensions at 8 and 14 Months

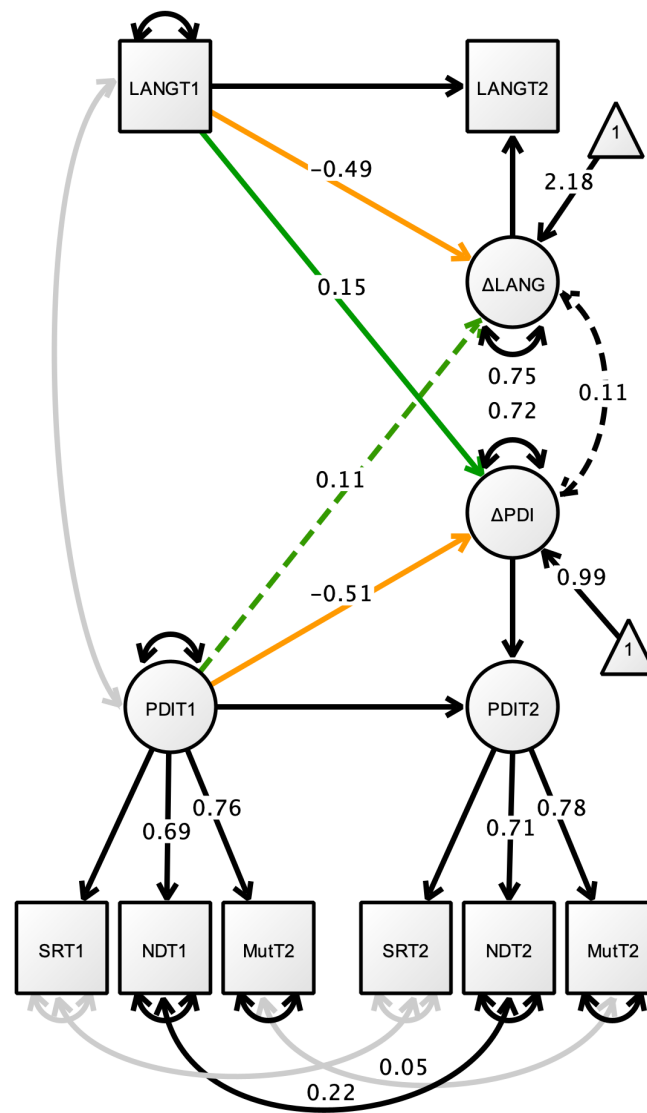
Following the identified significant associations of PDI change with language and social communication at 36 months, these associations were examined between 8 and 14 months through two separate bivariate LCS models. The aim was to explore how these relationships unfolded earlier and to examine whether there are associations with concurrent change in these variables. For the parameter estimates of the univariate LCS models for language and social communication, refer to **Tables A4.17** and **A4.18** in the Appendix. The fit indices of the language and social communication univariate models are not reported as these models are just-identified.

4.3.5.1 PDI and Language. The PDI and language bivariate model fitted the data well: $\chi^2(22) = 46.324$, $p = .002$, CFI = 0.969, RMSEA = 0.072, 90% CI [0.041, 0.102], SRMR=0.045. First, there was no association between PDI and language at 8 months (Est = 0.03, $SE = 0.70$, $z = 0.44$). Next, language scores at 8 months significantly predicted the rate of change in PDI (Est = 0.15, $SE = 0.01$, $z = 2.25$). However, the rate of change in language scores was only marginally dependent on PDI at 8 months ($\beta = 0.11$, $SE = 0.56$, $z = 1.82$). Therefore, those with high scores in language at 8 months showed a greater rate of change in PDI between 8 and 14 months. After accounting for this association and self-feedback pathways (**orange arrows, Figure 4.4**), changes in PDI and language over 8 to 14 months were only marginally associated ($\beta = 0.11$, $SE = 0.75$, $z = 1.67$). A schematic of the model is shown in **Figure 4.4**. **Table A4.19** provides

detailed statistics of the model. Combined with the results of the main model, these findings indicate that infant language ability shapes and is shaped by PDI across time.

Figure 4.4

Bivariate Latent Change Score Model for PDI and Language at 8 and 14 months

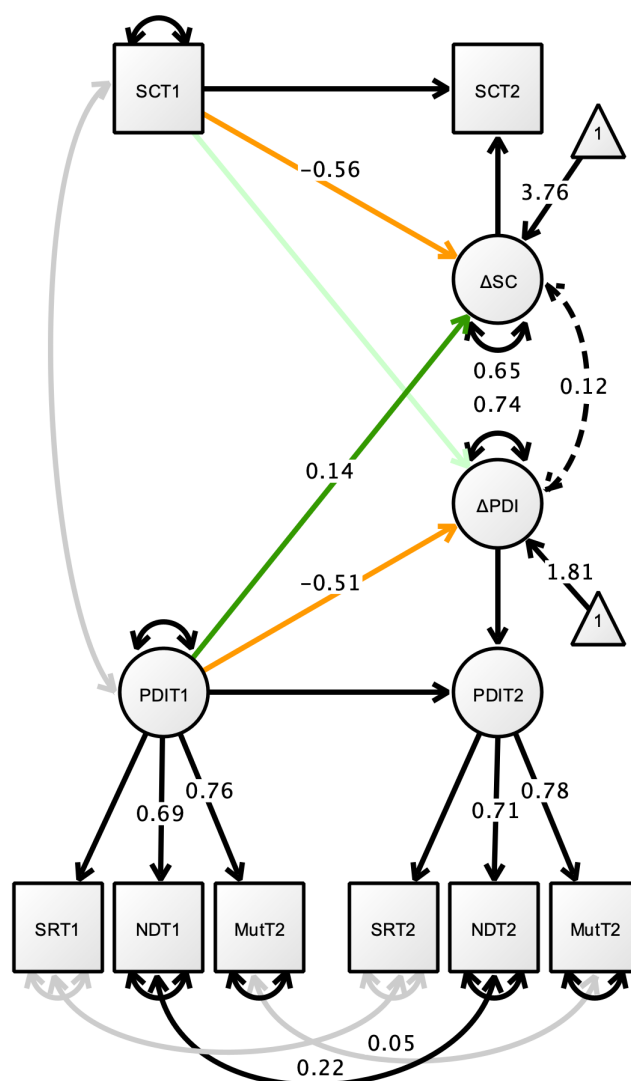


Note. Δ PDI: The latent variable representing the change in parent-dyadic interaction between 8 and 14 months. Δ LANG: The latent variable representing the change in language skills between 8 and 14 months. PDIT1: Parent-dyadic interaction assessed at 8 months. LANGT1: Infant language skills assessed at 8 months. PDIT2: Parent-dyadic interaction assessed at 14 months. LANGT2: Infant language skills assessed at 14 months. Mut: Mutuality; ND: Nondirectiveness; SR: Sensitive responsiveness. Black arrows with no values indicate relationships where

parameters are fixed. Solid lines indicate significant relationships. Grey arrows indicate nonsignificant relationships. The green lines indicate cross-domain coupling parameters (PDI to language and vice versa). Orange lines indicate within-domain couplings. Dashed arrows indicate marginal relationships. Circles indicate latent variables and squares indicator/observed variables. The triangles indicate the intercepts of the Δ PDI and Δ LANG latent factors. Standardised estimates are reported.

4.3.5.2 PDI and Social Communication. The PDI and social communication bivariate model fitted the data well: $\chi^2(22) = 44.149$, $p = .003$, CFI = 0.972, RMSEA = 0.071, 90% CI [0.040, 0.101], SRMR=0.045. There was no association between PDI and social communication at 8 months (Est = -0.08, $SE = 1.19$, $z = -1.14$). Further, social communication at 8 months was not a significant predictor of the rate of change in PDI (Est = 0.003, $SE = 0.006$, $z = 0.05$). In contrast, the rate of change in social communication skills was significantly dependent on PDI at 8 months ($\beta = 0.14$, $SE = 0.54$, $z = 2.44$). Therefore, those with high scores in PDI at 8 months showed *greater gains* in their social communication skills between 8 and 14 months. After accounting for this association and self-feedback pathways (orange arrows, **Figure 4.5**), changes in PDI and social communication over 8 to 14 months were only marginally correlated ($\beta = 0.12$, $SE = 0.80$, $z = 1.67$). A schematic of the model is shown in **Figure 4.5**. **Table A4.20** provides detailed statistics of the model. Taking into account the primary model, these results suggest that higher scores in PDI quality from as early as 8 months are linked to a positive change in social communication and later social communication skills at 3 years. They also provide an indication that greater PDI change relates to a change in social communication between 8-14 months.

Bivariate Latent Change Score Model for PDI and Social Communication at 8 and 14 months



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(PDI to SC and vice versa). Orange lines indicate within-domain couplings. Dashed arrows indicate marginal relationships. Circles indicate latent variables and squares indicator/observed variables. The triangles indicate the intercepts of the Δ PDI and Δ SC latent factors. Standardised estimates are reported.

4.3.6 Multigroup LCS models – Testing the Protective Value of PII

Following the main analyses, additional analyses were run to examine possible group (TL, EL-no ASD, EL-ASD) differences in the significant associations found in 8-month PII / PII change from 8 to 14 months and dimensional outcomes at 36 months. Although measurement invariance (at least partial strong measurement invariance) was not achieved across all the steps of the multigroup measurement invariance testing, the analyses for possible group differences were carried out. It has been suggested that, instead of rejecting a noninvariant model, testing group differences if it makes sense to do so and interpreting the results of noninvariance should be embraced as they can be very informative of the functioning of a construct across the groups (Putnick & Bornstein, 2016). Thus, analyses for the investigation of group differences were undertaken to examine the research question of interest whilst acknowledging the limitations and bearing in mind that the results should be interpreted with caution.

In the PDI LCS model, results showed that the association between PDI change and dimensional outcomes differed between the groups, as constraining the regression paths between 8-14-month PDI change and externalising behaviour, social communication and language at 36 months led to a significant drop in model fit $\Delta\chi^2(8) = 23.37, p = .003$). In the TL group, greater change in PDI was significantly related to lower scores in externalising behaviour ($\beta = -0.49, SE = 0.23, z = -3.05, p = .002$). In the EL-no ASD group, there was only a marginal effect of PDI change on externalising behaviour ($\beta = -0.21, SE = 0.19, z = -1.95, p = .05$) while no significant association was observed in the EL-ASD group ($\beta = 0.03, SE = 0.40, z = 0.107, p = .92$). In PDI change and language,

no associations were found in the TL and EL-ASD groups (TL: $\beta = 0.16$, $SE = 0.76$, $z = 1.16$, $p = .25$; EL-ASD: $\beta = 0.26$, $SE = 2.88$, $z = 1.03$, $p = .30$), while there was a marginal positive association in the EL-no ASD group ($\beta = 0.21$, $SE = 0.89$, $z = 2.00$, $p = .05$). Furthermore, PDI change in the TL group was marginally associated with higher social communication scores ($\beta = 0.30$, $SE = 0.65$, $z = 2.26$, $p = .02$), compared to the EL-no ASD and EL-ASD groups (EL-no ASD: $\beta = 0.17$, $SE = 0.77$, $z = 1.72$, $p = 0.09$; EL-ASD: $\beta = -0.02$, $SE = 2.08$, $z = -0.10$, $p = .92$).

In the attentiveness (infant attentiveness to parent) model, constraining the regression path led to a significant drop in model fit $\Delta\chi^2(2) = 7.82$, $p = 0.02$). The identified effects of infant attentiveness change on externalising behaviour differed between the groups. Of the three groups, a significant effect was only found for the TL group (TL: $\beta = -0.33$, $SE = 0.17$, $z = -3.10$, $p = .002$; EL-no ASD: $\beta = -0.11$, $SE = 0.14$, $z = -1.22$, $p = .22$; EL-ASD: $\beta = 0.15$, $SE = 0.20$, $z = 1.11$, $p = .27$).

4.4 Discussion

Autism spectrum disorder is characterised by substantial variability in developmental trajectories, and the quality of PII in the first months of life can play an important role in EL infants' developmental route. Yet, there has been limited prospective research into the early role of global PII aspects in infant dimensional outcomes in the context of ASD susceptibility. The present study aimed to extend the findings of the previous chapter and add to the existing literature by examining how changes between 8 and 14 months in global aspects of infant, parent and dyadic interaction that differed between EL and TL groups in the previous study (**Chapter 3**), contributed to ASD-related traits, adaptive behaviour and language/social communication dimensions at 36 months in an enriched sample of infants at EL and TL for ASD diagnosis. Focusing on change in PII qualities rather than PII at distinct time points allowed the tracking of the trajectory

of PII development as well as of the variability in change, offering a more accurate picture of how PII unfolded between 8-14 months and how this development was linked to different dimensional outcomes. This would not be achieved through a cross-sectional investigation.

As hypothesised, average scores in PDI, attentiveness and affect increased from 8 to 14 months across the whole sample. In addition, as predicted, 8- to 14-month change in infant attentiveness differed between the EL and TL groups, such that positive changes in attentiveness to parent were smaller for the EL group, while no group differences were observed in PDI and affect change. Consistent with what was predicted, across the whole sample, greater change in PDI was linked to less externalising behaviour and better language and social communication at 36 months. In particular, higher language scores at 8 months were associated with greater gains in PDI quality from age 8 to age 14, while higher initial quality of PDI was only marginally associated with greater gains in language from 8 to 14 months. In contrast, higher PDI at 8 months was linked to greater improvements in social communication from 8 to 14 months, while the opposite was not observed. This suggests that early language ability is more likely to drive changes in PDI, whilst early PDI is more likely to be a driver of developmental change in social communication skills.

Regarding infant interactional aspects, greater 8- to 14-month change in attentiveness and affect was linked to lower scores in externalising behaviour (though the effect was marginally nonsignificant for the affect scale). Supplementary analyses revealed an association between infant negative affect and externalising behaviour. However, in contrast to what was hypothesised, no associations were found between these PII scales and the other dimensions. Furthermore, as expected, infants at EL had higher scores in internalising/externalising behaviour, SRS and SCQ, and lower scores in language/social communication at 36 months compared to the TL group. Multigroup

analysis for possible protective effects of PII in developmental outcome revealed that the aforementioned associations between changes in attentiveness/PDI and the dimensional outcomes differed between the TL, EL- no ASD and EL-ASD groups.

4.4.1 8 to 14-Month PII Change Predicting Dimensional Outcomes at 36 months

In this enriched sample for varying developmental trajectories, the identified relationship between PDI change and dimensional outcomes aligns with previous findings showing that parental sensitivity, attunement to the child's behaviours, as well as dyadic synchrony, are related to the development of greater social communication and language skills, and the reduction of externalising behaviours in both neurotypically developing and autistic individuals (Bradley & Corwyn, 2007; E. W. Lindsey et al., 2009; R. A. Lindsey et al., 2020; Northrup & Iverson, 2015; Soares et al., 2018; Tamis-LeMonda et al., 2001; Valentovich et al., 2018; Zampella et al., 2020). In addition, PDI at 8 months significantly predicted these dimensions (marginally for social communication), which underscores that not solely PDI changes, but also the quality of PDI at baseline was already a significant contributor to these outcomes. Although infants at EL had lower scores in language/social communication and higher scores in externalising behaviour than TL infants at 36 months, highlighting these infants' susceptibility to poorer developmental outcomes, the results suggest some continuity of PDI in TL and EL infant developmental trajectories and are consistent with propositions that sensitively responsive, nondirective parenting, and mutual PII from the first months of life can support the development of children's language and social communication and adaptive behaviour ability (NICHD Early Child Care Research Network, 1999; Rocha et al., 2020). Although it is worth noting that it cannot be ascertained from this study whether these associations are causative, the results are very informative for designing

early parent-targeted interventions that could perhaps target these components of PII to optimise children's developmental outcomes.

Contrary to the study's hypothesis, no associations were found between 8-month PDI or PDI change and internalising behaviour as well as ASD-related traits, even though TL infants had significantly lower scores in these dimensions compared to the EL group. In particular, the lack of association between PDI and internalising behaviour converges with previous research showing no links between the latter and dyadic flexibility in 3- to 6-year-old children (Rozenblatt-Perkal & Zaidman-Zait, 2020). One possibility for the lack of these associations could be that the PDI aspects are less directly relevant to the SRS, SCQ measures and internalising behaviour and they may instead be more sensitive predictors of language, social communication and externalising behaviour measures. Another possibility is that at the ages of 8-14 months, infants may not be displaying behaviours that could affect PII linked to later ASD-related traits and internalising behaviour, but these associations are likely to become more profound later, when infants begin to exhibit more behaviours their parents could respond to. For instance, previous studies have found links between PII aspects (i.e. parent intrusiveness, dyadic reciprocity, parent engagement) and internalising behaviour in children or older infants (Ding et al., 2021; Kok et al., 2013; Steenhoff et al., 2021; Valentovich et al., 2018).

The absence of association with ASD-related traits did not converge with the findings from the previous chapter which found differences in these interactional aspects with respect to ASD outcome status. Although an increase in attentiveness to parent was found for the TL relative to the EL group, which agrees with the previous chapter's findings, there are different possible explanations for the absence of an association with ASD-related traits. First, this could be because this study included an additional sample of infants (combined Phase 1 and 2 samples), while the previous study included only a part of this sample (Phase 2), which may have reduced any possible effects. Second, the

studies differed in the analytical/methodological approaches implemented. Compared to the study from **Chapter 3**, parent sensitive responsiveness, nondirectiveness and mutuality were combined to form a latent factor in this study and different relationships were modelled through somewhat complex LCS models involving many parameters. In addition, relations with ASD outcome status in the previous study is a somewhat different approach to the one used here looking at relations with measures of ASD symptom severity with the SRS and SCQ variables. Last, this study examined associations including the whole sample, while the previous chapter's study investigated PII differences based on ASD outcome status groups.

Furthermore, greater 8-to-14-month change in infant attentiveness to parent, and to a lesser extent, infant affect, was only related to lower externalising behaviour at 36 months. On one hand, this shows some degree of specificity of these infant interactional aspects to externalising behaviour. This specificity might reflect the development of self-regulatory processes which are important for the child's ability to control and regulate behaviour and emotions to events happening in the environment. Children's ability to regulate their attention has been shown to be a predictor of lower externalising behaviour at later ages (Belsky et al., 2007), whereas children's inability to control their emotions (i.e. anger) has been associated with increments in aggressive behaviour (Deater-Deckard et al., 2010). Thus, the development of attention and emotion regulation may have played a role in the links of these interactional aspects with externalising behaviour in particular. On the other hand, it is also important to note that links between infant behavioural attention or positive affect and the other dimensions, such as language/social communication skills have been observed in previous empirical work (Laake & Bridgett, 2014; Morales et al., 2000; Mundy et al., 2007; Young et al., 2009). The discrepancy in the findings could be explained by the populations included, age ranges or methods used in different studies. For example, Mundy et al. (2007) found infant responses to and

initiations of joint attention at 12 and 18 months, respectively, were related to language skills at 24 months. However, the current study examined 8-14-month changes to infant attentiveness in relation to language ability at 36 months. Laake & Bridgett (2014) used parent reports to measure infant positive affect at 10 months, while Young et al. (2009) used the still-face paradigm to measure infant gaze behaviour and affect at 6 months.

Nevertheless, the identified predictive relationship between these specific infant interactive behaviours and later externalising behaviour presents similarities with previous empirical work, showing an association between infant initiations/responses to joint attention and higher positive affect early on being related to lower scores in externalising behaviour at a later age in neurotypical development (Moore et al., 2001; Van Hecke et al., 2007). Importantly, infant attentiveness was also a significant mediator in the relationship between ASD likelihood status and 36-month externalising behaviour. These results highlight that infant positivity and the ability to attend to the parent in interactions can be important indicators of the development of externalising behaviour. The propensity to orient and attend to others' activities as well as engage in social interactions with positive affect can create social learning opportunities. This, in the context of PII, can enable infants to develop adaptive behaviour abilities which they can then transfer to their social interactions with peers or other less familiar adults (Mundy & Willoughby, 1996).

Interestingly, although scores on infant affect increased over time and a change in affect across the whole sample marginally predicted lower externalising behaviour, supplementary analyses with a smaller sample size showed the opposite effect. There was an average increase in negative affect from 8-14 months and greater change in this variable predicted higher externalising behaviour. This reduced EL and TL infant sample likely involved infants who displayed more negative affect during PII. These infants later exhibited higher externalising behaviours. These results are consistent with past research

showing that infant negative engagement is related to subsequent externalising behaviour (Ding et al., 2021), and again, highlight that early infant affect can be a significant indicator of later maladaptive behaviour.

The results also highlight the individual heterogeneity that exists in PII. This is not surprising considering that the sample involved both infant sibling groups at TL and EL for ASD. However, it underscores the significance of taking into account individual differences early on in development, and that group effects are not necessarily generalisable to the individual (at least for this study). This can also be shown through the significant individual differences in change that was found across all the LCS models, despite the observed average increase in the scores of all the domains between 8 to 14 months across the whole sample.

4.4.2 Bidirectional Associations Between PDI and Language/Social Communication

The findings from the language bivariate LCS models indicated a positive coupling between 8-month language and 8-14-month change in PDI, suggesting that infants with high language scores at 8 months had an improvement in the quality of PDI between 8 and 14 months. The coupling between PDI at 8 months and 8-to-14-month change in language only approached significance but also had a positive coefficient and a similar effect size. Although marginally non-significant, these findings provide an indication that PDI early in infancy may play a role in later language ability and resonate with substantial evidence suggesting that the quality of PII (i.e. parent responsiveness, affect synchrony and others) contributes towards the development of children's language skills in both neurotypical and ASD development (Baker et al., 2010; Feldman & Greenbaum, 1997; Huttenlocher et al., 1991; Tamis-LeMonda et al., 2001). Combined with the univariate models showing links between 8-14-month PDI change and 36-month

language ability, these results also indicate that the effect of PDI in language development becomes stronger with time.

Moreover, the findings suggest that not only PDI, but also infants contribute with their early language skills towards shaping PDI over time, which, in turn, contributes to 36-month language skills (as shown in the univariate model). This is the first study to show this relationship at that age using global PII and an LCS modelling approach, including a diverse sample of TL and EL infants. Along similar lines, previous research shows that the characteristics of the child affect parent responses or input (Albert et al., 2018; Choi et al., 2020; Fusaroli et al., 2019; Luo & Tamis-LeMonda, 2017; Warlaumont et al., 2014). For instance, using naturalistic audio recordings from PII, Warlaumont and colleagues (2014) found that speech-related vocalisations (i.e. babbling, singing, speech) of children with and without ASD (ages 8-48 months) were associated with an increase in the probability of parent responses compared to when vocalisations were not speech-related. Parent responses to child speech-related vocalisations, in turn, increased the probability of the child's subsequent vocalisations being speech-related. Importantly, the results support the transactional model of development, positing that the children's developmental trajectories are influenced by both the infant characteristics and the environment (i.e. caregivers) in a reciprocal manner (Sameroff, 2009).

The positive coupling found between PDI at 8 months and 8-to14-month social communication change suggested that a high quality of PDI contributed to an improvement in infant social communication skills between 8 and 14 months. In contrast to language skills, 8-month social communication abilities did not predict a developmental change in PDI quality. Similarly, previous research showed that the development of infant social expressiveness in the first months of life did not predict the degree of parent responses to these infants' behaviours (Murray et al., 2016). In fact, the VABS social communication (averaged socialisation and communication) scale involves

the assessment of everyday skills not only in language but also in communication, play and interpersonal relationships. On the other hand, the language (expressive and receptive) scale focuses more on the assessment of verbal ability, language production and the processing of linguistic input. It is possible that while early language production and understanding could stimulate more parent sensitive responses, nondirectiveness, and dyadic mutuality, facilitating later PII, 8-month socialisation and communication skills measured through the VABS may not be a driver of the developmental progression of PDI. The age of 8 months may have been too early for infants to show social behaviours that could influence PDI changes over time, or other biological or contextual factors may have been implicated in this association. Although outside the scope of this study, future research would be interesting to test whether social communication skills at a later age predict changes in PDI, as infants' behavioural repertoire tends to increase with development. Instead, the results highlight that, from as early as 8 months, the quality of PDI exerts an influence on infants' 8-to-14-month change in everyday social communication ability, and that 8-to-14-month PDI change continues to contribute to this skill at 36 months (as shown in the univariate model). This finding agrees with past studies revealing that parent responsiveness and synchronous interactions contribute to children's social communication development (Lindsey et al., 2009; Murray et al., 2016; Soares et al., 2018; Zampella et al., 2020).

Moreover, an absence of concurrent relationships between PDI and language/social communication at 8 months was found, while, after accounting for baseline levels of the constructs and the regression pathways between and within them, the changes in PDI and language/social communication were marginally positively associated. While PDI does not seem to be a correlate of language/social communication at 8 months, the results provide some indication that changes (or improvements) in PDI and language/social communication over a 6-month period go in tandem, even after

controlling for other effects. Although future replication studies with larger sample sizes are needed to consolidate these correlations given the marginal effects, these results provide a hint that changes in PDI and language/social communication are inextricably connected.

4.4.3 Evaluating the Protective Value of PII in Developmental Outcomes

The findings revealed that groups differed in the regression paths linking PDI change and externalising behaviour, language and social communication. Group differences also emerged in infant attentiveness change and externalising behaviour. This meant that TL infants with greater improvements in PDI and attentiveness had lower scores in externalising behaviour and higher scores in social communication skills (marginal effect). No associations were observed in the EL-ASD group, which could perhaps be explained by the considerably smaller sample size of this group compared to the other two groups, possibly reducing the power to detect any significant effects. Interestingly, the EL-no ASD group showed a marginal effect of PDI change on externalising behaviour in the same negative direction as the TL group and a positive predictive relationship between PDI change and language ability that approached significance, compared to the other two groups which did not show this association. PDI change in this group predicted higher language skills and lower externalising behaviour, suggesting that the PDI aspects could serve as protective factors against genetic/familial susceptibility for ASD diagnosis. These findings agree with propositions that gains in the quality of PII can modify EL infant developmental trajectories towards a more neurotypical path, acting as protective factors, and that these improvements can be reflected in different dimensions, such as language development (Elsabbagh, 2020). These findings can contribute towards informing early interventions focusing on PII.

4.4.3.1 A Note on Multigroup Measurement Noninvariance. The results regarding group differences should be interpreted with caution since multigroup measurement invariance was not fully achieved. However, the aspect of noninvariance warrants further discussion. Longitudinal measurement invariance of the PDI factor was achieved when the groups were collapsed. This highlights that the absence of measurement invariance may not necessarily be due to the inconsistency of the PDI construct itself, rather than that the construct may be changing in composition in one or more of the groups. Indeed, the strong intercorrelations between the PII items in the whole sample appear to change when these are examined by group (with low intercorrelations of some of the PII items shown for the EL-ASD group; see **Table A4.21**). This may have contributed to noninvariance. It has been postulated that “noninvariance can be informative and may lead researchers to important conclusions about how different groups interpret the same construct” (p.19, Putnick & Bornstein, 2016). Therefore, an interesting question for future research would be to examine whether PDI is interpreted the same way in the EL-ASD dyads as in the other sibling groups. For instance, is PDI experienced in the same way for the EL-ASD group as the TL and EL-no ASD groups? Nevertheless, it is also highly possible that measurement invariance was not achieved due to group uneven sample sizes.

4.4.4 Limitations and Future Directions

This study has several limitations that need to be acknowledged when interpreting the results. Firstly, even though this study was one of the largest prospective studies exploring PII in relation to later dimensional outcomes, the sample size of the infant sibling subgroups was uneven, which may have led the estimates to be driven by the largest groups’ data. For instance, it is one possibility that the absence of associations in the EL-ASD group may be explained by this aspect. In addition, the marginally

nonsignificant relationships observed may indicate that including a larger overall sample size would increase statistical power to detect significant effects. Due to ASD heterogeneity, future studies including infant sibling groups require larger sample sizes, as this can enhance the studies' translational potential into clinical practice (Lombardo et al., 2019; Szatmari et al., 2016).

In addition, one methodological limitation to interpreting the results of the study is that multigroup measurement invariance was not fully achieved across all the steps of testing measurement invariance of the PDI latent factor, which may be an indication that the PDI construct measured was not the same/did not have the same meaning across the groups. As mentioned, the issue of noninvariance should be investigated further. Employing a similar study design in future replication studies would also help clarify this issue. Moreover, while investigating PDI change with 2 time points was informative of how these aspects developed and how this change was linked to later outcomes, looking at 2 time points is still limiting when examining change and bidirectional relationships of different domains across time. Investigating these over several time points in time would provide a wider developmental window for a more comprehensive view of how social interactions change and their influence on dimensional measures. Furthermore, although a longitudinal design was used through an LCS modelling approach which allows the examination of causal associations, no direct causal inferences can be drawn. Causal effects can be determined through experimental studies targeting these PDI aspects and their links to later developmental outcome in vulnerable populations.

In addition, the study did not examine the possible confounding effects of other variables in the observed associations, such as parent age, socio-economic status or psychological distress. Research suggests that these factors play a role in PDI (Barnes et al., 2014; Koşkulu et al., 2021; Loncarevic et al., 2023), thus including these domains in future studies should be considered.

4.5 Conclusion

This study is one of the first to investigate 8-to-14-month changes in global qualities of PII and their relationship to different dimensional outcomes later in development in TL and EL infants. Therefore, it adds to the existing literature by showing that PDI at 8 months as well as changes in PDI over time are linked to the development of externalising behaviour, language and social communication skills. The study also demonstrates that infant interactional aspects (attentiveness to parent and affect) specifically have an influencing role in later externalising behaviour and stressed the reciprocal relationships between infant language skills and PDI development. In addition, it highlights that positive changes in PDI in infants at EL with no subsequent ASD diagnosis contribute towards better language ability and lower externalising behaviour. All in all, the findings of this study support the transactional model of development by showing that the bidirectional effects of both parent input and infant characteristics shape infant developmental trajectories. They provide a better understanding of the interactional processes linked to dimensional outcomes rather than solely ASD diagnosis, and thus, of the developmental trajectories of EL and TL infants. They suggest that PII aspects can serve as protective factors in mitigating later social communication difficulties and maladaptive behaviour, as well as ASD diagnosis. This is important for infants at EL for ASD outcome as well as those at EL for other comorbid conditions. Last, the findings underscore the importance of studying developmental dimensions in the context of unstructured PII. The results carry implications for early identification of infants who have increased vulnerability for later maladaptive behaviour and for designing early interventions targeting particular PII aspects to support vulnerable infants and their families.

4.6 Appendix

4.6.1 Assessment of ASD Outcome at 36 Months

Details of the assessment procedure are provided in section A around their third birthday, children were seen for assessment by experienced clinical researchers to determine ASD diagnosis. Children were administered the ADOS (24 and 36 months), a semi-structured observational measure, and the ADI-R, a structured parent interview of children's ASD symptoms. Particularly, in phase 1, 52 of the 54 EL infants were seen for assessment at 24 months while 53 were seen at 36 months. Regarding the ADOS assessment, 50 infants at EL were administered Module 1, and two Module 2 at 24 months. At 36 months, in both groups of infants, three were administered Module 1 and 98 Module 2. Regarding the TL infants, they were not administered the ADI-R in Phase 1, while in Phase 2 they were administered the ADOS and ADI-R for outcome assessment at 36 months. None of the infants showed any signs of atypical behaviour or ASD.

4.6.2 Examination of Age Intervals in the LCS Models

Across all the models, the autoregressive parameter between PDI at 8 and 14 months was fixed to unity, assuming that the age intervals are equidistant across individuals. There were no outcome group (TL, EL-no ASD, EL-ASD) differences in age interval ($F(2,236) = .835, p = .435, \eta_p^2 = .007$). There were no risk group (EL, TL) differences in age interval either $t(237) = 1.23, p = .220, d = .17$. The variance in age interval (months) was considered low ($M = 6.33, SE = 0.74$).

However, 15 participants had an interval greater than 2 *SD* below/above the mean, thus, they were excluded. Analyses were re-run with the excluded participants and no considerable changes were found. The results were similar to the main results:

In the multiple indicator LCS model, the same results were found in the association between PDI and dimensional outcomes: PDI change only was significantly related to externalising behaviour (PDI T1: $\beta = -0.17, p = .026$; PDI change: $\beta = -0.29, p < .001$), both PDI change and PDI at 8 month were significantly related to language (PDI 8 months: $\beta = 0.23, p = .002$; PDI change: $\beta = .26, p = .001$) and social communication (PDI 8 months: $\beta = 0.19, p = .014$; PDI change: $\beta = 0.24, p < .001$). The ASD likelihood group was a significant predictor of all dimensional outcomes ($p < .001$) except externalising behaviour ($\beta = 0.11, p = .077$). Group was also a non-significant predictor of PDI change ($\beta = -0.04, p = .532$).

Similarly, in the attentiveness LCS model, attentiveness change was significantly related to externalising behaviour ($\beta = -0.19, p = .003$). ASD likelihood group was a significant predictor of attentiveness change ($p = .006$) and dimensional outcomes (all $ps < .001$) except externalising behaviour ($\beta = 0.10, p = .124$). Furthermore, in the affect model, no significant relationships were found between affect change and dimensional outcomes (all $ps > .026$).

In addition to the above, analysis was re-run with age interval as a covariate of the change factor across all the models in order to account for differences in age interval across the two time points. Again, the results were similar across the models: PDI change significantly predicted externalising behaviour ($\beta = -0.29, p < .001$), language ($\beta = 0.26, p = .001$) and social communication ($\beta = 0.24, p < .001$). Parent-dyadic interaction at 8 months was predictive of language ($\beta = 0.23, p = .002$) and marginally predictive of social communication outcomes ($\beta = 0.17, p = .024$). Attentiveness change was associated with externalising behaviour ($\beta = -0.20, p = .002$), while affect was not related to any of the dimensional outcomes (all $ps > .025$). Age difference was a non-significant predictor of change in all the models (PDI: $\beta = 0.09, p = .127$; Attentiveness: $\beta = 0.06, p = .290$; Affect: $\beta = -0.04, p = .426$).

4.6.3 Missing Data Evaluation

Missing data analysis was performed across phase 1 and 2 separately at 8 and 14 months in order to investigate whether data used in this study were MAR, MCAR, or neither. Firstly, the variables that contained missing data were dummy-coded. Further, descriptive statistics of missing data were examined, and logistic regressions were performed with missing data indicators as the dependent variable and elevated likelihood for ASD (EL, TL), biological sex, age, verbal and non-verbal developmental level, Vineland internalising and externalising behaviours, SRS and SCQ as the independent variables. Correlations between the independent variables were also examined before they were included in the models to ensure there was no high collinearity between them.

Logistic regressions revealed that ASD likelihood group was a significant predictor of missingness in 14-month sensitive responsiveness, nondirectiveness, attentiveness, mutuality ($Exp(B) = 0.12$, $SE = 1.05$, $Wald = 4.25$, $p = .04$) and affect ($Exp(B) = 0.09$, $SE = 1.04$, $Wald = 5.59$, $p = .02$). In addition, at 14 months, females had more missing data in affect than males ($Exp(B) = 3.66$, $SE = 0.64$, $Wald = 4.12$, $p = .04$). Therefore, missing data were considered as MAR and Full Information Maximum Likelihood (FIML) was used. To handle missing data, FIML method calculates the likelihood function for each individual case based on the data that are available from that case and was preferred over 'listwise deletion' which is one of the most common methods used to deal with missing data. The rationale for using FIML was that, under MAR, FIML has shown to produce less biased parameter estimates (Enders & Bandalos, 2001).

4.6.4 Multigroup Measurement Invariance

Initially, measurement invariance across groups at each time point was tested. At the 8-month time-point, the configural and metric invariance models showed acceptable

standalone fit and negligible change in the alternative fit indices, except a non-negligible change in SRMR (> 0.025). In addition, the configural model resulted in a negative variance estimate for one of the observed variables (sensitive responsiveness), which was manually fixed to zero. Metric invariance was accepted as the rest of the fit indices were acceptable and it has been suggested that SRMR tends to over-reject an invariant model in small sample sizes (F. F. Chen, 2007). Further testing of the scalar invariance model showed an acceptable standalone fit (mediocre fit for RMSEA: > 0.08 but < 0.01) but a non-negligible change in the alternative fit indices. Partial scalar invariance was run after inspection of the modification indices, where the parameters of the PII item 'nondirectiveness' were free to vary across the groups. The partial scalar invariance model provided an acceptable standalone fit and a negligible change in the alternative fit indices. Last, a partial strict invariance model was tested but standalone fit and the alternative fit indices were above the acceptable threshold, thus, partial scalar invariance was concluded. **Table A4.6** shows the results of the measurement invariance for the PDI factor across groups at 8 months.

Subsequently, measurement invariance across groups at the 14-month time point was tested. The configural invariance model showed acceptable standalone fit and negligible change in the alternative fit indices but resulted in a negative variance estimate for the 'sensitive responsiveness' observed variable. The variance was manually fixed to zero. The metric invariance model was run next which led to an unacceptable fit and a non-negligible change in fit indices. After the inspection of the modification indices, partial metric invariance was run in which the parameters of the PII item 'mutuality' were free to vary across the groups. The partial metric invariance model provided an acceptable standalone fit and a negligible change in fit indices except for Δ RMSEA (> 0.010) and Δ SRMR (> 0.025). However, considering that both of these indices tend to over-reject an invariant model when the sample size is small and Δ RMSEA can also be affected by

model complexity (F. F. Chen, 2007), partial metric invariance was accepted. Further, partial scalar invariance was run and provided an unacceptable standalone fit and alternative fit indices. The modification indices were inspected again, and partial scalar invariance was run, freeing the parameters of the item ‘sensitive responsiveness’ across groups. Partial scalar invariance provided an unacceptable model fit and a non-negligible change in the alternative fit indices. Therefore, partial scalar measurement invariance was not supported. No further constraints were released, as only one invariant indicator would not be sufficient to establish the comparability of the PII constructs across the groups. Since partial scalar invariance was not achieved, partial strict invariance was not tested. **Table A4.7** shows the results of the measurement invariance for the PDI factor across groups at 14 months.

Next, measurement invariance was tested over time within each group. In the TL group across time, the configural invariance model showed an acceptable standalone fit but resulted in a negative variance estimate for the ‘sensitive responsiveness’ PII item. The variance was fixed to zero. The metric invariance model showed an acceptable standalone fit and a negligible change in fit indices, except RMSEA (RMSEA: 0.117, Δ RMSEA > 0.010). Considering that RMSEA has been suggested to be affected by small sample sizes and given that the sample size of the model was relatively small, metric invariance was accepted. The scalar invariance model resulted in a worsening of fit and a non-negligible change in the fit indices. Releasing an equality constraint (sensitive responsiveness intercept) after inspection of the modification indices led to an improvement in model fit and a negligible change in the alternative fit indices, thus, partial scalar invariance was supported. The partial strict invariance model resulted in a worsening of model fit and change in fit indices (CFI > 0.005, RMSEA > 0.010). Based on the modification indices, the constraints of the item ‘mutuality’ were freed, which led to an improvement in model fit compared to the prior model and a negligible change in

fit indices. Thus, partial strict longitudinal measurement invariance was concluded for the TL group. **Table A4.8** shows the results of the measurement invariance for the TL group across time.

In the EL-no ASD group, the configural, metric and scalar invariance models resulted in a negligible change in fit indices and an acceptable standalone fit. Strict invariance testing provided an acceptable model fit except $\Delta\text{RMSEA} (> 0.010)$. Considering RMSEA's sensitivity to sample size and given that the rest of the fit indices provided an acceptable fit, strict measurement invariance was concluded for the EL-no ASD group. **Table A4.9** shows the results of the measurement invariance for the EL-no ASD group across time.

Last, in the EL-ASD group, the configural and metric invariance models showed an acceptable fit and a negligible change in fit indices except for RMSEA and SRMR. However, metric invariance was accepted, given the sensitivity of these indices to sample size. Scalar invariance provided an unacceptable model fit and a non-negligible change in all the fit indices. Partial scalar invariance was run with the parameters of the 'mutuality' item freed following inspection of the modification indices. This model provided an acceptable model standalone fit but a non-negligible change in the alternative fit indices ($\Delta\text{CFI} > 0.005$; $\Delta\text{RMSEA} > 0.010$; $\Delta\text{SRMR} > -0.005$). Thus, partial scalar invariance was not supported. No further constraints were released, as only one invariant indicator would not be sufficient to establish the comparability of the PII constructs across time. Since partial scalar invariance was not achieved, partial strict invariance was not tested. **Table A4.10** shows the results of the measurement invariance for the EL-ASD group across time.

