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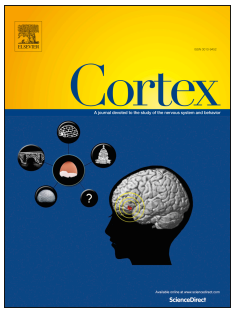

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Author contributions

Borja Blanco: Conceptualization, Formal analysis, Visualization, Writing – Original Draft, Writing – Review & Editing.

Sarah Lloyd-Fox: Conceptualization, Methodology, Investigation, Data Curation, Methodology, Writing – Review & Editing, Supervision.

Jannath Begum-Ali: Investigation, Data Curation, Project Administration.

Laura Pirazzoli: Investigation, Data Curation.

Amy Goodwin: Investigation.

Luke Mason: Software, Methodology.

Greg Pasco: Investigation, Data Curation.

Tony Charman: Conceptualization, Writing – Review & Editing, Supervision, Funding Acquisition.

Emily J.H. Jones: Conceptualization, Writing – Review & Editing, Supervision, Funding Acquisition.

Mark H. Johnson: Conceptualization, Methodology, Writing – Review & Editing, Supervision, Funding Acquisition.

Cortical Responses to Social Stimuli in Infants at Elevated Likelihood of ASD and/or ADHD: a Prospective Cross-Condition fNIRS Study

Borja Blanco[1], Sarah Lloyd-Fox[1], Jannath Begum-Ali[2], Laura Pirazzoli[3,4], Amy Goodwin[5], Luke Mason[2,5], Greg Pasco[5], Tony Charman[5], Emily J.H. Jones[2], Mark H. Johnson[1,2] & The BASIS/STAARS Team

[1]Department of Psychology, University of Cambridge, UK
[2]Centre for Brain & Cognitive Development, Birkbeck, University of London, UK
[3]Laboratories of Cognitive Neuroscience, Division of Developmental Medicine, Department of Medicine, Boston Children's Hospital, Boston, MA, USA
[4]Harvard Medical School, Boston, MA, USA
[5]Institute of Psychiatry, Psychology & Neuroscience, Kings College London, UK

Corresponding author: Borja Blanco, bb579@cam.ac.uk

Abstract

Autism spectrum disorders (ASD) and attention-deficit hyperactivity disorder (ADHD) are highly prevalent neurodevelopmental conditions that often co-occur and present both common and distinct neurodevelopmental profiles. Studying the developmental pathways leading to the emergence of ASD and/or ADHD symptomatology is crucial in understanding neurodiversity and discovering the mechanisms that underpin it. This study used functional near-infrared spectroscopy (fNIRS) to investigate differences in cortical specialization to social stimuli between 4- to 6-month-old infants at typical and elevated likelihood of ASD and/or ADHD. Results showed that infants at both elevated likelihood of ASD and ADHD had reduced selectivity to vocal sounds in left middle and superior temporal gyrus. Furthermore, infants at elevated likelihood of ASD showed attenuated responses to visual social stimuli in several cortical regions compared to infants at typical likelihood. Individual brain responses to visual social stimuli were associated with later autism traits, but not ADHD traits. These outcomes support our previous observations showing atypical social brain responses in infants at elevated likelihood of ASD and align with later atypical brain responses to social stimuli observed in children and adults with ASD. These findings highlight the importance of characterizing antecedent biomarkers of atypicalities in processing socially relevant information that might contribute to both phenotypic overlap and divergence across ASD and ADHD conditions and their association with the later emergence of behavioural symptoms.

Keywords: ASD, ADHD, fNIRS, social stimuli, infants

Introduction

Neurodevelopmental conditions have onsets in early development and affect children's brain development and function, impairing their ability to reach developmental milestones in cognitive, social, and emotional domains (Johnson et al., 2015; Jones et al., 2014; Mikami et al., 2019). The heterogenous aetiology and highly overlapping symptomatology across neurodevelopmental conditions makes it sometimes difficult to draw clear diagnostic boundaries between conditions (Astle et al., 2022). Co-occurrence of neurodevelopmental conditions is also common, indicating the importance of considering cross-condition research on neurodevelopmental conditions (Thapar et al., 2017). Research that focuses on studying potentially shared developmental pathways is needed to uncover the mechanisms that underpin neurodevelopmental diversity (Johnson et al., 2015; Parenti et al., 2020). Autism spectrum disorders (ASD) and attention-deficit hyperactivity disorder (ADHD) are two of the most prevalent neurodevelopmental conditions, and can commonly co-occur (e.g., Joshi et al., 2017; Salazar et al., 2015; Stevens et al., 2016). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) ASD is mainly characterized by impairments in social interaction and communication, and the presence of restricted and repetitive behaviours (American Psychiatric Association, 2013). ADHD is characterized by a persistent pattern of inattention and hyperactivity-impulsivity symptoms (American Psychiatric Association, 2013). Recent research has found considerable overlapping features between ASD and ADHD, particularly in attention-related problems, impulsivity, and impairments in social communication (Mayes et al., 2012; Rommelse et al., 2011; Sokolova et al., 2017; van der Meer et al., 2017), and changes within DSM-5 now allow for a simultaneous diagnosis of both conditions. Developmental pathways leading to the emergence of ASD and/or ADHD symptomatology early in development remain largely unexplored, but recent research has focused on trying to ascertain the mechanisms underlying their overlapping and distinct neurobiological profiles.