Table A4.1*Intra-Class Correlation Coefficients (ICC) Between Coders for The MACI Items*

		8 months		14 months	
		Phase 1	Phase 2	Phase 1	Phase 2
		(N 25%)	(N 10%)	(N 26%)	(N 10%)
<i>Parent</i>	Sensitive Responsiveness	0.66	0.88	0.74	0.67
	Non-directiveness	0.63	0.68	0.75	0.67
<i>Infant</i>	Attentiveness	0.58	0.82	0.69	0.73
	Positive affect (MACI version 1)	0.82	-	0.77	-
	Positive affect (updated MACI version)	-	0.70	-	0.71
	Negative affect (updated MACI version)	-	0.81	-	0.71
	Mutuality	0.80	0.75	0.83	0.70

Note. Values ≥ 0.60 indicate good to excellent ICC.*Abbreviations:* MACI: Manchester assessment of caregiver-infant Interaction.

Table A4.2

Results of the Shapiro-Wilk Tests Assessing the Normality of the Distribution of Scores of the Variables Used in the Latent Change Score Models

Variable	<i>W</i>	<i>p</i>
<i>8 months</i>		
Parent sensitive responsiveness	0.909	< 0.001
Parent nondirectiveness	0.923	< 0.001
Infant attentiveness	0.927	< 0.001
Infant affect	0.968	< 0.001
Dyadic mutuality	0.930	< 0.001
Language	0.990	0.179
Social communication	0.978	0.004
<i>14 months</i>		
Parent sensitive responsiveness	0.914	< 0.001
Parent nondirectiveness	0.917	< 0.001
Infant Attentiveness	0.921	< 0.001
Infant affect	0.960	< 0.001
Dyadic mutuality	0.911	< 0.001
Language	0.970	< 0.001
Social communication	0.987	0.063
<i>36 months</i>		
SRS Total	0.812	< 0.001
SCQ Total	0.742	< 0.001
Internalising behaviour	0.822	< 0.001
Externalising behaviour	0.811	< 0.001
Language	0.978	0.006
Social communication	0.950	< 0.001

Abbreviations. SCQ: Social communication questionnaire; SRS: Social responsiveness scale; W: Shapiro-Wilk test.

Table A4.3*Sample Demographic and Clinical Characteristics by Clinical Outcome Group at 36 Months*

	Total	TL	EL-no ASD	EL-ASD	F/H	Group comparisons
Participants, N	243	27	96	17		
	Mean (SD)					
Age	38.42 (2.35)	38.40 (2.65)	38.50 (2.28)	38.15 (1.94)	0.30	-
MSEL ELC	107.61 (24.47)	117.04 (15.91)	106.71 (21.65)	89.78 (28.35)	17.25*** ^a	TL>EL-noASD/EL-ASD; EL-noASD>EL-ASD
VABS ABC	98.73 (12.92)	106.44 (8.11)	98.23 (10.95)	83.63 (15.12)	40.72*** ^a	TL>EL-noASD/EL-ASD; EL-noASD>EL-ASD
ADOS-2 Social Affect Total Score ^b	4.58 (4.11)	4.21 (3.45)	3.85 (3.60)	8.30 (5.30)	5.76*** ^a	TL<EL-ASD; EL-noASD<EL-ASD
ADOS-2 RRB Total Score ^b	1.36 (1.50)	0.99 (1.15)	1.20 (1.37)	2.79 (1.83)	28.03*** ^a	TL<EL-ASD; EL-noASD<EL-ASD
ADOS-2 CSS ^b	2.95 (2.40)	2.67 (2.0)	2.56 (2.11)	5.15 (3.08)	21.16*** ^a	TL<EL-ASD; EL-noASD<EL-ASD
ADI-R Social	3.43 (4.76)	0.96 (1.49)	2.06 (2.73)	10.94 (5.69)	67.63*** ^a	TL<EL-ASD; EL-noASD<EL-ASD
ADI-R Communication	3.60 (4.58)	0.48 (1.05)	2.63 (3.33)	9.97 (5.08)	68.44*** ^a	TL<EL-noASD/EL-ASD; EL-noASD<EL-ASD
ADI-R Behaviours/Repetitive interests ^d	1.30 (2.18)	0.08 (0.28)	0.72 (1.38)	4.63 (2.56)	73.95*** ^a	TL<EL-ASD; EL-noASD<EL-ASD

^a The Kruskal-Wallis test was used for variables with non-normally distributed scores based on histograms, Q-Q plots and Shapiro-Wilk tests. Differences between groups have been adjusted by the Bonferroni correction for multiple comparisons.

Abbreviations. ADI-R: Autism Diagnostic Interview-revised; ADOS: Autism Diagnostic Observation Schedule; ASD: Autism spectrum disorder; CSS: ADOS-2 Calibrated Severity Scale; EL: Elevated likelihood; H: Kruskal-Wallis test; MSEL ELC: Mullen Scales of Early Learning Early Learning Composite; RRB: Restricted and Repetitive Behaviours; SRS: Social Responsiveness Scale; TL: Typically developing infants; VABS: Vineland Adaptive Behaviour Scales.

* $p < 0.05$. ** $p < 0.001$.

Table A4.4*Sibling Group Means on the PII and Dimensional Outcome Variables Used in the Study*

			8 months			14 months						
			Mean (<i>SD</i>)									
			Total	TL	EL	EL-no ASD	EL-ASD	Total	TL	EL	EL-no ASD	EL-ASD
			<i>N</i> = 216	<i>n</i> = 71	<i>n</i> = 145	<i>n</i> = 115	<i>n</i> = 30	<i>N</i> = 221	<i>n</i> = 74	<i>n</i> = 147	<i>n</i> = 120	<i>n</i> = 27
Parent Sensitive												
responsiveness			3.70 (1.26)	3.93 (1.37)	3.59 (1.19)	3.67 (1.20)	3.27 (1.26)	4.17 (1.33)	4.38 (1.40)	4.06 (1.29)	4.19 (1.28)	3.48 (1.19)
Parent												
Nondirectiveness			3.72 (1.31)	4.10 (1.22)	3.53 (1.31)	3.64 (1.31)	3.10 (1.27)	4.04 (1.32)	4.51 (1.32)	3.80 (1.26)	3.89 (1.28)	3.41 (1.08)
Dyadic mutuality			3.34 (1.29)	3.42 (1.42)	3.30 (1.22)	3.34 (1.84)	3.17 (1.37)	3.82 (1.38)	4.26 (1.41)	3.61 (1.32)	3.78 (1.31)	2.81 (1.04)
Infant attentiveness			3.99 (1.27)	3.92 (1.30)	4.02 (1.26)	4.01 (1.21)	4.03 (1.45)	4.48 (1.21)	4.80 (1.21)	4.32 (1.19)	4.48 (1.16)	3.59 (1.05)
Infant affect			4.26 (1.22)	4.01 (1.14)	4.38 (1.24)	4.33 (1.24)	4.58 (1.22)	4.56 (1.23)	4.40 (1.07)	4.65 (1.30)	4.80 (1.23)	3.96 (1.41)
Infant positive affect ^a			3.56 (1.62)	3.29 (1.30)	3.63 (1.69)	3.40 (1.57)	4.81 (1.83)	4.64 (1.70)	4.38 (1.65)	4.71 (1.71)	4.74 (1.68)	4.50 (1.95)
Infant negative affect ^a			2.46 (1.65)	2.38 (1.56)	2.48 (1.67)	2.33 (1.61)	3.25 (1.84)	2.57 (1.58)	2.27 (1.25)	2.65 (1.65)	2.60 (1.67)	2.93 (1.59)
Lang ^b			49.24 (8.36)	49.64 (7.51)	49.05 (8.74)	49.70 (8.18)	46.45 (10.43)	45.24 (10.28)	47.96 (10.02)	43.99 (10.19)	45.34 (10.03)	38.84 (9.19)
				102.35	96.13	96.70						
SC ^c			98.09 (12.91)	(12.17)	(12.80)	(12.51)	93.99 (13.82)	97.18 (11.25)	101.0 (8.84)	95.41 (11.81)	97.12 (11.50)	88.88 (10.84)
Dimensional												
outcomes	at	36	Total	TL	EL	EL-no ASD	EL-ASD					
months			<i>N</i> = 243	<i>n</i> = 77	<i>n</i> = 166	<i>n</i> = 132	<i>n</i> = 34					
Internalising 36 ^d			14.31 (2.59)	13.32 (1.85)	14.76 (2.75)	14.01 (2.29)	17.87 (2.30)					
Externalising 36 ^d			13.19 (2.50)	12.72 (2.30)	13.40 (2.57)	12.86 (2.36)	15.63 (2.21)					

			35.62	28.96	
SRS 36 ^e	30.54 (23.45)	19.81 (9.24)	(26.29)	(20.23)	62.70 (30.75)
SCQ 36 ^f	5.27 (6.14)	2.89 (2.38)	6.36 (6.98)	4.63 (5.46)	13.80 (7.94)
			50.75	52.62	
Lang 36 ^g	53.10 (12.11)	58.37 (8.52)	(12.74)	(11.17)	43.33 (15.76)
		106.87	96.24	99.12	
SC 36 ^h	99.48 (12.31)	(7.59)	(12.59)	(10.48)	84.56 (13.82)

^a Only Phase 2 data available for positive and negative affect (124 infants provided data for these variables at 8 months and 126 infants at 14 months).

^b Missing data for one infant at 8 months and 5 infants at 14 months.

^c Missing data for five infants at 8 months and 10 infants at 14 months.

^d Missing data for 18 infants.

^e Missing data for 19 infants.

^f Missing data for 11 infants.

^g Missing data for six infants.

^h Missing data for 10 infants.

Abbreviations. ASD: Autism Spectrum Disorder; EL: Elevated likelihood; Lang: language; SC: Social communication; SCQ: Social communication questionnaire; SRS: Social responsiveness scale; TL: Typical likelihood.

Table A4.5

Tests of Longitudinal Measurement Invariance for the PII Multiple-indicator Univariate Latent Change Score Model Across the Whole Sample

Model	parameters	Fit Indices				Comparison of fit indices between nested models					Decision
		χ^2 (<i>df</i>)	CFI	RMSEA [90% CI]	SRMR	Model comp	$\Delta\chi^2$ (Δdf)	Δ CFI	Δ RMSEA	Δ SRMR	
M1: Configural invariance (no constraints) ^a	22	24.141 (7)	0.978	0.105 [0.058, 0.156]	0.038	-	-	-	-	-	-
M2: Metric invariance (factor loadings constrained) ^a	22	24.421 (9)	0.980	0.089 [0.045, 0.134]	0.039	M1	-0.280 (2)	-0.002	0.016	-0.001	Accept
M3: Scalar invariance (factor loadings and intercepts constrained) ^a	22	25.633 (11)	0.980	0.079 [0.038, 0.121]	0.040	M2	-1.212 (2)	0.000	0.010	-0.001	Accept
M4: Residual invariance	22	24.675 (12)	0.981	0.074 [0.031, 0.115]	0.038	M3	0.958 (1)	-0.001	0.005	0.002	Accept

(factor loadings,
intercepts and
residual variances
constrained)^a

Note. $N = 247$ (243 used); Method: Full information Maximum Likelihood. ^a Running the configural model resulted in a negative variance estimate for the ‘sensitive responsiveness’ variable. The variance was manually fixed to zero.

Abbreviations. χ^2 : chi-square test; CFI: comparative fit index; RMSEA: root mean squared error of approximation; CI: confidence interval; SRMR: standardised root mean squared residual; Model comp: model comparison; Δ : denotes change value; $\Delta \chi^2$: chi-square difference test; Δdf : degrees of freedom difference; $\Delta CFI / \Delta RMSEA / \Delta SRMR$: alternative fit indices; ΔCFI : change in comparative fit index; $\Delta RMSEA$: change in root mean squared error of approximation; $\Delta SRMR$: change in standardised root mean squared residual.

Table A4.6*Tests of Measurement Invariance Across Groups at 8 Months*

Model	parameters	Fit Indices				Comparison of fit indices between nested models					Decision
		χ^2 (<i>df</i>)	CFI	RMSEA [90% CI]	SRMR	Model comp	$\Delta\chi^2$ (Δdf)	Δ CFI	Δ RMSEA	Δ SRMR	
M1: Configural invariance (no constraints) ^a	24	3.881 (3)	0.997	0.064 [0.000, 0.220]	0.014	-	-	-	-	-	-
M2: Metric invariance (factor loadings constrained) ^a	24	8.447 (7)	0.995	0.054 [0.000, 0.165]	0.061	M1	-4.566 (4)	0.002	0.010	-0.047	Accept
M3: Scalar invariance (factor loadings and intercepts constrained) ^a	26	16.873 (11)	0.978	0.086 [0.000, 0.163]	0.040	M2	-8.426 (4)	0.017	-0.032	0.021	Reject
M4: Partial scalar invariance (factor loadings and intercepts constrained) ^a	26	10.412 (9)	0.995	0.047 [0.000, 0.163]	0.064	M2	-1.965 (2)	0.000	0.007	-0.003	Accept

^b

M5:	26	16.312	0.988	0.059	0.077	M4	-5.900	0.007	-0.012	-0.013	Reject
Partial residual invariance (factor loadings, intercepts and residual variances constrained) ^{a b}		(13)		[0.000, 0.137]			(4)				

Note. $N = 247$ (243 used); Method: Full information Maximum Likelihood.

^a Negative variance estimate for the PII item ‘sensitive responsiveness’. The variance was manually fixed to zero.

^b The ‘nondirectiveness’ item’s parameters free to vary across groups.

Abbreviations. χ^2 : chi-square test; CFI: comparative fit index; RMSEA: root mean squared error of approximation; CI: confidence interval; SRMR: standardised root mean squared residual; Model comp: model comparison; Δ : denotes change value; $\Delta \chi^2$: chi-square difference test; Δdf : degrees of freedom difference; $\Delta CFI / \Delta RMSEA / \Delta SRMR$: alternative fit indices; ΔCFI : change in comparative fit index; $\Delta RMSEA$: change in root mean squared error of approximation; $\Delta SRMR$: change in standardised root mean squared residual.

Table A4.7*Tests of Measurement Invariance Across Groups at 14 Months*

Model	parameters	Fit Indices				Comparison of fit indices between nested models					Decision
		χ^2 (<i>df</i>)	CFI	RMSEA [90% CI]	SRMR	Model comp	$\Delta\chi^2$ (Δdf)	Δ CFI	Δ RMSEA	Δ SRMR	
M1: Configural invariance (no constraints) ^a	24	5.740 (3)	0.995	0.085 [0.000, 0.220]	0.015	-	-	-	-	-	-
M2: Metric invariance (factor loadings constrained) ^a	24	18.954 (7)	0.972	0.137 [0.048, 0.225]	0.095	M1	-13.214 (4)	0.023	-0.052	-0.08	Reject
M2: Partial Metric invariance (factor loadings constrained) ^{a b}	24	8.038 (5)	0.995	0.066 [0.000, 0.194]	0.056	M1	-2.298 (2)	0.000	0.019	-0.041	Accept
M3: Partial scalar invariance	26	43.576 (9)	0.908	0.217 [0.148, 0.291]	0.138	M2	-35.718 (4)	0.087	-0.151	0.082	Reject

(factor loadings
and intercepts
constrained)^{a b}

M4:	26	14.428	0.981	0.111	0.081	M2	-6.390	0.014	-0.045	-0.025	Reject
Partial scalar invariance		(7)		[0.000, 0.207]			(2)				

(factor loadings
and intercepts
constrained)^{a b c}

Note. $N = 247$ (243 used); Method: Full information Maximum Likelihood. Strict invariance was not tested as partial scalar invariance was not achieved.

^a Negative variance estimate for the PII item ‘sensitive responsiveness’. The variance was manually fixed to zero.

^b The ‘mutuality item’s parameters free to vary across groups.

^c The ‘sensitive responsiveness’ item’s parameters free to vary across groups.

Abbreviations. χ^2 : chi-square test; CFI: comparative fit index; RMSEA: root mean squared error of approximation; CI: confidence interval; SRMR: standardised root mean squared residual; Model comp: model comparison; Δ : denotes change value; $\Delta \chi^2$: chi-square difference test; Δdf : degrees of freedom difference; $\Delta CFI / \Delta RMSEA / \Delta SRMR$: alternative fit indices; ΔCFI : change in comparative fit index; $\Delta RMSEA$: change in root mean squared error of approximation; $\Delta SRMR$: change in standardised root mean squared residual.

Table A4.8

Tests of Measurement Invariance within groups across time: TL group

Model	parameters	Fit Indices				Comparison of fit indices between nested models					Decision
		χ^2 (<i>df</i>)	CFI	RMSEA [90% CI]	SRMR	Model comp	$\Delta\chi^2$ (Δdf)	Δ CFI	Δ RMSEA	Δ SRMR	
M1: Configural invariance (no constraints) ^a	21	21.997 (8)	0.959	0.142 [0.060, 0.226]	0.059	-	-	-	-	-	-
M2: Metric invariance (factor loadings constrained) ^a	21	21.177 (10)	0.965	0.117 [0.030, 0.195]	0.060	M1	820 (2)	-0.006	0.025	-0.001	Accept
M3: Scalar invariance (factor loadings and intercepts constrained) ^a	21	35.645 (12)	0.924	0.158 [0.094, 0.224]	0.085	M2	-14.468 (2)	0.041	-0.041	-0.025	Reject
M4:	21	21.537 (11)	0.964	0.113 [0.025, 0.187]	0.063	M2	-0.36 (1)	0.001	0.004	-0.003	Accept

**Partial scalar
invariance**
(factor loadings
and intercepts
constrained)^{a, b}

M5:	21	30.213	0.939	0.141	0.065	M4	-8.676	0.025	-0.028	-0.002	Reject
Partial strict invariance		(12)		[0.073, 0.210]			(1)				

(factor loadings,
intercepts and
residual
variances
constrained)^{a, b}

M6:	21	22.692	0.959	0.121	0.064	M4	-1.155	0.005	-0.008	-0.001	Accept
Partial strict invariance		(11)		[0.040, 0.195]			(0)				

(factor loadings,
intercepts and
residual
variances
constrained)^{a, b, c}

Note. $N = 77$; Method: Full information Maximum Likelihood

^aNegative variance estimate for the PII item ‘sensitive responsiveness’. The covariance between sensitive responsiveness at 8 and 14 months was manually fixed to zero. The variance of the item at 8 and 14 months was also fixed to zero.

^b The ‘sensitive responsiveness item’s parameters free to vary.

^c The ‘mutuality’ item’s parameters free to vary.

Abbreviations. χ^2 : chi-square test; CFI: comparative fit index; RMSEA: root mean squared error of approximation; CI: confidence interval; SRMR: standardised root mean squared residual; Model comp: model comparison; Δ : denotes change value; $\Delta \chi^2$: chi-square difference test; Δdf : degrees of freedom difference; $\Delta CFI / \Delta RMSEA / \Delta SRMR$: alternative fit indices; ΔCFI : change in comparative fit index; $\Delta RMSEA$: change in root mean squared error of approximation; $\Delta SRMR$: change in standardised root mean squared residual.

Table A4.9*Tests of Measurement Invariance within groups across time: EL-no ASD group*

Model	parameters	Fit Indices				Comparison of fit indices between nested models					Decision
		χ^2 (df)	CFI	RMSEA [90% CI]	SRMR	Model comp	$\Delta\chi^2$ (Δdf)	Δ CFI	Δ RMSEA	Δ SRMR	
M1: Configural invariance (no constraints) ^a	23	8.263 (6)	0.996	0.048 [0.000, 0.136]	0.015	-	-	-	-	-	-
M2: Metric invariance (factor loadings constrained) ^a	23	8.269 (8)	1.000	0.000 [0.000, 0.108]	0.019	M1	-0.006 (2)	-0.004	0.048	-0.004	Accept
M3: Scalar invariance (factor loadings and intercepts constrained) ^{a, b}	22	10.412 (11)	1.000	0.000 [0.000, 0.092]	0.027	M2	-2.143 (3)	0.000	0.000	-0.008	Accept

M4:	22	13.480	0.996	0.034	0.037	M3	-3.068	0.004	-0.034	-0.010	Accept
Strict invariance		(12)		[0.000, 0.107]			(1)				
(factor loadings, intercepts and residual variances constrained) ^{a, b}											

Note. $N = 132$ (130 used); Method: Full information Maximum Likelihood.

^aNegative variance estimate for the PII item ‘sensitive responsiveness’. The covariance between sensitive responsiveness at 8 and 14 months was manually fixed to zero.

^bNegative variance estimate for the PII item ‘sensitive responsiveness’ at 8 months. The variance was manually fixed to zero.

Abbreviations. χ^2 : chi-square test; CFI: comparative fit index; RMSEA: root mean squared error of approximation; CI: confidence interval; SRMR: standardised root mean squared residual; Model comp: model comparison; Δ : denotes change value; $\Delta \chi^2$: chi-square difference test; Δdf : degrees of freedom difference; $\Delta CFI / \Delta RMSEA / \Delta SRMR$: alternative fit indices; ΔCFI : change in comparative fit index; $\Delta RMSEA$: change in root mean squared error of approximation; $\Delta SRMR$: change in standardised root mean squared residual.

Table A4.10*Tests of Measurement Invariance within groups across time: EL-ASD group*

Model	parameters	Fit Indices				Comparison of fit indices between nested models					Decision
		χ^2 (<i>df</i>)	CFI	RMSEA [90% CI]	SRMR	Model comp	$\Delta\chi^2$ (Δdf)	Δ CFI	Δ RMSEA	Δ SRMR	
M1: Configural invariance (no constraints) ^a	22	9.773 (7)	0.971	0.095 [0.000, 0.136]	0.097	-	-	-	-	-	-
M2: Metric invariance (factor loadings constrained) ^a	22	14.666 (9)	0.933	0.128 [0.000, 0.270]	0.130	M1	-0.006 (2)	-0.004	0.048	-0.004	Accept
M3: Scalar invariance (factor loadings and intercepts constrained) ^a	22	19.587 (11)	0.882	0.153 [0.000, 0.276]	0.152	M2	-4.921 (2)	0.051	-0.025	-0.022	Reject
M4: Partial scalar invariance	22	10.354 (10)	1.000	0.000 [0.000, 0.101]	0.026	M2	10.312 (1)	-0.067	0.128	0.104	Reject

(factor loadings
and intercepts
constrained)^{a, b}

Note. $N = 34$ (32 used); Method: Full information Maximum Likelihood. Strict invariance was not tested as partial scalar invariance was not achieved.

^a Negative variance estimate for the PII item ‘sensitive responsiveness’. The covariance between sensitive responsiveness at 8 and 14 months was manually fixed to zero. The variance of the item at 8 and 14 months was also fixed to zero.

^b The ‘mutuality’ item’s parameters free to vary.

Abbreviations. χ^2 : chi-square test; CFI: comparative fit index; RMSEA: root mean squared error of approximation; CI: confidence interval; SRMR: standardised root mean squared residual; Model comp: model comparison; Δ : denotes change value; $\Delta \chi^2$: chi-square difference test; Δdf : degrees of freedom difference; ΔCFI / $\Delta RMSEA$ / $\Delta SRMR$: alternative fit indices; ΔCFI : change in comparative fit index; $\Delta RMSEA$: change in root mean squared error of approximation; $\Delta SRMR$: change in standardised root mean squared residual.

Table A4.11*Parameter Estimates of the Univariate Latent Change Score Model for Parent-Dyadic Interaction*

Latent variables						CI	CI	
	Indicator	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	lower	upper	β
PDIT1	SRT1	1				1	1	1
PDIT1	NDT1	0.707	0.035	20.484	<0.001	0.64	0.775	0.693
PDIT1	MutT1	0.801	0.03	26.946	<0.001	0.742	0.859	0.764
PDIT2	SRT2	1				1	1	1
PDIT2	NDT2	0.707	0.035	20.484	<0.001	0.64	0.775	0.714
PDIT2	MutT2	0.801	0.03	26.946	<0.001	0.742	0.859	0.783
dPDI	PDI	1				1	1	1.063
						CI	CI	
Regressions	Predictors	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	lower	upper	β
PDIT2	PDIT1	1				1	1	0.943
PDI change	PDIT1	-0.573	0.064	-8.972	<0.001	-0.698	-0.448	-0.508
						CI	CI	
Covariances	Covariates	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	lower	upper	β
SRT1	SRT2	0				0	0	NaN
NDT1	NDT2	0.188	0.066	2.864	0.004	0.059	0.317	0.22
MutT1	MutT2	0.037	0.052	0.708	0.479	-0.065	0.139	0.051
						CI	CI	
		<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	lower	upper	β
PDI change	Intercept	2.598	0.256	10.166	<0.001	2.097	3.099	1.835
PDIT1	Intercept	3.697	0.085	43.635	<0.001	3.531	3.863	2.944
PDI change	Variance	1.487	0.122	12.191	<0.001	1.248	1.727	0.742
PDIT1	Variance	1.577	0.122	12.923	<0.001	1.338	1.816	1

Note. Negative variance estimate for the SR indicator. The variance of SR was manually fixed to zero. No further adjustments made. Method: Full information maximum likelihood with robust standard errors.

Abbreviations. Mut: Dyadic mutuality; ND: Parent nondirectiveness; PDI: Parent-dyadic interaction; SR: Parent sensitive responsiveness; T1: Time 1 (8 months); T2: Time 2 (14 months).

Table A4.12

Parameter Estimates of the Univariate Latent Change Score Model for Parent-Dyadic Interaction with Dimensional Outcomes

Latent variables						CI		
	Indicator	B	SE	z	p	lower	upper	β
PDIT1	SRT1	1				1		1
PDIT1	NDT1	0.707	0.035	20.484	<0.001	0.64	0.775	0.693
PDIT1	MutT1	0.801	0.030	26.946	<0.001	0.742	0.859	0.764
PDIT2	SRT2	1						1
PDIT2	NDT2	0.707	0.035	20.484	<0.001	0.64	0.775	0.714
PDIT2	MutT2	0.801	0.030	26.946	<0.001	0.742	0.859	0.783
dPDI	PDI	1						1.062
						CI		
Regressions	Predictors	B	SE	z	p	lower	upper	β
PDIT2	PDIT1	1				1	1	0.942
								-
PDI change	PDIT1	-0.572	0.063	-9.086	<0.001	-0.696	-0.449	0.508
SC 36	PDIT1	1.668	0.728	2.290	0.022	0.241	3.095	0.169
Lang 36	PDIT1	2.144	0.688	3.115	0.002	0.795	3.493	0.224
Internalising								-
36	PDIT1	-0.262	0.157	-1.667	0.096	-0.57	0.046	0.124
Externalising								-
36	PDIT1	-0.382	0.154	-2.477	0.013	-0.685	-0.08	0.189
								-
SRS 36	PDIT1	-1.416	1.354	-1.046	0.296	-4.069	1.238	0.076
								-
SCQ 36	PDIT1	-0.452	0.381	-1.188	0.235	-1.199	0.294	0.092
SC 36	PDI change	1.701	0.59	2.885	0.004	0.545	2.857	0.195
Lang 36	PDI change	1.938	0.636	3.049	0.002	0.692	3.184	0.228
Internalising								-
36	PDI change	-0.192	0.134	-1.436	0.151	-0.454	0.07	0.102
Externalising								-
36	PDI change	-0.512	0.148	-3.455	0.001	-0.802	-0.221	0.285
								-
SRS 36	PDI change	-1.187	1.208	-0.983	0.326	-3.555	1.181	0.072

								-
SCQ 36	PDI change	-0.129	0.354	-0.363	0.717	-0.823	0.566	0.029
								-
SC 36	Group	-10.481	1.321	-7.936	<0.001	-13.069	-7.892	0.394
								-
Lang 36	Group	-7.005	1.377	-5.089	<0.001	-9.703	-4.307	0.271
Internalising								
36	Group	1.482	0.313	4.735	<0.001	0.869	2.095	0.26
Externalising								
36	Group	0.661	0.33	2.002	0.045	0.014	1.307	0.121
SRS 36	Group	15.409	2.298	6.705	<0.001	10.905	19.914	0.307
SCQ 36	Group	3.432	0.617	5.561	0	2.222	4.641	0.258
							CI	CI
Covariances	Covariates	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	lower	upper	β
SRT1	SRT2							
NDT1	NDT2	0.188	0.066	2.864	0.004	0.059	0.317	0.22
MutT1	MutT2	0.037	0.052	0.708	0.479	-0.065	0.139	0.051
Lang 36	SCQ 36	80.915	11.713	6.908	<0.001	57.958	103.872	0.645
Internalising								-
36	SCQ 36	-13.16	2.464	-5.342	<0.001	-17.988	-8.331	0.465
Externalising								-
36	SCQ 36	-6.237	1.989	-3.136	0.002	-10.135	-2.339	0.230
		-				-		-
SRS 36	SCQ 36	130.638	25.475	-5.128	<0.001	180.568	-80.707	0.529
								-
SCQ 36	SCQ 36	-32.734	6.752	-4.848	<0.001	-45.968	-19.501	0.494
Internalising								-
36	Lang 36	-7.566	2.353	-3.215	0.001	-12.179	-2.954	0.265
Externalising								-
36	Lang 36	-3.203	2.148	-1.491	0.136	-7.413	1.006	0.117
						-		-
SRS 36	Lang 36	-58.422	22.506	-2.596	0.009	102.532	-14.312	0.235
								-
SCQ 36	Lang 36	-13.525	6.125	-2.208	0.027	-25.529	-1.521	0.202
Externalising	Internalising							
36	36	3.077	0.51	6.033	<0.001	2.077	4.076	0.497

	Internalising							
SRS 36	36	33.948	6.254	5.428	<0.001	21.691	46.206	0.603
	Internalising							
SCQ 36	36	8.593	1.562	5.501	<0.001	5.531	11.654	0.568
	Externalising							
SRS 36	36	24.943	4.908	5.082	<0.001	15.323	34.563	0.462
	Externalising							
SCQ 36	36	6.755	1.275	5.298	<0.001	4.256	9.253	0.466
SRS 36	SCQ 36	115.115	18.325	6.282	<0.001	79.198	151.032	0.874
						CI	CI	
		B	SE	z	p	lower	upper	β
PDI change	Intercept	2.588	0.252	10.256	<0.001	2.093	3.082	1.829
PDIT1	Intercept	3.698	0.085	43.543	<0.001	3.532	3.865	2.945
PDI change	Variance	1.486	0.121	12.237	<0.001	1.248	1.725	0.742
PDIT1	Variance	1.576	0.122	12.928	<0.001	1.337	1.815	1

Note. Negative variance estimate for the SR indicator. The variance of SR was manually fixed to zero. No further adjustments made. “Group” refers to ASD likelihood group (EL, TL). Method: Full information maximum likelihood with robust standard errors.

Abbreviations. Lang: Language; Mut: Dyadic mutuality; ND: Parent nondirectiveness; PDI: Parent-dyadic interaction; SC: Social communication; SCQ: Social communication questionnaire; SR: Parent sensitive responsiveness; SRS: Social responsiveness scale; T1: Time 1 (8 months); T2: Time 2 (14 months).

Table A4.13*Parameter Estimates of the Univariate Latent Change Score Model for Infant Attentiveness*

Latent variables	Indicator	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	CI	CI	β
						lower	upper	
Att change	AttT2	1				1	1	1.279
Regressions	Predictors	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	CI	CI	β
						lower	upper	
AttT2	AttT1	1				1	1	1.047
Att change	AttT1	-0.79	0.068	-11.636	<0.001	-0.923	-0.657	-0.647
		<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	CI	CI	β
						lower	upper	
Att change	Intercept	3.647	0.286	12.748	<0.001	3.086	4.208	2.355
AttT1	Intercept	3.993	0.086	46.539	<0.001	3.825	4.162	3.151
Att change	Variance	1.395	0.11	12.742	<0.001	1.181	1.61	0.582
AttT1	Variance	1.606	0.131	12.297	<0.001	1.35	1.862	1

Note. Method: Full information maximum likelihood with robust standard errors.*Abbreviations.* Att: Infant attentiveness; T1: Time 1 (8 months); T2: Time 2 (14 months).

Table A4.14*Parameter Estimates of the Univariate Latent Change Score Model for Infant Attentiveness with Dimensional Outcomes*

Latent variables	Indicator	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	CI lower	CI upper	β
Att change	AttT2	1				1	1	1.279
Regressions	Predictors	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	CI lower	CI upper	β
AttT2	AttT1	1				1	1	1.045
Att change	AttT1	-0.791	0.069	-11.487	<0.001	-0.926	-0.656	-0.646
Internalising 36	Att change	-0.157	0.119	-1.318	0.188	-0.391	0.077	-0.092
Externalising	Att change	-0.293	0.103	-2.837	0.005	-0.496	-0.091	-0.179
SRS 36	Att change	-1.463	0.934	-1.566	0.117	-3.294	0.368	-0.097
SCQ 36	Att change	-0.408	0.272	-1.502	0.133	-0.94	0.124	-0.102
SC 36	Att change	1.011	0.522	1.938	0.053	-0.012	2.034	0.126
Lang 36	Att change	0.587	0.535	1.096	0.273	-0.462	1.636	0.075
Internalising 36	Group	1.468	0.32	4.581	<0.001	0.84	2.096	0.257
Externalising 36	Group	0.597	0.341	1.753	0.08	-0.07	1.265	0.109
SRS 36	Group	14.937	2.323	6.429	<0.001	10.384	19.491	0.298
SCQ 36	Group	3.335	0.623	5.35	<0.001	2.113	4.556	0.251
SC 36	Group	-10.344	1.375	-7.524	<0.001	-13.038	-7.649	-0.387
Lang 36	Group	-7.275	1.438	-5.058	<0.001	-10.094	-4.456	-0.28
Att change	Group	-0.492	0.165	-2.985	0.003	-0.815	-0.169	-0.148
Covariances	Covariates	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	CI lower	CI upper	β
Externalising 36	Internalising 36	3.132	0.516	6.075	<0.001	2.121	4.142	0.497
SRS 36	Internalising 36	33.835	6.235	5.426	<0.001	21.614	46.056	0.602
SCQ 36	Internalising 36	8.549	1.563	5.47	<0.001	5.485	11.612	0.566

SC 36	Internalising 36	-13.373	2.386	-5.604	<0.001	-18.05	-8.696	-0.467
Lang 36	Internalising 36	-8.069	2.377	-3.394	0.001	-12.728	-3.409	-0.275
SRS 36	Externalising 36	24.922	4.914	5.072	<0.001	15.291	34.553	0.456
SCQ 36	Externalising 36	6.629	1.275	5.198	<0.001	4.13	9.129	0.451
SC 36	Externalising 36	-6.878	2.012	-3.419	0.001	-10.821	-2.935	-0.247
Lang 36	Externalising 36	-4.29	2.141	-2.003	0.045	-8.486	-0.093	-0.15
SCQ 36	SRS 36	114.107	18.115	6.299	<0.001	78.602	149.611	0.872
SC 36	SRS 36	-130.644	24.737	-5.281	<0.001	-179.128	-82.16	-0.526
Lang 36	SRS 36	-60.682	22.464	-2.701	0.007	-104.712	-16.653	-0.239
SC 36	SCQ 36	-32.416	6.697	-4.841	<0.001	-45.541	-19.29	-0.486
Lang 36	SCQ 36	-13.888	6.306	-2.202	0.028	-26.248	-1.529	-0.203
Lang 36	SC 36	85.206	12.05	7.071	<0.001	61.587	108.824	0.657
		<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	CI lower	CI upper	β
Att change	Intercept	3.972	0.295	13.482	<0.001	3.394	4.549	2.564
AttT1	Intercept	3.992	0.086	46.521	<0.001	3.823	4.16	3.154
Att change	Variance	1.345	0.111	12.069	<0.001	1.126	1.563	0.56
AttT1	Variance	1.602	0.13	12.339	<0.001	1.347	1.856	1

Note. “Group” refers to ASD likelihood group (EL, TL). Method: Full information maximum likelihood with robust standard errors.

Abbreviations. Att: Infant attentiveness; Lang: Language; SC: Social communication; SCQ: Social communication questionnaire; SRS: Social responsiveness scale; T1: Time 1 (8 months); T2: Time 2 (14 months).

Table A4.15*Parameter Estimates of the Univariate Latent Change Score Model for Infant Affect*

Latent variables						CI		
	Indicator	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	lower	upper	β
Aff change	AffT2	1				1	1	1.257
						CI		
Regressions	Predictors	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	lower	upper	β
AffT2	AffT1	1				1	1	0.989
Aff change	AffT1	-0.796	0.068	-11.681	<0.001	-0.93	-0.663	-0.627
						CI		
		<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	lower	upper	β
Aff change	Intercept	3.702	0.303	12.231	<0.001	3.109	4.295	2.399
AffT1	Intercept	4.263	0.083	51.67	<0.001	4.101	4.425	3.511
Aff change	Variance	1.445	0.122	11.829	<0.001	1.206	1.685	0.607
AffT1	Variance	1.474	0.131	11.255	<0.001	1.218	1.731	1

Note. Method: Full information maximum likelihood with robust standard errors.*Abbreviations.* Aff: Infant affect; T1: Time 1 (8 months); T2: Time 2 (14 months).

Table A4.16*Parameter Estimates of the Univariate Latent Change Score Model for Infant Affect with Dimensional Outcomes*

Latent variables	Indicator	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	CI lower	CI upper	β
Aff change	AffT2	1				1	1	1.259
Regressions	Predictors	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	CI lower	CI upper	β
AffT2	AffT1	1				1	1	0.988
Aff change	AffT1	-0.799	0.071	-11.266	<0.001	-0.938	-0.66	-0.627
Internalising 36	Aff change	-0.184	0.125	-1.473	0.141	-0.429	0.061	-0.107
Externalising	Aff change	-0.228	0.114	-1.996	0.046	-0.452	-0.004	-0.139
SRS 36	Aff change	0.584	1.22	0.479	0.632	-1.806	2.974	0.039
SCQ 36	Aff change	-0.019	0.332	-0.056	0.955	-0.67	0.632	-0.005
SC 36	Aff change	0.576	0.535	1.076	0.282	-0.473	1.624	0.072
Lang 36	Aff change	0.889	0.545	1.631	0.103	-0.179	1.956	0.114
Internalising 36	Group	1.553	0.31	5.016	<0.001	0.946	2.16	0.273
Externalising 36	Group	0.763	0.338	2.255	0.024	0.1	1.426	0.14
SRS 36	Group	15.873	2.327	6.82	<0.001	11.311	20.434	0.316
SCQ 36	Group	3.584	0.62	5.779	<0.001	2.369	4.8	0.269
SC 36	Group	-10.948	1.351	-8.103	<0.001	-13.596	-8.3	-0.41
Lang 36	Group	-7.605	1.386	-5.486	<0.001	-10.322	-4.888	-0.293
Aff change	Group	0.211	0.166	1.266	0.205	-0.115	0.537	0.063
Covariances	Covariates	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	CI lower	CI upper	β
Externalising 36	Internalising 36	3.142	0.512	6.131	<0.001	2.137	4.146	0.496
SRS 36	Internalising 36	34.575	6.269	5.515	<0.001	22.288	46.861	0.614
SCQ 36	Internalising 36	8.677	1.58	5.49	<0.001	5.579	11.774	0.573

SC 36	Internalising 36	-13.425	2.485	-5.402	<0.001	-18.295	-8.554	-0.467
Lang 36	Internalising 36	-7.776	2.408	-3.229	0.001	-12.495	-3.056	-0.267
SRS 36	Externalising 36	26.33	4.931	5.339	<0.001	16.664	35.995	0.476
SCQ 36	Externalising 36	6.922	1.278	5.416	<0.001	4.417	9.428	0.465
SC 36	Externalising 36	-7.219	2.067	-3.493	<0.001	-11.27	-3.169	-0.255
Lang 36	Externalising 36	-4.077	2.152	-1.894	0.058	-8.296	0.142	-0.142
SCQ 36	SRS 36	115.571	18.149	6.368	<0.001	80	151.143	0.874
SC 36	SRS 36	-135.344	25.275	-5.355	<0.001	-184.882	-85.807	-0.539
Lang 36	SRS 36	-64.012	22.768	-2.812	0.005	-108.636	-19.388	-0.252
SC 36	SCQ 36	-33.414	6.835	-4.888	<0.001	-46.811	-20.016	-0.495
Lang 36	SCQ 36	-14.379	6.333	-2.27	0.023	-26.792	-1.966	-0.21
Lang 36	SC 36	85.493	12.376	6.908	<0.001	61.236	109.75	0.657
		B	SE	z	p	CI lower	CI upper	β
Aff change	Intercept	3.576	0.302	11.826	<0.001	2.983	4.168	2.312
AffT1	Intercept	4.253	0.083	51.521	<0.001	4.091	4.415	3.501
Aff change	Variance	1.441	0.121	11.928	<0.001	1.204	1.677	0.602
AffT1	Variance	1.475	0.131	11.262	<0.001	1.218	1.732	1

Note. “Group” refers to ASD likelihood group (EL, TL). Method: Full information maximum likelihood with robust standard errors.

Abbreviations. Aff: Infant affect; Lang: Language; SC: Social communication; SCQ: Social communication questionnaire; SRS: Social responsiveness scale; T1: Time 1 (8 months); T2: Time 2 (14 months).

Table A4.17*Parameter Estimates of the Univariate Latent Change Score Model for Language*

Latent variables		Indicator	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	CI lower	CI upper	β
Lang change		LangT2	1				1	1	1.097
Regressions		Predictors	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	CI lower	CI upper	β
LangT2		LangT1	1				1	1	0.813
Lang change		LangT1	-0.654	0.077	-8.463	<0.001	-0.805	-0.502	-0.485
			<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	CI lower	CI upper	β
Lang change		Intercept	28.156	3.827	7.357	<0.001	20.655	35.657	2.502
LangT1		Intercept	49.22	0.536	91.785	<0.001	48.169	50.271	5.9
Lang change		Variance	96.846	10.424	9.29	<0.001	76.415	117.277	0.765
LangT1		Variance	69.6	6.092	11.425	<0.001	57.66	81.54	1

Note. Method: Full information maximum likelihood with robust standard errors.*Abbreviations.* Lang: Language; T1: Time 1 (8 months); T2: Time 2 (14 months).

Table A4.18*Parameter Estimates of the Univariate Latent Change Score Model for Social Communication*

Latent variables						CI		
	Indicator	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	lower	upper	β
SC change	SCT2	1				1	1	1.022
						CI		
Regressions	Predictors	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	lower	upper	β
SCT2	SCT1	1				1	1	1.132
SC change	SCT1	-0.518	0.061	-8.469	<0.001	-0.638	-0.398	-0.573
						CI		
		<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	lower	upper	β
SC change	Intercept	49.91	6.005	8.311	<0.001	38.14	61.681	4.288
SCT1	Intercept	98.132	0.832	117.898	<0.001	96.5	99.763	7.617
SC change	Variance	90.97	9.887	9.201	<0.001	71.593	110.348	0.672
SCT1	Variance	165.986	20.437	8.122	<0.001	125.93	206.042	1

Note. Method: Full information maximum likelihood with robust standard errors.*Abbreviations.* SC: Social communication; T1: Time 1 (8 months); T2: Time 2 (14 months).

Table A4.19

Parameter Estimates of the Bivariate Latent Change Score Model for Parent-Dyadic Interaction and Language

Latent variables		CI						
Indicator		<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	lower	CI upper	β
PDIT1	SRT1	1				1	1	1
PDIT1	NDT1	0.707	0.035	20.484	<0.001	0.64	0.775	0.693
PDIT1	MutT1	0.801	0.03	26.946	<0.001	0.742	0.859	0.764
PDIT2	SRT2	1				1	1	1
PDIT2	NDT2	0.707	0.035	20.484	<0.001	0.64	0.775	0.714
PDIT2	MutT2	0.801	0.03	26.946	<0.001	0.742	0.859	0.783
PDI change	PDI	1				1	1	1.066
Lang change	Lang	1				1	1	1.096
		CI						
Regressions	Predictors	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	lower	CI upper	β
PDIT2	PDIT1	1				1	1	0.943
LangT2	LangT1	1				1	1	0.813
Lang change	PDIT1	1.014	0.557	1.82	0.069	-0.078	2.105	0.113
Lang change	LangT1	-0.656	0.077	-8.561	<0.001	-0.806	-0.506	-0.487
PDI change	LangT1	0.025	0.011	2.253	0.024	0.003	0.046	0.146
PDI change	PDIT1	-0.582	0.063	-9.195	<0.001	-0.705	-0.458	-0.514
		CI						
Covariances	Covariates	<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	lower	CI upper	β
PDIT1	LangT1	0.312	0.702	0.444	0.657	-1.065	1.689	0.03
	Lang							
PDI change	change	1.247	0.748	1.667	0.096	-0.219	2.714	0.106
SRT1	SRT2	0	0	0	0			NaN
NDT1	NDT2	0.188	0.066	2.864	0.004	0.059	0.317	0.22
MutT1	MutT2	0.037	0.052	0.708	0.479	-0.065	0.139	0.051
		CI						
		<i>B</i>	<i>SE</i>	<i>z</i>	<i>p</i>	lower	CI upper	β
PDI change	Intercept	1.4	0.549	2.549	0.011	0.324	2.477	0.986
PDIT1	Intercept	3.697	0.085	43.527	<0.001	3.53	3.863	2.944
Lang change	Intercept	24.514	4.564	5.371	<0.001	15.569	33.459	2.181
LangT1	Intercept	49.216	0.537	91.702	<0.001	48.164	50.268	5.898
PDI change	Variance	1.448	0.117	12.406	<0.001	1.22	1.677	0.719

PDIT1	Variance	1.576	0.122	12.947	<0.001	1.338	1.815	1
Lang change	Variance	95.188	10.237	9.298	<0.001	75.123	115.253	0.753
LangT1	Variance	69.637	6.098	11.42	<0.001	57.685	81.589	1

Note. Negative variance estimate for the SR indicator. The variance of SR was manually fixed to zero. No further adjustments made. “Group” refers to ASD likelihood group (EL, TL). Method: Full information maximum likelihood with robust standard errors.

Abbreviations. Lang: Language; Mut: Dyadic mutuality; ND: Parent nondirectiveness; PDI: Parent-dyadic interaction; SCQ: Social communication questionnaire; SR: Parent sensitive responsiveness; SRS: Social responsiveness scale; T1: Time 1 (8 months); T2: Time 2 (14 months).

Table A4.20

Parameter Estimates of the Bivariate Latent Change Score Model for Parent-Dyadic Interaction and Social Communication

Latent variables		CI						
Indicator		B	SE	z	p	CI lower	upper	β
PDIT1	SRT1	1				1	1	1
PDIT1	NDT1	0.707	0.035	20.484	<0.001	0.64	0.775	0.693
PDIT1	MutT1	0.801	0.03	26.946	<0.001	0.742	0.859	0.764
PDIT2	SRT2	1				1	1	1
PDIT2	NDT2	0.707	0.035	20.484	<0.001	0.64	0.775	0.714
PDIT2	MutT2	0.801	0.03	26.946	<0.001	0.742	0.859	0.783
PDI change	PDI	1				1	1	1.063
SC change	SC	1				1	1	1.02

Regressions		CI						
Predictors		B	SE	z	p	CI lower	upper	β
PDIT2	PDIT1	1				1	1	0.942
SCT2	SCT1	1				1	1	1.13
SC change	PDIT1	1.305	0.535	2.438	0.015	0.256	2.353	0.141
SC change	SCT1	-0.505	0.06	-8.421	<0.001	-0.622	-0.387	-0.559
PDI change	SCT1	0	0.006	0.053	0.958	-0.012	0.013	0.003
PDI change	PDIT1	-0.573	0.064	-8.95	<0.001	-0.699	-0.448	-0.508

Covariances		CI						
Covariates		B	SE	z	p	CI lower	upper	β
PDIT1	SCT1	-1.349	1.185	-1.139	0.255	-3.671	0.973	-0.083
PDI change	SC change	1.345	0.804	1.673	0.094	-0.231	2.922	0.117
SRT1	SRT2	0				0	0	NaN
NDT1	NDT2	0.188	0.066	2.864	0.004	0.059	0.317	0.22
MutT1	MutT2	0.037	0.052	0.708	0.479	-0.065	0.139	0.051

		CI						
		B	SE	z	p	CI lower	upper	β
PDI change	Intercept	2.559	0.684	3.743	<0.001	1.219	3.899	1.807
PDIT1	Intercept	3.694	0.085	43.643	<0.001	3.528	3.86	2.942
SC change	Intercept	43.745	6.364	6.874	<0.001	31.272	56.219	3.763
SCT1	Intercept	98.149	0.834	117.749	<0.001	96.516	99.783	7.62
PDI change	Variance	1.488	0.122	12.178	<0.001	1.249	1.728	0.742
PDIT1	Variance	1.576	0.122	12.933	<0.001	1.338	1.815	1

SC change	Variance	88.377	9.244	9.56	<0.001	70.258	106.495	0.654
SCT1	Variance	165.927	20.426	8.123	<0.001	125.893	205.96	1

Note. Negative variance estimate for the SR indicator. The variance of SR was manually fixed to zero. No further adjustments made. “Group” refers to ASD likelihood group (EL, TL). Method: Full information maximum likelihood with robust standard errors.

Abbreviations. Mut: Dyadic mutuality; ND: Parent nondirectiveness; PDI: Parent-dyadic interaction; SCQ: Social communication questionnaire; SR: Parent sensitive responsiveness; SRS: Social responsiveness scale; T1: Time 1 (8 months); T2: Time 2 (14 months).

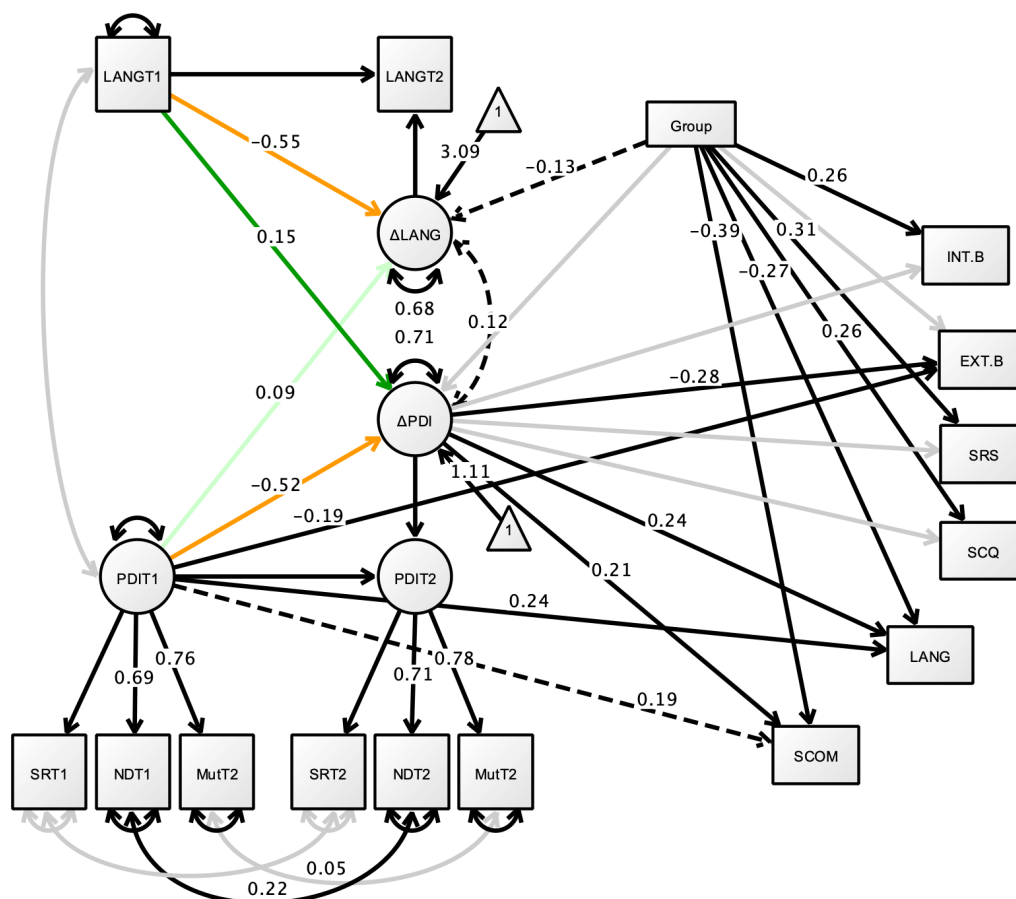
Table A4.21

Correlation Between the Global Parent and Dyadic Interaction Aspects by Infant Sibling Group (TL, EL-no ASD, EL-ASD) at 8 and 14 Months

<i>TL group</i>	Sensitive responsiveness	Nondirectiveness	Mutuality
<i>14 months</i>			
Sensitive responsiveness		.65**	.88**
Nondirectiveness	.72**		.49**
Mutuality	.77**	.50**	
<i>8 months</i>			
<i>EL-no ASD group</i>	Sensitive responsiveness	Nondirectiveness	Mutuality
<i>14 months</i>			
Sensitive responsiveness		.73**	.72**
Nondirectiveness	.75**		.55**
Mutuality	.80**	.60**	
<i>8 months</i>			
<i>EL-ASD</i>	Sensitive responsiveness	Nondirectiveness	Mutuality
<i>14 months</i>			
Sensitive responsiveness		.53**	.45*
Nondirectiveness	.64**		0.28
Mutuality	.74**	0.33	
<i>8 months</i>			

* $p < 0.05$ ** $p < 0.01$.

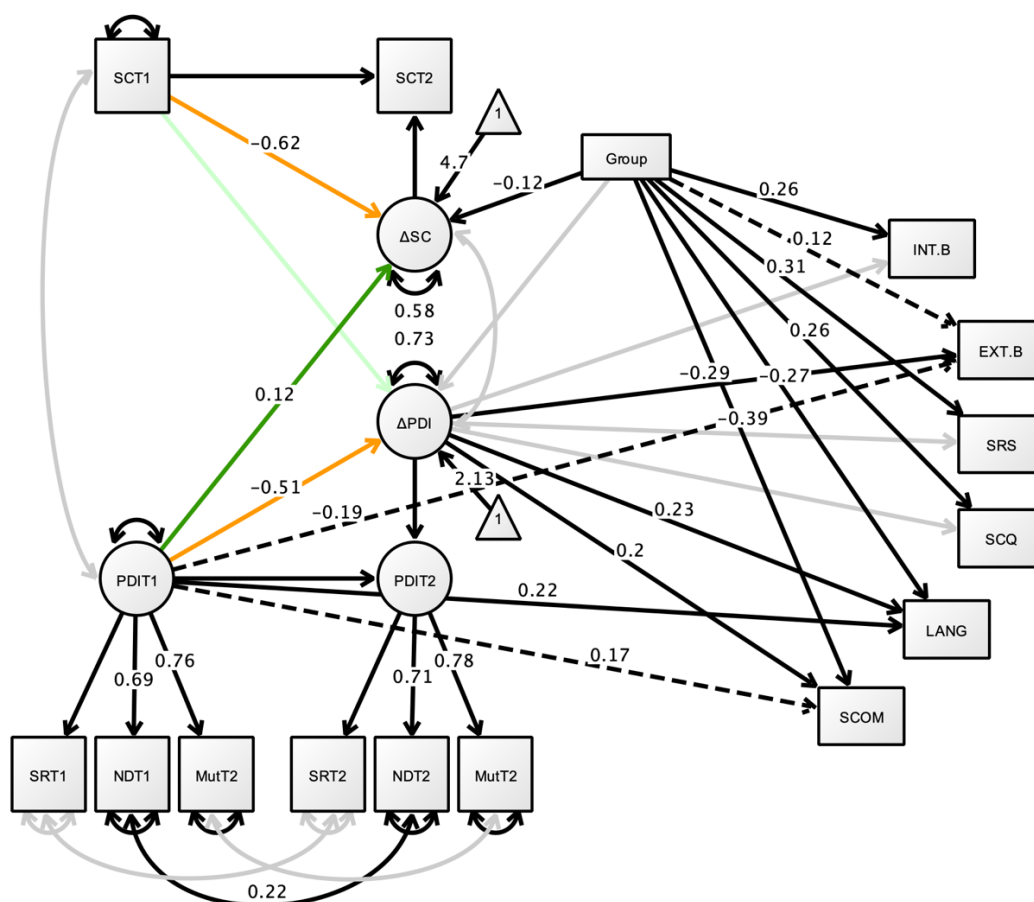
Bivariate Latent Change Score Model for PDI and Language with Dimensional Outcomes



Δ PD1: The latent variable representing the change in parent-dyadic interaction between 8 and 14 months. Δ LANG: The latent variable representing the change in language skills between 8 and 14 months. PDIT1: Parent-dyadic interaction assessed at 8 months. LANGT1: Infant language skills assessed at 8 months. PDIT2: Parent-dyadic interaction assessed at 14 months. LANGT2: Infant language skills assessed at 14 months. Group represents the ASD likelihood groups (EL, TL). Mut: Mutuality; ND: Nondirectiveness; SR: Sensitive responsiveness; EXT.B: Externalising behaviour; INT.B: Internalising behaviour; LANG: Language; SCOM: Social communication; SCQ: Social communication questionnaire; SRS: Social responsiveness scale. Black arrows with no values indicate relationships where parameters are fixed. Solid lines indicate significant relationships. Grey arrows indicate nonsignificant relationships.

The green lines indicate cross-domain coupling parameters (PDI to language and vice versa). Orange lines indicate within-domain couplings. Dashed arrows indicate marginal relationships. Circles indicate latent variables and squares indicator/observed variables. The triangles indicate the intercepts of the Δ PDI and Δ LANG latent factors. Standardised estimates are reported.

Bivariate Latent Change Score Model for PDI and Social Communication with Dimensional Outcomes



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Grey arrows indicate nonsignificant relationships. Green lines indicate cross-domain coupling parameters (PDI to SC and vice versa). Orange lines indicate within-domain couplings. Dashed arrows indicate marginal relationships. Circles indicate latent variables and squares indicator/observed variables. The triangles indicate the intercepts of the Δ PDI and Δ SC latent factors. Standardised estimates are reported.

Chapter 5. Neural Correlates of Infant Social Attention are Linked to Parent-Infant Interaction in 8-Month-Old Infants at Elevated Likelihood for ASD

5.1 Introduction

5.1.1 Early Neural Correlates of Differential Social Attention

As reviewed in **Chapter 1**, evidence from behavioural data shows that overt ASD signs in social communication and interaction, such as reductions in gesturing, social orienting and joint attention begin to appear after the first year. It is possible that a decline in the processing of social signals identified through behavioural tasks is related to earlier underlying atypicalities in gaze and face processing at the neural level (Amso & Scerif, 2015). Indeed, brain function measures of face and gaze processing have identified social attention differences between infants with and without a family history of ASD within the first year of life (Elsabbagh et al., 2012; Gui, Bussu, et al., 2021; Tye et al., 2020). Therefore, compared to behavioural tasks, measures of brain function may be able to capture possible early indicators of ASD before their later expression through infant behaviour.

5.1.1.1 Face Processing. Face processing has been shown to play a huge role in the way that brain mechanisms involved in social cognition in ASD operate (Dawson, Webb, & McPartland, 2005). Given that the neural systems related to the processing of faces and gaze develop from the very first months of life (Johnson, 2005), any atypicalities in these domains could be among the first indices of aberrant brain development in infants with a later ASD diagnosis.

Evidence from electrophysiological studies revealing social attention differences between infants with and without subsequent ASD place social processing (face/gaze) as a candidate, genetically driven neurodevelopmental trait of ASD, as it is also found to be atypical in parents of children with ASD (Dawson et al., 2005). An EEG study that examined neural responses to pictures of familiar and unfamiliar faces and objects in 10-month-old EL and TL infants suggested greater attention capture by objects relative to faces among the EL group. That is, the groups showed differential responses to faces relative to objects, with the EL group showing significantly faster N290 and P400 neural responses to objects (McCleery et al., 2009). However, the clinical outcome of the EL group was not known. Jones and colleagues (2016) extended on these findings in a longitudinal design that followed up to 3-year ASD diagnosis in a prospective longitudinal study and found that at 6, but not at 12 months, EL-ASD infants had faster P400 (suggested to be indicative of decreased attention) and shorter as well as shallower Nc (indicative of reduced sustained attention to stimuli) responses to faces compared to objects, as shown through an ERP paradigm. Consistent with these findings, recent research evidence by Gui et al. (2021) demonstrated that, compared to TL controls, 8-month-old infants with a family history of ASD had a decreased depth of Nc responses to faces relative to a non-social stimulus (visual noise), which was predictive of social skills at 3 years within the entire sample. Additionally, contrary to TL and EL-no ASD infants, the EL-ASD infants showed faster neural responses to the face (expressed through shorter Nc latencies) than the noise stimulus. Along similar lines, another study found a reduced N290 latency response differentiation to faces versus visual noise in 8-month-old EL-ASD infants than those at TL and EL-no ASD (Tye et al., 2020).

5.1.1.2 Eye Gaze Processing. Several studies have focused on the neural processing of eye gaze as a possible early marker responsible for the development of joint

attention skills. Elsabbagh et al. (2012) conducted a longitudinal study looking at ERPs evoked by dynamic eye gaze shifts in infants with and without familial likelihood for ASD at 6 to 10 months. Findings revealed that the TL group as well as the EL siblings with no ASD outcome had a differential P400 response to gaze shifts directed toward versus away from them compared to EL-ASD siblings who did not show a differentiation. The findings suggested that atypical brain responses of EL-ASD infants might be evident within their first year of life, before the emergence of clear behavioural signs. In a more recent prospective study, Tye et al. (2020) compared social and non-social neural responses in infants with and without familial ASD at a group level as well as individually through a machine learning approach. Results showed that, as opposed to infant groups with no ASD outcome, neural responses of EL-ASD infants were characterised by a longer P400 latency and a smaller amplitude to eye gaze shifts directed towards versus away from them. The above results suggested that atypicalities in engagement with social stimuli emerge early in development and may have implications for later social and communication skills in children with ASD.

The above findings illustrate the dynamic nature of incoming social information processing taking place in the infant brain, reflected through neural responses to perceptual and social stimuli (faces/gaze) in relation to non-social stimuli during development. They also point to eye gaze and face processing as potential neurodevelopmental markers for ASD that are particularly evident in early infancy before the emergence of clear behavioural signs in infants with a subsequent ASD diagnosis. These brain processing differences likely suggest an earlier emergence of atypicality that might impact socially in subtle ways, not yet seen in standardised behavioural measures. Understanding how ASD develops is essential for a clearer picture of the development of the condition that will in turn help in the refinement of early targeted interventions to improve the developmental trajectories of infants with emerging ASD.

5.1.2 Links Between Brain Function and PII

The IS theory posits that cognitive functions are accomplished through an activity-dependent collaboration within cortical regions and between the whole brain and the external environment (Johnson et al., 2005). One proposition is that early brain function differences can be exacerbated by atypicalities in interactions within different regions of the brain and the child's social environment, thereby producing a pattern of socio-cognitive development that gradually deviates from a typical trajectory (Elsabbagh & Johnson, 2010). For instance, typically developing infants are biased towards attending to socially relevant stimuli in the environment, which enables the formation of inter- and intraregional cortical connections and therefore, contributes to the emergence of a typical social brain network later in development (Johnson, 2001; Johnson et al., 2005). In the case of ASD, it is suggested that a deviation from the underlying processes contributing to these biases can lead to a delay or even a lack of subsequent cortical specialisation for social information. Any primary atypicalities may then be further amplified by the infant's social environment, leading to emerging disruptions in social communication and interaction. Considering this and evidence suggesting that early brain differences associated with later ASD diagnosis are evident before the emergence of early behavioural signs (Elsabbagh et al., 2012), linking brain function measures and quality of PII may help shed light on the early developmental processes leading to ASD outcome, as well as the mediating effect of PII in infant developmental trajectories (Green, 2022). Research on such links has focused mostly on normative populations, while there is very limited research examining them in the context of ASD (Ilyka et al., 2021).

For instance, in neurotypical populations, existing evidence suggests that normative variation in PII may exert an influence on infant neural processing of emotionally loaded social stimuli. A study investigated the role of experience in the

processing of facial expressions of emotion indirectly through measures of maternal emotional disposition (positive and negative affect) and ERP responses to facial expressions in 7-month-old infants (De Haan et al., 2004). Results indicated that infants with positive mothers (scoring high on positive affect) showed a larger Nc component to fearful compared to happy faces. These results stressed the role of emotional environment on infants' development of face processing. Other preliminary research using fNIRS revealed an association between cortical activation to vocal emotion (by a stranger) in the left anterior superior temporal cortex and caregiver nondirectiveness in free play interactions, such that stronger neural responses to angry vocalisations were linked to greater mother directiveness in 6-month-old infants (Zhao et al., 2019). Longitudinal research also indicated that more positive and less physically stimulating interactions between mothers and infants at 5 months were linked to high frontal resting EEG power at 10 and 24 months that increased between 5 and 10, as well as 10 and 24 months (Bernier et al., 2016).

Although limited, there is some evidence suggesting an association between brain function in response to social information and PII in the context of ASD within the first year of life. Elsabbagh et al. (2015) examined ERP responses to dynamic eye gaze shifts directed toward versus away from the infant and their association with PII in EL siblings relative to TL controls at 7 months of age (with a sub-sample of the sample included in the current study). The results revealed clear associations between brain responses to eye gaze and unstructured PII domains as measured through the MACI rating scheme. These relationships were shown in both EL and TL groups; greater positive affect (the degree of positive state) in EL infants was linked to greater P400 (latency) response difference to eye gaze shifts directed toward versus away from the infant but was stronger mostly in EL infants who did not later receive an ASD diagnosis. No such strong association was observed in the TL group. In contrast, the TL group showed a P100 (latency)

differentiation to eye gaze shifts associated with high parent sensitive responsiveness, suggesting that the neural mechanisms of infants at TL may interpret social information differently in their interactions with a parenting figure relative to the EL group.

A more recent study investigated the role of parental language input (through laboratory-based free-play interaction) in brain oscillatory activity (gamma power over frontal and temporal regions through resting EEG) and language development in toddlers at TL and EL for ASD (Romeo et al., 2022). The results revealed that higher parent quality input at 18 months was linked to lower baseline frontal and temporal gamma power at 24 months, which in turn was associated with higher expressive language skills. These effects were stronger for the EL infants, and particularly those who later received an ASD diagnosis. These findings possibly indicate EL infants' differential susceptibility to their language environment affecting their neural functioning in ways that promote language development.

In sum, although causation cannot be inferred and such associations are yet to be clearly defined, the above studies highlight the potential of combining brain function and PII measures for a better understanding of the developmental pathways leading to ASD. The brain shapes and is shaped by experience, and such possible bidirectional effects could have an impact on children's developmental trajectories. Therefore, the links between brain function and PII could help to elucidate the possible factors contributing to the emergence of ASD, enabling better detection and intervention.

5.1.3 Aims of the Study

As discussed earlier, atypical neural processing in a period of increasing neuroplasticity can affect infants' social experiences and responses to the external environment leading to reduced social attention and interaction, and thus, reduced opportunities for social learning, while at the same time, the quality of infants' social

environment (i.e., caregivers) can influence brain development in a feedforward fashion (Klin et al., 2020). Theory supported by evidence draws attention to the significance of the links between brain function and early caregiver-infant social interactions, and the important role they play in children's developmental outcomes (Elsabbagh, Bruno, Wan, Charman, Johnson, Green, & Team, 2015; Ilyka et al., 2021; A. J. Sameroff, 1993, 2009).

The aim of this study was to investigate the links between brain function (ERP measures) and unstructured PII between 8-month-old infants with and without familial likelihood for ASD. The ERPs of interest included the P1, P400, N290 and Nc, as they have previously differentiated infants at EL and TL within the first year. In particular, the depth of neural responses to social vs non-social stimuli (amplitudes, including dynamic eye gaze shifts and static faces vs. non-social stimuli) as well as the generic effects relating to the timing of neural responses to social and/or non-social stimuli between the two groups were examined. Both the depth and timing of neural responses were of interest since they have been shown to differ between EL and TL infants (as discussed earlier), with EL infants showing reduced depth of processing of social information. In addition, the timing of neural responses has been associated with PII measures in EL and TL infants in previous research which included a part of the sample from this study (Elsabbagh, Bruno, Wan, Charman, Johnson, Green, & The BASIS Team, 2015). The PII measures included parental (directiveness, sensitive responsiveness) and infant (attentiveness) aspects because they have previously distinguished infants in terms of ASD likelihood status.

More specifically, using an SEM approach, this study explored the mediating role of infant attentiveness in the relationship between brain response to social and non-social information and parental aspects of PII. It was hypothesised that infant neural responses to social stimuli would influence infants' attentiveness within PII, which would in turn influence patterns of parental interaction. For instance, greater attention capture and

neural processing of social stimuli in TL infants would be linked to higher attentiveness towards their parents who would likely be more responsive and non-directive. On the other hand, a reduced brain depth and speed of visual social processing in EL infants would relate to infant attentiveness to the parent, possibly sending less communicative signals during the interaction, which may be more challenging for parents to interpret and therefore respond appropriately to and may result in the parent introducing less sensitively responsive/more directive behaviours. If a mediation path exists and differentiates the two groups of infants at an age of maximal brain plasticity, it could help to better inform targets for parent-mediated interventions to improve children's developmental outcomes.

5.2 Methods

5.2.1 Participants

Details of the process of verification of ASD likelihood status in the older sibling are described in **Chapter 3** for Phase 2 and are the same for Phase 1. Confirmation of EL status in the older sibling was made through the DAWBA (Goodman, Ford, Richards, Gatward & Meltzer, 2000) and SCQ (Rutter, Bailey & Lord, 2003) assessments, reviewed by experienced research clinicians (TC and GP) in order to verify local clinical diagnosis. Infants in the TL group were recruited separately from a volunteer database at the Birkbeck Centre for Brain and Cognitive Development. The criteria for their inclusion were full-term birth (37-42 weeks), except one infant who was born prior to 37 weeks (Phase 2), normal birthweight and no ASD within first-degree relatives (information obtained through parent interview). In phase 1, most of the older siblings (hereafter, probands) of EL infants met criteria for ASD ($n = 44$). A small number of probands ($n = 4$) scored below instrument cut-off on the SCQ but were included after meeting threshold on the DAWBA and expert judgement. Two probands had available data for only 1 of the

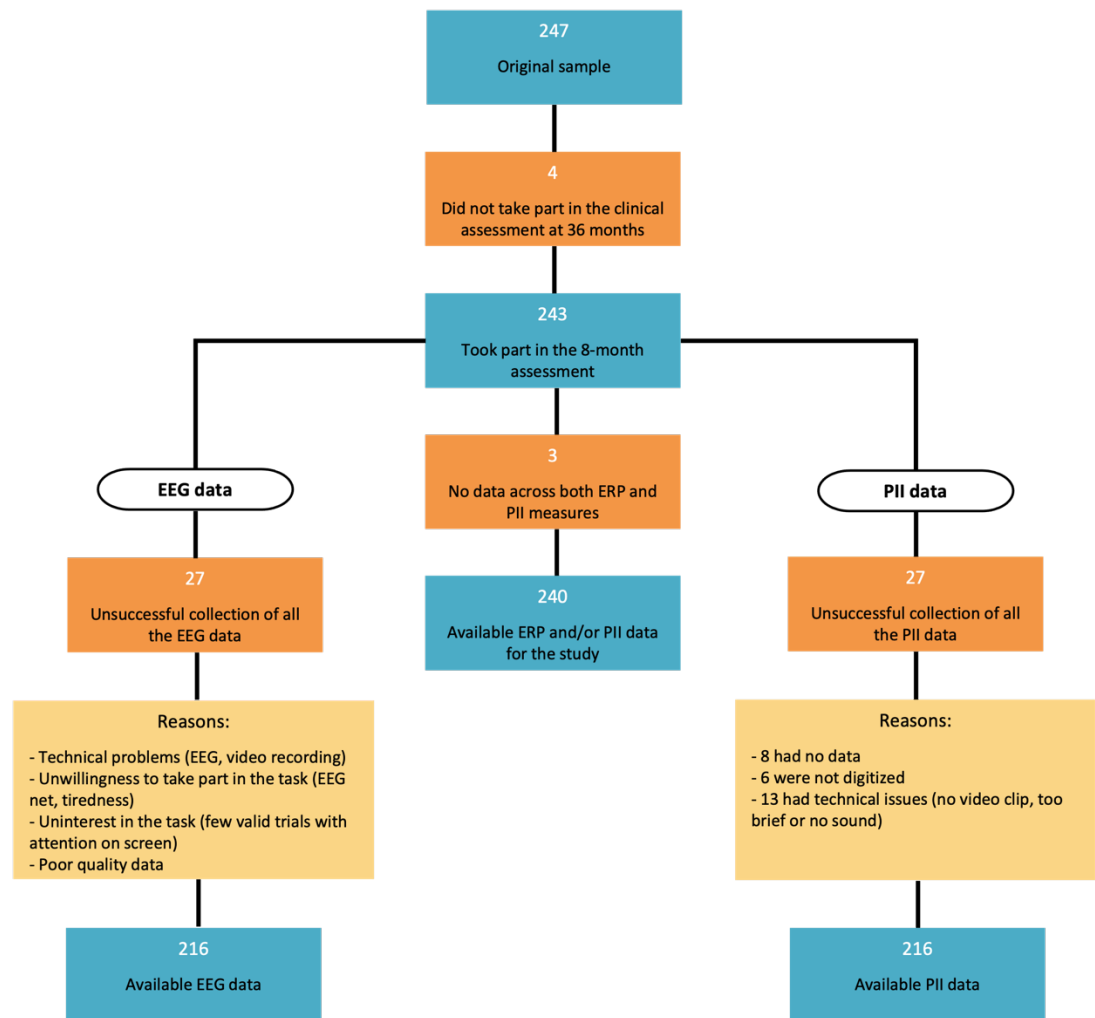
2 assessment measures. Only parent-confirmed local clinical ASD diagnosis was available for 4 probands. No exclusions were made after the examination of parent-reported medical history for significant medical conditions in probands and family members of EL infants. With regards to TL infants, results from the SCQ indicated that none of the older siblings scored above instrument cut-off for ASD (>15).

A total of 247 infants participated in the BASIS (two independent samples, ‘Phase 1’ and ‘Phase 2’ sample). The ‘Phase 2’ sample, as described in **Chapter 3 (section 3.2.1)** was combined with an independent ‘Phase 1’ sample that took part in the initial phase of BASIS recruitment and whose PIIs were studied partially previously in Wan et al. (2013). In Phase 2, 143 infants participated, consisting of 116 (64 male, 52 female) infants who had at least one older sibling with a community diagnosis of ASD (EL) and 27 (14 male, 13 female) infants (control group) with at least one older sibling and no family history of ASD (TL). Phase 1 included 104 infants, 54 (21 male, 33 female) who were EL infants while the other 50 (21 male, 29 female) infants were TL controls. Infants at TL were recruited from a volunteer database at the Centre for Brain and Cognitive Development. **Figure 5.1** provides information about the initial and final sample of participants of this study, with details of exclusions.

Overall, a total number of 240 participants (75 TL, 165 EL) were included in the current study because they provided available ERP and/or PII data (**Figure 5.1**). No data exclusions were made (apart from data that were missing across both ERP and PII measures), as missing data were handled within the chosen analytical method (described in later sections). Ethical approval for the BASIS was made available from the UK National Health Service National Research Ethics Service London (REC reference number: 08/H0718/76 and 06/MRE/02/73). Informed consent was given by one or both parents to participate in the study.

Figure 5.1

Flowchart of the Number of Participants Recruited as Part of the British Autism Study of Infant Siblings and Included in This Study with Details of Exclusions



Note. The number of participants that were initially recruited from the BASIS at 8 months is depicted at the top cell of the flowchart (Phases 1 and 2) with reasons for subsequent exclusions (orange cells for the number of participant exclusions and yellow cells for the reasons). The bottom middle cell (in blue) shows the number of participants with available data in the ERP and/or PII measures used in the study. The two bottom cells (in blue) show the number of participants with available ERP and PII data separately.

5.2.2 Measures

5.2.2.1 Electrophysiological Measure. **Chapter 2** provides detailed information on the EEG measure. To recapitulate, the ERP task followed the protocol described in Elsabbagh et al. (2012). Infants sat on their parents' laps in front of a 40 x 29cm computer screen that was 60cm away from them, and a video camera recorded infants' fixation on the screen during stimulus presentation. At the beginning of each trial block, a static colourful fixation stimulus preceded the appearance of an image of one of four colourful female faces with gaze directed either toward or away from the infant. In addition to faces, "visual noise" stimuli appeared in one third of the blocks, created from the female face stimulus by randomizing the phase spectra while keeping the amplitude and colour spectra constant (Halit et al., 2004). The faces were shown at the centre of the screen with the eyes positioned at the place of the fixation stimuli to ensure infants' concentration on the location of the eyes. In following trials of the same block, the face displayed on the screen remained and alternated direction of gaze towards and away from the infant three to six times. The faces spanned 21 x 14 degrees of visual angle. The fixation stimulus spanned roughly 1.6 x 1.6 degrees and was presented for 800 to 1,200 ms. The duration of each trial was 800 ms, succeeded by a 500 ms interval of no stimulus presentation. Overall, the task evaluated responses to the following stimuli: static faces with direct gaze, static faces with averted gaze, gaze shifts toward the infant, gaze shifts away from the infant and visual noise. The P100, P400, N290 and Nc components were averaged for each stimulus across occipito-temporal channels (frontal right and left for the Nc) quantified by their amplitude and latency, with a total of 36 ERP variables being used for the analysis. Refer to **Chapter 2** for a depiction of the experimental stimuli.

5.2.2.1.1 Electrophysiological Acquisition and Processing. Details of the EEG acquisition and processing are provided in the appendix (section 5.6.1).

5.2.2.2 PII Measure. The MACI (version 2.2) global coding scheme was used in this study for the evaluation of PII (see the General Methods Chapter for details about the measure). To briefly recapitulate, the MACI consists of 8 seven-point scales for the assessment of parental, infant and dyadic interaction. For this study, only parent sensitive responsiveness, parent nondirectiveness and infant attentiveness scales were included, as these scales have differentiated EL from TL infants in previous research (M. W. Wan et al., 2013) as well as in the previous study (**Chapter 3**). They were also the most relevant to test the research hypotheses: parent sensitive responsiveness refers to the extent to which the caregiver responds promptly and congruently to the infant's behaviours, parent nondirectiveness concerns the caregiver's acceptance of the infant's experience and behaviour instead of 'controlling' the infant's autonomy, and infant attentiveness refers to the infant's amount and quality of voluntary orientation to the caregiver, including, among others, shared attention and interest in the caregiver's activity, eye contact and initiated vocalisations.

5.2.2.2.1 PII Procedure. Briefly, the PII procedure involved a six-minute videotaped recording of unstructured play between the primary caregiver and the infant on a mat in a laboratory setting using a standard set of toys. The evaluation of videoclips was undertaken blinded to all participant information and started when there were no external distractions and after the researcher had left the room.

5.2.2.2.2 Inter-Rater Reliability. Blind coding of a proportion (10%) of the video clips used was undertaken to test for inter-rater agreement. Single measures intraclass

correlations using a two-way mixed effects model based on absolute agreement definition revealed moderate to strong agreement in all three items: parent sensitive responsiveness (Phase 1: $r = .66$, Phase 2: $r = .88$), parent non-directiveness (Phase 1: $r = .63$, Phase 2: $r = .68$, infant attentiveness (Phase 1: $r = 0.58$, Phase 2: $r = .82$).

5.2.2.3 Assessment Measures. Phase 1 participant details, measures of developmental level and atypical behaviour mirror those of phase 2 (**Chapter 3** provides a detailed description of the measures). A brief description of these measures is provided below.

5.2.2.3.1 Developmental Level and Adaptive Functioning. The MSEL standardised measure (Mullen, 1995) was used to evaluate infant cognitive capacity in five key domains: Gross and fine motor, visual reception, and receptive and expressive language (Mean = 50, $SD = 10$). The score of these areas (apart from gross motor skills) is combined to produce an ELC standard score (mean = 100, $SD = 15$). A higher MSEL score indicates greater developmental skill. The VABS (Sparrow et al., 2005) is a semi-structured parent-report measure (questionnaire at 8 months) that was employed to assess infant adaptive functioning. The VABS evaluates everyday personal and social abilities in four main domains, such as communication, daily living skills, socialisation and motor skills. A maladaptive behaviour index is also offered which is optional. The four main domains can then be combined to yield an ABC score (mean = 100, $SD = 15$), a standardised measure of general adaptive behaviour. Lower scores indicate greater difficulties in adaptive behaviour. The VABS ABC and MSEL ELC were used in this study for participant background characterisation.

5.2.2.3.2 Assessment of ASD Outcome at 3 Years. In terms of assessment of categorical outcome, in phase 1, infants followed the same assessment measures as those in phase 2. At around their third birthday, children were seen for assessment by experienced clinical researchers to determine ASD diagnosis according to DSM-5 (American Psychiatric Association, 2013). Autism Spectrum Disorder diagnosis was estimated based on, among other measures, 24- and 36-month results from assessments using the ADOS-G – Second Edition (Lord, Rutter, et al., 2012). ADOS-2 total scores were calculated using the ADOS-G raw item scores. Particularly, at phase 1, 52 of the 54 EL infants were seen for assessment at 24 months while 53 were seen at 36 months. Fifty infants at EL were administered Module 1, and two Module 2 at 24 months. In Phase 2, 116 children were administered Module 2 while 20 were administered Module 1. At 36 months, in both groups of infants, three were administered Module 1 and 98 Module 2. Calibrated Severity Scores for Social Affect, and RRB were used (Gotham, et al., 2009) as standardised measures of ASD severity taking into account differences in module applied, age and verbal ability.

The ADI-R (Rutter, Le Couteur, et al., 2003) for the assessment of ASD symptoms was also completed. This assessment (semi-structured interview) was conducted with infants' parents and focused on three domains (aggregated totals of specific items based on the ICD-10 and the DSM-IV criteria): Reciprocal Social Interactions, Communication and RRB. Estimation of standard algorithm scores was undertaken for the three domains of the ADI-R. The TL infants were not administered the ADI-R in Phase 1, while in Phase 2 they were administered both the ADOS and ADI-R for outcome assessment at 36 months.