As ASD and ADHD are both highly heritable (Ghirardi et al., 2019; Tick et al., 2016), a suitable approach for studying early brain developmental pathways in these conditions is through prospective longitudinal studies of infants at elevated likelihood (EL) of developing ASD and/or ADHD by virtue of having a first degree relative with one or both conditions. Comparing prospective data from infants who might later meet diagnostic criteria for neurodevelopmental conditions provides the opportunity to identify antecedent biomarkers associated with the later emergence of behavioural symptoms in a dimensional way (Jones et al., 2014). Previous studies have examined transdiagnostic phenotypes in ASD and ADHD, including early motor function, sensory processing, and visual attention to faces. Studies on infants within the first two years of life have shown similar profiles of early motor atypicalities in both conditions (Begum Ali et al., 2020; Reetzke et al., 2022), while alterations in sustained attention to faces at 14 months was more strongly associated with later ADHD than ASD profiles (Gui et al., 2020). Reduced neural repetition suppression of tactile stimulation (vibrotactile

stimuli) was observed in infants at EL of ASD, but not ADHD (Piccardi et al., 2021). Using electroencephalography (EEG), a reduced theta-beta ratio (balance between lower and higher frequencies) during viewing of naturalistic dynamic videos (social and non-social) in ten-month-old infants at EL of ADHD was linked to temperamental traits at two years, but this reduction was not observed in infants at EL of ASD (Begum-Ali et al., 2022). Finally, Miller et al., (2020) showed a high co-occurrence between elevated ASD symptoms and elevated symptom ratings of attention and behaviour dysregulation in the preschool period, with children with high ASD symptomatology also showing high levels of parent-/examiner-rated ADHD symptoms, indicative of a high dimensional overlap between ASD and ADHD phenotypes. The presence of both divergent and overlapping profiles between conditions across different cognitive domains supports the importance of considering dimensional measures when studying neurodevelopmental conditions (Johnson et al., 2015). Identifying early behavioural and neural markers that could serve as general indicators of atypical neurodevelopment may encourage the use of transdiagnostic approaches and treatment efforts that recognize neurodevelopmental diversity (Astle et al., 2022; Manzini et al., 2021; Talbott & Miller, 2020).

In the present paper we aim to characterize antecedent biomarkers of atypicalities in processing socially relevant information that might contribute to both phenotypic overlap and divergence across ASD and ADHD conditions. Social understanding and communication are fundamental attainments during early development and precursors of a successful ability to engage in complex social interactions, with impairments in this ability significantly affecting several aspects of everyday life. Impairments in social interaction and communication are one of the core diagnostic symptoms of ASD, and significant impairments in social cognition have been observed in studies assessing children with ADHD or co-occurring ASD+ADHD (de Boo & Prins, 2007; Factor et al., 2017; Rao & Landa, 2014; Salley et al., 2015). In the mature brain, research examining the neural substrates of ASD has largely focused on a set of brain regions that collectively constitute the 'social brain' (Johnson et al., 2005; Müller & Fishman, 2018) and which process various social functions (e.g., face and eye gaze perception, emotion recognition or social communication). Brain regions that have been identified as part of the social brain network include the superior temporal sulcus (STS), middle and superior temporal gyrus (MTG and STG), temporoparietal junction (TPJ), inferior frontal gyrus (IFG), fusiform gyrus, amygdala and insula among others (Adolphs, 2009). Converging neuroimaging evidence in children and adults demonstrate atypical functional brain activity (mostly hypoactivation) in areas of the social brain network associated with ASD (Müller & Fishman, 2018). In the social cognition domain, altered brain responses in individuals with ASD have been observed during face processing tasks (Ammons et al., 2021; Leung et al., 2018; Safar et al., 2021), eye contact behaviour (Jiang et al., 2020; Senju & Johnson, 2009) and joint attention (Delbruck et al., 2019; Franchini et al., 2017; Mundy, 2018). Recent studies have further demonstrated a reduced functional connectivity in large-scale networks during social cognition tasks and between social brain regions in ASD (Shephard et al., 2019;

Yao et al., 2021), with this reduction being associated with the severity of social difficulties (Jung et al., 2019; Odriozola et al., 2019). Research investigating the neural consequences of ADHD in relation to social cognition is more limited, but some works have reported impaired neural responses during facial emotion processing (Ibáñez et al., 2011), hyperconnectivity during social cognition tasks (Shephard et al., 2019) and associations between altered functional connectivity and social and communication impairments (Chen et al., 2020).