The SRS (Constantino & Gruber, 2012) questionnaire (pre-school form) measuring symptom severity in the social domain was also completed by parents, alongside the VABS and SCQ. Each item is scored on a 4-point Likert Scale and takes

approximately 15-20 minutes to complete. A total score measuring the severity of ASD social impairment is generated. Furthermore, scores from five sub-scales (AWR, COG, COMM, MOT, RRB) are produced. Each of these domains' raw scores are aggregated with their total converted into the SRS-2 Total T-score. Two additional scales are included in the measure, corresponding to DSM-5 criteria: SCI and RRB. Scores range from zero to 195, with higher scores indicating greater severity of social impairment.

Last, parents completed the 25-item questionnaire named Q-CHAT which assesses ASD-related behaviours based on ICD-10 and DSM-IV domains. Each Q-CHAT item is scored on a 5-point scale (0-4), with higher scores indicating greater ASD traits. A total Q-CHAT score can be calculated by the summation of each item score.

In the total sample, 239 children took part in the 36-month visit. Four EL children were absent for the 36-month visit and therefore were excluded from the analysis. Four TL controls dropped out but were included based on assessments in previous visits. The remaining sample comprised 243 infants (EL = 166; TL = 77). Of the 166 EL infants, 34 (20%) met criteria for ASD diagnosis (EL-ASD) based on ICD-10 criteria (Phase 1) and DSM-5 (Phase 2), 88 (53%) were identified as typically developing (EL-TD) and 44 (27%) were classified as having other developmental concerns (EL-Aty), scoring above the ASD threshold on the ADOS-G and ADI-R as well as scoring below -1.5 standard deviations on the MSEL ELC score.

5.2.3 Analyses

5.2.3.1 Data Reduction. The P1, N290, P400 and Nc components, averaged by their amplitude and latency provided a large number of potential ERP variables (amplitudes and latencies per component per condition). Therefore, as a first step, exploratory factor analysis (EFA) was used in order to reduce the number of ERP

variables and identify their underlying structure. EFA is a data-driven method for the identification of common factors that explain patterns of associations between variables that share common variance (Norris & Lecavalier, 2010). The variables were first standardised because the ranges of amplitudes and latencies differ. In particular, two separate EFAs were conducted:

- 1) Using the brain response differences between the stimulus conditions (amplitudes and latencies: static face directed toward versus away (FD vs FA); static face directed toward versus noise (FD vs N); eye gaze shifting toward versus away (SD vs SA)).
- 2) Using absolute latencies of each ERP component for each condition.

In order to undertake the first EFA, analysis using the condition contrasts led to a further reduction in the ERP variables (from 36 to 22 in total, as individual variables (e.g., FD and FA) were combined to form one variable (e.g., FD vs. FA) representing infant brain response difference). The rationale for computing the amplitude and latency response difference between the conditions was: (1) ERPs are often quantified based on their difference scores to discern brain activity in response to one condition stimulus relative to another, (2) this approach can also be used for variable reduction as the stimulus contrast can be considered as a single variable for testing associations, and (3) it was preferable in order to test the hypotheses for this study based on previous research in ASD that has used the classic ERPs approach of condition differences. As already mentioned, these condition contrasts have been used by a number of studies and have differentiated infants with a subsequent ASD diagnosis relative to those who develop typically, showing group effects (Elsabbagh et al., 2009; Elsabbagh et al., 2012; Gui,

Bussu, et al., 2021; Tye et al., 2020). The second EFA included all the latencies for each ERP component across the different conditions (18 variables in total).

To determine how many factors to extract, scree plots and Kaiser's criterion were examined, where appropriate (A. Field, 2013). Briefly, the scree plot presents the eigenvalues (the amount of variance in the data) of factors in descending order with a point of inflexion which is used as a criterion for factor retainment (Cattell, 1966). Under Kaiser's criterion, only factors with eigenvalues greater than one were included in the model, as they represent a large amount of variation (A. Field, 2013; H. F. Kaiser, 1960). Although this approach can lead to overestimation of factors, evidence suggests that it is more precise with less than 30 variables and when communalities after extraction are above .7 (A. Field, 2013), which was taken into consideration for this analysis. EFA analyses were performed using IBM SPSS software.

5.2.3.2 SEM. Using the latent factors derived from the EFA analyses (shown below), SEMs were conducted to analyse whether the ERP measures were associated with parental aspects of PII directly, or whether this relationship was mediated by infant attentiveness, an infant aspect of the PII measure. SEM is a multivariate technique used for the specification and estimation of linear relationships of latent and observed variables (Bollen, 1989). This method of data analysis was preferred as it is a flexible approach that could help address the research questions of interest. It can be used to investigate direct and indirect effects in a single frame and test multivariate relationships using latent constructs that can have various indicator variables, taking into account measurement error and thus, reducing bias when investigating the relationships (Bollen, 1989; Tomarken & Waller, 2005). This cannot be achieved with traditional methods (e.g., ANOVA) which are based on default models, have limitations in the number of associations that can be specified and assume no measurement error. In addition,

compared to traditional measures, the SEM approach resolves any issues with multicollinearity by using latent constructs. At the same time, it provides approaches for dealing with missing data and violations of normality assumptions and allows for the comparison of SEM models between groups while inspecting measurement invariance across the groups (MacCallum & Austin, 2000; Tomarken & Waller, 2005). Model fit was assessed by using the same absolute goodness of fit indices described in more detail in **Chapter 4**: the χ^2 statistic, CFI, RMSEA and SRMR. To recapitulate, general rules of thumb exist in terms of what can be considered an acceptable model fit. The following values were used to indicate acceptable fit: Chi-square p-value > 0.05, CFI > 0.95 or > 0.90 (for acceptable fit), RMSEA < 0.06 or < 0.07 (or less conservatively, < 0.08) and SRMR < 0.08 (Hu & Bentler, 1999; Schermelleh-Engel et al., 2003; Steiger, 2007). SEM analyses was performed in ‘lavaan’ R package (version 4.2.2) using the ‘sem’ function (Rosseel, 2012).

Shapiro-Wilk tests revealed evidence of non-normality ($ps < 0.01$, **Table A5.2**). However, variable transformation was not performed for the following reasons: 1) transforming the data would have implications for the interpretation of the results, 2) it can be problematic, as the transformed data cannot mimic the original data and transformation may not necessarily lead to a more normal distribution (Feng et al., 2014; Grayson, 2004). Instead, Maximum Likelihood estimation with robust standard errors was used (this approach has also been used in previous research conducting mediation analysis including part of the sample of the current study (e.g., Chapter 3 in Gui, 2019).

Overall, two SEMs were performed. In each SEM, as a first step, the whole sample ($N = 243$) was used, which is a necessary step to ensure model convergence and fit. Subsequently, two groups of infants were used (infants at TL, $n = 77$; infants at EL for ASD, $n = 166$) employing a multi-group comparison, after ensuring that the same construct was measured across the groups through measurement invariance testing

(Beaujean, 2014). Only two groups were used as any attempts to include clinical outcome groups led to model non-convergence. Furthermore, including two groups would increase statistical power (considering the complexity of the models and sample size), as separating the sample into clinical outcome groups (> 3 groups) would reduce the sample size for each group even further, which could limit the power to observe true relationships in the data, if any. One of the two separate SEMs conducted included the brain response difference scores (the factors extracted from the first EFA were modelled as predictors of the first SEM) and the other included the overall components (the single factor extracted from the second EFA was modelled as a predictor of the second SEM). Details about the factors are given below. Regarding the experimental outcome, the parental variables (sensitive responsiveness and non-directiveness) were highly correlated ($r = .733$, $p < .001$) therefore they were constrained to load into a single factor named “parent sensitivity”. For model identification purposes, the ‘marker variable’ method was used, meaning that the latent variables’ scales were set by fixing the factor loading of one indicator variable to 1 for each latent variable (Beaujean, 2014).

Both SEMs tested whether there was a significant direct association between the brain measures (experimental predictors) and parent sensitivity (outcome) between the two groups of infants at 8 months, and whether this relationship was mediated by infant attentiveness. Infant age was included as a predictor of the brain measures, infant attentiveness and parent sensitivity as it varied across phases. Since age was controlled for, phase was not included as a further covariate, as age also accounts for possible differences in phase. Last, additional analyses with Wald tests were conducted to test the equality of the standardised regression coefficients of interest between the two sibling groups by setting up equality constraints (using the `lavTestWald` function, Klopp, 2019).

5.2.3.3 Measurement Invariance Testing. As the aim of this research was to test the hypothesised model across two different groups of infants, measurement invariance testing was a necessary step of multi-group analysis. Measurement invariance is used to indicate that the construct measured is equivalent across the groups, which is important for the study's validity and interpretation. That is, when investigating group differences, it determines whether differences in variables reflect differences between groups or whether these differences are due to differences in the instrument(s) used (Beaujean, 2014). Measurement invariance testing was conducted through Multigroup Confirmatory Factor Analysis (MG-CFA) which involved a series of tests that constrain parameters of interest in hierarchical order and compare one model to the next (Beaujean, 2014; Gana & Broc, 2019). The tests of measurement invariance included:

- 1) Configural invariance testing: the least restrictive model that tests whether the groups have the same factor structure.
- 2) Metric or weak invariance testing: the factor loadings are constrained to be equal across the groups.
- 3) Scalar or strong invariance testing: the factor loadings and intercepts are constrained to be equal across the groups.
- 4) Residual or strict invariance testing: the factor loadings, intercepts and error variances are assumed to be equal across the groups. Of note, the strict invariance level is not a requisite to imply measurement invariance (Mackinnon et al., 2022; Putnick & Bornstein, 2016).

Before testing the above models, a simple CFA was applied to each group separately in order to ensure that the hypothesized model fitted well in both groups (Gana & Broc, 2019). Measurement invariance was evaluated through the use of alternative fit

indices for nested model comparisons: ΔCFI , ΔRMSEA , ΔSRMR and $\Delta\chi^2$, though keeping in mind that chi-square tests are sensitive to sample size and violation of normality and can lead to model rejection even with negligible discrepancies (Bollen, 1989). As mentioned in **Chapter 4**, the cut-off criteria used based on $N \leq 300$ and unequal sample sizes were: $\text{CFI} \geq .905$, $\text{RMSEA} \leq .010$, $\text{SRMR} \leq .025$ for testing loading invariance, and $\text{CFI} \geq .905$, $\text{RMSEA} \leq .010$, $\text{SRMR} \leq .025$ for testing intercept or residual invariance (F. F. Chen, 2007). In addition, in the case that the models showed an unacceptable fit, an inspection of the modification indices and partial invariance would be tested, where/if necessary. The use of partial invariance testing is controversial (Steinmetz, 2013; Widaman & Reise, 1997), but it is generally deemed justifiable (Putnick & Bornstein, 2016). Again, in order to scale the latent variables, the factor loadings of the first indicator variable of each latent variable were fixed to 1. Measurement invariance testing was performed in ‘lavaan’ R (version 4.2.2) package (Rosseel, 2012) using the ‘cfa’ function.

5.2.3.4 Missing Data Evaluation. The missing data evaluation procedure is described in section **5.6.2**.

5.3 Results

5.3.1 Participant Demographic Characteristics

Table 5.1 shows the demographic and clinical characteristics of the sample, comparing the EL and TL infant groups. It provides information on the sample, age range, general adaptive behaviour measured through the VABS composite score, and cognitive abilities measured through the MSEL composite score. The groups differed significantly in the MSEL and VABS, with TL infants having higher scores than EL infants (MSEL p

= .03; VABS $p < .001$). **Table A5.3** provides the mean scores of the ERP and PII variables used in the study in the EL and TL groups.

Table 5.1

Demographic Characteristics and Mean Scores on Developmental Measures, Collected at 8 Months Across the Whole Sample. Infants at Typical Likelihood are Compared to Those at Elevated Likelihood for ASD

	Mean (SD)			$t(df) / \chi^2$	p	Cohen's d
	Total $N = 243$	TL $N = 77$	EL $N = 166$			
Age	8.13 (1.21)	7.91 (1.34)	8.22 (1.15)	-1.85 (240)	.066	-0.26
Sex M/F	119/124	35/42	84/82	0.56	.271 ^a	0.05 ^b
MSEL ELC ^c	103.96 (15.0)	107.3 (12.6)	102.7 (15.8)	2.21 (240)	.028	0.30
VABS ABC ^d	95.59 (13.40)	100.7 (12.8)	93.3 (13.1)	4.06 (236)	< 0.001	0.57
AOSI Total	8.30 (4.81)	6.47 (3.86)	9.13 (4.96)	-4.16 (241)	< 0.001	4.64

^a Fisher's exact test was used.

^b Cramer's V statistic was used as a measure of effect size.

^c One missing value in the EL group.

^d Two missing values in the TL group and three missing values in the EL group.

Abbreviations. EL: Elevated Likelihood; MSEL: Mullen Scales of Early Learning; TL: Typical Likelihood; VABS: Vineland Adaptive Behaviour Scales.

5.3.2 Missing Data Analysis

The results from the logistic regressions revealed significant relationships between age and some of the categorical indicator variables (**Table A5.4**). Therefore, missing data were considered as MAR and FIML was used.

5.3.3 Exploratory Factor Analysis

5.3.3.1 EFA 1: ERP Response Differences Between Stimulus Conditions.

Section **5.6.3** in the appendix provides a detailed description of the EFA 1 results. The scree plot showed inflexions that would justify retaining two factors (**Figure A5.1**). The variables clustered on factors suggested that factor one represented infant ‘face processing’ and factor two ‘gaze processing’. As all the variables loading on the two factors were amplitudes, both gaze and face processing factors represented the strength of brain response to the stimulus condition differences (**Table A5.3** provides details on the mean scores of the amplitudes in EL and TL infants).

5.3.3.2 EFA 2: ERP Absolute Responses to Stimulus Presentation. Section **5.6.4** in the appendix provides a detailed description of the EFA 2 results. After examining the scree plot (**Figure A5.2**) and factor loadings after rotation, one factor was retained. The variables clustered on factor 1 suggested that the factor represented the overall infant ‘brain response speed’ to both social and non-social stimuli (see **Table A5.3** for mean scores of the latencies in the EL and TL infant groups).

5.3.4 Investigating Brain and PII Associations Across the Whole Sample

5.3.4.1 SEM 1: Face and Gaze Processing as Predictors of PII. The results of SEM 1 are described in detail in section **5.6.5**. Overall, infant attentiveness significantly predicted parent sensitivity ($\beta = 0.36, p < .001$). Age was a significant predictor of parent sensitivity ($\beta = 0.10, p < .001$) and infant attentiveness ($\beta = 0.14, p = .03$). No other associations were observed. There was no mediation effect of infant attentiveness in the path between face/gaze processing and parent sensitivity ($ps > .50$).

5.3.4.2 SEM 2: Speed of Brain Response as Predictor of PII. The results of SEM 1 are described in detail in section **5.6.5**. Overall, the regressions showed that parent

sensitivity was significantly predicted by infant attentiveness ($\beta = 0.37, p < .001$), such that higher infant attentiveness was linked to more accepting and non-directive parent behaviour towards the infant. Age predicted infant attentiveness ($\beta = 0.14, p = .03$) and parent sensitivity ($\beta = 0.26, p < .001$). No other associations were observed. There was no mediation effect of infant attentiveness in the path between brain response speed and parent sensitivity ($p > .60$).

5.3.5 Investigating Brain and PII Associations by ASD Likelihood Group

5.3.5.1 Measurement Invariance Testing: Face and Gaze Processing Factors.

As already mentioned, measurement invariance testing was performed in five steps. Initially, regarding the face and gaze processing factors, two CFAs were conducted for the TL and EL group separately. The residual correlations that had been included in the SEM model using the whole group (**section 5.3.4.1**) were retained in the present CFAs and to later test measurement invariance, as after their inclusion and based on modification indices the models showed adequate fit, with no substantial discrepancies between them (TL group: $\chi^2(17) = 22.75, p = .16$, CFI = 0.981, SRMR = 0.091, RMSEA = 0.066, 90% CI [0.000, 0.131]; EL group: $\chi^2(17) = 26.971, p = .06$, CFI = 0.981, SRMR = 0.065, RMSEA = 0.065, 90% CI [0.000, 0.110]), compared to when there were no residual correlations in the model (TL group: $\chi^2(20) = 43.64, p = .002$, CFI = 0.920, SRMR = 0.100, RMSEA = 0.124, 90% CI [0.074, 0.174]; EL group: $\chi^2(19) = 78.22, p < .001$, CFI = 0.892, SRMR = 0.078, RMSEA = 0.147, 90% CI [0.114, 0.182]). The factor loadings showed satisfactory magnitude (ranging from .54 to .97) and were statistically significant ($p < .001$).

Next, measurement invariance was tested (see **Table A5.11** for details of the models tested, degrees of freedom, fit indexes, model comparison statistics and decisions

based on the models compared). Initial run of the model resulted in a negative variance estimate for the indicator variable ‘N290 amplitude SD vs. SA’. The variance was manually fixed to 0. Subsequent run of the model resulted in a negative variance estimate for the indicator variable ‘N290 amplitude FD vs. N’. The variance was manually fixed to 0. No further adjustments made. As shown in Table A.11, goodness of fit indices demonstrated that model fit was good across all the measurement invariance tests, except SRMR which had an acceptable value only for the configural model, based on Hu's and Bentler's (1999) suggested cut-off criteria. However, it is worth noting that SRMR can over-reject an invariant model in small samples (F. F. Chen, 2007), whereas CFI, which indicated a good fit, performs well when sample sizes are smaller (Hu & Bentler, 1998). The comparison of fit indices across nested models showed measurement invariance, indicating a similar amount of change given the cut-off criteria suggested by Chen (2007) for small sample sizes ($N \leq 300$). In addition, the chi-square difference tests for model comparisons were nonsignificant (model 1 to model 2: $p = .6009$; model 2 to model 3: $p = .18$; model 3 to model 4: $p = .30$; refer to **Table A5.11** for χ^2 values and df). Model 4 had the lowest AIC/BIC value (Model 1: AIC = 7177.1, BIC = 7359.4; Model 2: AIC = 7170.1, BIC = 7332.1; Model 3: AIC = 7165.7, BIC = 7300.7; Model 4: AIC = 7164.1, BIC = 7278.9), thus, concluding that metric, scalar and residual invariance was supported in this dataset. Overall, the combination of fit statistics above indicated that measurement invariance was achieved for the face and gaze processing factors.

5.3.5.2 Face and Gaze Processing as Predictors of PII Between EL and TL Infants. After establishing measurement invariance across the two groups, additional analysis was conducted to examine whether the same associations that were found in the whole group SEM were held between the variables of model one across the two groups of infants (EL and TL infants). This was followed by the calculation of Wald tests to

compare which paths were or weren't significantly different between the groups. An initial run of the model resulted in a negative variance estimate for the indicator variable 'sensitive responsiveness'. The variance was manually fixed to 0. Subsequent run of the model resulted in negative variance estimate for the indicator variable 'N290 amplitude SD vs. SA'. No further adjustments were made. The model provided an acceptable fit to the data ($\chi^2(92) = 129.637, p = .006$, CFI = 0.966, SRMR = 0.103, RMSEA = 0.057, 90% CI [0.031, 0.079]).

In the TL group, all the indicator variables loaded strongly on the face processing, gaze processing and parent sensitivity factors ($p < .001$, **Table A5.12**). There was a non-significant direct effect of the neural measures on parent sensitivity (face processing: $\beta = -0.17, p = .12$; gaze processing: $\beta = -0.095, p = .28$). While a non-significant association was observed between the neural measures and infant attentiveness (face processing: $\beta = 0.16, p = .28$; gaze processing: $\beta = -0.12, p = .38$), the latter significantly predicted parent sensitivity ($p < .001$). Additionally, the following pairs of variables co-varied significantly: P100 and P400 amplitudes to FD vs FA ($\beta = 0.51, p = .001$), P400 amplitude to FD vs N and P400 amplitude to FD vs FA ($\beta = 0.30, p = .01$), P1 amplitude to FD vs N and FD vs FA respectively ($\beta = 0.32, p = .03$).

Regarding the EL group, all the indicator variables loaded strongly on the latent variables, though most, not as strongly as in the TL group ($p < .001$, **Table A5.13**). No significant direct effect was observed between the neural measures and parent sensitivity (face processing: $\beta = -0.00, p = 1.0$, gaze processing: $\beta = 0.11, p = .15$). Contrary to the TL group, face processing was significantly associated with infant attentiveness ($p = .04$) but gaze processing was not ($\beta = 0.01, p = .95$). However, as with the TL group, infant attentiveness was significantly associated with parent sensitivity ($p = .001$) and there was a significant covariance between the variables mentioned in the TL group description above (P100 and P400 amplitudes to FD vs FA: $\beta = 0.52, p < .001$; P400 amplitude to

FD vs N and P400 amplitude to FD vs FA: $\beta = 0.41, p = .002$; P100 amplitude to FD vs N and FD vs FA: $\beta = 0.40, p = .01$).

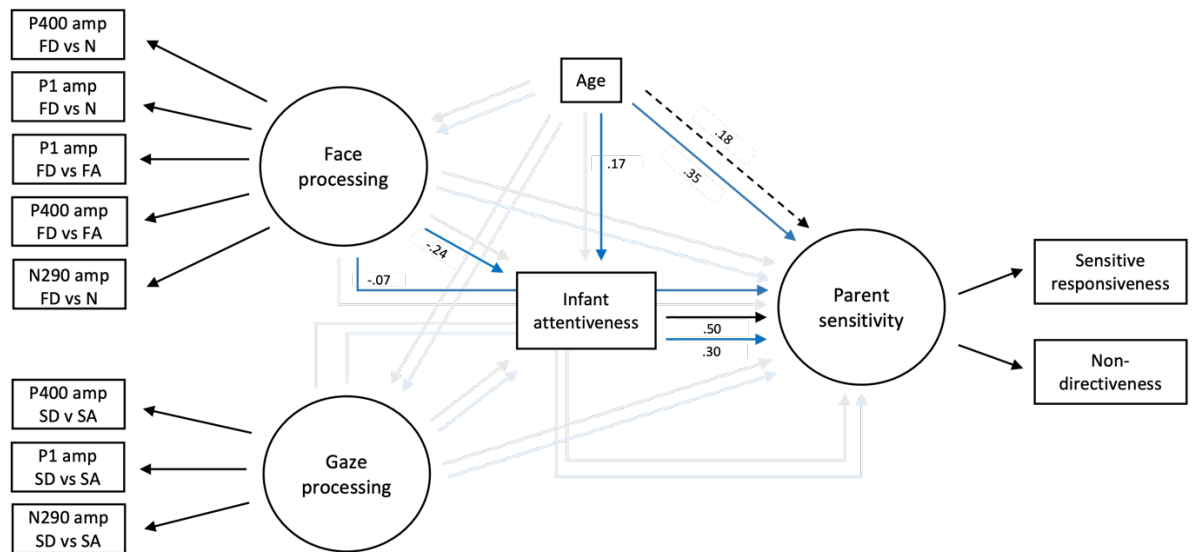
In the EL, but not in the TL group, age significantly predicted parent sensitivity and attentiveness (parent sensitivity: $p < .001$; infant attentiveness: $p = .02$). **Figure 5.4** illustrates significant paths in black/blue solid lines for the TL/EL infants, respectively, and trends of association ($p < .1$) in dashed lines. All standardised and unstandardised estimates with robust standard errors are shown in **Tables A5.12 and A5.13**.

The mediation model testing for the effect of infant attentiveness in the path between neural measures and parent sensitivity showed that there was a significant indirect effect of infant attentiveness, but only on the path between face processing and parent behaviour for the EL group (face processing, EL group: $\beta = -0.07, SE = 0.006, z = -2.023, p = .04$; TL group: $\beta = 0.08, SE = 0.014, z = 1.034, p = .30$; gaze processing, EL group: $\beta = 0.001, SE = 0.009, z = 0.059, p = .95$; TL group: $\beta = -0.06, SE = 0.030, z = -0.0847, p = .40$).

Further analysis was conducted by calculating Wald tests to investigate group differences across the different paths. The overall Wald test to identify group differences across all paths showed that ‘group’ was a significant moderator ($\chi^2(5) = 13.16, p = .02$). Inspecting specific group differences revealed that the groups differed in the path between face processing and attentiveness ($\chi^2(1) = 4.70, p = .03$).

Figure 5.2

Face and Gaze Processing Multigroup Model Depicting the Regression Paths in the TL and EL group



Note. Face and gaze processing structural equation model predicting parent sensitivity mediated by infant attentiveness in the TL (black arrows) and EL (blue arrows) groups. Covariances between the indicator variables are omitted for clarity. Black and blue arrows indicate significant relationships at $p < .05$. Dashed arrows indicate marginal relationships ($p < .1$). Grey and light blue arrows indicate nonsignificant relationships. Standardised betas are reported.

5.3.5.3 Measurement Invariance Testing: Speed of Brain Response Factor.

Measurement invariance testing of the factor concerning the speed of brain response across the EL and TL infants was also performed in five steps. Firstly, two CFAs were conducted for each group separately. The residual correlations that had been included in the model when examining the whole group were retained in the present CFAs and for later testing measurement invariance, as after their inclusion and based on modification indices the models showed better fit, with no substantial discrepancies between them (TL group: $\chi^2(1) = 2.19$, $p = .14$, CFI = 0.988, SRMR = 0.021, RMSEA = 0.108, 90% CI [0.000, 0.309]; EL group: $\chi^2(1) = 0.118$, $p = .73$, CFI = 1.000, SRMR = 0.006, RMSEA

= 0.000, 90% CI [0.000, 0.187]) compared to when there were no residual correlations in the model (TL group: $\chi^2(2) = 1.74$, $p = .42$, CFI = 1.000, SRMR = 0.027, RMSEA = 0.000, 90% CI [0.000, 0.237]; EL group: $\chi^2(2) = 11.694$, $p = .003$, CFI = 0.858, SRMR = 0.077, RMSEA = 0.230, 90% CI [0.115, 0.365]). The ERP variables loaded moderately to strongly on the factor (ranging from .50 to .89) and were statistically significant ($p < .001$), except P100 latency to Noise that had a weak factor loading in both groups (EL group: $\beta = 0.21$, $p = .08$; TL group: $\beta = .27$, $p = .12$).

As a next step, measurement invariance testing was performed (see **Table A5.14** for details of the models tested, degrees of freedom, fit indexes, model comparison statistics and decisions based on the models compared). All the measurement invariance tests indicated good model fit. The comparison of fit indices across nested models showed measurement invariance, indicating similar amount of change given the aforementioned cut-off criteria suggested by Chen (2007). The amount of change in SRMR comparing model 3 to model 4 was slightly above the acceptable threshold. However, as already mentioned, SRMR can be affected by sample size and can over-reject an invariant model, especially when testing loading and residual invariance (F. F. Chen, 2007), while CFI is more reliable with small samples (Hu & Bentler, 1998). Furthermore, chi-square difference tests for model comparisons were nonsignificant (model 1 to model 2: $p = .96$; model 2 to model 3: $p = .28$; model 3 to model 4: $p = .77$; refer to **Table A5.14** for χ^2 values and df). Model 4 had the lowest AIC/BIC value (Model 1: AIC = 5236.1, BIC = 5318.4; Model 2: AIC = 5230.5, BIC = 5303.3; Model 3: AIC = 5227.9, BIC = 5291.2; Model 4: AIC = 5221.7, BIC = 5272.4), showing that metric, scalar, and residual invariance was supported in this dataset. Overall, the combination of fit statistics above indicated that measurement invariance was achieved for the brain response speed factor.

5.3.5.4 Speed of Brain Response as a Predictor of PII Between EL and TL

Infants. After establishing measurement invariance for the brain response speed factor, additional analysis was conducted to examine associations between EL and TL infants on the variables of model two. An initial run of the model resulted in a negative variance estimate for the indicator variable ‘sensitive responsiveness’. The variance was manually fixed to 0. No further adjustments were made. The model provided a good fit to the data ($\chi^2(32) = 42.313, p = .11$, CFI = 0.974, SRMR = 0.050, RMSEA = 0.050, 90% CI [0.000, 0.088]).

All items loaded moderately to strongly on the brain response speed and parent behaviour factors in both groups ($p < .001$), except P1 latency to Noise which loaded weakly across groups ($p > .05$, **Tables A5.15 and A5.16**).

Regarding the TL group, the direct path between the brain measure and parent behaviour was non-significant ($\beta = .04, p = .78$). However, there was a borderline significant association between brain response speed and infant attentiveness ($p = .05$), such that faster brain responses to visual stimuli were related to higher attentiveness to the parent. Consistent with the previous models, infant attentiveness significantly predicted parent sensitivity ($p < .001$). In addition, there was a non-significant covariance between N290 and P1 latency to Noise ($\beta = 0.14, p = .43$). Considering the EL group, similarly to the TL group, no significant direct effect was observed between the brain measure and parent sensitivity ($\beta = 0.19, p = .07$). There was a non-significant relationship between brain response speed and infant attentiveness ($p = .301$) but infant attentiveness significantly predicted parent sensitivity ($p = .001$), though to a lesser extent than in the TL group. A significant covariance was observed between N290 and P1 latency to Noise ($\beta = 0.37, p < .001$). Furthermore, age was a significant predictor of parent sensitivity for the EL group only (TL group: $p = .08$; EL group: $p < .001$). **Figure 5.5** illustrates the significant paths in black/blue solid lines for the TL/EL infants,

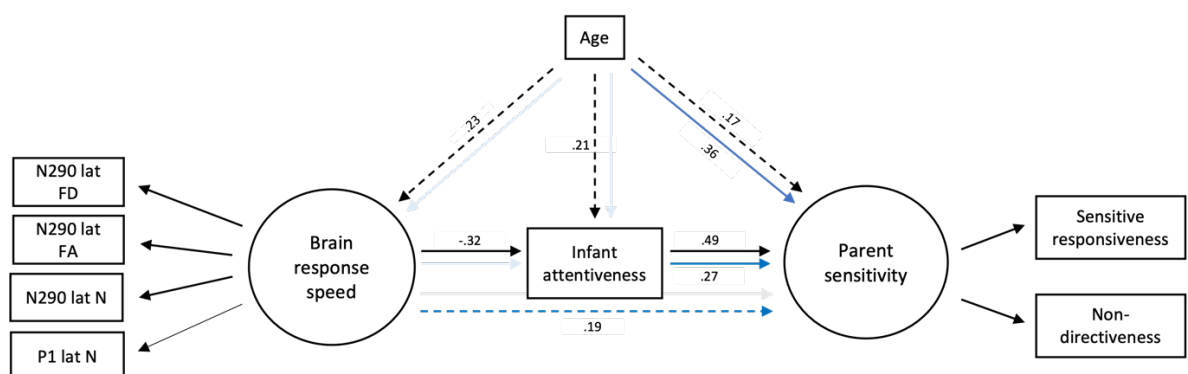
respectively, and trends of association ($p < .1$) in dashed lines. All standardised and unstandardised estimates with robust standard errors are shown in **Tables A5.15 and A5.16**.

The examination of the mediating effect of infant attentiveness on the path between speed of brain response and parent sensitivity showed no significant indirect effect in any of the two groups (TL group: $\beta = -0.159$, $SE = 0.006$, $z = -1.779$, $p = .08$; EL group: $\beta = 0.038$, $SE = 0.003$, $z = 1.002$, $p = .32$).

Additional analysis involved the calculation of Wald tests to investigate group differences across the different paths in the SEM model. The overall Wald test to identify group differences across all paths was significant ($\chi^2(3) = 8.28$, $p = .04$). Inspecting specific group differences through Wald tests revealed that the differences between the two groups in the path between brain response speed and attentiveness were significant ($\chi^2(1) = 4.45$, $p = .04$). Furthermore, the path between infant attentiveness and parent behaviour was marginally significantly different between the groups ($\chi^2(1) = 4.00$, $p = .05$).

Figure 5.3

Brain Response Speed Model Depicting the Regression Paths in the TL and EL Group



Note. Brain response speed structural equation model predicting parent sensitivity mediated by infant attentiveness in the TL (black arrows) and EL (blue arrows) group. Covariances

between the indicator variables are omitted for clarity. Black and blue arrows indicate significant relationships at $p < .05$. Dashed arrows indicate marginal relationships ($p < .1$). Grey and light blue arrows indicate nonsignificant relationships. Standardised betas are reported.

5.4 Discussion

It has been suggested that early neural differences possibly underlying disrupted neural processing of social attention in infants at EL, may influence the quality of social interactions between infants and their caregivers, which could have downstream effects on subsequent development. However, research on the links between brain function and PII in the context of ASD susceptibility has been limited. The present study aimed to add to and extend previous findings by investigating the links between infant neural measures of visual attention and measures of unstructured parent-infant interaction in 243 8-month-old infants with and without an EL for ASD who took part in BASIS phase 1 and 2. In terms of the neural measures, the study focused on the examination of infant brain processing of faces with an emphasis on the magnitude of neural responses to 1) faces with gaze directed toward versus away from the infant or versus visual noise, 2) eye gaze shifts directed toward versus away from the infant. Additionally, the investigation of the general speed of infant brain response to both social and non-social stimuli was of interest. Parent-infant interaction measures involved infant attentiveness to parent and parent sensitivity towards the infant (measured as sensitive responsiveness and non-directiveness).

The findings suggest an association between brain function and PII in EL and TL infants, consistent with previous preliminary research that incorporated a sub-sample (Phase 1 sample) of infants included in the current study (Elsabbagh, Bruno, Wan, Charman, Johnson, Green, & Team, 2015). Compared to previous research by Elsabbagh and colleagues (2015), the larger sample size in the current study allowed the inclusion

of additional variables, and thus, the flexibility of testing different theoretically based relationships between variables, extending previous research. The findings revealed non-significant relationships between the neural measures and infant attentiveness as well as parent sensitivity across the whole sample. The results from the multigroup SEM showed a negative association between face processing and infant attentiveness in the EL group, while a marginally significant trend towards faster responses to both social and non-social stimuli linked to greater attentiveness to parent in the TL group was observed. Wald tests revealed EL and TL group differences in these regression paths (and between attentiveness and parent sensitivity in the brain response speed model, though only at a trend level). In addition, across all SEMs, infant attentiveness was positively associated with parent sensitivity. No direct associations were observed between the neural measures and parent sensitivity in any of the models. There was a mediation effect of infant attentiveness in the relationship between face processing depth and parent sensitivity only for the EL group. No mediation effect was observed in the brain response speed multigroup SEM model. The sections below consider possible explanations of the study results.

Overall, the results agree with theoretical propositions that the ability of the infant's brain to process social information relates to infant social engagement/attention to the external environment (the parent during play interactions), which in turn, relates to the way the parent responds to the infant (Elsabbagh & Johnson, 2010; Johnson et al., 2005). They also provide evidence for differences in brain-PII relationships between EL and TL infants. These differences in the patterns of association between ERP and PII measures may reflect alternative developmental pathways underpinning brain development in EL and TL infants. The sections below discuss the study results in more detail.

5.4.1 Face processing and PII

The findings revealed that infants at EL had greater responses to faces compared to non-faces/faces averted from the infant, which was linked to lower infant attentiveness to parent, and infant attentiveness was in turn associated with increased parent sensitivity. This mediating effect of infant attentiveness on brain function and parent sensitivity contrasts with the initial hypothesis that greater attention capture and neural processing of faces would be linked to higher infant attentiveness, and in turn to higher parent sensitivity in the TL group, as this link was not observed in TL infants. Different factors may contribute to the present finding, which are discussed next.

5.4.1.1 Social Brain Specialisation Differences. It is possible that greater face processing amplitude through the P1, N290 and P400 components, which are linked to lower attentiveness may underpin a developmental delay in the EL group's social development as manifested initially within the social brain network (Johnson et al., 2005). This is supported by the finding that the mediation effect was applied to static faces (vs. non-face/face directed away) only and not to dynamic eye gaze shifts, the latter of which are considered to be more developmentally sophisticated. This may also explain EL infants' lower developmental level score (MSEL ELC) compared to the TL infants' score (**Table 5.1**).

More specifically, each of these paradigms relays two different types of communicative information: The former signals communicative intent through direct eye contact whereas the latter conveys referential information through the direction of gaze to the referent object or location of interest (Csibra & Gergely, 2006). Evidence suggests that both are present very early in infancy and the former is a prerequisite in order for the latter to follow (Farroni et al., 2004; Senju et al., 2008). In particular, the dynamic eye gaze shift stimulus is closely linked to shared attention in naturalistic contexts and

involves the recruitment of more social attention processing mechanisms in the brain than static gaze (Conty et al., 2007). Shared attention in infants develops from a simple face orienting into a more sophisticated engagement in joint attention activities with others. Infant attention capture by simple stimuli decreases while it increases with more dynamic ones with developmental time (Richards, 2010) and infants become more involved in episodes of shared attention with others, following or directing gaze to share a mutual reference point (Mundy, 2018). In fact, joint attention facilitates social learning, it is crucial for socio-cognitive development and has been shown to be atypical in EL-ASD infants, with atypicalities emerging from 7 months of age, analogous to the time of the development of joint attention skills in typically developing infants (Braithwaite et al., 2020; Carpenter et al., 1998; E. J. H. Jones et al., 2014; Mundy, 2018). These findings are consistent with previous research showing no neural response differentiation to dynamic eye gaze shifts in 6 to 10-month-old EL-ASD infants compared to EL-no ASD and TL infants (Elsabbagh et al., 2012), indicative of possible disruptions in the processing of social stimuli. Although no significant effects were shown for the TL group either, this is likely due to EL infant overrepresentation in this study. Thus, it is likely that the differences in EL infant patterns of neural activation to social vs. non-social stimuli compared to TL infants may suggest that EL infants engage in alternative neural processing pathways to interpreting social information due to delayed brain specialisation, which relates to infant social attention in the context of play interaction, affecting parental responses. In fact, if the study results indeed reflect a delayed social brain specialisation, this can have important implications for intervention, as prolonged neural plasticity (due to delayed perceptual narrowing) may extend sensitive periods within which early interventions could be implemented to improve infants' developmental trajectories (Johnson, Jones, et al., 2015).

5.4.1.2 Inefficient Face Processing. A second plausible explanation is that the finding may reflect inefficient face processing, such that it may be more effortful for EL infants' brains to process social vs non-social stimuli reflected in lower attentiveness to parent during play. Previous research using different measures has shown similar patterns of results. For instance, an eye-tracking study using a face pop-out paradigm demonstrated that infants at EL with and without a subsequent ASD diagnosis showed longer peak look durations to a static face stimulus than TL infants at 14 months (Hendry et al., 2018), while the same results were found in 15-month-old infants at EL with a later ASD outcome in a previous similar study (Elsabbagh, Gliga, et al., 2013). Hendry et al. (2018) also found that prolonged attention to faces was linked to difficulties in effortful control at 3 years in the EL group. Other studies using a habituation task revealed that EL-ASD infants exhibited longer peak looks to faces than objects compared to TL controls at 12 months (Jones et al., 2016; Jones, Dawson, Kelly, Estes, & Webb, 2017), while longer habituation to faces in toddlers with ASD has been linked to lower social and verbal skills (Webb et al., 2010). These findings also extend to research examining attention-deficit/hyperactivity disorder (ADHD) outcome in EL and TL infants, since the two conditions genetically overlap (Rommelse et al., 2010), with the ADHD group showing longer looking times on screen regardless of the stimulus presented than the TL group, early during the first year (M. Miller et al., 2018). Therefore, the present ERP responses likely signify disruptions in attention engagement and processing of social stimuli that possibly affect infants' behavioural social attention within unstructured PII.

Although this is one possible explanation, it should also be acknowledged that "longer looking" is difficult to interpret. For instance, longer peak look duration could also be interpreted as a preference rather than as something more effortful. Considering this, it cannot be strongly concluded that the interpretation of longer peak look duration as reflecting a difficulty in attention engagement holds for the current study's findings

that were based on brain data. Thus, this interpretation cannot be strongly supported but it may be a possibility.

5.4.1.3 Context Complexity. Another factor that possibly contributes to this finding is that EL infants' social attention ability may differ depending on the context (neural social attention in a structured environment vs. social attention to the parent within the context of play). The important distinction here is that the brain measure involved the use of specific static social/non-social stimuli presented under a highly structured, controlled environment. On the other hand, the assessment of attentiveness within PII did not just involve attention to the face or eye contact; it also considered the use of gestures, infant's responses to caregiver's vocalisations, shared attention, proximity, and others. While these infants may be able to adapt to the former environment due to lesser complexity, in a dynamic, less predictable social environment with multiple competing stimuli, such as the early social environment involving interactions with caregivers, infants' own brain processing capabilities may pose limitations to their level of attentiveness to their parents. This possibly explains the negative indirect effect observed between brain function and PII. This result is consistent with previous research showing that infants or toddlers who develop ASD attend less to scenes or experimental contexts involving various social stimuli (Chawarska et al., 2012; Shic et al., 2014). The present result might reflect an adaptive response to disrupted neural signal processing (Johnson, 2017; Johnson, Jones, et al., 2015) or it might be related to infants' motivation to attend to social cues in different conditions (Chevallier et al., 2012). Given the cross-sectional design of this study, it is difficult to disentangle the underlying processes related to the present finding. Future longitudinal research examining these links, perhaps incorporating additional measures (e.g., eye-tracking) might help elucidate the developmental mechanisms underpinning the present associations.