Using EEG, studies assessing social brain function early in life have revealed that atypical neural responses to faces and dynamic eye gaze shifts in 6- to 10- month-old infants were predictive of ASD traits and diagnosis at 36 months (Elsabbagh et al., 2012; Gui et al., 2020; Shephard et al., 2020; Tye et al., 2020). Neuroimaging techniques looking at the brain's haemodynamic response can provide increased spatial resolution to study potential alterations in core social brain regions. Using functional near-infrared spectroscopy (fNIRS), previous research has shown a reduced activation to visual and auditory social stimuli in social brain regions (i.e., MTG, IFG, STS and TPJ) in 4- to 6-month-old infants at EL of ASD, compared to infants at typical likelihood (TL) for this condition (Blasi et al., 2015; Braukmann et al., 2018; Lloyd-Fox et al., 2013, 2017). Bhat et al., (2019) showed a decrease in intra- and interhemispheric functional connectivity during a naturalistic parent-infant social interaction task in 6- to 9-month-old infants at EL for ASD compared to typically developing infants. These results are in line with the hypoconnectivity observed in large-scale functional networks during a social cognition task in children at EL for ASD (Shephard et al., 2019). Overall, current results raise the possibility that atypicalities in processing socially relevant information in infants at EL of ASD can be observed early in life, and that these alterations may be related with an atypical developmental trajectory of the social brain network. However, fewer prospective studies have focused on evaluating potential behavioural and neural markers of atypicalities in emerging social abilities in infants at EL of ADHD.

Here, we present an expansion of our previous fNIRS studies (Lloyd-Fox et al., 2013, 2017) where we showed a reduced activation to social stimuli in 4- to 6-month-old infants at EL of ASD. Concretely, infants at EL of ASD showed decreased selectivity to visual and auditory social stimuli than TL infants in left STS and right STS regions respectively (Lloyd-Fox et al., 2013). In addition, those infants who went on to develop ASD at 3 years, showed reduced brain responses to social stimuli that were associated with parental reports of ASD symptomatology (Lloyd-Fox et al., 2017). Considering the importance of understanding the dimensional nature of neurodevelopmental conditions, in this prospective study we use the same fNIRS paradigm to examine the brain responses to visual and auditory social and non-social stimuli in infants at typical and EL of ASD and/or ADHD. Our heterogenous sample, including a broader range of neurodevelopmental conditions, enables us to investigate the presence of relevant transdiagnostic factors that may extend across conditions, which in turn might help improve the specificity of current models of atypical development. The current study includes a larger sample than our previous reports, an updated fNIRS data preprocessing pipeline, and analysis methods to target specific hypotheses.

In this extended sample we aim to assess early specialization to social stimuli by describing common and distinct markers of brain response patterns in TL and EL infants. Previous neuroimaging research in infants aged 4-7 months has shown that specific areas of the temporal lobe can be activated by social auditory stimuli (vocal sounds) as well as non-social sounds, but regions in the MTG/STG, particularly in the anterior portion, show increased activation when exposed to vocalizations and auditory communicative cues (Blasi et al., 2011; Grossmann et al., 2010; Minagawa-Kawai et al., 2011). Additionally, fNIRS studies with infants aged 6 months and younger have found enhanced activation in prefrontal, IFG, and STG regions when exposed to dynamic visual social stimuli, such as facial eye and mouth movements, and nursery rhymes as compared to non-social videos and static images (Correia et al., 2012; Farroni et al., 2013; Lloyd-Fox et al., 2009). In contrast, atypical perception of vocal sounds and a lack of vocally selective regions when compared to environmental sounds has been observed in infants (Blasi et al., 2015), children (Čeponienė et al., 2003; Klin, 1991) and adults (Gervais et al., 2004; Rutherford et al., 2002) with ASD. Atypical cortical responses in individuals with ASD has also been observed during the presentation of visual social human actions (Pelphrey & Carter, 2008). These findings suggest that the typical developmental specialization towards vocal sounds and visual social stimuli may be altered in ASD. For this reason, and following the same approach as in our previous research (Lloyd-Fox et al., 2013, 2017), here we focused on the contrast assessing vocal vs non-vocal selectivity and in the visual social condition presenting dynamic visual social stimuli.

First, we will describe responses to these conditions within each likelihood group (i.e., TL and EL), which will also allow us to report similarities with the outcomes observed in our previous works (Lloyd-Fox et al., 2013, 2017). Our second goal will be to probe the specificity of the observed responses across likelihood subgroups (i.e., TL, ASD, ADHD, ASD+ADHD). We predict that group-level comparisons on the brain responses to visual and auditory social stimuli will reveal differences between infants in the TL group and infants in the EL group. Specifically, we predict a higher selectivity for auditory vocal stimuli as compared to auditory non-vocal stimuli (i.e., vocal selectivity) in TL infants observed in MTG and STG, as opposed to a higher selectivity for auditory non-vocal stimuli as compared to auditory vocal stimuli (i.e., non-vocal selectivity) in the EL ASD group over the STS and TPJ regions. We also expect higher activation to visual social stimuli in TL infants compared to infants in the EL ASD group, observed in IFG and STS-TPJ brain areas. It is challenging to draw specific hypotheses about the brain response patterns to social stimuli in infants at EL of ADHD due to the limited number of previous studies on this group. We investigate whether infants at EL of ADHD might exhibit similar atypical brain responses as those observed in infants at EL of ASD, which could suggest a transdiagnostic factor, or rather if their responses will resemble those of TL infants, suggesting that the altered brain responses to the social cognition task observed in infants at EL of ASD might be condition specific. Infants at EL of ASD+ADHD might display an additive effect (Tye et al., 2013, 2014), showing a combination of the altered response profiles observed in EL ASD and EL ADHD groups. We assess to what extent these differences are driven by infants' EL subgroups (i.e., ASD,