5.4.2 Brain Response Speed and PII

Contrary to one of the study's hypotheses, the results revealed no mediation effect of attentiveness in the path between the timing of infant brain responses and parent sensitivity. However, the EL and TL groups differed in the path between the speed of brain response to social and non-social stimuli and infant attentiveness to parent. A borderline significant effect of generally faster brain responses to both social and non-social stimuli linked to greater attentiveness to parent was observed in the TL group, while the EL group did not show a relationship between the two measures. There is research evidence showing that, compared to children with no ASD, children with an ASD diagnosis show slower neural information-processing speed compared to those with no ASD, which is linked to impairments in social attention (Dawson, Webb, & McPartland, 2005). Infants at EL with and without a subsequent ASD diagnosis also show prolonged neural responses to visual social stimuli compared to those with no family history of ASD (Elsabbagh et al., 2009; Elsabbagh et al., 2012). However, in a more recent study, the opposite effect was found in infants with later ASD reflected through the P400 component, which was interpreted as a reduced depth of processing (E. J. H. Jones et al., 2016).

Considering previous findings, although the observed association in this study did not represent a strong effect size, the trend shown towards faster brain response speed in the TL group might mean that this type of brain response reflects a general trend toward fast and more efficient perceptual processing and encoding ability regardless of the stimulus presented. This was then linked to greater infant attentiveness towards the parent during play interaction, which was related to higher parent sensitivity towards the infant. Although replication is necessary with a larger sample size given the marginal association, these results are again consistent with theoretical propositions supporting the

relationship between brain and experience (Champagne & Curley, 2005; A. J. Sameroff, 2009). More efficient neural processing provides the potential to enhance social interest and can increase the quality of infant social experiences (reflected here in higher attentiveness to the parent), which can influence parental responses.

The fact that brain response speed was not associated with parent sensitivity was somewhat surprising, considering that previous research has found links between P100 latency response difference and parent sensitive responsiveness in a subsample of TL infants included in this study (Elsabbagh, Bruno, Wan, Charman, Johnson, Green, & The BASIS Team, 2015). However, differences in methodology, study design and sample size between the studies likely explain the inconsistency in the findings.

5.4.3 Infant Attentiveness and Parent Sensitivity

The study results revealed that greater infant attentiveness was related to higher parent sensitivity in all SEM models across both groups. In the multigroup SEM, this relationship was stronger in the TL group compared to the EL group (as was also shown in Chapter 3), but Wald tests revealed that the differences between both groups in this relationship were non-significant in the face processing model and marginally significant in the brain response speed model. These findings indicate that parents may be reacting in a similar way to similar behaviour (attentiveness) in their child, which is consistent with the proposition that parents adjust their social behaviours to their infants' characteristics and developmental level. Considering that the quality of early caregiver-infant interactions can have an effect on infant brain function, possibly altering infants' developmental routes (Champagne & Curley, 2005), this finding can be central and can help inform parent training interventions. Indeed, interventions delivered to parents of infants at EL for ASD (interventions delivered when infants aged between 7 to 10 and 9 to 14 months) have shown treatment effects, with increases in parent non-directiveness and

infant attentiveness (Green, Charman, Pickles, Wan, Elsabbagh, Slonims, Taylor, Mcnally, et al., 2015; Green et al., 2017) and with EL and TL infants having similar ERP (P400) responses to faces and objects post-intervention (intervention delivered between 9 and 11 months of age, Jones et al., 2017). Whether the quality of infant social interactions with caregivers and, particularly, parental responses contribute to changes in infant social attention within play interactions and to neural processing and cortical specialisation at later points in time remains to be found through a longitudinal design investigating how brain-PHI co-develop across time in EL and TL infants.

5.4.4 Limitations and Future Directions

This study has contributed to a better understanding of the nature of the relationship between brain function and PHI in the context of ASD. However, some methodological limitations need to be considered in the interpretation of the results that would inform areas for future research direction. Firstly, although this study was the largest combining brain function measures with measures of PHI in the context of ASD, the sample size was still not sufficient to examine how brain and PHI relationships unfolded based on 3-year ASD diagnosis. Any attempts to include clinical outcome groups led to model non-convergence. Even though no rules of thumb exist around the specific sample size required to use SEM as this depends on many factors, such as model complexity, missing data, the number of indicators or the factor loadings' size (Wolf et al., 2013), SEM generally requires large sample sizes (Kline, 2015). It has been suggested that having a very small sample could possibly affect the accuracy of the parameter estimates (Kline, 2015; Wolf et al., 2013), and given that the EL-ASD group size was small ($n = 34$) in itself and compared to the other two groups (TL: $n = 77$; EL-no ASD: $n = 132$), multigroup SEM using the two likelihood groups was considered as the best option. Therefore, given the potential of the findings, the marginal associations observed

and the implications they may have for ASD emergence, replication of the study with a larger sample size is needed, which would increase the model's statistical power, allowing the inclusion of an EL group with a later diagnosis. This would enable the interpretation of the findings with greater confidence. Furthermore, considering that the study did not examine the identified relationships in the EL group in relation to ASD outcome, it is not possible to discount the possibility that these associations may have been driven by the EL group who did not go on to be diagnosed with ASD. It should also be noted that no adjustment for multiple comparisons was performed in the multigroup SEM, as EL and TL group differences were jointly evaluated in all the regression paths that were asking different questions. However, it should be acknowledged that correcting for multiple comparisons or adjusting the p-value threshold to a stricter criterion (e.g., $p < 0.01$) may have led to a nonsignificant difference between the groups, specifically in the paths between face processing/brain response speed and infant attentiveness.

It would also be of interest to explore how the relationships unfold in EL infants who develop neurotypically and those who develop other clinical conditions, which would provide further important clues about the heterogeneity of the condition, the possible underlying mechanisms and the protective factors associated with ASD. In addition, controlling for the effects of other environmental (i.e., parental socioeconomic status, parental stress, parental autistic traits) or genetic (i.e., polygenic scores) factors on brain and PII relationships in ASD would be an interesting avenue for future research.

Moreover, the basis for using SEM was that it is a very flexible approach, as it allowed the use of different measured and latent constructs to test the hypothesised direct and indirect relationships in a single model that would otherwise be undertaken in a stepwise manner. However, it was not without its challenges. Due to the occurrence of negative estimates of variances, specific modifications in the model were necessary to aid convergence. Furthermore, although theoretically and methodologically justifiable,

certain modifications based on modification indices were required to improve model fit. Therefore, replication with an independent sample is needed to rule out model overfitting and to evaluate the models' generalisability to other samples.

Finally, the observed relationships cannot necessarily imply causality between the particular measures of brain function and the caregiver-infant interaction aspects. These links regarding both typical and atypical development are yet to be established. Further work employing a longitudinal design would be required to advance our understanding of the possible causal mechanisms between neural social attention and caregiver-infant interaction processes involved in ASD outcome and to determine the sensitivity of these measures to early parent-mediated intervention effects (Green et al., 2017; E. J. H. Jones et al., 2017).

5.5 Conclusion

The present study has contributed to filling the gap that exists in literature by showing that neural measures of social attention are related to qualitative aspects of PII in 8-month-old infants at TL and EL for ASD, supporting theoretical propositions for the importance of early infant brain-environment interactions (Elsabbagh & Johnson, 2010; Johnson et al., 2005; Klin et al., 2020). The study results are consistent with a model of diverging neurodevelopmental pathways to visual attention in relation to social attention within the context of play in EL infants. They could possibly play a role in early emerging signs of ASD, as these findings might be an indication of face processing inefficiencies or delays in the EL group that may compromise infant interactional attentiveness to the parent during social interactions, which, in turn, influences the way caregivers respond to their infants. This evidence offers significant insights into the possible factors contributing to ASD outcome and the role that PII can play in these children's developmental trajectories, which could contribute towards developing or enriching early

parent-targeted interventions in the future. It provides a stepping-stone towards a better understanding of how measures of brain function relate to naturalistic interactions between infants and their parents and whether they could both play a predictive role in assessing the risk of clinical diagnosis in early childhood. Dissecting these associations through a longitudinal design would provide a clearer view of the early social interaction dynamics as well as the developmental processes related to ASD outcome.

5.6 Appendix

5.6.1 *Electrophysiological Acquisition and Processing*

For EEG recording, a 128 channel Hydrocel Sensor Net was placed on infants' head while they were sitting on their parents' laps in front of the computer screen. Brain activity was measured during trial presentation which included 50 trials, presented continuously when the infants paid attention to the screen. The electrode used as a reference was located at the vertex (Cz in the conventional 10/20 system). EGI NetAmps 200 was used (gain = 1,000). EEG data pre-processing was conducted by M. Elsabbagh (Phase 1) and C.Tye (Phase 2). The signal was digitized at a sampling rate of 500Hz and a band-pass filter between 0.1-1000Hz was applied.

EGI Netstation software 4 (for Phase 1) and 5 (for Phase 2) was used for offline data storage and analysis using the same protocol as Elsabbagh et al. (2012). In the trials used, infants were focusing their gaze on the centre of the screen throughout the 800 ms segment after stimulus presentation using the concurrent video recording. Artifacts such as infant gaze shifts, head movement and blinking during or 100 ms before stimulus presentation were excluded through video coding. Following from this, data were corrected to the -200 ms baseline. Segments with significant artifacts were removed through automated artifact rejection. In particular, for each segment, the channels removed due to bad signal recording were those with EEG signal $>400 \mu\text{V}$. Data with the signal reaching amplitudes $>400 \mu\text{V}$ for 1,000 ms were removed for constituting eye-blinks, while data for 160 samples were removed for constituting eye movements. Channels in which more than 75% of the data were counted as artifacts were considered bad. Subsequently, experienced EEG researchers (M. Elsabbagh and C. Tye) examined each trial visually for manual rejection of EEG data that contained artifacts. The

interpolation of missing data from 12 or fewer channels was undertaken or the whole trial was rejected. Next, data were rereferenced to the average.

Stimulus-locked epochs (-200 to 800 ms peri-stimulus window for the face with Direct Gaze condition, -200 ms to 795 ms for the Face with Averted Gaze and Noise) were averaged within each presentation block. Averages were calculated for each participant based on a minimum of 10 trials per stimulus. There was no difference in the valid trials used for each outcome group. Additionally, occipito-temporal montages used by (Elsabbagh et al., 2012) were used in this study and were confirmed through visual examination of grand averages. **Table A5.1** shows the mean number of valid trials per group for each condition.

5.6.2 Missing Data Evaluation

The Missing data were examined to determine whether they were MAR, MCAR or neither. Firstly, the variables that contained missing data were dummy-coded, creating categorical indicator variables that separated the subjects with missing values from the subjects with observed values. Then, each indicator variable was included in a logistic regression model as the dependent variable, with the variables in the analysis, including infant sex, age in months (8 months), ASD likelihood group, as well as verbal and non-verbal developmental level at 8 months as the independent variables. In addition, bivariate correlations were performed between the independent variables to examine possible high intercorrelations between them. Owing to the high intercorrelations between parent sensitive responsiveness and nondirectiveness, they were included separately in the regression models as predictors.

5.6.3 EFA 1: ERP Response Differences Between Stimulus Conditions

The first EFA was conducted using principal axis factor analysis on the 22 ERP measures. An initial scan of the correlation matrix showed that some variables were not correlated or were correlated slightly ($r < .3$), while others correlated very highly with each other ($r > .8$) with the determinant value indicating an issue of multicollinearity (Determinant = 7.86E-006, smaller than the necessary value of 0.00001) and some of the diagonals of the anti-image correlation matrix were below the acceptable value of .5. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy had a mediocre value according to Hutcheson and Sofroniou (1999), (KMO = .62). The Bartlett's test of sphericity was significant ($\chi^2(231) = 1373.2, p < .05$). Some of the communalities were below .3 verifying that some items did not share common variance with others.

After the elimination of 11 variables in total that showed low correlations, a principal axis factor analysis was run on the 11 remaining variables using both orthogonal and oblique rotations. Because the oblique rotation displayed a low association between the extracted factors, the orthogonal rotation (varimax) was selected (Pedhazur and Schmelkin, 2013). The KMO measure verified the sampling adequacy for the analysis (KMO = .70) and the Bartlett's test of sphericity was significant ($\chi^2(55) = 759.9, p < .05$). All KMO values for individual items were greater than .64, which is above the acceptable limit of .5 (A. Field, 2013).

Three factors had eigenvalues over Kaiser's criterion of one and in combination explained 69.52% of the variance (**Table A5.5**). The scree plot showed inflexions that would justify retaining two factors (**Figure A5.1**). Given that the sample size was not large enough (When $N > 250$, Kaiser's criterion is considered to be more accurate, Field, 2013) and that not all communalities after extraction exceeded .7, these criteria under Kaiser's rule were considered inappropriate. Thus, the scree plot was used and two factors were retained (see **Table A5.6** for factor loadings after rotation).

5.6.4 EFA 2: ERP Absolute Responses to Stimulus Presentation

The second EFA was also conducted using principal axis factor analysis and included 18 items that were all latencies so as to obtain the variables that best mapped onto latency in order to investigate the overall speed of infant brain response to social/non-social stimuli. As before, the analysis was run using both orthogonal and oblique rotations. The orthogonal rotation (varimax) was preferred due to negligible associations between the extracted factors (Pedhazur and Schmelkin, 2013). The KMO measure of sampling adequacy was acceptable (KMO = .65, 'mediocre', according to Hutcheson & Sofroniou, 1999). The Bartlett's test of sphericity was significant ($\chi^2(153) = 631.130, p < .05$). All KMO values for individual items were greater than .51, which is above the acceptable limit of .5 (A. Field, 2013).

Six factors had eigenvalues over Kaiser's criterion of one, and together they explained 63.68% of the variance (**Table A5.7**). Not all communalities after extraction exceeded the value of .7. The scree plot showed inflexions that would justify retaining two or four factors (**Figure A5.2**). Finally, only one factor was retained, firstly, because it explained most of the variance relative to the other factors (**see Table A5.8 for factor loadings after rotation**), and secondly, because the variables connected to that factor satisfied the investigation of the hypothesis of interest.

5.6.5 SEM 1: Face and Gaze Processing as Predictors of PII

Firstly, the hypothesised model that face and gaze processing predicts parent sensitivity, mediated by infant attentiveness (to parent) and controlling for infant age, was assessed for fit using the entire sample. An initial run of the model resulted in a negative variance estimate for the indicator variable 'sensitive responsiveness'. The variance was manually fixed to 0. Subsequent run of the model resulted in a negative variance estimate for the indicator variable 'N290 amplitude SD vs. SA'. The variance was manually fixed

to 0. No further adjustments were made. The model provided a poor fit to the data ($\chi^2(48) = 155.96$, $p < .001$, CFI = 0.904, RMSEA = 0.093, 90% CI [0.077, 0.110], Akaike Information Criterion, (AIC) = 9340.619, Bayesian Information Criterion (BIC) = 9480.832). Based on modification indices, adding three residual correlations concurrently (P1 amplitude FD vs. FA correlated with P400 amplitude FD vs. FA, P400 amplitude FD vs. N correlated with P400 amplitude FD vs. FA, P100 amplitude FD vs. N correlated with P100 amplitude FD vs. FA) provided better fit to the data ($\chi^2(45) = 69.004$, $p = .01$, CFI = 0.978, SRMR = 0.089, RMSEA = 0.046, 90% CI [0.022, 0.066], AIC = 9264.581, BIC = 9415.311), considering that the chi-square statistic is sensitive to sample size and model rejection could occur even with minimal discrepancies (Bollen, 1989; Tucker & Lewis, 1973). Therefore, the latter model was retained. The justification for altering the model by adding the particular residual correlations was that the correlated variables share similar properties, as they all measure the strength of brain response to the same stimulus (static face directed toward the infant) versus non-social stimulus conditions (face looking away or visual noise) and two of the three residual correlations are between the same ERP components (P100 and P400 amplitudes). Additionally, both the P100 and P400 components have consistently shown to be modulated in tasks involving processing and encoding of faces, therefore their correlation is justifiable (de Haan et al., 2003; Halit et al., 2003).

In the model (**Figure A5.3**), all the indicator variables loaded strongly on the face processing, gaze processing and parent sensitivity factors ($p < .001$; **Table A5.9**). There was a significant covariance between P100 amplitude and P400 amplitude FD vs. FA ($\beta = 0.51$, $p < .001$), P400 amplitude FD vs. Noise and P400 amplitude FD vs. FA ($\beta = 0.38$, $p < .001$), P100 amplitude FD vs Noise and P1 amplitude FD vs FA ($\beta = 0.39$, $p = .002$). Additionally, the neural measures were neither directly associated with parent sensitivity (face processing: $\beta = -0.03$, $p = .718$; gaze processing: $\beta = -0.02$, $p = .71$) nor infant

attentiveness (face processing: $\beta = -0.09$, $p = .492$; gaze processing: $\beta = -0.03$, $p = .78$). In turn, infant attentiveness significantly predicted parent sensitivity ($p < .001$), while age was a significant predictor of parent sensitivity ($p < .001$) and infant attentiveness ($p = .03$).

The model testing the mediating effect of infant attentiveness in the path between face/gaze processing and parent sensitivity showed that there was no indirect effect of infant attentiveness (face processing: $\beta = -0.02$, $SE = 0.007$, $z = -0.689$, $p = .49$; gaze processing: $\beta = -0.007$, $SE = 0.010$, $z = -0.272$, $p = .79$). Therefore, the face and gaze processing mediation model using the entire sample was not supported.

5.6.6 SEM 2: Speed of Brain Response as Predictor of PII

In the next step, the model that speed of brain response predicts parent sensitivity, mediated by infant attentiveness and controlling for age, was assessed for fit using the entire sample. An initial run of the model resulted in an improper solution with a negative variance estimate for the indicator variable ‘sensitive responsiveness’. The variance was manually fixed to 0. Based on the modification indices, the model indicated a better fit after the inclusion of covariance between the indicator variables of the latent variable ‘speed’ (N290 latency to Noise correlated with P100 latency to Noise) ($\chi^2(16) = 23.002$, $p = .11$, CFI = 0.981, RMSEA = 0.042, 90% CI [0.000, 0.078] than without the covariance ($\chi^2(17) = 35.29$, $p = .006$, CFI = 0.950, SRMR = 0.051, RMSEA = 0.068, 90% CI [0.035, 0.099], according to Hu and Bentler’s cut-off criteria (Hu & Bentler, 1999). Therefore, the former model was retained. As in the previous model, altering this model by adding the particular residual correlation was also considered justifiable both methodologically and theoretically because the associated variables share similar properties: a) they both measure the timing of brain response to the same stimulus (visual noise) and b) both P100

and N290 components are elicited in response to visual stimuli (de Haan et al., 2003; Halit et al., 2003).

Factor loadings (**Table A5.10**) were higher for N290 latency to FD ($\beta = 0.79$), FA ($\beta = 0.91, p < .001$), Noise ($\beta = 0.53, p < 0.001$) and parent non-directiveness ($\beta = 0.74, p < .001$) than P100 latency to Noise ($\beta = 0.20, p = .06$). Furthermore, in the model (**Figure A5.4**), the results from the regressions showed that parent sensitivity was significantly predicted by infant attentiveness ($p < .001$), but not by infant brain response speed ($\beta = 0.09, p = .27$), such that higher infant attentiveness was linked to more accepting and non-directive parent behaviour towards the infant. Additionally, infant brain response speed did not predict infant attentiveness ($\beta = -0.05, p = .62$). Age predicted infant attentiveness ($p = .03$) and parent sensitivity ($p < .001$) but not infant brain response speed ($\beta = 0.06, p = .51$).

The mediation model testing for the indirect effect of infant brain response speed on parent sensitivity (via infant attentiveness) controlling for age revealed that no indirect effect was observed ($\beta = -0.02, p = .62$). Therefore, as with the previous model, a mediation model using the whole sample was not supported by the data here.

Table A5.1

Valid Trials of the Participants for Each Condition of the ERP Analysis by ASD Likelihood Group and by Phase

Phase	Condition		TL	EL
Phase 1	<i>Total sample</i>		<i>n</i> = 50	<i>N</i> = 54
	Face direct gaze	Trials	35.0	35.3
		Valid	20.8	22.6
	Face averted gaze	Trials	35.0	35.5
		Valid	20.7	23.2
	<i>n</i>		32	32
	Gaze shift toward	Trials	128.6	127.5
		Valid	58.7	63.0
	Gaze shift away	Trials	129.1	125.9
		Valid	59.8	63.6
	<i>n</i>		45	50
	Noise	Trials	46.8	45.9
		Valid	26.5	26.7
	<i>n</i>		35	41
Phase 2	<i>Total sample</i>		<i>n</i> =27	<i>n</i> =116
	Face direct gaze	Trials	25.6	26.5
		Valid	14.1	16.5
	Face averted gaze	Trials	25.1	26.6
		Valid	14.7	16.8
	<i>n</i>		9	68
	Gaze shift toward	Trials	99.7	105.4
		Valid	44.5	51.1
	Gaze shift away	Trials	101.3	105.5
		Valid	43.7	50.5
	<i>n</i>		23	102
	Noise	Trials	37.5	39.3
		Valid	19.3	22.2
	<i>n</i>		20	84

Abbreviations. TL: Typical likelihood group; EL: Elevated likelihood group.

Table A5.2

Results of the Shapiro-Wilk Tests Assessing the Normality of the Distribution of Scores of the Variables Used in the SEMs

Variable	W	p
<i>Total N/missing= 247/129</i>		
<i>ERP</i> P400 amplitude FD vs. Noise	0.971	0.012*
N290 amplitude FD vs. Noise	0.986	0.268
P100 amplitude FD vs. Noise	0.99	0.526
P400 amplitude FD vs. FA	0.99	0.526
P100 amplitude FD vs. FA	0.992	0.745
P100 amplitude SD vs. SA	0.988	0.416
N290 amplitude SD vs. SA	0.989	0.444
P400 amplitude SD vs. SA	0.985	0.229
N290 latency FD	0.979	0.068 ⁺
N290 latency FA	0.983	0.144
N290 latency Noise	0.968	0.007*
P100 latency Noise	0.988	0.374
<i>PII</i> Infant attentiveness	0.942	<0.001*
Parent Sensitive responsiveness	0.909	<0.001*
Parent non-directiveness	0.939	<0.001*

Abbreviations. PII: Parent-infant interaction; ERP: Event-related potential; FD: face with direct gaze; FA: face with averted gaze; SD: gaze shifts directed toward; SA: gaze shifts directed away; W: Shapiro-Wilk test; p: p-value of the Shapiro-Wilk statistic.

* p<0.05. ⁺ p<0.1.

Table A5.3*Mean Scores of the Variables Used in the Study by ASD Likelihood Group, Collected at 8 Months*

	Mean (SD)		
	Total	TL	EL
<i>PII and ERP measures</i>	<i>N = 243</i>	<i>n = 77</i>	<i>n = 166</i>
P400 amplitude FD vs. Noise	-6.10 (9.0)	-5.91 (9.46)	-6.19 (8.84)
N290 amplitude FD vs. Noise	-5.84 (7.84)	-7.02 (7.77)	-5.40 (7.82)
P100 amplitude FD vs. Noise	-3.22 (6.57)	-4.11 (6.31)	-2.82 (6.78)
P400 amplitude FD vs. FA	-0.47 (7.95)	1.02 (8.09)	-0.83 (7.54)
P100 amplitude FD vs. FA	-0.07 (6.0)	0.17 (5.24)	0.07 (6.32)
P100 amplitude SD vs. SA	-0.53 (3.21)	-1.09 (2.84)	-0.30 (3.39)
N290 amplitude SD vs. SA	-1.0 (3.76)	-1.68 (3.56)	-0.69 (3.85)
P400 amplitude SD vs. SA	-1.21 (4.09)	-2.36 (3.62)	-0.69 (4.24)
N290 latency FD	266.4 (20.49)	265.9 (23.07)	266.9 (19.67)
N290 latency FA	266.8 (20.68)	265.3 (23.62)	267.9 (19.50)
N290 latency Noise	256.7 (19.44)	253.81 (19.37)	258.0 (19.41)
P100 latency Noise	175.1 (18.25)	176.2 (19.97)	174.5 (17.76)
Infant attentiveness	3.99 (1.27)	3.92 (1.30)	4.02 (1.26)
Parent Sensitive responsiveness	3.70 (1.26)	3.93 (1.37)	3.59 (1.19)
Parent non-directiveness	3.72 (1.31)	4.10 (1.22)	3.53 (1.31)

Abbreviations. PII: Parent-infant interaction; ERP: Event-related potential; TL: Typical likelihood; EL: Elevated likelihood; FD: face with direct gaze; FA: face with averted gaze; SD: gaze shifts directed toward; SA: gaze shifts directed away; SD: standard deviation;

Table A5.4

Results of the Logistic Regression Analyses Testing for the Relationship Between Variables in the Analysis (Independent Variables) and Categorical Indicator Variables (Dependent Variables). Only Significant Relationships are Reported. Unstandardised Beta (B), Standard Error (SE.), Degrees of Freedom (df), The Exponentiation of The Beta Coefficient/Odds Ratio (Exp(B))

Indicator	Predictor	B	SE	Wald	df	p	Exp(B)
N290 Lat FD	Constant	2.22	1.37	2.64	1	0.10	9.22
N290 Lat FA	Age	-0.32	0.13	6.37	1	0.01	0.72
P100 amp FD vs. FA	Constant	2.22	1.37	2.64	1	0.10	9.22
P4 amp FD vs. FA	Age	-0.32	0.13	6.37	1	0.01	0.72
P100 amp FD vs. N	Constant	2.38	1.37	3.03	1	0.08	10.84
P4 amp FD vs. N	Age	-0.36	0.13	7.70	1	0.006	0.70
N290 amp FD vs. N							
N290 lat FD	Constant	2.24	1.37	2.67	1	0.10	9.34
N290 lat FA	Age	-0.32	0.13	6.19	1	0.01	0.73
P100 amp FD vs. FA							
P4 amp FD vs. FA							
P100 lat N	Constant	1.62	1.52	1.14	1	0.29	5.05
N290 lat N	Age	-0.31	0.14	4.74	1	0.03	0.73
P100 amp SD vs. SA	Constant	3.60	2.15	2.81	1	0.09	36.53
N290 amp SD vs. SA	Age	-0.02	0.21	0.01	1	0.92	0.98

Abbreviations. Lat: Latency; amp: Amplitude; FD: Face with Direct Gaze; FA: Face with Averted Gaze; N: Noise; SD: Eye Gaze Shift Directed toward the infant; SA: Gaze Shift Directed Away from the infant.

Table A5.5

The Eigenvalues, Percentages of Variance and Cumulative Percentages Associated with Each Factor for the 11 Items Used in the First Exploratory Factor Analysis

Factor	Eigenvalue	% of variance	Cumulative %
1	4.00	36.33%	36.33%
2	2.34	21.28%	57.60%
3	1.31	11.92%	69.52%

Note. Extraction method: Principal Axis Factoring.

Table A5.6

Factor Loadings and Communalities of the First Exploratory Factor Analysis for the 11 Items Constituting Brain Response Differences Between the Stimulus Conditions

	Factor loading			Communality
	1	2	3	
P100 amp FD vs. N	.87			.77
N290 amp FD vs. N	.79			.71
P100 amp FD vs. FA	.71			.54
P400 amp FD vs. N	.61		.43	.57
P400 amp FD vs. FA	.52		.43	.47
P100 lat FD vs. FA	-	-	-	.08
N290 amp SD vs. SA		.98		.97
P400 amp SD vs. SA		.84		.70
P100 amp SD vs. SA		.77		.60
Nc amp FD vs. FA			-0.743	.59
Nc amp FD vs. N			-0.694	.53

Note. $N = 247$ (126 used due to missing data). Factor loadings $< .3$ are suppressed; Extraction method: Principal Axis Factoring; Rotation method: Varimax with Kaiser Normalisation.

Abbreviations. Amp: Amplitude; lat: Latency; FD: Face with Direct Gaze; FA: Face with Averted Gaze; N: Noise; SD: Eye Gaze Shift Directed toward the infant; SA: Gaze Shift Directed Away from the infant.

Table A5.7

The Eigenvalues, Percentages of Variance and Cumulative Percentages Associated with Each Factor for the 18 Latencies Used in the Second Exploratory Factor Analysis

Factor	Eigenvalue	% of variance	Cumulative %
1	3.66	20.34%	20.34%
2	2.05	11.41%	31.75%
3	1.81	10.06%	41.81%
4	1.65	9.15%	50.96%
5	1.19	6.63%	57.59%
6	1.10	6.09%	63.68%

Note. Extraction method: Principal Axis Factoring.

Table A5.8

Factor Loadings and Communalities of the Second Exploratory Factor Analysis for the 18 Latencies Across the Different Conditions

Factor							Communality
	1	2	3	4	5	6	
N290 lat FD	0.826						0.75
N290 lat FA	0.749						0.62
N290 lat N	0.608						0.52
P100 lat N	0.312						0.18
P400 lat FA	0.373	0.76					0.75
P400 lat FD	0.329	0.687					0.62
Nc lat FD		0.494					0.31
Nc lat FA		0.406					0.2
P100 lat FD			0.898				0.86
P100 lat FA			0.707				0.51
P400 lat N				0.82			0.8
Nc lat N				0.497			0.34
P100 lat SA					0.697		0.56
N290 lat SA					0.472		0.29
P100 lat SD					0.443		0.22
N290 lat SD					0.369		0.24
P400 lat SD						0.82	0.71
P400 lat SA						0.431	0.25

Note. $N = 247$ (126 used due to missing data). Factor loadings $< .3$ are suppressed; Extraction method: Principal Axis Factoring; Rotation method: Varimax with Kaiser Normalisation.

Abbreviations. Lat: Latency; FD: Face with Direct Gaze; FA: Face with Averted Gaze; N: Noise; SD: Eye Gaze Shift Directed toward the infant; SA: Gaze Shift Directed Away from the infant.

Table A5.9

Summary of the SEM Results Using the Whole Sample, with Face and Gaze Processing Factors as the Predictors and Parent Sensitive Responsiveness as the Outcome Variable. Unstandardised Beta Coefficients (B), Robust Standard Errors (SE), Z-Values, P-Values and Standardised Beta Coefficients (β) are Presented for Each Path

Latent variables	Indicator variables	B	SE	z	p	β
face processing	P400 amp FD vs. N	1	-	-	-	0.749
face processing	P100 amp FD vs. N	0.771	0.085	9.093	<0.001**	0.792
face processing	P100 amp FD vs. FA	0.499	0.075	6.639	<0.001**	0.563
face processing	P400 amp FD vs. FA	0.581	0.094	6.165	<0.001**	0.489
face processing	N290 amp FD vs. N	1.111	0.106	10.482	<0.001**	0.954
Gaze processing	P400 amp SD vs. SA	1	-	-	-	0.833
Gaze processing	P100 amp SD vs. SA	0.738	0.064	11.469	<0.001**	0.786
Gaze processing	N290 amp SD vs. SA	1.083	0.090	12.026	<0.001**	0.986
Parent sensitivity	Sensitive responsiveness	1	-	-	-	1
Parent sensitivity	Non-directiveness	0.775	0.044	17.770	<0.001**	0.738
Regressions	Predictors	B	SE	z	p	β
Parent sensitivity	face processing	-0.005	0.013	-0.362	0.718	-0.026
Parent sensitivity	gaze processing	0.008	0.022	0.377	0.706	0.023
Parent sensitivity	Infant Attentiveness	0.358	0.065	5.515	<0.001**	0.360
Parent sensitivity	Age	0.279	0.060	4.647	<0.001**	0.099
Infant Attentiveness	face processing	-0.013	0.018	-0.686	0.492	-0.067
Infant Attentiveness	gaze processing	-0.008	0.028	-0.274	0.784	-0.021
Infant Attentiveness	Age	0.147	0.066	2.211	0.027*	0.141
face processing	Age	0.800	0.475	1.683	0.092 ⁺	0.144
Gaze processing	Age	0.006	0.189	0.029	0.977	0.002
Covariances	covariates	B	SE	z	p	β
P100 amp FD vs. FA	P400 amp FD vs. FA	17.447	2.275	7.670	<0.001**	0.508
P400 amp FD vs. N	P400 amp FD vs. FA	15.943	3.999	3.987	<0.001**	0.384
P100 amp FD vs. N	P1 amp FD vs. FA	7.693	2.468	3.117	0.002*	0.391

Note. Initial run of the model resulted in negative variance estimate for indicator variable ‘Sensitive responsiveness’. The variance was manually fixed to 0. Subsequent run of the model resulted in negative variance estimate for the indicator variable ‘N290 amplitude SD vs. SA’. The variance was manually fixed to 0. No further adjustments made.

Abbreviations. FD: face with direct gaze; FA: face with averted gaze; N: visual noise; SD: eye gaze shift directed toward; SA: eye gaze shift directed away.

****** $p < 0.001$. ***** $p < 0.05$. ⁺ $p < 0.1$.

Table A5.10

Summary of the SEM Results Using the Whole Sample, with Brain Response Speed Factor as the Predictor and Parent Sensitive Responsiveness as the Outcome Variable. Unstandardised Beta Coefficients (B), Robust Standard Errors (SE), Z-Values, P-Values and Standardised Beta Coefficients (β) are Presented for Each Path

latent variable	Indicator variables	B	SE	z	p	β
Brain response						
speed	N290 lat FD	1	-	-	-	0.788
Brain response						
speed	N290 lat FA	1.162	0.203	5.733	<0.001**	0.907
Brain response						
speed	N290 lat N	0.637	0.114	5.611	<0.001**	0.528
Brain response						
speed	P1 lat N	0.221	0.118	1.870	0.062 ⁺	0.195
Parent sensitivity	Sensitive responsiveness	1	-	-	-	1
Parent sensitivity	Non-directiveness	0.775	0.044	17.770	<0.001**	0.738
Regressions	Predictors	B	SE	z	p	β
Parent sensitivity	Brain response speed	0.007	0.007	1.095	0.274	0.094
Parent sensitivity	Infant attentiveness	0.364	0.063	5.764	<0.001**	0.366
Parent sensitivity	Age	0.269	0.059	4.529	<0.001**	0.260
Infant						
attentiveness	Brain response speed	-0.004	0.008	-0.492	0.622	-0.048
Infant						
attentiveness	Age	0.140	0.064	2.173	0.030*	0.135
Brain response						
speed	Age	0.812	1.224	0.664	0.507	0.061
Covariances	covariates	B	SE	z	p	β
N290 lat N	P1 lat N	89.193	26.422	3.376	0.001	0.303

Note. Initial run of the model resulted in negative variance estimate for indicator variable ‘Sensitive responsiveness’. The variance was manually fixed to 0.

Abbreviations. FD: face with directed gaze; FA: face with averted gaze; N: visual noise.

⁺*p* < 0.1. **p* < 0.05. ***p* < 0.001.

Table A5.11

Tests of Measurement Invariance Between the TL and EL Group for the Face and Gaze Processing Model

Model	parameters	Fit indices				Comparison of fit indices between nested models					Decision
		χ^2 (<i>df</i>)	CFI	RMSEA [90%CI]	SRMR	Model Comp	$\Delta \chi^2$ (Δdf)	Δ CFI	Δ RMSEA	Δ SRMR	
M1: Configural invariance (No constraints)	54	41.61 (34)	0.991	.046 [.000, 0.088]	0.076	-	-	-	-	-	-
M2: Metric invariance (Factor loadings constrained)	54	45.10 (40)	0.993	.038 [.000, 0.080]	0.084	M1	4.56 (6)	-.002	.008	-.008	Accept
M3: Scalar invariance (Factor loadings and intercepts constrained)	54	57.42 (48)	0.988	.043 [.000, 0.080]	0.095	M2	11.46 (8)	-.005	-.005	-.011	Accept

M4:	54	64.73	0.986	.044	0.098	M3	7.28	.002	-.001	-.003	Accept
Residual invariance (Factor loadings, intercepts and residual variances constrained)		(54)		[.000, 0.080]			(6)				

Note. Total $N = 243$, TL group $n = 77$ (68 used); EL group $n = 166$ (148 used); Method: Full Information Maximum Likelihood. Initial run of the model resulted in negative variance estimate for indicator variable ‘N290 amplitude SD vs. SA’. The variance was manually fixed to 0. Subsequent run of the model resulted in negative variance estimate for the indicator variable ‘N290 amplitude FD vs. N’. The variance was manually fixed to 0. No further adjustments made.

Abbreviations. CFI: comparative fit index; RMSEA: root mean squared error of approximation; CI: confidence interval; SRMR: standardised root mean squared residual; Model comp: model comparison; $\Delta \chi^2$: chi-square difference test; Δdf : degrees of freedom; $\Delta CFI / \Delta RMSEA / \Delta SRMR$: alternative fit indices, ΔCFI : change in comparative fit index; $\Delta RMSEA$: change in root mean squared error of approximation; $\Delta SRMR$: change in standardised root mean squared residual.

Table A5.12

Summary of the Multigroup SEM Results for the TL Group, with Face and Gaze Processing Factors as Predictors and Parent Sensitive Responsiveness as the Outcome Variable. Unstandardised Beta Coefficients (B), Robust Standard Errors (SE), z-values, p-values and Standardised Beta Coefficients (β) are Presented for Each Path

latent variable	Indicator variables	B	SE	z	p	β
face processing	P400 amp FD vs N	1	-	-	-	0.787
face processing	P1 amp FD vs N	0.730	0.102	7.183	<0.001**	0.861
face processing	P1 amp FD vs FA	0.459	0.096	4.770	<0.001**	0.650
face processing	P400 amp FD vs FA	0.633	0.134	4.719	<0.001**	0.570
face processing	N290 amp FD vs N	1.015	0.130	7.811	<0.001**	0.975
Gaze processing	P400 amp SD v SA	1	-	-	-	0.828
Gaze processing	P1 amp SD vs SA	0.653	0.114	5.714	<0.001**	0.704
Gaze processing	N290 amp SD vs SA	1.163	0.131	8.899	<0.001**	1
Parent sensitivity	Sensitive responsiveness	1	-	-	-	1
Parent sensitivity	Nondirectiveness	0.639	0.063	10.090	<0.001**	0.715
Regressions	Predictors	B	SE	z	p	β
Parent sensitivity	face processing	-0.032	0.021	-1.565	0.117	-0.174
Parent sensitivity	gaze processing	-0.042	0.039	-1.082	0.279	-0.095
Parent sensitivity	Infant Attentiveness	0.522	0.097	5.371	<0.001**	0.497
Parent sensitivity	Age	0.180	0.099	1.817	0.069 ⁺	0.177
Infant Attentiveness	face processing	0.027	0.025	1.079	0.280	0.156
Infant Attentiveness	gaze processing	-0.049	0.056	-0.875	0.382	-0.116
Infant Attentiveness	Age	0.135	0.126	1.067	0.286	0.139
face processing	Age	0.238	0.928	0.256	0.798	0.043
Gaze processing	Age	-0.099	0.248	-0.401	0.689	-0.043
Covariances	Covariates	B	SE	z	p	β
P1 amp FD vs FA	P400 amp FD vs FA	13.505	4.112	3.284	0.001*	0.511
P400 amp FD vs N	P400 amp FD vs FA	11.383	4.455	2.555	0.011*	0.295
P1 amp FD vs N	P1 amp FD vs FA	3.949	1.815	2.176	0.030*	0.317

Note. Initial run of the model resulted in negative variance estimate for indicator variable ‘Sensitive responsiveness’. The variance was manually fixed to 0. Subsequent run of the model resulted in negative variance estimate for the indicator variable ‘N290 amplitude SD vs. SA’. The variance was manually fixed to 0. No further adjustments made.

Abbreviations. Amp: amplitude; FD: face with directed gaze; FA: face with averted gaze; N: visual noise; SD: eye gaze shift directed toward; SA: eye gaze shift directed away.

$**p < 0.001$. $*p < 0.05$. $^+p < 0.1$.