ADHD, ASD+ADHD) and phenotypic outcomes of ASD and ADHD traits at 36 months. We predict that differences in early patterns of brain activation to social stimuli will associate with later social abilities, with reduced activation to social stimuli relating to ASD/ADHD traits. Combining these sources of information can help us define underlying phenotypic subtypes in our sample, potentially providing a complementary way to explain the diversity of profiles that exist within neurodevelopmental conditions.

Methods

Participants and ethical considerations

Ethical approval was granted by the UK National Health Service National Research Ethics Service London REC 13/LO/0751, 08/H0718/76 and 06/MRE02/73). All methods and experimental protocols were approved and carried out in accordance with the NHS and Birkbeck, University of London Ethics Committee guidelines and regulations. One or both parents/legal guardians gave informed consent for the participation in the study.

The data used to support the findings of this study are stored in the British Autism Study of Infant Siblings (BASIS) Network Data Repository. The conditions of our ethics approval do not allow public archiving of pseudonymised study data. The data cannot be fully anonymized due to the nature of combined sources of information, such as neuroimaging, sociodemographic and clinical outcome measures, making it possible to attribute data to specific individuals, and hence, falling under personal information, the release of which would not be compliant with GDPR guidelines unless additional participant consent forms are completed. Our data sharing procedures were created in consultation with stakeholders (Begum-Ali et al., 2023). To access the data, interested readers should contact the BASIS network coordinator at basis@bbk.ac.uk. Access will be granted to named individuals following ethical procedures governing the reuse of sensitive data. Specifically, requestors must pre-register their proposal, and clearly explain the purpose of the analysis so as to ensure that the purpose and nature of the research is consistent with that to which participating families originally consented. Additionally, requestors must complete and sign a data sharing agreement to ensure data is stored securely. Approved projects would need to adhere to the network's policies on Ethics, Data Sharing, Authorship and Publication. Please refer to the BASIS data sharing policies available at https://www.basisnetwork.org/collaboration-and-project-affiliation/index.html for further details on the data access process and requirements. Legal copyright restrictions prevent public archiving of MSEL, SRS-2 and CBCL-P which can be obtained from the copyright holders in the cited references. No part of the study procedures or analysis plans was preregistered prior to the research being conducted.

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. Participants were recruited for a longitudinal study running from 2008 to

2019. Inclusion criteria included full-term birth (gestational age>36 weeks), and no known medical or developmental condition. Participants belonged to two different recruitment phases of the BASIS project (i.e., Phase 2 and Phase 3). Sample sizes for Phase 3 were based on power analyses of corresponding measures in the Phase 2 cohort. A total of 172 four- to six-month-old infants participated in this study (Phase 2, n = 65, Phase 3, n = 107). Ninety-one participants were excluded based on the following exclusion criteria: not having enough trials for analysis (at least three trials per condition) based on offline coding of looking times (n = 30); technical issues (i.e., equipment failure or experimenter error, n = 10); infant not compliant with the task or fussy (n = 17); incorrect cap positioning (n = 5); artifacts in the signal during data acquisition (n = 13); not enough trials (at least three trials per condition) after data preprocessing (n = 15); not enough channels (more than 10 of the 26 fNIRS channels rejected) after data preprocessing (n = 1).

Data from 81 infants were available for data analysis (**Table 1**). The final sample presents partially overlapping datasets, as 30 of these participants, those belonging to recruitment Phase 2 of the BASIS project, were included in previous publications by our group (Lloyd-Fox et al., 2013, 2017). Infants were assigned a binary rating based on the confirmed presence or absence of a first-degree relative with ASD (i.e., 1, 0), ADHD (i.e., 0, 1), or both (i.e., 1, 1), and therefore being at an EL of either one or both conditions. Participants with no first-degree relatives with either diagnosis were assigned a TL for ASD and/or ADHD (i.e., 0, 0). As ASD and ADHD diagnoses often co-occur, this approach allowed us to test condition specific effects, and their interaction. In each phase, and at the time point of fNIRS data collection, the four likelihood subgroups showed similar chronological age and developmental ability (according to the Mullen Scales of Early Learning, MSEL, Mullen, 1995) all within the average range (**supplementary materials**). From the 172 infants that participated in the study, 50 were part of the TL group. From these, 23 infants were included in the final sample (46 %). From the 122 participants assigned to the EL group, 58 were included in the final sample (47.5 %).

During the 36-month visit, a battery of clinical research measures was administered. ASD traits were assessed using total scores from the Social Responsiveness Scale (SRS-2, Constantino & Gruber, 2012). Emerging ADHD traits were measured using raw scores from the ADHD sub-scale of the Child Behaviour Checklist-Preschool (CBCL-P, Achenbach & Ruffle, 2000). Experienced researchers of the BASIS/STAARS team reviewed all information and agreed consensus ASD diagnostic outcome according to DSM-5 (American Psychiatric Association, 2013) for 7 participants (Phase 2 = 4, Phase 3 = 3).

Experimental procedure

fNIRS data acquisition

Infants were tested with the UCL-NIRS topography system (Everdell et al., 2005), which uses two continuous wavelengths of source light at 770 and 850 nm with a sampling frequency of 10 Hz. The custom-built fNIRS headgear (Lloyd-Fox et al., 2010) consists of two source-detector arrays placed

bilaterally (5 sources and 5 detectors each, source-detector separation = 2 cm), containing a total of 26 channels for each haemoglobin oxygenation state (i.e., oxyhaemoglobin HbO and deoxyhaemoglobin HbR) covering frontal and temporal areas. The fNIRS headgear was aligned with standard 10–20 positions using anatomical scalp landmarks. We used this information to approximate the underlying cortical anatomy using an MRI-fNIRS co-registration method (Lloyd-Fox et al., 2014). This approach

	TL	EL-ASD	EL-ADHD	EL-ASD+ADHD	Total
N	23	37	12	9	81
Gender	15m, 8f	19m, 18f	4m, 8f	6m, 3f	44m, 37f
Age in days (SD)	163 (24)	167 (25)	166 (16)	166 (24)	166 (23)

Table 1. Participant characteristics. Female (f), male (m).

ensures that the fNIRS cap is positioned over specific regions of the social brain network, allowing comparisons to be drawn with previous findings from infant and adult populations.

Infants were tested in a dimly lit and sound-attenuated room while sitting on their parent's lap. Parents were instructed to refrain from interacting with the infant during the stimuli presentation unless the infant became fussy or sought their attention. Visual stimuli were displayed on a 117-cm plasma screen at approximately 100 cm from the participants. Auditory stimuli were presented by two external speakers located behind the screen.

Stimuli

The experimental paradigm **(Figure 1)** was the same as the one used in (Lloyd-Fox et al., 2017) and in previous research by our group (Lloyd-Fox et al., 2013). Briefly, infants were presented with three experimental conditions. The visual social condition consisted of full-colour, life-size (head and

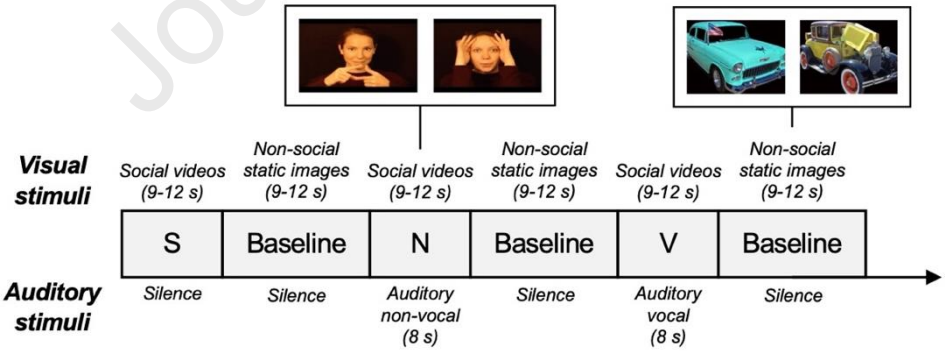

Figure 1. Illustration of the experimental paradigm showing the presentation order and duration of the visual and auditory stimuli for the three experimental conditions (V = vocal, N = non-vocal and S = visual social) and the baseline condition. Experimental conditions were presented in the same order across infants (S, N, V, S, V, N, S, V, N, S, N, V).

shoulders only) videos of 8 seconds duration. Videos were displayed for 9–12 seconds by adding a random (1-4 seconds) delay at the end of each trial. Each trial consisted of two video clips of a female adult who performed one of three different sequences (i.e., moved their eyes left or right, or performed hand games, 'Peek-a-boo' and 'Incy Wincy Spider'). In each trial, the videos were drawn from a

selection of six different videos to avoid inducing anticipatory brain activity and to control for effects of attention.

During the two auditory conditions, visual social auditory vocal condition and the visual social auditory non-vocal condition, social videos were presented following the same approach as in the visual social condition. In these trials, auditory stimuli were presented concurrently with the social videos. Auditory stimuli had a duration of 8 seconds, including four different sounds (of vocal or non-vocal stimuli) presented for 0.37–2.92 seconds and interleaved by periods of silence (of 0.16–0.24 seconds). The vocal condition consisted of four communicative and non-communicative non-speech adult vocalizations (i.e., coughing, yawning, laughing, and crying). The non-vocal condition included four naturalistic environmental sounds likely to be familiar to infants of this age (i.e., running water, rattles, squeaky toys, bells). The two auditory conditions were equivalent in terms of average sound intensity and duration ($P > 0.65$). Vocal and non-vocal stimuli were chosen from the Montreal Affective Voices audio collection (for more detail, see Belin et al., 2008).