Table A5.13

Summary of the Multigroup SEM Results for the EL Group, with Face and Gaze Processing Factors as Predictors and Parent Sensitive Responsiveness as the Outcome Variable. Unstandardised Beta Coefficients (B), Robust Standard Errors (SE), z-values, p-values and Standardised Beta Coefficients (β) are Presented for Each Path

Latent variable	Indicator variables	B	SE	z	p	β
face processing	P400 amp FD vs N	1	-	-	-	0.743
face processing	P1 amp FD vs N	0.779	0.116	6.688	<0.001**	0.755
face processing	P1 amp FD vs FA	0.544	0.108	5.047	<0.001**	0.569
face processing	P400 amp FD vs FA	0.538	0.123	4.376	<0.001**	0.459
face processing	N290 amp FD vs N	1.128	0.153	7.380	<0.001**	0.946
Gaze processing	P400 amp SD v SA	1	-	-	-	0.817
Gaze processing	P1 amp SD vs SA	0.783	0.080	9.753	<0.001**	0.802
Gaze processing	N290 amp SD vs SA	1.110	0.096	11.617	<0.001**	1
Parent sensitivity	Sensitive responsiveness	1	-	-	-	1
Parent sensitivity	Nondirectiveness	0.830	0.058	14.396	<0.001**	0.748
Regressions	Predictors	B	SE	z	p	β
Parent sensitivity	face processing	-0.000	0.019	-0.006	0.995	-0.001
Parent sensitivity	gaze processing	0.038	0.026	1.451	0.147	0.112
Parent sensitivity	Infant Attentiveness	0.285	0.084	3.380	0.001*	0.301
Parent sensitivity	Age	0.362	0.071	5.120	0.000**	0.350
Infant Attentiveness	face processing	-0.046	0.022	-2.059	0.039*	-0.238
Infant Attentiveness	gaze processing	0.002	0.031	-0.059	0.953	0.005
Infant Attentiveness	Age	0.186	0.081	2.307	0.021*	0.171
face processing	Age	1.065	0.670	1.591	0.112	0.187
Gaze processing	Age	0.047	0.256	0.182	0.855	0.015
Covariances	Covariates	B	SE	z	p	β
P1 amp FD vs FA	P400 amp FD vs FA	18.946	2.897	6.54	<0.001**	0.536
P400 amp FD vs N	P400 amp FD vs FA	16.236	5.071	3.202	0.001*	0.408
P1 amp FD vs N	P1 amp FD vs FA	8.67	3.596	2.411	0.016*	0.385

Note. Initial run of the model resulted in negative variance estimate for indicator variable ‘Sensitive responsiveness’. The variance was manually fixed to 0. Subsequent run of the model resulted in negative variance estimate for the indicator variable ‘N290 amplitude SD vs. SA’. The variance was manually fixed to 0. No further adjustments made.

Abbreviations. FD: face with directed gaze; FA: face with averted gaze; N: visual noise; SD: eye gaze shift directed toward; SA: eye gaze shift directed away.

****** $p < 0.001$. ***** $p < 0.05$. **+** $p < 0.1$.

Table A5.14

Tests of Measurement Invariance Between the TL and EL Group for the Brain Response Speed Model

Model	parameters	Fit Indices				Comparison of fit indices between nested models					Decision
		χ^2 (<i>df</i>)	CFI	RMSEA [90% CI]	SRMR	Model comp	$\Delta\chi^2$ (Δdf)	Δ CFI	Δ RMSEA	Δ SRMR	
M1: Configural invariance (no constraints)	26	1.52 (2)	1.00 0	0.000 [0.000, 0.182]	0.011	-	-	-	-	-	-
M2: Metric invariance (factor loadings constrained)	26	1.62 (5)	1.00 0	0.000 [0.000, 0.065]	0.016	M1	0.31 (3)	0.000	0.000	-0.005	Accept
M3: Scalar invariance (factor loadings and intercepts constrained)	27	5.22 (8)	1.00 0	0.000 [0.000, 0.091]	0.032	M2	3.86 (3)	0.000	0.000	-0.016	Accept
M4: Residual invariance	27	7.04 (12)	1.00 0	0.000 [0.000, 0.060]	0.042	M3	1.83 (4)	0.000	0.000	-0.010	Accept

(factor
loadings,
intercepts and
residual
variances
constrained)

Note. Total $N = 247$, TL group $n = 77$ (55 used); EL group $n = 166$ (120 used). Method: Full information Maximum Likelihood.

Abbreviations. CFI: comparative fit index; RMSEA: root mean squared error of approximation; CI: confidence interval; SRMR: standardised root mean squared residual; Model comp: model comparison; $\Delta \chi^2$: chi-square difference test; Δdf : degrees of freedom; $\Delta CFI / \Delta RMSEA / \Delta SRMR$: alternative fit indices, ΔCFI : change in comparative fit index; $\Delta RMSEA$: change in root mean squared error of approximation; $\Delta SRMR$: change in standardised root mean squared residual.

Table A5.15

Summary of the Multigroup SEM Results for the TL Group, with Brain Response Speed as the Predictor and Parent Sensitive Responsiveness as the Outcome Variable. Unstandardised Beta Coefficients (B), Robust Standard Errors (SE), Z-values, P-values and Standardised Beta Coefficients (B) are Presented for Each Path

Latent variable	Indicator variables	B	SE	z	p	β
Brain response speed	N290 lat FD	1.000	-	-	-	0.862
Brain response speed	N290 lat FA	1.051	0.197	5.329	<0.001**	0.886
Brain response speed	N290 lat N	0.624	0.141	4.425	<0.001**	0.633
Brain response speed	P1 lat N	0.217	0.191	1.133	0.257	0.213
	Sensitive					
Parent behaviour	responsiveness	1.000	-	-	-	1
Parent behaviour	Nondirectiveness	0.639	0.063	10.090	<0.001**	0.715
Regressions	Predictors	B	SE	z	P	β
Parent behaviour	Brain response speed	0.003	0.011	0.282	0.778	0.043
Parent behaviour	Infant attentiveness	0.519	0.107	4.837	<0.001**	0.492
Parent behaviour	Age	0.173	0.098	1.766	0.077 ⁺	0.169
Infant attentiveness	Brain response speed	-0.021	0.011	-1.975	0.048 [*]	-0.323
Infant attentiveness	Age	0.203	0.119	1.704	0.088 ⁺	0.210
Brain response speed	Age	3.302	1.934	1.707	0.088 ⁺	0.226
Covariances	Covariates	B	SE	z	P	β
N290 lat N	P1 lat N	38.795	49.253	0.788	0.431	0.135

Note. Initial run of the model resulted in negative variance estimate for indicator variable ‘Sensitive responsiveness’. The variance was manually fixed to 0.

Abbreviations. FD: face with directed eye gaze; FA: face with averted eye gaze; Lat: latency; N: visual noise.

** $p < .001$. * $p < 0.05$. ⁺ $p < 0.1$.

Table A5.16

Summary of the Multigroup SEM Results for the EL Group, with Brain Response Speed Factor as the Predictor and Parent Sensitive Responsiveness as the Outcome Variable. Unstandardised Beta Coefficients (B), Robust Standard Errors (SE), Z-values, P-values and Standardised Beta Coefficients (β) are Presented for Each Path

Latent variable	Indicator variables	B	SE	z	p	β
Brain response speed	N290 lat FD	1	-	-	-	0.752
Brain response speed	N290 lat FA	1.193	0.320	3.730	<0.001**	0.904
Brain response speed	N290 lat N	0.632	0.164	3.863	<0.001**	0.479
Brain response speed	P1 lat N	0.280	0.145	0.053	0.062 ⁺	0.233
Parent behaviour	Sensitive responsiveness	1	-	-	-	1
Parent behaviour	Non-directiveness	0.830	0.058	14.396	<0.001**	0.747
Regressions	Predictors	B	SE	z	P	β
Parent behaviour	Brain response speed	0.016	0.009	1.821	0.069 ⁺	0.194
Parent behaviour	Infant attentiveness	0.258	0.075	3.453	0.001*	0.272
Parent behaviour	Age	0.373	0.070	5.326	<0.001**	0.362
Infant attentiveness	Brain response speed	0.012	0.011	1.034	0.301	0.138
Infant attentiveness	Age	0.259	0.229	1.128	0.259	0.096
Brain response speed	Age	-0.446	1.896	-0.235	0.814	-0.035
Covariances	Covariates	B	SE	z	P	β
N290 lat N	P1 lat N	109.865	31.318	3.508	<0.001**	0.374

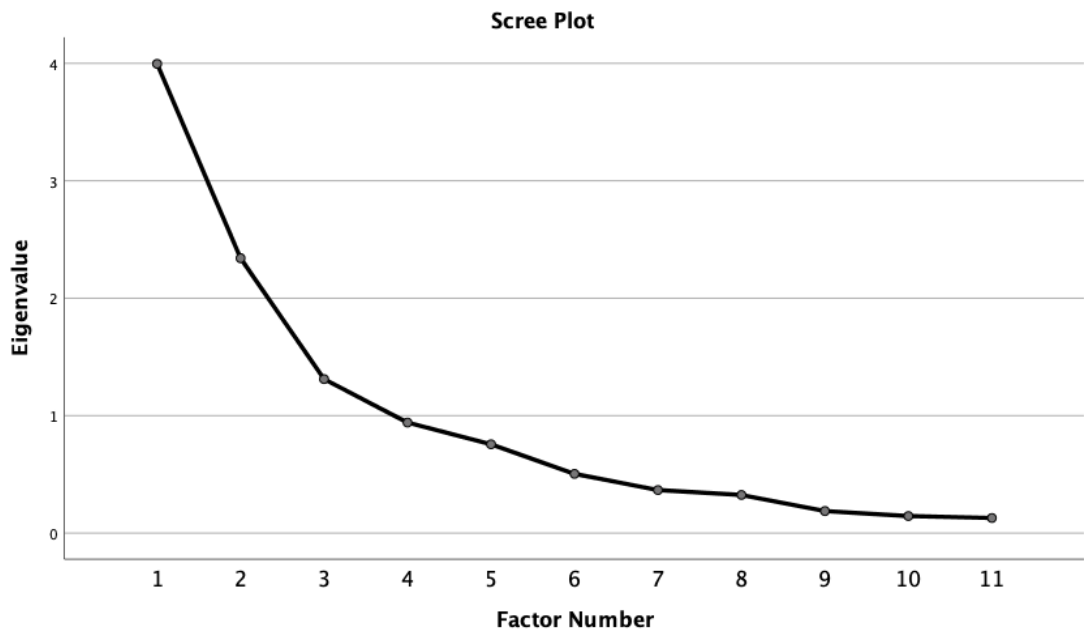
Note. Initial run of the model resulted in negative variance estimate for indicator variable ‘Sensitive responsiveness’. The variance was manually fixed to 0.

Abbreviations. FD: face with directed eye gaze; FA: face with averted eye gaze; Lat: latency; N: visual noise.

** $p < 0.001$. * $p < 0.05$. ⁺ $p < 0.1$.

Figure A5.1

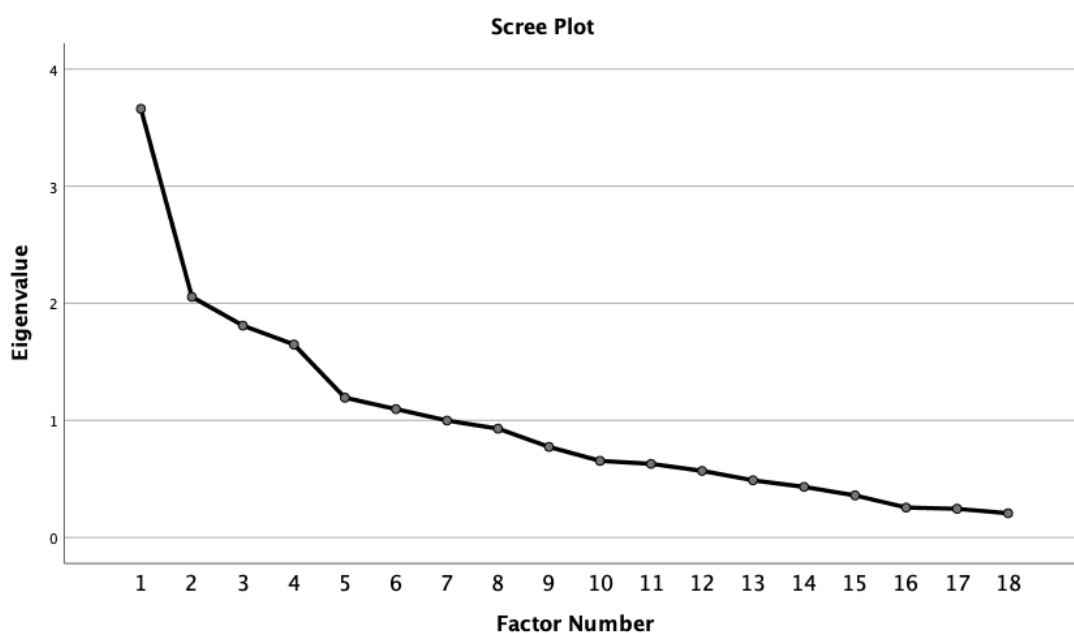
A Scree Plot of the First Exploratory Factor Analysis Using the Brain Response Differences Between the Stimulus Conditions



Note. A scree plot of the first exploratory factor analysis showing the eigenvalues (y axis) and their associated factors (x axis) corresponding to the number of variables (brain response difference) in the analysis in descending order.

Figure A5.2

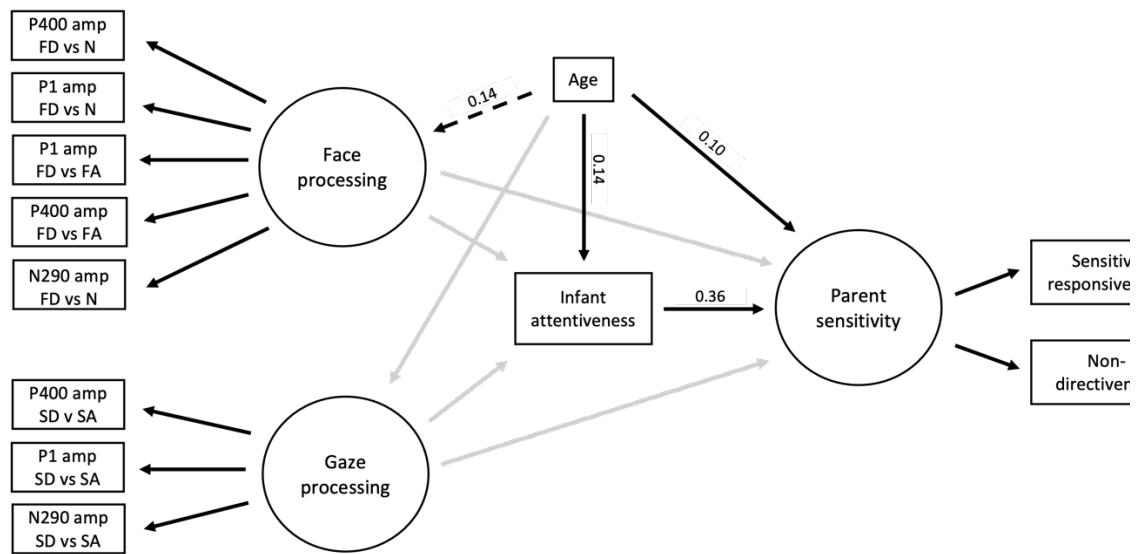
A Scree Plot of The Second Exploratory Factor Analysis Using Absolute Latencies of Each ERP Component for Each Condition



Note. A scree plot of the second exploratory factor analysis showing the eigenvalues (y axis) and their associated factors (x axis) corresponding to the number of variables (latencies) in the analysis in descending order.

Figure A5.3

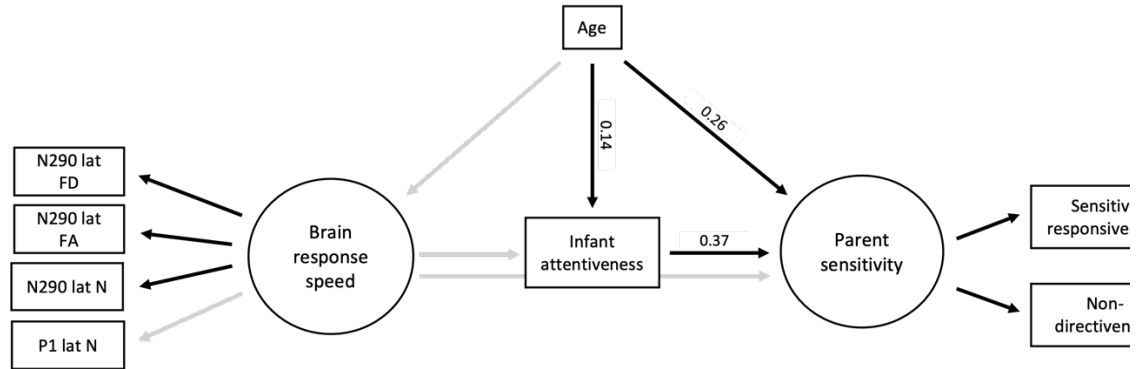
Face and Gaze Processing Model Depicting the Regression Paths in the Whole Sample



Note. Face and gaze processing structural equation model predicting parent sensitivity mediated by infant attentiveness in the whole sample. Covariances between the indicator variables are omitted for clarity. Black arrows indicate significant relationships at $p < .05$. Dashed arrows indicate marginal relationships ($p < .1$). Grey arrows indicate nonsignificant relationships. Standardised betas are reported.

Figure A5.4

Brain Response Speed Model Depicting the Regression Paths in the Whole Sample



Note. Brain response speed structural equation model predicting parent sensitivity mediated by infant attentiveness in the whole sample. Covariances between the indicator variables are omitted for clarity. Black arrows indicate significant relationships at $p < .05$. Grey arrows indicate nonsignificant relationships. Standardised betas are reported.

Chapter 6. Parent-Infant Interaction in Infants at Elevated Likelihood of ASD: Exploring Infant Brain Function Correlates Using a Data-Driven Approach

6.1 Introduction

Autism Spectrum Disorder is characterised by great variability between individuals in behavioural and biological expressions as well as in developmental trajectories which indicates the involvement of many underlying mechanisms leading to the development of the condition (Constantino et al., 2010; E. J. H. Jones et al., 2014; Lai et al., 2013). Apart from the relatively late appearance in early childhood of robust ASD traits, the high heterogeneity of ASD could possibly explain why it is not usually detectable before the age of two. Capturing this heterogeneity could possibly be obscured by focusing only on one or two domains, as mechanisms underlying ASD could affect different areas of functioning across development. Therefore, integrating multi-modal data can parse out the heterogeneity that characterises the condition and can provide a better understanding of the biological processes involved in the expression of clinical outcome by looking at how these impact different psychological functions early in infancy.

6.1.1 Integrating Brain and PII Measures to Understand ASD Development

The current study seeks to examine the relationship between brain function and PII in infants at EL for ASD, following a data-driven approach through an integrated analysis of multiple brain and PII measures. Integrating features from different brain and

PII measures within the first year of life and examining their relationship to 3-year clinical outcome can help to identify the mechanisms underlying ASD, expressed through intrinsic patterns of variation in these domains. Autism Spectrum Disorder likely emerges from a complex interaction between genetic and environmental factors that can alter the function and structure of the developing brain, reducing infants' ability to learn from their environment (Johnson, 2011). In turn, the quality of parent-child interactions can further affect these brain mechanisms (Elsabbagh, Bruno, Wan, Charman, Johnson, Green, & The BASIS Team, 2015; Elsabbagh & Johnson, 2010; Ilyka et al., 2021). It has been empirically established that atypicalities in the social domain, such as decreased social interest and social orienting, represent one of the core symptoms of ASD emergence that become more robust in behaviour after the first year of life (Ozonoff et al., 2010; Zwaigenbaum et al., 2005). However, measures of brain function in infancy have proven to be more sensitive predictors of ASD, as they have differentiated infants with and without a family history of ASD within the first year, before the appearance of overt behavioural signs of ASD (Elsabbagh et al., 2012; McCleery et al., 2009; Tye et al., 2020). For instance, converging evidence identifies face processing as a leading candidate domain in ASD, as neural responses to faces measured through ERP components, such as the P100, P400, N290 and the Nc have differentiated EL from TL infants in the first months of life before overt signs of ASD in behaviour and social interactions become apparent between the groups (Elsabbagh et al., 2012; Gui et al., 2021; Jones et al., 2016; Tye et al., 2020). This points to the necessity of examining these measures further to gain a greater understanding of the underlying processes leading to ASD. In addition, some links between specific ERP responses to faces and PII features have already been

observed by Elsabbagh et al. (2015) and can be useful to better understand the possible influence that PII can have on developmental trajectories.

Previous research linking specific neural features of face processing and PII aspects by ASD likelihood group has focused on a case-control comparison, top-down approach (Elsabbagh, Bruno, Wan, Charman, Johnson, Green, & The BASIS Team, 2015). Similarly, the previous chapter took a theory-based approach, focusing on linking specific neural features of face/gaze processing and PII qualities, such as infant attentiveness and parent sensitivity. While this offered the advantage of building on existing knowledge and theory of brain-PII relationships to derive a model to accurately examine the hypotheses of interest, relying solely on a priori knowledge may have obscured information (e.g., important distinctions based on individual variability) that may not be easily apparent from a theory-based approach using a limited number of variables. Thus, a further examination of how face/gaze processing is related to PII considering the heterogeneity of the condition is valuable. Firstly, although the traditional group comparison approach employed by previous research is useful for identifying the possible early markers of ASD, implementing a data-driven approach is advantageous because it allows the examination of the extracted patterns from the data without previous knowledge of clinical categories, and then it enables the investigation of how these relate to different clinical outcomes. This approach is different from the former which is based on clinical categories ad hoc. Thus, a data-driven approach can help gain a better insight into ASD variability and has the potential to create more comparable subgroups that could form targets for early intervention. Secondly, investigating possible alterations in many different face-processing aspects reflected in different components and caregiver-infant interactional aspects from several PII domains, considering how these are present at an

individual level can be even more informative in decoupling these associations and understanding individual heterogeneity. It can also reinforce their predictive value to identify early signals of subsequent ASD diagnosis. Furthermore, examining these links through an approach that is less driven by theoretical assumptions can help inform the theoretical models that have been mostly based on typical development, as little is known about brain function differences and their links to naturalistic PII in the context of ASD susceptibility and diagnosis.

6.1.2 Unsupervised Data-Driven Methods: Linked Independent Component Analysis

Unsupervised data-driven approaches aim to capture the structural properties and patterns of the data without a priori knowledge of their labels or sample groupings (Hinton & Sejnowski, 1999), therefore, they are not driven by hypotheses regarding data structure. In particular, Linked ICA is an unsupervised learning method that integrates multiple measures based on shared variation between subjects with the aim of identifying independent components of multimodal variability (Groves et al., 2011). Linked ICA is used in neuroimaging (Francx et al., 2016; Groves et al., 2012; Itahashi et al., 2015; Wolfers et al., 2017) but can be equally applied to instances where multiple modalities (e.g., ERP, behavioural measures) are used across the same sample (Bussu et al., 2020).

The technique was initially developed to overcome the difficulty of finding approaches that could fuse data across multiple modalities (for MRI) to model covariances across subjects and characterise inter-subject variability. The spatial concatenation approach can also analyse multimodal data by bringing together each subject's data into a single dataset. However, each modality's contribution to the ICA cost function depends on the scaling, thus, the difference in modalities' noise levels and

number of voxels makes concatenating multimodal data challenging. A scaling mismatch can lead to ICA being controlled by the modalities with the largest variance or the most voxels (e.g., in this case, the modality (ERP or PII) with the most features) (Groves et al., 2011). Another approach, tensor ICA, can be used and assumes that each component has one spatial map for all modalities, applied to each modality with different weightings. However, this may not be appropriate in cases where there is a different number of voxels or different modalities have different spatial maps (Groves et al., 2011). Within a Bayesian framework, Linked ICA allows for either tensor ICA or spatially-concatenated ICA, or their combination. All the modalities share the same subject-loading matrix, such that each component comprises a single subject-course and one spatial map in each of the modalities. The information from all the modalities is balanced in the subject-weighting matrix (Groves et al., 2011). In other words, the information from different measures is brought together to produce components through participant loadings and non-Gaussian spatial maps across modalities. Independent component analysis' effectiveness is that it seeks non-Gaussian spatial sources representing real structured features in the data. Non-Gaussian independent sources are then turned into more Gaussian observed signals, such that the original independent sources can be isolated (Groves et al., 2011). In addition, compared to approaches such as principal component analysis or factor analysis which look for Gaussian data and for a high co-variance between a group of variables that do not correlate with variables outside of that group, the ICA mixing matrix vectors are not forced to be orthogonal to each other. Therefore, they can explain common variance of variables that are external to the ICA. Last, Linked ICA provides an advantage over traditional case-control comparison approaches as it is not based on a priori knowledge

of sample subgroups and considers individual variability. This is the first study to use this approach combining brain and PII data in the context of ASD.

Previous research by Bussu et al. (2020) used Linked ICA to integrate developmental measures with electrophysiological measures of neural sensitivity to eye gaze in the same sample of 8-month-old infants included in the current study. Their findings identified a pattern showing greater neural responses to eye gaze shifts linked to high levels of functioning which was more strongly present in the TL group compared to the ASD group. They also identified a high overlap between the groups. Therefore, this novel approach can be used to combine brain and PII data without having pre-defined clinical categories, which can advance our understanding of ASD heterogeneity and the PII and brain development dynamics in the first years of life. This cannot be achieved with theory-driven approaches, such as those implemented in previous studies. For instance, while previous research has identified infant sibling group differences in specific areas of PII, these areas in particular might not necessarily be related to face processing aspects. Thus, a data-driven approach offers the flexibility to address this question by integrating multiple modalities, compared to previous studies that have focused on emerging group differences in specific brain or PII features over time.

6.1.3 Aims of the Study

In this study, Linked ICA was used to prospectively link brain and PII measures irrespective of clinical categories set a priori. The aim was to use this novel approach in order to discover common features and patterns in various unlabelled PII and brain data to better understand the dynamics of early brain function and PII in the context of ASD. Event-related-potential responses to social and non-social stimuli that have previously

differentiated EL from TL infants, such as the P100, N290, P400 and the Nc components were integrated with all the scales (parental, infant and dyadic) from the MACI global rating scheme at 8 months to identify patterns that were linked across the different domains. A second objective was to examine their association with 3-year clinical outcomes, as this helped to elucidate the possible underlying processes expressed in these domains early on and how these led to different clinical outcomes post hoc, taking into account individual variability. Looking only at the data structure to identify emerging patterns and then investigate how these lead to later clinical outcomes can enhance our understanding of individual heterogeneity and improve the predictive value of these measures identifying subgroups of infants who may benefit from early intervention.

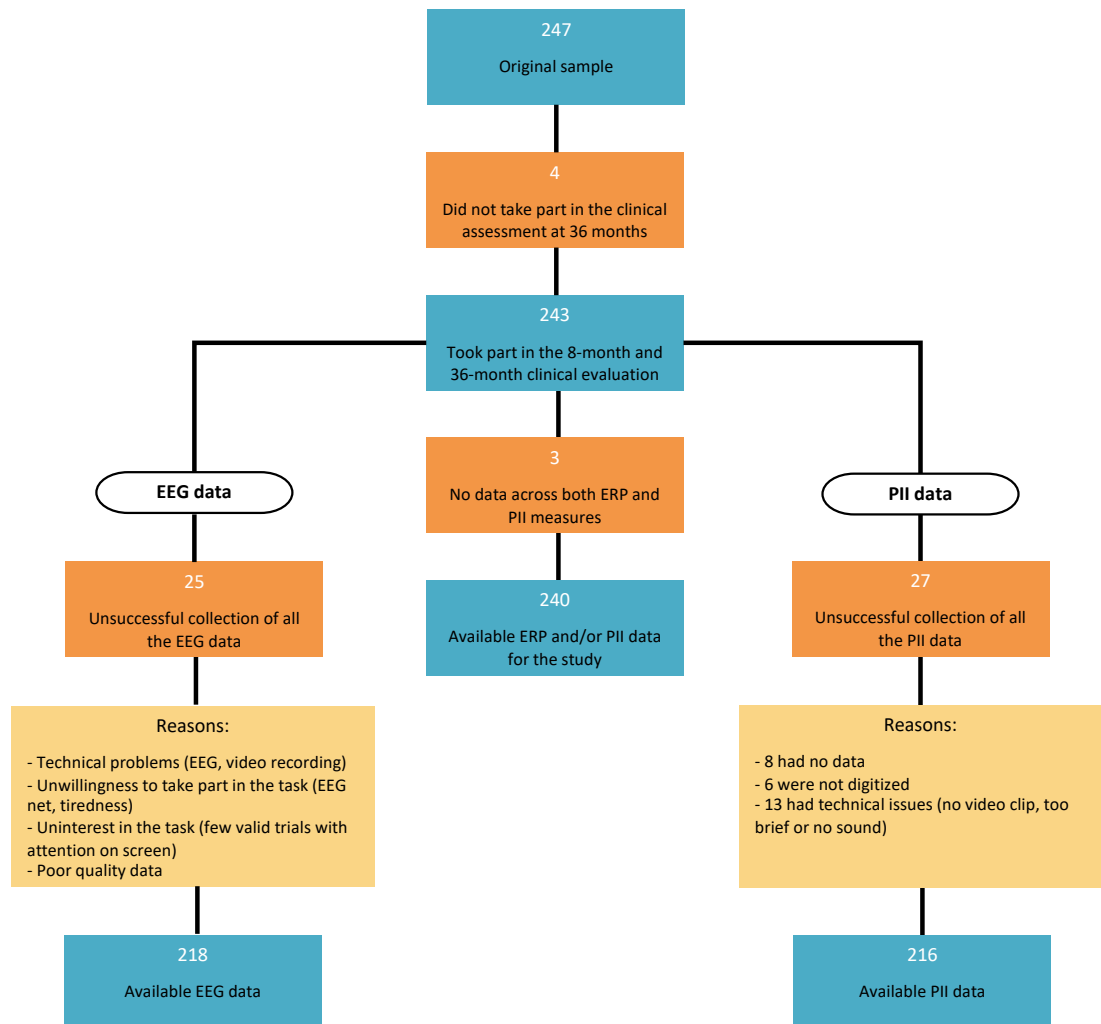
6.2 Methods

6.2.1 Participants

Figure 6.1 provides information about the initial and final sample of participants of this study, with details of exclusions. Data were collected from participants recruited in phases 1 and 2 of the BASIS. Overall, a total number of 240 participants (75 TL, 165 EL) were included in the current study because they provided available ERP and/or PII data. Ethical approval was made available from the UK National Health Service National Research Ethics Service London (REC reference numbers: 06/MRE02/73, 08/H0718/76). Informed consent for participation in the study was provided by one or both parents. Assessments were undertaken blind to infant clinical outcome but the experimenters were aware of the infants' ASD likelihood status. Upon enrolment, the infants had not been diagnosed with any developmental condition.

Figure 6.1

Flowchart of the Number of Participants Recruited as Part of the British Autism Study of Infant Siblings and Included in This Study with Details of Exclusions



Note. The number of participants that were initially recruited from the BASIS at 8 months is depicted at the top cell of the flowchart (Phases 1 and 2) with reasons for subsequent exclusions (orange cells for the number of participant exclusions and yellow cells for the reasons). The bottom middle cell (in blue) shows the number of participants with available data in the ERP and/or PII measures used in the study. The two bottom cells (in blue) show the number of participants with available ERP and PII data separately.

6.2.2 Measures

6.2.2.1 Electrophysiological Measure. The ERP task was the same as the one used by Elsabbagh et al. (2012) and is described in more detail in Chapters 2 and 5. Briefly, the task was designed to evaluate responses to a) static faces with direct gaze, b) static faces with averted gaze, c) gaze shifts toward the infant, d) gaze shifts away from the infant and e) visual noise. The average of the P100, P400, N290 and Nc components was taken for each stimulus across occipito-temporal channels (frontal right and left for the Nc). The components were quantified by their amplitude and latency, which resulted in a total of 36 ERP variables being used for the multimodal analysis.

6.2.2.1.1 Electrophysiological Acquisition and Processing. The procedure of electrophysiological acquisition and processing is described in detail in **Chapters 2 and 5**.

6.2.2.2 PII Measure. The MACI (version 2.2) is a global rating scheme that evaluates qualities of PII, consisting of 8 items with a rating scale ranging from 1 to 7 points for the assessment of the qualitative aspects of the caregiver, infant and dyadic play interaction. Due to the data-driven nature of this study, all 8 items were used. In Phase 1, PII assessment had been undertaken using an earlier version of the MACI (version 1). In Phase 2, the video clips were assessed using the updated version of the MACI (version 2.2). The main difference between the two versions is that the updated version of MACI considers the evaluation of ‘infant affect’ into ‘positive’ and ‘negative’, compared to the earlier version that did not make this differentiation, with both ‘positive’

and ‘negative’ affect being incorporated into one single item named ‘infant affect’. For this study, only the affect scales from MACI version 2.2 are considered in data analysis. This is to avoid inconsistencies in terms of analysing infant affect. In addition, by separating affect, more detailed and accurate information of the interaction can be obtained and higher inter-rater reliability can be achieved. Independent rating of a portion of the PII video clips blind to all participant information was undertaken.

6.2.2.2.1 PII Procedure. In the PII assessment, unstructured play between infants and their parents was video recorded in a laboratory setting after a period of familiarisation. To briefly recapitulate, the dyad was sat on a mat with a small set of selected toys and was instructed to engage in free play with their infants as they would normally do at home, with or without the use of toys as they preferred. The video clips were evaluated for 6 minutes from the moment the researcher left the room, blind to all participant information.

6.2.2.2.2 Inter-Rater Reliability. Single measures intraclass correlation (two-way mixed effects model using an absolute agreement definition) was used. When necessary, both raters re-reviewed the video clips in areas that were disagreements until a common agreement in the ratings was reached. The results from the intra-class correlations revealed moderate to high inter-rater agreement in all the PII scales ($r_s > 0.63$, all $p_s < .001$; refer to **Table A6.1** in the appendix for details).

6.2.2.3 Assessment Measures. Chapter 3 provides a detailed description of the assessment measures. A brief description of these measures is provided below.

6.2.2.3.1 Developmental Level. The MSEL standardised measure (Mullen, 1995) was used to evaluate infant cognitive functioning in five key domains: Gross and fine motor, visual reception, and receptive and expressive language (Mean = 50, $SD = 10$). The score from these areas, except gross motor skills, was combined to produce an Early Learning Composite (ELC) standard score (mean = 100, $SD = 15$).

6.2.2.3.2 Adaptive Functioning. The Vineland Adaptive Behavior Scales – second edition (VABS-II, Sparrow et al., 2005), a semi-structured parent-report measure (questionnaire at 8 and 14 months and parent semi-structured interview at 36 months) of adaptive behaviour was used, which evaluates everyday personal and social abilities in four main domains, such as communication, daily living skills, socialisation and motor skills, as well as a maladaptive behaviour index (optional). The four main domains were combined, yielding an ABC (mean = 100, $SD = 15$), a standardised measure of general adaptive behaviour.

6.2.2.3.3 Assessment of ASD Outcome at 3 Years. The Autism Observation Scale for Infants (AOSI, Bryson et al., 2008), a semi-structured observational assessment was used for the detection of early behavioural signs of ASD at 8 months. In addition, a battery of clinical assessments was used for the assessment of ASD outcome at 3 years: the Autism Diagnostic Observation Schedule-Generic (ADOS-G)-Second Edition (Lord, Rutter, et al., 2012), an observational assessment that is centred around the child's social behaviours, the Autism Diagnostic Interview-Revised (ADI-R, Rutter et al., 2003) interview conducted with parents, the Social Responsiveness Scale (SRS) and The

Quantitative CHecklist for Autism in Toddlers (Q-CHAT, Allison et al., 2008) questionnaires concerning the child's symptom severity and social skills. Based on these standardised clinical assessments, the infants at EL were categorised into infants with ASD outcome (EL-ASD), infants with atypical development but no ASD (EL-Atyp) and infants with typical development (EL-TD). Of the 165 EL infants who took part in this study, 87 were classified as EL-TD, 44 as EL-Atyp and 34 as EL-ASD.

6.2.3 Statistical Analysis

6.2.3.1 Linked Independent Component Analysis. Linked ICA is an unsupervised learning method based on Bayesian independent component analysis for identifying independent modes of variation in the data (Smith et al., 2004). Linked ICA allows for concurrent multimodal data fusion and analysis (i.e., of behavioural and brain data) based on their common features on the same experimental subjects, producing a number of independent components of multimodal variability (Groves et al., 2011, 2012). All the modalities share the same subject loading matrix; each identified component has a single form of variability and contains a shared subject loading indicating how much variation is explained by each component for the individual subject, a spatial map for component for each modality group indicating the weights of experimental measures (i.e., how ERP (or PII) measures relate to each other for the component) and weightings of the different modalities (i.e., ERP and PII) contributing to each component (**Figure 6.2**). The model in algebraic form:

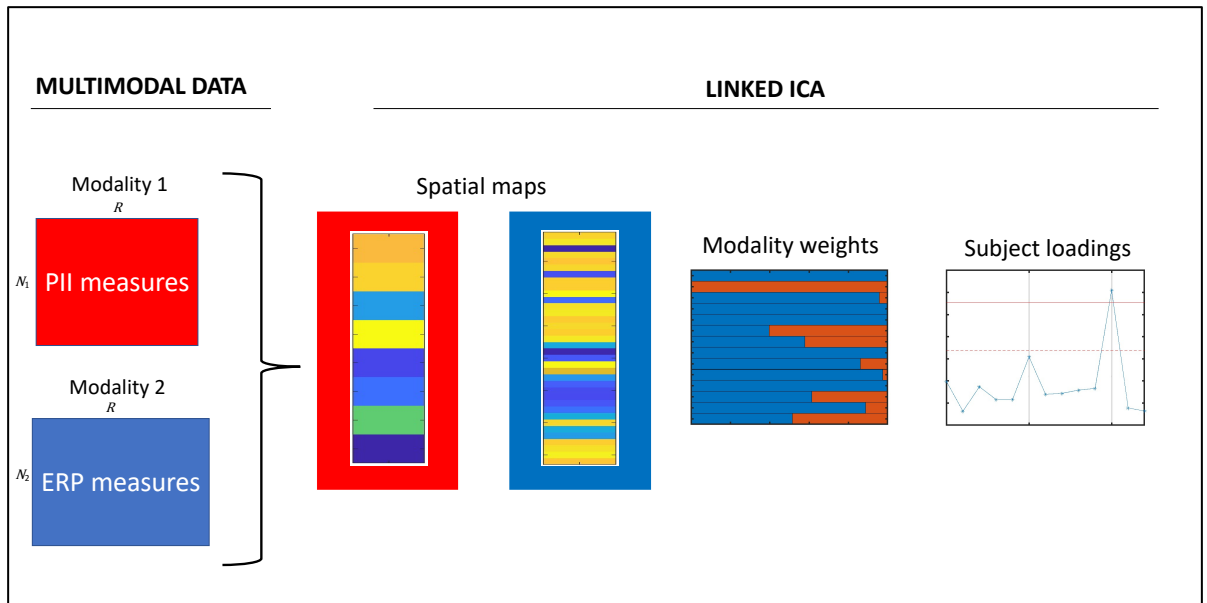
$$\mathbf{Y}_{n,t,r}^{(k)} = \sum_{i=1}^L \mathbf{X}_{n,i}^{(k)} \mathbf{W}_{t,i}^{(k)} \mathbf{H}_{i,r} + \mathbf{E}_{n,t,r}^{(k)}$$

(Equation 6.1)

where $\mathbf{Y}$ represents the multimodal data which are the ERP and PII measures in this study with modality t , subject r , voxel (here the PII/ERP features) n and modality group k (ERP and PII groups). The data of each modality group is a sum of components, with $i = 1 \dots L$ representing each component that is made up of spatial maps $\mathbf{X}_{n,i}^{(k)}$ in modality group k , modality weights $\mathbf{W}_{t,i}^{(k)}$ in modality t for modality group k , a shared weighted matrix $\mathbf{H}$ (used for all the modality groups) in subject r , and additive noise $\mathbf{E}$ (see Groves et al., 2011 for a detailed description of the method).

Figure 6.2

The Linked ICA Analysis Procedure



Note. Initially (left to right), different modalities including different features per subject were decomposed into Linked ICA, producing: a) spatial maps for each modality group

indicating the weights of the experimental measures for component compared to estimated noise in individual variation; b) modality weights indicating the relative weightings of modalities in each component; c) a subject loading showing how much variation is explained by a component per individual subject. PII: parent-infant interaction; ERP: Event-related potential.

6.2.3.2. Multimodal Patterns of ERP and PII Data. Data analysis was performed in MATLAB using the FLICA exploratory analysis tool, and the code from the FSL website (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FLICA>) was used for implementation. The analysis included data integrated from PII and ERP measures (a total of 8 and 36 features respectively) at 8 months. For the identification of independent components, the examination of the eigenvalues of the covariance matrix showed that 21 components were needed to explain 85% of the variance, but convergence could not be reached with more than 15 components. Therefore, linked ICA decomposition ran with 14 estimated components that explained 70% of the variance in the data. The extracted components were assessed with linear regression for an association with clinical outcome at 36 months using Holm-Bonferroni correction for multiple comparisons (correction for the number of components) to identify the patterns related to ASD outcome. Clinical outcome was used as the independent variable and individual subject loadings as the dependent variable. The following covariates were accounted for: age, sex, verbal and nonverbal developmental level at 8 months. Phase was also controlled for to account for possible phase-related differences, but it did not make any difference to the results. The decision to control for the effect of Phase was made on the basis that there may have been a possibility that the MACI rating scheme used for the evaluation of aspects of PII slightly differed between Phases, as minor amendments had been made in an updated version of

MACI for video coding that was used in Phase 2 (version 2.2). In addition, by controlling for Phase, it was possible to control for differences in phase-related age differences, as the participants in Phase 1 were slightly younger on average than the participants in Phase 2. When a significant association with clinical outcomes was observed, differences of clinical outcome groups on component loadings were tested via t-tests with Holm-Bonferroni correction for multiple comparisons with an alpha level of .05 used as a significance criterion and were considered significant ($p = .008$; tests = 6).