Between each trial, acting as baseline condition, infants were presented with visual static non-social images. The baseline stimuli set consisted of twelve different full-colour still images of different types of transport (e.g., cars and helicopters). During each baseline trial, images were randomly selected (4-8 images) and presented for a pseudorandom duration (1–3 seconds) for a total duration of 10-12 seconds. The loop of trials was repeated until the infant became bored or fussy (see example of a stimulus presentation sequence in **Figure 1** caption). Copies of the research materials including social videos, auditory stimuli and baseline images necessary to conduct an independent replication of this study are available on https://github.com/borjablanco/BASIS. Task code can be obtained from copyright holders by contacting the BASIS network coordinator at basis@bbk.ac.uk.

Data processing and analysis

fNIRS data processing and analysis were performed using in-house scripts developed in MATLAB (R2020b, MathWorks, MA, USA) and third-party toolboxes (i.e., Homer2, Huppert et al., 2009) and algorithms (Pollonini et al., 2016). Analysis code used in this study can be accessed in https://github.com/borjablanco/BASIS. Before data processing, infants' looking times for each experimental trial (vocal, non-vocal and visual social conditions) were extracted from video recordings of the session. Trials were excluded if valid looking time was below 60% of total trial duration.

The different steps of the data processing pipeline, and the specific parameters used in each of them are illustrated in **Figure 2**. First, changes in optical density (OD) were calculated from raw intensity data. Channels were rejected based on the scalp coupling index (SCI) and peak power of the OD signals at both wavelengths in the cardiac pulse frequency range [1.5, 3.5] Hz (Pollonini et al., 2016). Participants with more than ten channels (~40%) rejected per wavelength (equivalent channels were rejected in both wavelengths) were excluded from further analysis. Motion correction was performed following guidelines for infant fNIRS research (Di Lorenzo et al., 2019; Frijia et al., 2021).

Motion artifacts were identified on a channel-by-channel basis based on changes in signal amplitude and/or standard deviation (Huppert et al., 2009). The output of this step served as input for a motion correction procedure based on spline interpolation (Scholkmann et al., 2010), which was followed by a second motion correction step consisting of a wavelet-based despiking method (Molavi & Dumont, 2012). The presence of residual motion artifacts after motion correction was evaluated by an additional motion detection step. The information from this step was used to discard trials that still contained segments of data affected by motion artifacts. Participants contributing fewer than three trials per condition (vocal, non-vocal or visual social) were excluded for further analysis at this point (Lloyd-Fox et al., 2013, 2017). OD data were converted into HbO and HbR concentration changes by means of the modified Beer-Lambert Law (Delpy et al., 1988), using wavelength and age dependent differential pathlength factors (Scholkmann & Wolf, 2013). Finally, data was low pass filtered to frequencies below 0.6 Hz to reduce the contribution of high-frequency physiological noise sources (e.g., cardiac pulse). After data preprocessing, valid trials were baseline corrected and block-averaged within channels for each condition. Average HbO and HbR concentration change channel time courses for each infant were used in subsequent group-level analyses.

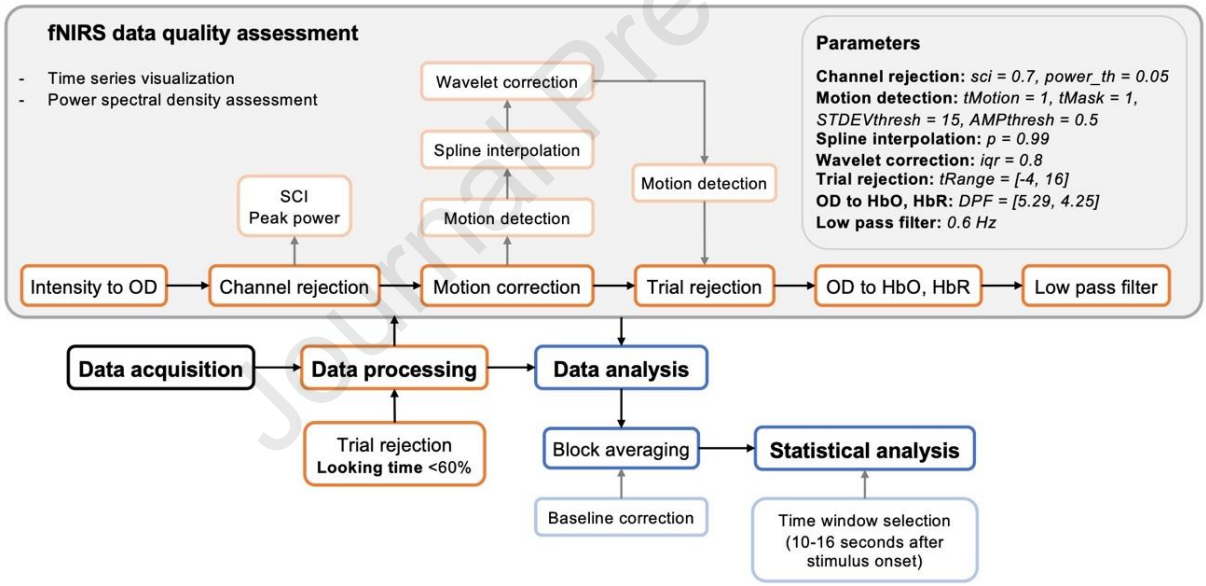

Figure 2. fNIRS data processing pipeline. Optical density (OD); scalp coupling index (SCI); differential pathlength factor (DPF).

Within-group analyses (TL and EL)

All the analyses were computed for HbO and HbR and results for both chromophores are presented in the main text or in **supplementary materials** when appropriate. First, to look at common markers of infants' brain responses to social stimuli and for comparison with our previous works, group-level analyses were computed for TL and EL groups separately. In this set of analyses, the EL group included all participants across EL subgroups (i.e., ASD, ADHD, ASD+ADHD). Group-level haemodynamic responses for each condition (i.e., vocal, non-vocal and visual social) were computed

by averaging the individual haemodynamic responses across all infants in the group. A time window was selected between 10-16 seconds post-stimulus onset to extract regions showing cortical activation for each experimental condition of interest on average haemodynamic responses from individual infants (i.e., vocal – non-vocal contrast and visual social condition). The average concentration change within this time window was used for conducting analyses within each group and for subsequent statistical comparisons between experimental groups. Details about the procedure employed for determining the time window of interest are provided in **supplementary materials**.

We used a cluster-based permutation approach (Abboub et al., 2016; Lloyd-Fox et al., 2019) to identify three-channel cluster candidates showing activation changes for each experimental condition on each experimental group. Three-channel clusters were formed by adjacent channels. Statistical tests (one-sample *t* tests) on the mean change within the selected time window were conducted for each channel and summed to get a cluster *t*-value. The statistical significance of the observed *t*-value was tested by means of non-parametric permutation testing by randomly interchanging channel positions and computing the cluster *t*-value across several permutations on the permuted set (N = 1000 permutations). The obtained values were used to generate a distribution from which the significance of the *t*-value of each original cluster candidate could be assessed. The significance of every three-channel cluster candidate in the fNIRS channel setup was evaluated. This approach can be used to derive regions of interest in a data-driven way and provides control for multiple comparisons. For results description, macro-anatomical regions underlying fNIRS channels were inferred from previous publications (Lloyd-Fox et al., 2014). Complementary results analysing functional activation across experimental conditions on a channel-by-channel basis are provided in **supplementary materials**.

Statistical comparisons between likelihood subgroups

A cluster-based permutation approach was used to identify regions showing differential responses across TL and EL groups. This analysis aimed to identify significant clusters that define regions of interest (ROIs) for later comparisons between likelihood subgroups where the specificity of the observed differences can be tested. In this initial analysis for ROI identification the EL group included all participants across EL subgroups (i.e., ASD, ADHD, ASD+ADHD). Overlapping clusters were considered part of the same ROI. The cluster-based permutation approach followed the same steps as above, but this time an independent two-sample *t*-test was used to compare TL and EL groups, and in each permutation the labels of each participant (i.e., TL or EL) were randomly exchanged to estimate the null distribution (N = 1000 permutations). Haemodynamic responses within each ROI were averaged across channels and on the time window of interest. This value was used in a two-way ANOVA to test the effect of likelihood subgroup and their interaction, considering for this analysis each likelihood subgroup separately (i.e., TL, ASD, ADHD and ASD+ADHD). Post-hoc *t*-tests corrected for multiple comparisons were conducted using Tukey's method. Statistical analysis

presented in this section were conducted using JASP statistical software (Version 0.17.1: JASP Team, 2023).

Results

In the final sample, the mean number of discarded channels per participant was 1.61 (SD = 1.63). The mean number of included trials for the vocal condition was 4.32 (SD = 0.94), 4.39 (SD = 0.9) for the non-vocal condition and 4.6 (SD = 1.03) for the visual social condition. Infants in the TL and EL subgroups (i.e., ASD, ADHD and ASD+ADHD) did not differ in terms of number of channels discarded or number of trials included per condition (**supplementary materials**).