6.2.4 Missing Data Evaluation

Details of missing data evaluation are provided in section **6.6.1** of the appendix.

6.3 Results

6.3.1 Participant Demographic Characteristics

Details of demographic and clinical characteristics of the sample used in the study are shown in **Table 6.1** (refer to **Table A6.2** for the demographic and clinical characteristics of the sample at 36 months). No differences in age were shown between the groups. There were significantly more males than females in the EL-ASD group than in the EL-Atyp, EL-TD and TL groups: $\chi^2(3) = 13.26, p = .004$. Differences also emerged between the groups in the assessment measures. **Table A6.3** provides the mean scores of the variables used in the study by clinical outcome group.

Table 6.1*Sample Demographic and Clinical Characteristics*

	Total	TL	EL-TD	EL-Atyp	EL-ASD	F/χ^2	Group comparisons
Participants, <i>N</i>	240	75	87	44	34		
	Mean (SD)						
<i>8 months</i>	min-max						
Sex (M/F)	119/121	35/40	35/52	23/21	26-8	13.26*	EL-ASD>EL-TD/EL-Atyp/TL
Age (months)	8.13 (1.22)	7.93 (1.34)	8.24 (1.21)	8.30 (1.03)	8.06 (1.17)	1.20	-
MSEL ELC	103.94 (14.90)	106.73 (12.33)	106.23 (15.63)	99.77 (13.26)	97.12 (17.44)	5.28*	TL/EL-TD>EL-ASD ^b
VABS ABC	95.46 (13.14)	100.25 (11.85)	96.30 (13.16)	89.91 (11.43)	90.32 (13.80)	22.33** ^a	EL-Atyp<EL-TD/TL; EL-ASD<TL
AOSI Total	8.32 (4.81)	6.51 (3.89)	8.49 (4.71)	9.36 (4.85)	10.53 (5.57)	7.20** ^b	TL<EL groups

^a The Kruskal-Wallis test was used for variables with non-normally distributed scores based on histograms, Q-Q plots and Shapiro-

^b Hochberg's GT2 test was used where homogeneity of variance was met but sample sizes were unequal.

Abbreviations: ADI-R: Autism Diagnostic Interview-revised; ADOS: Autism Diagnostic Observation Schedule; ASD: Autism spectrum disorder; Atyp: Infant siblings with atypical development but no ASD; CSS: ADOS-2 Calibrated Severity Scale; EL: Elevated likelihood; MSEL ELC: Mullen Scales of Early Learning Early Learning Composite; min-max: minimum-maximum values; RRB: Restricted and Repetitive Behaviours; SRS: Social Responsiveness Scale; TD: Infant siblings with typical development; TL: Typically developing infants; VABS: Vineland Adaptive Behaviour Scales.

* $p < 0.01$; ** $p < 0.001$.

6.3.2 Missing Data Analysis

Following statistical analysis, missing data were considered as MAR. Refer to section 6.6.1 of the appendix for a detailed description of the missing data analysis.

6.3.3 Identified Patterns of ERP and PII Measures

Of the 14 components, only one integrated component was significantly associated with clinical outcome at 36 months (IC6 $\beta = -0.25$, $p < .001$). The weight of the IC6 component was composed of 40% ERP and 60% PII measures. Individual loadings for component IC6 were examined for possible outliers. One outlier that was outside of the upper robust range (mean $[-0.036] + 3 \times \text{std} [1.001]$) was excluded to limit analyses to robust comparisons.

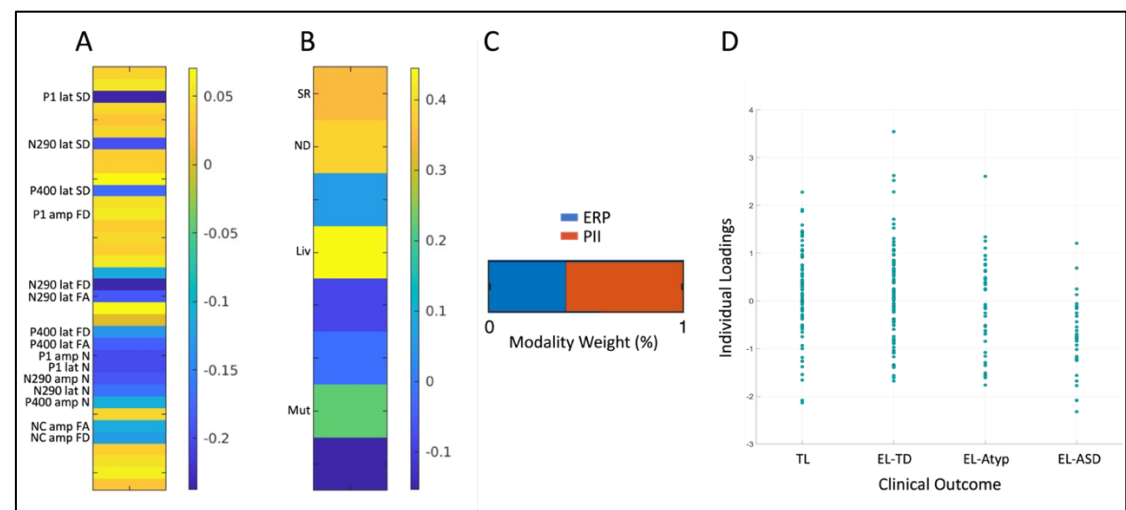
The pattern identified in the ERP features generally showed a stronger effect towards negative values and consisted of: shorter P1, N290 and P400 latencies in response to eye gaze shifting towards the infant; shorter N290 and P400 latencies in response to direct and averted eye gaze; shorter P1 and N290 latencies in response to visual noise; greater P1 amplitude in response to direct eye gaze; greater Nc amplitude in response to eye gaze directed toward and away from the infant; smaller P1, N290, and P400 amplitudes in response to visual noise.

In addition, the linked PII pattern showed a stronger effect towards positive values and consisted of high parent sensitive responsiveness, parent non-directiveness, infant liveliness and dyadic mutuality. Results from the comparison of clinical outcome groups on individual participant loadings controlling for age, sex, verbal and nonverbal developmental level at 8 months revealed significant differences between the EL-ASD group and all the other groups (TL: $p < .001$; EL-TD: $p < .001$; EL-Atyp: $p = .007$; refer

to **Table 6.2** for detailed statistics). Further, the individual loadings were negatively associated with clinical outcome ($\beta = -0.25$), showing a significantly lower expression in individuals within the EL-ASD group compared to the other groups (**Figure 6.3**).

Figure 6.3

Linked ICA of Brain and PII Data and Association with Clinical Outcome



Note. This figure presents the independent component linked across the ERP and PII measures, significantly associated with 3-year clinical outcome. A and B indicate the spatial maps that show the weights of the ERP and PII measures compared to estimated noise by subject. C indicates the relative weights of modalities in each component. D shows component individual loadings associated with 3-year clinical outcome.

Abbreviations: Amp: Amplitude; ASD: Autism spectrum disorder; EL: Elevated likelihood; FD: Face with direct gaze; FA: Face with averted gaze; Liv: Infant liveliness; lat: Latency; Mut: dyadic mutuality; N: Visual noise; ND: Parent nondirectiveness; Atyp: Infant siblings with atypical development but no ASD; SD: Eye gaze shift directed toward the infant; SR: Parent sensitive responsiveness; TD: Infant siblings with typical development; TL: Typically developing infants.

Table 6.2

Group Comparisons of the Linked Component, Significantly Associated with Clinical Outcome at 36 Months

Clinical outcome groups		Independent Component 6		
TL vs.		<i>df</i>	<i>t</i>	<i>p</i>
	EL-TD	165	0.71	0.48
	EL-Atyp	121	1.80	0.075
	EL-ASD	110	4.97	<0.001**
EL-TD vs.				
	EL-Atyp	132	1.26	0.21
	EL-ASD	121	4.47	<0.001**
EL-Atyp vs.				
	EL-ASD	77	2.75	0.007*

Note. Bonferroni correction was applied for multiple comparisons (6 tests = 0.008).

Abbreviations: ASD: Autism spectrum disorder; Atyp: Infant siblings with atypical development but no ASD; EL: Elevated likelihood; TD: Infant siblings with typical development; TL: Typically developing infants.

* $p < 0.01$. ** $p < 0.001$.

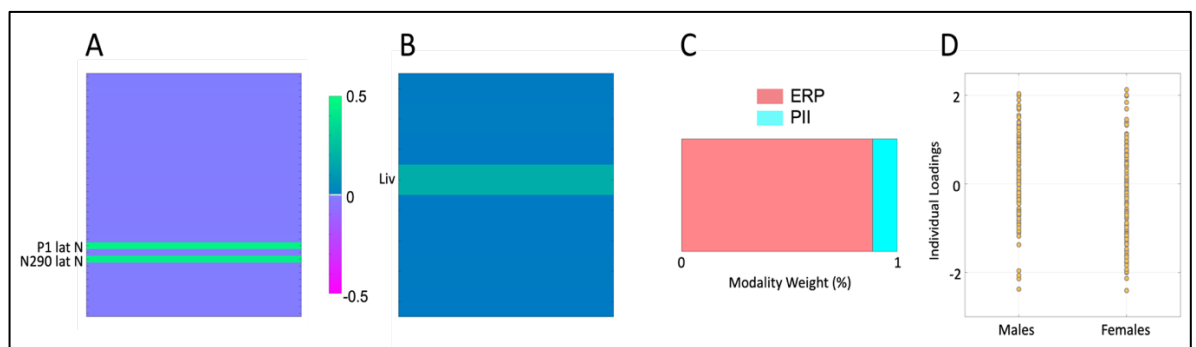
6.3.4 Identified Patterns of ERP and PII Measures in Relation to Biological Sex

Since the participants differed by sex, the already extracted components were examined post hoc for possible associations with sex while accounting for the following covariates: age, clinical outcome, verbal and nonverbal developmental level at 8 months. The aim of this supplementary analysis was to further investigate whether the identified components reflected possible protective effects. Considering the male prevalence of ASD (Baio et al., 2018) and the differential liability model according to which female-specific protective effects decrease females' susceptibility to ASD compared to males

(Robinson et al., 2013), if IC6 that differed by clinical outcome was less expressed in males, this may have been an indication of this linked ERP and PII pattern being a possible protective factor. The results revealed that the IC6 which was the only component that differed by clinical outcome group was unrelated to sex. Instead, independent component 13 (IC13) was the only one significantly associated with sex ($\beta = -0.10$, $p = .002$), correcting for multiple comparisons ($n = 14$ components tested) (**Figure 6.4**). Although there was substantial individual overlap, IC13 was more expressed in males than females (**Panel D**) and was strongly dependent on the ERP features (more than PII, **Panel C**). The pattern identified in the ERP features was composed of longer P100 and N290 latencies to visual noise while other ERP weights were negative and near zero (**Panel A**). The linked PII pattern was characterised by positive values for infant liveliness and negative values, approximating zero, for the rest of the PII items (**Panel B**).

Figure 6.4

Linked ICA of Brain and PII Data and Association with Biological Sex



Note. This figure presents the independent component linked across the ERP and PII measures, significantly associated with biological sex. Panels A and B indicate the spatial maps illustrating the weights of the ERP and PII measures compared to estimated noise by

subject. Panel C indicates the relative weights of modalities in each component. Panel D shows component individual loadings associated with biological sex.

Abbreviations: Lat: Latency; Liv: Infant liveliness; N: Visual noise.

6.4 Discussion

This study aimed to delineate the early dynamics of brain function and PII in the context of ASD and the developmental processes associated with 3-year clinical diagnoses using a data-driven approach. To our knowledge, this is the first study to link different electrophysiological measures and PII qualities at 8 months using multivariate data-driven analysis, and particularly, Linked ICA in ASD. This approach initially allowed the integration of different ERP and PII data to identify co-varying patterns in these domains, followed by their examination in relation to clinical outcomes. Even though some of the domains used here have been previously related to ASD outcome (Elsabbagh et al., 2012; Wan et al., 2013), the present study examined these associations further using a hypothesis-free data-driven approach, with a focus on bringing together multiple modalities and look at the data structure independent of a priori assumptions regarding clinical categories, thus, taking into account individual heterogeneity that characterizes the condition.

A two-stage approach was taken by initially identifying a developmental process through integrating brain and PII data, extracting patterns of variation linked across the two measures. Then, the association of this process with 3-year clinical outcome was examined. One integrated component was identified, significantly associated with clinical outcome and showing a nice integration between brain and PII measures. This component did not differ in relation to biological sex. The component revealed a pattern consisting of faster and greater infant neural responses to social and non-social stimuli, and higher

ratings in qualities of parental, infant and dyadic aspects of free play interaction. The PII measure consisted of higher parent sensitive responsiveness, parent nondirectiveness, higher infant liveliness and dyadic mutuality. The electrophysiological measures consisted of faster P1, N290 and P400 responses to eye gaze shifts. It also consisted of faster N290, P400 as well as increased P1 responses to faces with direct eye gaze, and Nc responses to faces with direct and averted gaze. It also involved faster and smaller P1, N290 as well as decreased P400 responses to a non-face stimulus. This pattern of ERP responses was indicative of faster attention capture of dynamic eye gaze shifts as well as greater engagement of attention to faces. It was also suggestive of greater attention capture but reduced depth of processing of non-faces. The integrated pattern explained more individual variation in infants at TL, with lower individual loadings in the EL-TD, EL-Atyp and EL-ASD groups, meaning that it was associated with typical development. Importantly, it was less expressed in the EL-ASD group compared to the other groups, suggesting a neurotypical process that was mostly absent in infants at EL with a subsequent ASD diagnosis.

6.4.1 Electrophysiological Pattern of Social Information Processing

The ERP pattern involved different social brain mechanisms, encompassing early and later stages of social information processing, consistent with previous research findings (Tye et al., 2020), thus, converging with other research evidence suggesting face processing as an important marker in the developmental pathways underlying ASD.

A study by Bussu et al. (2020) involving the same participants, method and ERP components as in this study (excluding the Nc) showed a similar pattern of results in ERP responses, linked to low levels of ASD symptomatology and higher scores on

developmental level, again present in infants at TL (Bussu et al., 2020). Other work using a case-control comparison approach has shown that EL-ASD infants show the opposite effects in their neural responses to social or non-social stimuli. For instance, Elsabbagh et al. (2012) revealed differences between 8-month sibling groups in neural responses to dynamic gaze shifts involving the P400 amplitude component, with TL being able to differentiate their responses compared to EL-ASD infants who did not show a differentiation (Elsabbagh et al., 2012). Although the pattern observed here showed stronger effects towards P400 latency than amplitude involving additional ERP features, this might be explained by the difference in the approach used in the current study. The present results are also in line with further evidence suggesting decreased Nc responses to faces (E. J. H. Jones et al., 2016) and prolonged or diminished P400 responses to eye gaze shifts in infants at EL-ASD relative to those at TL (Tye et al., 2020).

It is also noteworthy that the overall pattern of ERP responses revealed faster ERPs to both social and non-social stimuli (non-faces) linked to PII. The development of effective communication skills requires the child's brain to be able to process visual information adequately fast in order to respond appropriately to various dynamic signals during social interactions (Laycock et al., 2020). Thus, the present effect might reflect a generally fast neural processing and encoding ability of the infants' brains that is not specific to social stimuli *per se* but could enable them to rapidly detect and interpret social cues in interactions, contributing to typical social functioning.

Furthermore, the study's result showed enhanced/faster attention to a simpler task, involving greater and faster responses to static faces and to a more complex task, such as dynamic gaze shifts. Neural responses to static faces are related to face encoding and reflect communicative intent (Csibra & Gergely, 2006). In turn, sensitivity to dynamic

gaze shifts is thought to involve the recruitment of a wide range of social attention processes, including those responsible for attributing mental states to others (Conty et al., 2007), it is crucial for the development of joint attention skills (Johnson et al., 2005) which, in turn, facilitate later socio-cognitive development (Farroni et al., 2002). Thus, the present effect might signify typically developing infants' brain processing ability to rapidly shift attention, which could help them to timely respond to parental invitations as well as to incoming multisensory information from their social environment.

6.4.2 Patterns of Integrated Brain and PII Measures

Greater attention capture by faces as well as dynamic gaze shifts and faster brain processing of both social and non-social stimuli were linked to higher scores in qualities of infant interactions with parents. Propositions considering the experience-dependent nature of the infant brain support the idea that infant social development is a product of reciprocal interactions between infant brain function and the early caregiving environment, mutually reinforcing one another (Klin et al., 2020; Shultz et al., 2018). Specifically, it has been suggested that typically developing infants' brains orient to social stimuli in their social environment, which is a process requiring both caregivers' engagement of their infants' brains in social interactions and the infants' brain processing capabilities to effectively respond to their parents' social communication bids (Johnson, 2014). Mutual adaptation to caregiver-infant actions and responses within the interaction in the first months of life is crucial for infant socio-communicative development as it can guide infants' subsequent social learning (Shultz et al., 2018). The present results likely show that typically developing infant brains are able to engage with and adapt quickly to the complexities and dynamic nature of the social environment, which could further

strengthen infant predictability of caregiver cues or actions, a fundamental element for social behaviour (Grossmann, 2015). Typically developing infant brain adaptability could also be explained by their higher overall cognitive functioning level compared to the other groups (as measured by the MSEL, **Table 6.1**). In turn, this may be detected by their social partners, even subtly, enhancing the fluency and timing of the caregiver responses, thus leading to greater sensitive responsiveness, nondirectiveness (greater acceptance of infant behaviours and experience) and mutuality within the interaction. In agreement with the study's findings, previous research using a sub-sample of this study comparing EL and TL groups at 7 months showed that higher parent sensitive responsiveness was associated with faster P1 responses to dynamic eye gaze shifts in infants at TL (Elsabbagh, Bruno, Wan, Charman, Johnson, Green, & The BASIS Team, 2015). In terms of PII measure, previous findings comparing EL with TL infants have revealed a deviation from the observed PII pattern shown in this study for the former group, revealing lower parent sensitive responsiveness, nondirectiveness and dyadic mutuality in EL compared to TL infants in the first year of life, with mutuality predicting 3-year ASD outcome (M. W. Wan et al., 2012, 2013). Lower parent sensitivity and dyadic mutuality have also been linked to higher ASD behaviours in infants at 36 months (Loncarevic et al., 2022).

Interestingly, no direct link between the infant brain responses to faces and parent sensitivity was observed in the previous chapter's findings for either the TL or the EL group. This might be explained by the difference in the statistical approach used between the studies. Linked ICA provided the advantage of integrating many different modalities to discover common features based on individual variability without inferring a structure in the data. In turn, the SEM approach implemented in the previous study (**Chapter 5**)

provided the flexibility to model different relationships comparing the EL and TL groups. In addition, the ERP and parent interactional behaviour variables were included in the SEM model as latent factors (using the condition contrasts for the face/gaze processing SEM), compared to the current study which included individual variables and only absolute amplitudes and latencies of each ERP component. These factors may have played a role in the discrepancy in the findings. Perhaps a larger sample size in the SEM approach may have increased statistical power to detect a significant association.

In addition, greater attention engagement with faces and faster processing of faces and eye gaze shifts were related to higher infant motor activity, as measured by the liveliness scale. Previous research has shown that motor experiences like object grasping in 3-month-old infants have been linked to a visual preference for faces over objects (Libertus & Needham, 2014), while infant processing of faces has been associated with their sitting ability (Cashon et al., 2013). By actively exploring their environment through walking, crawling, and changing positions, among others, infants can create opportunities for social communication and learning. Indeed, motor development has been shown to be linked with the development of important skills for social interactions, such as shared attention and social referencing (Campos et al., 2000). It is likely that infants' increasing motor experiences facilitate greater attention to faces and triadic exchanges with parents, linked to faster neural processing of faces. In turn, it may also be that infants' own face-processing capabilities linked to higher liveliness in the interaction facilitate social-communication opportunities, important for the development of social cognition. Siblings with a later ASD diagnosis experience delays in their motor skills (E. J. H. Jones et al., 2014) Past research using part of the sample used in this study has shown that EL infants

have decreased fine and gross motor skills (Leonard et al., 2014) and are less lively in their interactions with parents (M. W. Wan et al., 2012) compared to infants at TL.

6.4.3 Relation of Component Individual Loadings with Clinical Outcome – Evidence for Protective Effects?

Individual component loadings on clinical outcome groups showed significant differences between the EL-ASD and all the other groups. Of note, the groups seemed to overlap and were not clearly dissociated, as TL, EL-TD and EL-Atyp infants did not differ. This highlights the individual variability that exists in the condition, showing that infants who may have similar patterns of responses in behaviour and brain function may not receive the same clinical diagnosis later in development. However, the present finding reflects some degree of specificity with regard to ASD, as results clearly distinguished EL-ASD infants from the other groups, demonstrating that the linked patterns of brain and PII measures were less expressed in this group of infants. The fact that the identified process was absent in the EL-ASD group in relation to the other groups may represent a protective factor, possibly related to a compensatory activity or to what is referred to as ‘canalisation’ (Elsabbagh & Johnson, 2010; M. D. Kaiser et al., 2010). It likely reflects the part of a process of brain adaptive changes across development that work as compensatory and protective mechanisms from genetic and environmental susceptibilities of developing ASD, during which parents could have an influencing role when interacting with their infants. Indeed, altering the external environment in a period where infant brain plasticity is at its peak can shape brain function, consequently optimising infant developmental trajectories. For instance, high parent sensitivity and acceptance of infant’s behaviour could serve as a protective factor, possibly altering the

course of the developing brain. However, it would be interesting to examine whether EL siblings with no ASD outcome at 36 months received a clinical diagnosis later in life. In addition, investigating infant brain and behaviour over developmental time would possibly be able to capture more accurately the interactions between risk and protective factors that promote resilience, leading to alternative phenotypic expressions and the variability in developmental outcomes (Elsabbagh, 2020; Johnson et al., 2021).

On the other hand, component selection based on sex revealed that the integrated component associated with clinical outcome did not differ by sex, while sex differences emerged in a different independent component not associated with clinical outcome. This suggests that the identified patterns of linked ERP and PII measures associated with clinical outcome are not driven by sex. Thus, the present brain and PII relationships in terms of ASD diagnosis do not support the hypotheses for female-specific protective effects in relation to clinical outcome (at least in this study).

Overall, compared to previous work examining only a few ERP or PII features in relation to ASD outcome, the present study extended previous findings by using a novel data-driven approach showing patterns that involved different aspects of caregiver-infant interaction and face processing. Furthermore, individual loadings on the integrated component showed lower expression in the EL-ASD group with the identified patterns being mostly present in TL infants. This result might represent a developmental process underlying typical development that EL-ASD infants are lacking. Combined with evidence from previous research suggesting differences between infants at EL-ASD and TL in some of the ERP and PII features, it possibly underpins EL-ASD infants' divergence from this process.

6.4.4 Limitations and Future Directions

This study has employed a novel method integrating multiple ERP and PII data based on individual variability to inform an understanding of the underlying processes related to ASD outcome. However, several limitations need to be considered.

First, the subsample of infant siblings with a 3-year diagnosis of ASD investigated in this study was small, while the majority were those who developed typically based on clinical assessment at 36 months. This may explain why pattern extraction was weighted more towards typically developing infants. During data analysis, pattern extraction was made not only in terms of the variance-covariance matrix across measures and modalities but also considering the variance explained within individuals. Sample size may have also played a role in how pattern selection was related to clinical outcome, where the integrated component was different in the EL-ASD group compared to all the other groups, possibly due to this group having significantly lower individual weights for that component. Therefore, a prospective study of infant siblings with a more balanced design in terms of sample size in the groups (through multi-site collaboration) would allow a better encapsulation of the whole variation in brain responses and interactions in atypically developing infants.

Second, the study sought to identify modes of covariance between multiple ERP components measuring brain responses to social and non-social stimuli and different parent-infant interactional aspects using a cross-sectional design. Given the complexity and heterogeneity of ASD, this provided novel insights into how brain and PII measures co-acted early in development and how they were expressed in different outcome groups. However, the electrophysiological data were only available at 8 months and not collected longitudinally. Thus, it was not possible to investigate how the identified patterns

unfolded across different developmental stages. Future research should use a longitudinal design and the same analytical approach in an independent sample of infants to examine these associations. This would offer a better view of the dynamic relations between brain function and parent-child interaction and how these lead to different clinical outcomes. It would also offer important information on the possible protective factors driving variability in developmental outcomes.

Last, the findings do not necessarily imply a causative relationship between the processes measured through infant ERP responses to social and non-social cues and unstructured parent-child interactions. Further research employing longitudinal designs and additional domains (i.e., measures of developmental level, eye-tracking or genetic data) would possibly help to clarify causal links. It would also prove useful for a more homogenous categorization, which can be important for early intervention.

6.5 Conclusion

Using a data-driven approach, the study identified patterns of linked ERP and PII data that were less expressed in the EL-ASD infants, underpinning typical development. This can inform our understanding of the possible mechanisms leading to different clinical outcomes and of the dynamic nature of early caregiver-infant interactions and infant brain function. It also provides an important addition to the existing literature by showing that linking multiple measures of brain and PII data can help obtain greater insights into the developmental processes acting early in development before overt clinical symptoms of ASD appear. This novel approach provided an advantage to this study as it allowed the extraction of patterns of variation in brain and PII data without prior knowledge of clinical categories, considering individual variability. Investigating

associations between the brain and behaviour across time points in infancy to early childhood and integrating data from additional measures would enable the identification of possible causal or protective factors related to clinical outcome with greater confidence. It would also create a better view of the pathways involving genetic susceptibility, brain mechanisms and behaviour.

6.6 Appendix

6.6.1 Missing Data Evaluation and Analysis

Missing data were evaluated with logistic regressions including each categorical indicator variable as the dependent variable in the model, and infant sex, age in months (8 months), clinical outcome group, as well as verbal and non-verbal developmental level at 8 months as the independent variables.

Logistic regressions revealed age as a significant predictor of missingness for the P1, P400, and N290 ERP components in the static face conditions (Model: $\chi^2(1) = 5.22$, $p = .02$). The other predictors were non-significant, but age was significant at the 5% level ($Wald = 5.08$, $p = .02$), with an odds ratio (OR) of 0.78 (95% CI [0.63, 0.97]). In addition, age significantly predicted missingness for the Nc component across the conditions (Model: $\chi^2(1) = 7.46$, $p = .006$). Age was significant at the 1% level ($Wald = 7.17$, $p = .007$), with an OR of 0.74 (95% CI [0.58, 0.92]). Therefore, missing data were considered as MAR. To handle missing data, imputation through expectation maximization was performed on SPSS, where missing values were imputed with a simulated value to create a complete dataset. Assuming the shape of the distribution for the missing data, expectation-maximization is an iterative process where the algorithm aims to find the estimate of a parameter that maximizes the observed data log-likelihood (Gold & Bentler, 2000). By replacing missing values, all cases are maintained. This approach is advantageous over other approaches, such as listwise deletion which can introduce bias and affect the sample representativeness, as it excludes any case in the dataset that has a missing value.

Table A6.1*Intra-Class Correlation Coefficients Between Coders for The MACI Items*

		8 months	
		Phase 1 (N 25%)	Phase 2 (N 10%)
<i>Parent</i>	Sensitive Responsiveness	0.66	0.88
	Non-directiveness	0.63	0.68
<i>Infant</i>	Attentiveness	0.58	0.82
	Liveliness	0.66	0.64
	Positive affect	-	0.70
	Negative affect	-	0.81
<i>Dyad</i>	Mutuality	0.80	0.75
	Engagement intensity	0.68	0.78

Note. Values ≥ 0.60 indicate good to excellent ICC.

Abbreviations: MACI: Manchester assessment of caregiver-infant Interaction.

Table A6.2*Sample Demographic and Clinical Characteristics by Clinical Outcome Group at 36 Months*

	Total	TL	EL-TD	EL-Atyp	EL-ASD	F/H	Group comparisons
Participants, <i>N</i>	240	75	87	44	34		
	Mean (<i>SD</i>)						
Age	38.44 (2.36)	38.44 (2.68)	38.71 (2.38)	38.14 (2.05)	38.15 (1.94)	0.78	-
MSEL ELC	107.37 (22.71)	116.69 (15.97)	114.20 (15.22)	91.80 (24.82)	89.78 (28.35)	26.50*** ^a	EL-ASD/EL-Atyp<TL/EL-TD
VABS ABC	98.61 (12.92)	106.20 (8.11)	101.92 (8.54)	91.05 (11.79)	83.63 (15.12)	59.65*** ^b	TL>all others; EL-TD>EL-Atyp/ASD ^c
ADOS-2 Social Affect Total Score^e	4.56 (4.11)	4.08 (3.39)	2.21 (1.68)	7.09 (4.18)	8.30 (5.30)	22.05*** ^a	EL-TD<all others; TL<EL-Atyp/ASD
ADOS-2 RRB Total Score^e	1.37 (1.50)	1.01 (1.15)	0.87 (1.04)	1.86 (1.71)	2.79 (1.83)	38.91*** ^a	EL-TD/TL<EL-Atyp/ASD; EL-Atyp<EL-ASD
ADOS-2 CSS^e	2.95 (2.40)	2.62 (1.99)	1.55 (0.89)	4.57 (2.39)	5.15 (3.08)	65.62*** ^a	EL-TD<all others; TL<EL-Atyp/ASD
ADI-R Social^d	3.81 (4.98)	-	1.50 (1.91)	3.16 (3.67)	10.94 (5.69)	66.08*** ^a	EL-TD<EL-Atyp/ASD; EL-Atyp<EL-ASD

ADI-R Communication^d	4.07 (4.74)	-	1.81 (2.10)	4.20 (4.56)	9.97 (5.08)	56.81*** ^a	EL-TD<EL-Atyp/ASD; EL-Atyp<EL-ASD
ADI-R Behaviours/Repetitive interests^d	1.49 (2.29)	-	0.48 (0.90)	1.20 (1.95)	4.63 (2.56)	65.17*** ^a	EL-ASD>EL-TD/Atyp
SRS Total Score	30.51 (23.52)	19.82 (9.30)	26.42 (17.51)	34.03 (24.68)	62.70 (30.75)	47.63*** ^a	TL<EL-Atyp/ASD; EL- ASD>EL-TD/Atyp

^a The Kruskal-Wallis test was used for variables with non-normally distributed scores based on histograms, Q-Q plots and Shapiro-Wilk tests. Differences between groups have been adjusted by the Bonferroni correction for multiple comparisons.

^b Welch's F ratio was used because homogeneity of variance was not met.

^c Games-Howell post-hoc test was used where homogeneity of variance was not met and due to unequal sample sizes.

^d ADI-R not administered to TL group in Phase 1; statistical tests undertaken between EL subgroups.

^e ADOS-G item scores were used for the calculation of ADOS-2 total scores.

Abbreviations: ADI-R: Autism Diagnostic Interview-revised; ADOS: Autism Diagnostic Observation Schedule; ASD: Autism spectrum disorder; Atyp: Infant siblings with atypical development but no ASD; CSS: ADOS-2 Calibrated Severity Scale; EL: Elevated likelihood; H: Kruskal-Wallis test; MSEL ELC: Mullen Scales of Early Learning Early Learning Composite; min-max: minimum-maximum values; RRB: Restricted and Repetitive Behaviours; SRS: Social Responsiveness Scale; TD: Infant siblings with typical development; TL: Typically developing infants; VABS: Vineland Adaptive Behaviour Scales.

* $p < 0.01$; ** $p < 0.001$.

Table A6.3*Mean Scores of the Variables Used in the Study by Clinical Outcome Group*

	Total <i>N</i> = 240	Clinical outcome group mean (<i>SD</i>)			
		TL <i>n</i> = 75	EL-TD <i>n</i> = 87	EL-Atyp <i>n</i> = 44	EL-ASD <i>n</i> = 34
P100 amp SD	0.50 (2.52)	0.42 (2.49)	0.34 (2.70)	0.83 (2.23)	0.62 (2.53)
P100 amp SA	1.04 (2.61)	1.51 (2.68)	1.04 (2.41)	0.74 (2.47)	0.41 (2.95)
P100 lat SD	164.0 (11.83)	163.3 (12.12)	163.6 (9.94)	164.2 (14.53)	166.2 (12.17)
P100 lat SA	165.3 (12.59)	168.4 (12.50)	164.9 (12.39)	164.4 (12.79)	160.98 (11.97)
N290 amp SD	0.07 (3)	0.03 (2.97)	0.001 (3.14)	0.49 (2.70)	-0.16 (3.21)
N290 amp SA	1.07 (2.86)	1.71 (2.84)	0.98 (2.59)	0.73 (2.85)	0.36 (3.38)
N290 lat SD	257.4 (16.67)	258.7 (16.73)	255.8 (16.01)	256 (19.93)	259.9 (13.95)
N290 lat SA	255.7 (18.56)	257.8 (20.08)	254.2 (18.41)	254.1 (18.85)	256.5 (15.36)
P400 amp SD	1.83 (3.39)	1.45 (3.14)	1.86 (3.53)	2.51 (3.84)	1.74 (3.04)
P400 amp SA	3.04 (3.26)	3.81 (3.14)	3.01 (3.01)	2.65 (3.30)	1.98 (3.78)
P400 lat SD	421.4 (30.89)	421.1 (33.71)	419.5 (29.80)	417 (29.98)	431.4 (28.86)
P400 lat SA	422.2 (40)	426.5 (27.90)	423.1 (30.57)	416.9 (34.05)	417.7 (33.87)
P100 amp FD	3.24 (6.20)	1.74 (5.11)	4.01 (7)	5.30 (5.96)	2.05 (6.08)
P100 amp FA	3.14 (5.23)	1.57 (4.30)	3.56 (5.47)	4.69 (5.13)	3.48 (6.07)
P100 lat FD	158 (25.36)	146.8 (23.16)	161.5 (24.97)	168.4 (20.01)	160.8 (29.56)
P100 lat FA	160.6 (27.17)	153.6 (26.52)	165 (24.59)	166.5 (28.57)	158.1 (30.48)

N290 amp FD	3.72 (7.38)	3.26 (7.52)	3.77 (7.66)	5.06 (6.08)	2.85 (8.25)
N290 amp FA	4.20 (6.67)	3.04 (7.30)	4.40 (6.62)	4.47 (6.04)	5.79 (6.21)
N290 lat FD	266.6 (20.72)	266 (23.07)	266.5 (19.45)	265.6 (20.25)	269.5 (20.23)
N290 lat FA	267 (20.83)	265.3 (23.62)	266 (19.19)	269.9 (20.56)	269.6 (19.41)
P400 amp FD	7.54 (9.38)	7.62 (8.59)	7.18 (10.23)	10.19 (7.66)	4.85 (10.69)
P400 amp FA	7.78 (8.92)	6.60 (9.89)	7.76 (9.38)	9.80 (6.60)	7.75 (8.48)
P400 lat FD	413.3 (37.93)	410.4 (35.88)	414 (40.45)	416.5 (35.18)	413.8 (41.79)
P400 lat FA	411.8 (36.27)	408.1 (36.85)	412.1 (36.33)	411.6 (31.84)	418.8 (36.27)
P100 amp N	6.46 (5.71)	5.78 (5.68)	6.33 (5.97)	6.86 (5.72)	7.70 (5.21)
P100 lat N	175 (18.44)	176.2 (19.97)	171.9 (17.46)	175.2 (18.82)	180.1 (16.28)
N290 amp N	9.53 (7.33)	10.08 (8.61)	9.22 (6.43)	9.26 (7.14)	9.39 (6.93)
N290 lat N	256.7 (19.44)	253.8 (19.37)	254.5 (20.51)	255.6 (16.31)	269.5 (16.34)
P400 amp N	13.93 (8.54)	13.71 (8.63)	13.43 (8.71)	16.15 (7.97)	12.71 (8.61)
P400 lat N	412.8 (39.62)	405.4 (39.28)	412.4 (41.86)	416 (35.70)	425.7 (38.08)
Nc amp FD	-1.10 (5.73)	-1.21 (5.22)	-0.53 (5.89)	-3.13 (5.55)	0.24 (6.30)
Nc amp FA	-1.11 (5.18)	0.33 (5.13)	-1.34 (5.57)	-3.25 (4.51)	-0.84 (4.35)
Nc lat FD	474 (115.9)	471 (93.41)	482.4 (133.5)	451.6 (89.67)	487.8 (142.4)
Nc lat FA	482.6 (113.7)	475.7 (106.6)	479.5 (118)	476.7 (108.1)	512.7 (128.1)
Nc amp N	-2.84 (4.70)	-1.90 (5)	-3.23 (4.22)	-3.50 (5.75)	-3.02 (3.66)
Nc lat N	454.3 (104.5)	456 (98.87)	429.5 (96.98)	447.4 (90.69)	522.3 (126.4)
Parent sensitive responsiveness	3.70 (1.26)	3.93 (1.37)	3.72 (1.21)	3.57 (1.19)	3.27 (1.11)

Parent nondirectiveness	3.72 (1.31)	4.10 (1.22)	3.64 (1.29)	3.65 (1.36)	3.10 (1.27)
Infant attentiveness	3.99 (1.27)	3.92 (1.30)	4.00 (1.13)	4.05 (1.39)	4.03 (1.45)
Infant liveliness	4.19 (1.43)	4.39 (1.33)	4.22 (1.46)	4.14 (1.67)	3.72 (1.16)
Infant positive affect	3.56 (1.62)	3.29 (1.30)	3.28 (1.61)	3.67 (1.47)	4.81 (1.83)
Infant negative affect	2.46 (1.65)	2.38 (1.56)	2.25 (1.56)	2.52 (1.72)	3.25 (1.84)
Dyadic mutuality	3.34 (1.29)	3.42 (1.42)	3.36 (1.20)	3.30 (1.18)	3.17 (1.37)
Dyadic engagement intensity	3.98 (1.21)	3.96 (1.18)	3.90 (1.17)	3.97 (1.24)	4.27 (1.39)

Abbreviations. Amp: Amplitude; FA: Face with gaze averted from the infant; FD: Face with gaze directed towards the infant; Lat: Latency; N: Visual noise; SA: Eye gaze shift averted from the infant; SD: Eye gaze shift directed towards the infant

Chapter 7. General Discussion

From the moment of birth, social exchanges with parents are central in an infant's life and are believed to play a fundamental role in infant brain development (Champagne & Curley, 2005). The aim of the present PhD work was to prospectively examine early PII trajectories as well as PII-brain associations in the context of ASD susceptibility and developmental outcome. Previous research has provided valuable insights into these important aspects, especially in neurotypical development. Yet, there are no consistent data on early unstructured PII trajectories in infants at EL for ASD and their links to subsequent ASD or dimensional outcomes. In addition, the investigation of the links between aspects of parent-infant social exchanges and infant brain function (neural responses to social attention) within the first year in this population has been minimal. Investigating these further was significant for a greater understanding of the developmental processes underlying ASD and PIIs' contribution to children's developmental routes, which may enable earlier detection and earlier, improved access to intervention to support infants with early ASD signs and their families.

The research work undertaken in this Thesis aimed to fill this gap in literature. In particular, the experimental findings of this Thesis addressed a number of questions (set out in **Chapter 1**) which had not been sufficiently answered by previous research, and thus, warrant further investigation:

1. Are previous findings on PII differences in infants at EL for ASD replicable?
 - a) What are the trajectories of PII in infants with a subsequent ASD outcome compared to EL-no ASD and TL infants?

- b) What aspects of PII are similar or different between these groups over time?
- 2. How do early PII trajectories that differentiate EL from TL infants contribute to developmental outcomes other than ASD diagnosis?
- 3. How and what features of PII relate to measures of infant brain function within the first year?
 - a) Are any patterns of relationships similar or different between the groups?
 - b) How are these associations linked to ASD outcome?

This chapter summarises the findings of the research conducted in the current thesis with respect to the aforementioned aims and research questions. First, it provides a brief overview of the aims and findings of each study and then addresses the research questions. This is followed by a discussion of the key findings in relation to the broader literature and to the hypotheses that motivated this work. The implications of the findings are summarised. Finally, the limitations relevant to the findings are acknowledged, which provides the opportunity to put forward recommendations for future research.

7.1 Aims and Main Findings of Each Empirical Chapter

The findings emerging from the studies of this thesis shed light on the PII trajectories and brain-PII associations in ASD development and are outlined below.

Chapter 3 aimed to replicate previous findings to evaluate 8-14-month unstructured PII in a larger, independent cohort of EL and TL infants and assess whether PII differences between the sibling groups were associated with 3-year ASD diagnosis. Examining the replicability of previously reported effects including a larger non-overlapping sample was important for the improvement of the consistency and reliability

of research findings. The results partially replicated previous findings. They revealed group differences in parent and dyadic aspects of PII as well as decreases in social attention between 8-14 months in EL-ASD infants. Parent, infant and dyadic PII qualities predicted later ASD outcome.

Chapter 4 was an extension of **Chapter 3**. It extended previous findings by examining whether 8- to 14-month change in the PII qualities that differentiated EL from TL infants in **Chapter 3** was associated with 3-year dimensional outcomes (ASD-related traits, language, social communication, maladaptive behaviour) in the whole sample. It also explored earlier (between 8 and 14 months) associations between PII and language/social communication. Further, it examined whether any patterns of associations between PII change and 3-year dimensional outcomes differed between EL-ASD, EL-no ASD and TL infants to test the protective effects of PII aspects in later development. Parent/dyadic interaction change emerged as a significant predictor of language, social communication and externalising behaviour, and infant attentiveness to parent and affect change (marginally for affect change) was related to later externalising behaviour. In addition, language and social communication dimensions were linked to parent/dyadic interaction aspects between 8-14 months. Last, the associations between infant attentiveness, parent/dyadic interaction changes with the aforementioned dimensional outcomes differed between the TL, EL-no ASD and EL-ASD groups. These findings provide important insights into the interactional processes linked to dimensional outcomes rather than solely ASD diagnosis.

Chapter 5 investigated whether infant neural responses to social cues (faces, eye gaze) related to infant attentiveness to parent, and whether this was linked to parent sensitivity at 8 months. This study's hypothesis was based on theory suggesting that EL

infants' brain processing capabilities may affect their interactions with their proximal caregiving environment. Findings revealed a relationship between neural social attention and parent sensitivity, mediated by infant attentiveness to parent in the EL group, while borderline positive associations were found between infant brain responses to social and non-social stimuli and attentiveness to parent in the TL group. These findings provide evidence that infant brain processing capabilities may have an effect on the quality of PII.

Building on the study from Chapter 5, **Chapter 6** aimed to gain a better understanding of the brain-PII relationship at 8 months by following a data-driven approach (independent of a priori assumptions regarding clinical categories) considering individual heterogeneity, which has not previously been assessed. It integrated several measures of brain function (neural responses to faces, eye gaze and non-social cues) and parent, infant and dyadic aspects of PII. Then, it sought to examine whether/how these emerging brain-PII patterns related to clinical outcomes. A pattern of brain-PII association was found and was less expressed in EL-ASD infants compared to other clinical outcome groups (TL, EL-no ASD, EL-Atyp). These novel findings offer important insights into the developmental processes linked to ASD outcome.

7.2 Synthesis of Key Findings Addressing the Research Questions

7.2.1 Are Previously Observed Differences in PII Between EL and TL Infants Replicable?

Examining the replicability of previous research reporting PII differences between EL and TL infants and PII associations with later ASD outcome was one of the main goals of the current PhD work. It was considered essential for the improvement of the

validity of existing research findings, and thus, for a more enriched understanding of early ASD development as well as the role of parent-infant social exchanges in children's developmental trajectories. Establishing the consistency of previous findings using the same methodology and including a larger independent and non-overlapping cohort provided a strong replicability test. Indeed, **Chapter 3** replicated some of the previously reported findings by Wan et al. (2013), strengthening the existing evidence for PII differences between EL and TL infants. In addition to Wan et al.'s study, differences in aspects of PII have also been found in other studies. For instance, several studies have reported a directive tendency in social play from parents of EL infants compared to parents of infants at TL (Harker et al., 2016; Srinivasan & Bhat, 2020; Steiner et al., 2018; M. W. Wan et al., 2019a). Although the findings contrast with other research presenting a lack of differences in parent responsive or directive behaviour (Baker et al., 2010; Campbell et al., 2015), it is not surprising considering the small sample sizes previously employed which may have hindered any potential effects. Furthermore, dyadic aspects of PII were also affected in infants at EL for ASD, as mutuality was lower in this group compared to the TL group. Previous research has also found that the degree of reciprocal interactions between EL-ASD infants and their parents was lower than that of TL dyads (Campbell et al., 2015). Importantly, the current study not only replicated Wan et al.'s finding for differences in infant attentiveness after the first year but also offered a novel finding by showing earlier (8-month) alterations in EL-ASD infants' social attention, decreasing from 8 to 14 months compared to TL and EL-no ASD groups, which was not previously reported. In addition to Wan and colleagues, these results are consistent with research showing lower infant joint attention behaviours or responses to parents around

the first year linked to later ASD symptomatology (Kellerman et al., 2020; Rozga et al., 2011).

Moreover, consistent with the study replicated, lower dyadic mutuality and infant attentiveness at 14 months, and not at 8 months, were associated with an increased probability of 3-year diagnosis, indicating that differences in infant social attention and mutuality become more pervasive with development in EL-ASD dyads. Mutuality has been predictive of ASD severity in other studies (Campbell et al., 2015; Loncarevic et al., 2022). In addition, this is the first study to show that parent directiveness at 8 months predicted 3-year ASD outcome. Both this and the surprising result showing high positivity at 8 months as predictor of ASD outcome offer significant insights into the early dynamics of PII in ASD development (discussed later).

Overall, these findings strengthen and extend previous research showing emerging alterations in PII quality becoming more prevalent over time. They provide evidence for earlier predictive effects of PII on ASD diagnosis and a divergent trajectory in infant attentiveness starting from 8 months.

7.2.2 Do Early PII Trajectories Contribute to Developmental Outcomes Other Than ASD Diagnosis?

Findings from **Chapter 4** provide evidence indicating that positive changes in PII qualities between 8-14 months are related to 3-year dimensional outcome. Thus, patterns of PII across development are not only associated with ASD outcome but extend to other behavioural dimensions and subclinical traits. These findings highlight that sensitively responsive, nondirective parenting and mutual PII early on can support children's social development and adaptive behaviour, and agree with previous research showing

associations between parental sensitivity, attunement to the child's behaviours and dyadic synchrony with social communication/language skills and externalising behaviours in both neurotypically developing and autistic individuals (Bradley & Corwyn, 2007; E. W. Lindsey et al., 2009; R. A. Lindsey et al., 2020; Northrup & Iverson, 2015; Soares et al., 2018; Tamis-LeMonda et al., 2001; Valentovich et al., 2018; Zampella et al., 2020). Importantly, parent and dyadic aspects of interaction at 8 months were also significant contributors to changes in language and social communication skills earlier, between 8-14 months, highlighting that from as early as 8 months, the quality of parent and dyadic behaviours exerted an influence on the long-term development of infants' language and social communication ability in this enriched sample of TL and EL infants. Links between dyadic synchrony and language skills in EL infants (Kellerman et al., 2020) and between parent responsiveness/dyadic synchrony and language/social skills in neurotypically developing infants (E. W. Lindsey et al., 2009; Soares et al., 2018; Tamis-LeMonda et al., 2001) have been previously shown, though at later time points. Infant language skills at 8 months also contributed to 8-14-month changes in these interactional domains, underscoring that infants contribute with their own language skills towards shaping PII over time.

Furthermore, infant attentiveness to parent and affect (especially negative affect) were particularly associated with later externalising behaviour, pinpointing that infant attentiveness to parent and affect display within social interactions in the first year of life might reflect regulatory processes and could be a developmental precursor of later externalising behaviour skills. These findings are in conjunction with previous research showing that infant initiations/responses to joint attention and positive affect are linked to lower scores in externalising behaviour at a later age in neurotypical development

(Moore et al., 2001; Van Hecke et al., 2007). The findings underscore that attending to and engaging in social interactions in the context of PII early on sets the stage for social learning opportunities, enabling children to develop adaptive skills which they can then transfer to other social contexts.

7.2.3 How and What Features of PII Relate to Measures of Infant Brain Function Within the First Year?

This question was addressed by first conducting mediation analysis to investigate whether infant attentiveness to parent mediated the relationship between a) the strength of brain responses to faces with direct gaze toward the infant vs. non-faces/faces with averted gaze, b) 'the speed of brain responses to both social and non-social stimuli (faces and non-faces) and parent sensitivity (**Chapter 5**) at 8 months. A data-driven approach was then followed, which allowed the integration of multiple brain and several PII features (**Chapter 6**) at the same time point. In **Chapter 5**, it was found that infant attentiveness mediated the relationship between infant brain function and parent sensitivity in infants at EL, suggesting that infants' brain processing capabilities may affect their behavioural social attention, which, in turn, may influence parental responses toward the infant during play interactions. On the other hand, in TL infants, a pattern of faster brain responses to social and non-social cues was found, linked to higher infant attentiveness to parent (borderline effect). The novel method applied in **Chapter 6** identified an integrated component consisting of faster and greater infant neural responses to both social and non-social cues linked to higher ratings in qualities of parent, infant and dyadic qualities of PII (parent sensitive responsiveness, parent nondirectiveness, higher infant liveliness and dyadic mutuality). This developmental process was less

expressed in EL-ASD infants and was mostly associated with neurotypical development. Overall, these findings provide evidence for a differential pattern of brain and PII association between TL and EL infants and offer an important addition to existing preliminary research showing relationships between brain function and PII in infants at EL for ASD (Elsabbagh, Bruno, Wan, Charman, Johnson, Green, & The BASIS Team, 2015).

7.3 Emerging Themes

7.3.1 The Role of PII in Infant Developmental Trajectories

Across chapters, different parent, infant and dyadic global aspects of unstructured social interaction were evaluated, which provided the opportunity to identify PII domains that surfaced as particularly “relevant” in that they consistently contributed to later developmental outcome and were linked with brain measures. A PII scale that stood out across the studies of this thesis is infant attentiveness to parent. This variable was central as infants at EL with later ASD showed a marked trajectory of decreasing attentiveness, starting from as early as 8 months and predicting 3-year ASD outcome at 14 months (**Chapter 3**). A greater increase in attentiveness (8-14 months) was related to infants’ lower externalising behaviour (especially in the TL group) at 36 months (**Chapter 4**) and also played a mediating role in the relationship between EL infants’ neural face processing capability and parent sensitivity at 8 months (**Chapter 5**). An association with the speed of brain processing in TL infants was found too, although less robustly. Interestingly, attentiveness was not linked with brain measures in **Chapter 6**. A possible explanation for this discrepancy is that the methods employed in the two studies were

very different incorporating different variables. In addition, in **Chapter 6**, the integrated pattern identified was mostly driven by TL infants.

Moreover, parent sensitive responsiveness, nondirectiveness and dyadic mutuality were three domains that appeared to be of particular importance. Between 8 and 14 months, sensitive responsiveness, nondirectiveness and mutuality ratings were higher in TL than EL infants (**Chapter 3**). Higher scores in these scales were also associated with more enhanced and faster infant neural responses to social/non-social cues at 8 months, and this pattern of association was absent in EL infants who developed ASD at 3 years, possibly indicative of a developmental process associated with neurotypical development (**Chapter 6**). In addition, higher ratings in all these domains (as a latent factor) at 8 months and positive changes between 8 and 14 months predicted improved social communication, language and lower externalising behaviour at 3 years (**Chapter 4**). This association was not shown in the EL-ASD group. Except for sensitive responsiveness that did not emerge as a significant predictor of ASD outcome in **Chapter 3** (a finding that agrees with previous research, Wan et al., 2013), low nondirectiveness and mutuality ratings at 8 and 14 months, respectively, were related to an increased probability for ASD diagnosis. Importantly, nondirectiveness was a particularly robust finding, as it remained a significant predictor even after controlling for infant behavioural atypicality and developmental level.

These results underscore that not only parental but also infant and dyadic aspects of interaction were affected in EL infants with a later ASD diagnosis, which provides further insight into the dynamics of PII. Parent responsiveness and sensitivity in PII are fundamental for children's socio-emotional development (Ainsworth et al., 1978). Infants are also active agents in the parent-infant relationship, initiating and responding to others'

bids for social interaction (Senju & Csibra, 2008; Trevarthen & Aitken, 2001), shaping the dynamics of PII. Thus, the behaviours of each interactive partner are dynamic and mutually affected, shaping the patterns of relationships that develop over time (Leclère et al., 2014). Considering the bidirectional nature of PII (Kochanska et al., 2008; Moore et al., 2013), the particular PII domains identified here are key: they highlight that pre-existing ASD susceptibilities (e.g., genetic factors interfering with brain functioning) are likely to alter EL-ASD infants' attentiveness during social play, which may, in turn, influence parental responses, leading to more directive behaviours to engage their infants in social interactions. More specifically, the attentiveness MACI scale is based on a combination of orientation, attachment-type behaviours and social-communicative behaviours (since the scale is based on the GRS scale which is focused on attachment theory, Murray et al., 1996)). Thus, the low attentiveness to parent presented by EL infants may be perceived as personal and "rejecting" by the parent, which may contribute toward lower sensitive responding and more directive behaviours. This may then affect the overall mutuality and reciprocity in interactions with cascading effects on later development.

It is also worth mentioning the infant positive and negative affect MACI scales that were found to be relevant in terms of their effects on later developmental outcome in two of the studies of the current thesis. In the PII replication study (**Chapter 3**), positive affect was a significant predictor of 3-year ASD outcome. In addition, in the study investigating the contribution of PII change to 3-year dimensional outcome (**Chapter 4**), affect (especially negative affect) was related to externalising behaviour. The direction toward greater change in infant affect (higher positive affect over time) linked to lower externalising behaviour may indicate that infants find the interaction more rewarding,

which can create opportunities for social learning, enabling them to develop their adaptive behaviour skills later in life. On the other hand, negative affect within PII possibly reflects a temperamental characteristic suggestive of emotional dysregulation which may be a significant indicator of higher externalising behaviour later in life. The surprising result of high positive affect as a predictor of ASD outcome may also be indicative of surgency, a temperamental characteristic. It may also signify a delay in EL-ASD infants' social play in that they are inclined towards more dyadic than triadic play styles (triadic interactions involve more sophisticated social skills related to joint attention), which may elicit episodes of positive arousal. Although more research is needed to better understand how affect within PII relates to later developmental outcome, the results from the current empirical work suggest that positive and negative affect are of high relevance.

The results underscore the predictive value of these PII domains early in development. In contrast to other more standardised behavioural measures that do not robustly show differences within the first year in infants who later develop ASD (e.g., Ozonoff et al., 2010), these PII aspects may be able to capture early emerging behavioural atypicalities more accurately. Any behavioural differences at such an early age may not be observable through standardised assessments, such as parent reports or structured observation measures. In addition to ASD diagnosis, these PII domains within the first year were shown to contribute to the development of language, social communication and adaptive behaviour, indicating that the way that PII unfolds early on could influence the development of socio-emotional and language skills. These findings are important as they can inform the development of parent-targeted interventions (discussed in following sections) not only for infants at EL for ASD but also for those with a risk for later social, emotional and behavioural difficulties.

7.3.2 The Protective Value of Brain and PII Features

Autism spectrum disorder is a complex condition characterised by high variability in its aetiology and phenotypic expression. This makes the identification of a linear trajectory between ASD liabilities, protective factors and phenotypic outcome difficult to disentangle. Risk and protective factors can be seen as interacting attributes that are measurable and increase the probability of a particular outcome (Elsabbagh, 2020). The investigation of groups of infants with a similar aetiology can provide more insights into these factors compared to large populations of unknown aetiology, as it can inform on the mechanisms underpinning variability in outcome. This is because it can allow researchers to track infant developmental trajectories and examine how two individuals who share the same susceptibility for ASD or have a similar initial phenotypic expression follow an alternative developmental course, with the one receiving an ASD diagnosis and the other developing neurotypically or having other sub-clinical traits (Elsabbagh, 2020; Szatmari, 2018). Thus, it can help to obtain a better understanding of the factors associated with ASD in particular and those driving “resilience”, leading to a differential developmental outcome. In this thesis, a similar approach was followed by looking at early patterns of PII and brain function aspects that have previously differentiated EL from TL infants and whether those linked to developmental outcomes.

Starting from the study using Linked ICA to integrate multiple PII and neural measures of social attention (**Chapter 6**), the linked pattern of brain and PII measures was less expressed in EL infants who were later diagnosed with ASD compared to TL and EL groups of infants who received a subsequent diagnosis of neurotypical development or sub-clinical traits. In turn, the identified brain-PII pattern was mostly

expressed in TL individuals, and this group did not differ from EL-TD and EL-Atyp infants. Thus, this identified pattern that was absent in the EL-ASD group in relation to the other groups likely reflects a protective mechanism, representing the part of a process of brain adaptive changes across development that work as compensatory and protective factors from genetic and environmental susceptibilities of developing ASD, during which the quality of caregiver-infant interaction experience could have an influencing role. Greater attention capture by faces as well as dynamic gaze shifts and faster brain processing of both social and non-social stimuli were linked to higher ratings in qualities of infant interactions with parents. Specifically, the potential protective effect involved the EEG measure consisting of: faster P1, N290 and P400 responses to eye gaze shifts; faster N290, P400, increased P1 responses to faces with direct eye gaze and Nc responses to faces with direct and averted gaze; faster and smaller P1, N290 as well as decreased P400 responses to non-faces. In addition, the PII measure consisted of higher parent sensitive responsiveness, parent nondirectiveness, higher infant liveliness and dyadic mutuality. Thus, an enhanced quality of early PII experiences in a period of heightened brain plasticity could potentially shape brain function, consequently optimising infant developmental trajectories. Of note, the integrated component associated with clinical outcome did not differ by sex, indicating that, at least in this research work, the identified brain and PII relationships do not support the hypotheses for female-specific protective effects in relation to clinical outcome.

More specifically, the studies of this thesis provided evidence highlighting that an enhanced PII quality may aid in enriching later development or may relate to a developmental trajectory other than ASD outcome. In the PII replication study (**Chapter 3**), parent directive behaviour was lower in EL-no ASD infants compared to EL infants

with later ASD between 8-14 months, and infant attentiveness remained stable across time while it decreased for the latter group. Similarly, descriptive analysis showed that the EL-Atyp group generally had higher PII ratings than the EL-ASD group. However, EL-Atyp and EL-ASD infants had initially similar scores in some PII aspects, such as their level of attention to parent during free play interaction and mutuality which were then increased for the EL-Atyp group at 14 months. Furthermore, in the study investigating PII change in relation to 3-year dimensional outcomes (**Chapter 4**), group differences were also observed in the paths between developmental change in PII and externalising behaviour, language and social communication. Specifically, in the TL group, a trend towards greater improvement in parent-dyadic and attentiveness domains between 8-14 months linked to lower scores in externalising behaviour and better social communication skills was found. Similarly, a trend towards greater positive change in parent-dyadic domains predicting higher language skills and lower externalising behaviour was shown in the EL-no ASD group. No associations were shown in the EL-ASD group. However, the possibility that sample size differences may have played a role in the absence of effects cannot be discounted. Nevertheless, infants who later develop ASD show increasing difficulties in language and adaptive skills over time (Bussu et al., 2018; Lord, Luyster, et al., 2012; Visser et al., 2017), and positive changes in parent-dyadic interaction qualities may have acted as protective factors that mapped on to enhanced adaptive behaviour and language ability later on in life. The above results indicate that infants at EL who have more positive social interaction experiences and are more socially engaged may not follow a developmental route leading to ASD diagnosis and that these improvements can be reflected in different dimensions.

7.4 How Linking Brain and PII measures help us understand the developmental paths underlying ASD development – Theoretical Implications

Considering the IS theory proposition, compared to neurotypical development, brain development in neurodiverse populations, such as ASD may follow an alternative developmental route. This can affect the brain mechanisms that bias infants to orient to social stimuli, leading to a delay in brain specialisation for social information, which may be further amplified through interactions with the external environment, contributing to later social communication difficulties (Elsabbagh & Johnson, 2010). The studies of this thesis linking brain and PII measures within the first year of life offer important information regarding this hypothesis (or regarding the possible developmental processes underlying ASD). The results from the mediation study in **Chapter 5** demonstrated that EL infants' level of attentiveness to parent plays a significant role in the path between neural processing of social stimuli (faces) and parent sensitivity. In addition, greater neural responses to faces compared to non-faces/faces averted from the infant were linked to lower infant attentiveness to parent, but links between eye gaze processing and attentiveness were not shown. Different possible explanations have been given for this finding (details in chapter), such as inefficient/more effortful face processing, infant brain adaptation based on the complexity of the experimental context or a delayed brain specialisation within the social brain network affecting infants' behavioural attention. Using a data-driven approach taking into account individual variability in **Chapter 6** to link additional brain and PII measures at the same age was very beneficial, as it provided further insights into the nature of brain-PII relationships.

The particular ERP pattern identified in **Chapter 6** was composed of an early stage of face processing, involving greater and faster responses to static faces as well as

neural responses to a more complex task, such as dynamic gaze shifts. It has already been discussed that sensitivity to dynamic gaze shifts is thought to involve the recruitment of various social attention processes and is important for the development of joint attention skills (Johnson et al., 2005). In fact, the dynamic eye gaze shift stimulus in relation to PII appears to be a critical feature, as it was mostly prevalent in infants at TL (along with neural responses to static faces, **Chapter 6**) and not shown in infants at EL (**Chapter 5**). Of note, although TL infants did not show an association between eye gaze processing and infant attentiveness either in **Chapter 5**, a much larger sample (an important aspect in SEM) may have increased statistical power to detect any possible effects. Thus, the present results could be an indication of neurotypically developing infants' brain processing ability to rapidly shift attention to incoming complex information from their social environment, enabling them to respond to parental invitations promptly (Elsabbagh, Bruno, Wan, Charman, Johnson, Green, & The BASIS Team, 2015). Interestingly, faster infant neural responses to social and non-social cues were linked to higher attentiveness to parent in this group (although marginally, **Chapter 5**). In turn, this may be detected by their caregivers, even subtly, enhancing the fluency and timing of their responses, leading to higher nondirectiveness, sensitive responses and mutuality in play (**Chapters 5 and 6**). In addition, it is likely that infant brain processing capabilities related to higher infant liveliness (**Chapter 6**) also facilitate more opportunities for triadic exchanges and social communication.

The absence of this neural process in infants at EL and those subsequently diagnosed with ASD is consistent with the hypothesis of an altered or delayed brain specialization (Johnson et al., 2005), possibly affecting behavioural attentiveness to the parent in unstructured play. Indeed, this also agrees with the finding of decreasing

behavioural attentiveness to parent across 8-14 months and lower parent sensitive responsiveness and higher nondirectiveness in the EL-ASD group compared to the TL group (**Chapter 3**). However, it is also important to consider that the pattern of ERP and PII associations was overlapping and not clearly dissociated between the different clinical groups and might constitute a process of brain adaptation due to poor signal processing (although not necessarily resulting in neurotypical outcome), allowing the influx of more predictable and manageable information from the complex/dynamic aspects of the social world (Johnson, 2017). Whether this pattern of association is a developmental precursor of ASD remains to be confirmed by future longitudinal studies.

Furthermore, the findings from this research work provide support for the transactional model of development which focuses on the adaptive relationship between the individual's characteristics and the external environment, proposing that both affect the individual's development continuously and bidirectionally (A. Sameroff, 2009). The results across the empirical chapters of this thesis suggest that early infant brain function differences in response to social cues (**Chapters 5 and 6**) may affect infant behavioural attentiveness in social interactions, which may influence parental responses and have cascading effects on later development. Indeed, this was reflected in the findings showing links between EL infants' face processing and attentiveness at 8 months (**Chapter 5**), with attentiveness declining between 8-14 months, predicting 3-year ASD outcome at 14 months (**Chapter 3**). This finding may be indicative of emerging infant social attention difficulties affecting EL-autism infants' attentiveness to parent during PII. Parental sensitive responsiveness, nondirectiveness and dyadic mutuality were also affected, being lower in EL-ASD infants at 8 and 14 months, with parent directiveness and mutuality being associated with later ASD diagnosis. At the same time, the findings from **Chapter**

4 demonstrated that an ameliorated interactional environment can contribute towards a more optimised developmental trajectory, extending beyond diagnostic categories. Additionally, it showed that infant intrinsic characteristics shape and are shaped by the quality of PII from very early on in life.

7.5 Limitations

This section considers the broader limitations of the present work, in addition to the limitations discussed specifically for each of the empirical chapters. Firstly, although the studies of this thesis employed one of the largest samples to date to investigate trajectories of PII and brain function-PII relationships in the context of ASD susceptibility and diagnosis, it should be acknowledged that the sample size of the infant sibling groups was still relatively small and uneven, which posed limitations to the analytical approaches undertaken and may explain why some of the group effects only approached significance. For instance, in **Chapter 3**, the TL group was small compared to the EL group, though some of this group's PII ratings were comparable to those of prior studies' baseline ratings and those that included a larger TL sample (M. W. Wan et al., 2013; Whitehouse et al., 2019). In **Chapter 6**, the uneven sample size may have played a role in pattern selection in relation to clinical outcome, as individual weights of each group were considered for the resulting component. Furthermore, two studies (**Chapters 4 and 5**) used an SEM approach and somewhat complex models, generally requiring large sample sizes (Kline, 2015). In addition, some borderline significant effects were observed across the studies (e.g., see effects in PII variables predicting ASD outcome in **Chapter 3**, the bivariate models in **Chapter 4** and the speed of brain response effect in the TL group in **Chapter 5**). Again, this could be attributed to the sample size differences between the ASD

likelihood groups. Despite this limitation, the advanced analytical approaches conducted across the studies allowed the flexibility to examine different possible effects and helped provide important insights into brain-PII relationships and the role of PII in developmental outcomes.

Moreover, as the present work utilised already collected data, the electrophysiological data were only available at 8 months and had not been collected longitudinally, which prevented the longitudinal investigation of neural social attention development. In addition, due to time constraints, to maximise the number of PII data available that could be linked with the electrophysiological measures and considering that examining PII and PII-brain associations early in development was of interest, PII data coding was focused on the 8- and 14-month time points. These time points alone represent critical periods of development and allowed the interrogation of the research questions of interest. In addition, investigating PII qualities across 8 and 14 months in relation to different developmental outcomes offered significant and novel information on the evolving patterns of PII across different developmental groups. However, given the complexity and heterogeneity of ASD, investigating how features of PII and brain function unfolded across several time points in development would offer a wider developmental window for a more comprehensive picture of the developmental pathways underlying ASD. It would enable the investigation of the continuous dynamics of these relationships across time and, thus, inferences on the possible factors driving variability in developmental outcomes would be made with more confidence and accuracy.

Another important issue that arose with the inclusion of the BASIS cohort for this research work was self-selection bias. In developmental cohort studies, volunteer samples usually involve more families from higher socio-economic backgrounds, and this was

likely to be the case for the sample included here. Self-selection bias can limit the generalizability of findings as the samples included in studies may not be representative of the general population. Therefore, self-selection bias is an important issue in research with developmental populations which necessitates the generation of accessible protocols that could be implemented in the community and at home (e.g., Troller-Renfree et al., (2021) for mobile, in-home EEG).

In addition, there is evidence showing that EL and TL group differences in PII are partly explained by parent educational level within the first year of life (Pijl et al., 2021) and that EL and TL infants differ in family socio-economic status (Choi et al., 2019), which underscores the importance of having considered the possible effect of socio-economic status in the studies of this thesis.

Other factors may have played a role in the observed associations but were not studied here. For instance, parent psychological distress (stress, anxiety or depression) or the BAP may have been associated with the patterns of PII found between the different groups or may have partly explained the brain-PII relationships. First-degree relatives of individuals with ASD are more likely to show ASD-related traits (Pisula & Ziegart-Sadowska, 2015, for a review), and BAP characteristics in parents have been associated with ASD severity in children (Loncarevic et al., 2021; Sasson et al., 2013). Subclinical traits in the parent have also been associated with children's language and socio-emotional development (Loncarevic et al., 2021; L. J. Taylor et al., 2013). Furthermore, parental depression and anxiety have been linked to children's language development and adaptive behaviour (Bagner et al., 2010; L. A. Quevedo et al., 2012; Wachs et al., 2009). Even more striking is that parental depression has been related to infant brain function: 3 to 6-month-old infants of depressed mothers have shown a right frontal EEG asymmetry

relative to infants of non-depressed mothers (Field et al., 1995), while parental psychological distress has been found to affect their degree of sensitivity in PII (Shin et al., 2008; Xu et al., 2005). Thus, based on previous research, the possible impact of these factors on the associations interrogated in the present research work can be inferred, which underscores the importance of considering their inclusion in future research.

Last, as stressed throughout the studies of this thesis, it is important to emphasise that the reported associations cannot assume causality and the current studies are considered observational. Potential causal effects can be assumed by intervention studies or by research designs investigating brain and PII over several time points in development including larger samples.

7.6 Clinical Implications

The empirical work conducted in this thesis converges with existing research evidence showing face/gaze processing and specific PII aspects as important indicators likely associated with increased vulnerability for ASD (Elsabbagh et al., 2012; Tye et al., 2020; M. W. Wan et al., 2013). More specifically, the findings from this thesis suggest the concurrent emergence of neural differences with differences in infant behavioural social attention and parent behaviour within the context of PII, starting from 8 months (a critical developmental window) and having longer-term consequences. If the identified results reflect a delayed brain specialisation, this might prolong neural plasticity, extending sensitive periods within which early interventions could be most effective (Johnson, Jones, et al., 2015). In turn, positive changes in PII qualities within the first year seem to support the development of better social communication and language

outcomes, which suggests that a more enriched PII environment can help optimise infant development.

The results indicate that the dynamics of early social interactions may be involved in the developmental pathway between early intrinsic social brain processing alterations and developmental outcome, which has significant implications for early parent-targeted interventions. They suggest that future early screening and design of interventions should involve the support of interactive and communicative behaviours of parents, particularly during the second half of the first year, in a period of increasing brain plasticity when interactive differences are emerging.

Different intervention strategies exist to promote EL children's socio-emotional development, most of them being parent-mediated (McGlade et al., 2023), with parents usually being taught in different formats including video feedback, homework assignments, coaching, and interventionist modelling (Hampton & Rodriguez, 2022). Strategies have been mainly based on two frameworks, taking either a Naturalistic Developmental and Behavioural Intervention (NDBI) approach which is based on the principles of applied behaviour analysis and uses different behavioural strategies to teach developmentally appropriate skills, or a developmental approach that focuses on supporting parent-infant interactional synchrony and reciprocity. A few pre-emptive interventions have taken a developmental approach such as the iBASIS-VIPP aiming to promote parent-infant interactional synchrony through video-feedback, where parents are supported to adapt to their infant's communication styles, enhance their sensitive responding, emotional attunement and verbal/nonverbal interaction. The results from these interventions (delivered between 9 to 14 months of age) have shown positive subsequent effects on social communication and autistic development (Green et al., 2017;

Watson et al., 2017; Whitehouse et al., 2021). The current research work underscores the benefit of implementing such developmental approaches even earlier in infancy (Grzadzinski et al., 2021). This proposition also coincides with research showing no treatment effect in terms of PII or early ASD symptoms in interventions starting at around 12 months (Whitehouse et al., 2019) compared to those beginning earlier (Green, Charman, Pickles, Wan, Elsabbagh, Slonims, Taylor, McNally, et al., 2015; Green et al., 2017). Furthermore, the findings from this thesis provide evidence suggesting that such developmental approaches could perhaps be enriched by focusing not only on parent behaviour but also on the infant, such as by concentrating on infant attentiveness to the caregiver and shared interest, possibly in ways that are compatible with a non-directive approach rather than a behavioural approach.

Last, although replication with an independent sample is warranted, the results provide important insights into the potential of the identified neural process associated with neurotypical development for use as an outcome marker of intervention effects. Previous research delivering parent-mediated intervention between 9 and 11 months of age in EL infants prior to the emergence of ASD symptoms has shown an improvement in infant neural metrics of social attention, mirrored in ERP responses to social and non-social cues (Jones et al., 2017).

7.7 Future directions

7.7.1 Need for More Repeated Measures to Examine Trajectories of Brain-PII Relationships

The repeated measures of PII and cross-sectional brain function-PII associations in relation to developmental outcomes studied in this thesis can be seen as providing a glimpse into the wider developmental landscape under which these dynamic processes unfold. Therefore, more repeated measures over a greater period of time would provide a better and more accurate view, broadening the developmental picture. In terms of PII trajectories examined in **Chapters 3 and 4**, looking at the role of PII across 8 and 14 months and ASD outcome prediction and examining 8-14-month developmental change in relation to developmental outcomes at 3 years was informative because it provided significant information on the early developing patterns of PII and their role on later outcome. However, future studies should focus on collecting further repeated measures data that would allow for an investigation of nonlinear forms of growth of the PII dimensions and how these influence long-term outcomes. This could not be achieved with only two time points. In addition, tracking longitudinally the potential contribution of directive and low-sensitive parental behaviours to reductions in infant attentiveness to the caregiver would strengthen the case for the role of parental interactive behaviour, which could further inform pre-emptive interventions discussed earlier.

Furthermore, future studies should build on the current findings to examine the extent to which and how brain and PII relationships impact each other across development, starting from the first months of life, before the emergence of early ASD symptoms. In addition to preliminary cross-sectional research showing brain and PII associations within the first year of life in ASD (Elsabbagh, Bruno, Wan, Charman, Johnson, Green, & The BASIS Team, 2015), **Chapters 5 and 6** support this proposition:

brain function and PII associations were found at 8 months and were linked to 3-year clinical outcome classification. Thus, the current findings highlight and confirm that these associations can be seen early on, which can form the basis for further investigation of how brain and PII measures unfold over time. This is important, considering that previous research has shown long-term associations between early interactional behaviours and brain development (Ilyka et al., 2021). In addition, brain structure appears to develop at different rates, and so it is affected differently by the external environment (e.g., parenting) at different periods of time (Belsky & Haan, 2011). Specifically, a latent trajectory modelling approach could be utilised to explore how early face/gaze processing and PII qualities co-develop over several time points, which would provide novel information on the trajectories of change of these processes. Further, it would have the potential to contribute to existing theories of ASD and would potentially offer new insights into the mechanisms underlying ASD development.

Testing nonlinear latent growth models and perhaps extending these to include predictors of change (P. J. Curran & Hussong, 2003) in brain function and PII links would also be valuable in elucidating the developmental processes linked to ASD outcome. Such predictors could include parental characteristics (psychological distress, the BAP) or socio-economic status, as they are likely to explain part of these associations. In addition, considering the role of genetic (e.g., polygenic scores) liability in these associations would be an interesting future research avenue as it would be useful for more homogenous categorisation and for a more fine-grained understanding of the developmental pathways underlying ASD.

Last, looking more broadly at the intersection of other factors that may pose a challenge to these relationships in ASD liability, such as cultural/contextual factors

namely families living in poverty, or even other aspects that are likely to be detrimental to family psychological well-being, such as discrimination and stigma (Recio et al., 2020) would provide a more comprehensive and holistic view of ASD development, and will contribute towards the generalisability of findings to different contexts/populations.

7.7.2 Specific PII and Brain-PII Effects Warrant Further Exploration

Somewhat unexpected findings of high positive affect within PII predicting 3-year ASD outcome (**Chapter 3**) and of enhanced face processing related to lower infant attentiveness to parent (**Chapter 5**) are worthy of further investigation. Different speculations were made regarding the interpretation of these findings (see corresponding chapters for details). In terms of the first finding, high positivity could be a temperamental characteristic related to surgency or it might reflect developmental delays in infants' social play. With regard to the latter finding, from the patterns of results shown across the chapters, a speculative interpretation was made of a delayed brain specialisation influencing infants' degree of social attention during PII. In order to gain further insights into the proposed suggestions, replication of the current findings with a larger, independent sample would be necessary. Longitudinal exploration of patterns of positive affect and face/gaze processing-attentiveness associations could also help obtain a more in-depth understanding of the processes underlying the identified results.

7.7.3 Deconstructing Heterogeneity

One of the most prominent aspects of ASD is the heterogeneity in its developmental trajectory, aetiology, manifestation, phenotype and neurobiology (Lombardo et al., 2019). For instance, variability in phenotypic expression can involve

not only the timing of ASD onset and symptom severity but also cognitive and language ability as well as the existence of co-occurring conditions (Constantino & Charman, 2016; Harris & Handleman, 2000; R. J. Landa et al., 2007). Indeed, heterogeneity was also evident in the current research work. In **Chapter 4**, individual differences in 8-14-month PII change were found across all the LCS models, despite the average increase in the scores of the PII qualities across the whole sample. In addition, although the identified PII and brain pattern in **Chapter 6** distinguished EL-ASD infants from the other infant groups, the groups seemed to generally overlap.

Thus, the current research work highlights that future research should focus on the application of methods that consider individual variability. Specifically, the value of utilising both supervised (theory-driven) and unsupervised (data-driven) approaches has been emphasised as both approaches can be complementary (Lombardo et al., 2019). The former allows building on existing knowledge on distinctive aspects of interest and the latter can offer additional insights that may be missed by a theory-driven approach and can help explain heterogeneity. This thesis combined both approaches to better understand PII and brain function associations in ASD. Indeed, the top-down approach employed in **Chapter 5** provided valuable information on early brain-PII links in ASD susceptibility. By conducting Linked ICA, integrating various brain and PII features in **Chapter 6**, it was possible to extract patterns from brain and PII data not based on a priori knowledge of clinical categories, considering their presence at an individual level. This enabled a more enriched and in-depth understanding of these processes taking into account individual heterogeneity. Future research could utilise these approaches, perhaps by integrating these and additional modalities (e.g., measures of developmental level, eye-tracking) through a longitudinal design and larger samples to further demystify how

these processes act together over time, which can help increase our understanding of the mechanisms underlying ASD.

Moreover, conducting a case-control comparison approach was valuable for identifying how PII unfolds in different sibling groups and how PII differences relate to ASD outcome. Extending the investigation of PII trajectories in relation to dimensional outcomes in **Chapter 4** provided a clearer view of the role of PII in the development of quantitative traits that are shared (or not) with other conditions and those contributing specifically to ASD or the BAP. A potentially interesting approach would be to examine whether the PII patterns identified are observed in individuals who are at EL for comorbid conditions, such as ADHD. This will be important for a better understanding of the heterogeneous manifestation of ASD and the factors associated with specific trajectories of development, which would help inform developmental mechanisms and targeted interventions.

7.8 Conclusion

The thesis offers novel findings and extends previous research on the interactional processes and brain-PII associations in infants at EL for ASD. First, it strengthens existing evidence for emerging differences in parent, infant and dyadic aspects of PII between EL and TL infants. Second, it provides novel evidence showing a trajectory of decreasing attentiveness to parent between 8-14 months in EL-ASD infants, and parent directiveness and infant positive affect at 8 months as predictors of 3-year ASD diagnosis. Third, it adds to the limited existing literature by showing that parent and dyadic interactional aspects at 8 months as well as 8-14-month positive change in these aspects is linked to the development of lower externalising behaviour as well as higher language and social

communication skills. It demonstrates that infant interactional qualities (attentiveness and affect) specifically relate to later externalising behaviour and that infant language skills and the development of parent/dyadic qualities are reciprocally affected within the first year of life. Fourth, the present work contributes toward filling the gap that exists in literature by presenting evidence for an association between neural measures of social attention and qualitative aspects of PII at 8 months in EL and TL infants. Through a novel data-driven approach, it further shows that patterns of brain and PII relationships based on individual heterogeneity differ between EL-ASD and TL, EL-TD and EL-Atyp groups, which has not been shown before.

These findings agree with the transactional model of development supporting that the bidirectional effects of both parental input and infant characteristics shape infant developmental trajectories. They are consistent with a model of diverging neurodevelopmental pathways to visual attention, possibly reflecting delayed brain specialisation, affecting infant behavioural social attention and parent/dyadic qualities within the context of play. This work highlights the predictive validity of particular qualities of PII in infant developmental outcome in the context of ASD and proposes that the quality of PII and the identified process of linked ERP and PII measures could possibly serve as protective factors, altering the course of development and optimising infant developmental trajectories. The above evidence holds important clinical implications for designing very early interventions that focus on the quality of the interpersonal and communication environment of the child.

All in all, by looking into the early interactional processes and their links to infant neural social attention in ASD susceptibility and outcome, the current work hopes to have offered a stepping-stone into the possible developmental mechanisms associated with

ASD emergence and the role of early parent-infant interactional dynamics in infant developmental trajectories. Future research should focus on extending the findings of this work through a longitudinal design to refine our understanding of how infant brain processing of social information and the parent, infant and dyadic interactional qualities co-develop and mutually influence each other over time. In addition, future studies could consider incorporating the possible impact of other factors in this relationship, such as socio-economic status and parent characteristics, or broader cultural/contextual factors, such as poverty, discrimination and stigma. Last, studies could combine the use of theory and data-driven approaches or perhaps examine how the associations unfold in other co-morbid conditions to help decompose ASD heterogeneity. This can provide a more holistic and clear understanding of the emergence of this complex neurodevelopmental condition.

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