Within-group results

A cluster-based permutation analysis was used to identify three-channel cluster candidates showing significant activation for the vocal – non-vocal contrast and for the visual social condition in each infant group. Infants in the TL group showed vocal selectivity (i.e., vocal > non-vocal) in a set of overlapping clusters covering left middle/superior temporal (MTG/STG) regions (HbO, **Figure 3**), and non-vocal selectivity (i.e., non > vocal) in a set of overlapping clusters located in left posterior inferior/middle temporal (pITG/pMTG) regions (HbR). Infants in the EL group (including all participants across EL subgroups) showed non-vocal specificity in one cluster located in the left MTG (HbO), one cluster located in left pITG/pMTG region (HbR) and in one cluster on the right IFG/STG region (HbO). For the visual social condition (**Figure 4**), infants in the TL group showed significant activation in a cluster in the left pITG/pMTG region (HbO) and in a set of overlapping clusters on the right hemisphere covering IFG and STG/MTG (HbR). Infants in the EL group showed functional activation in similar regions to the TL group (HbO) and significant deactivation (or inverted) responses in a set of overlapping clusters including the left IFG and left anterior aSTG/aMTG. Individual responses for the vocal – non-vocal contrast and for the visual social condition on each EL subgroup (i.e., ASD, ADHD and ASD+ADHD) for each significant cluster are provided in **supplementary materials.** Cluster statistics for each group and for each condition are also included in **supplementary materials**.

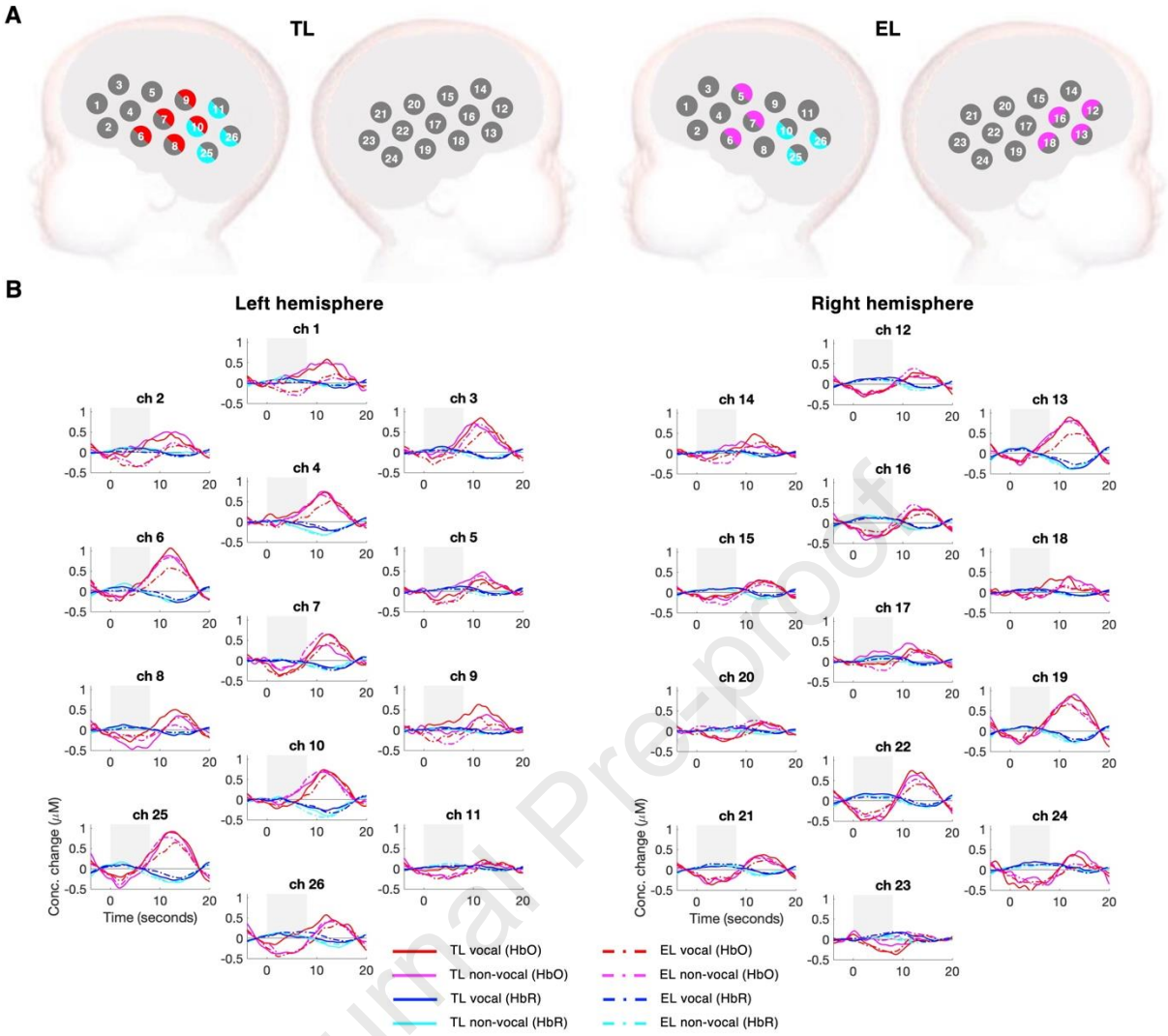

Figure 3. A) Clusters showing significant activation changes for the vocal – non-vocal contrast represented in a diagram of the infant head for each experimental group. In the diagrams colour describes the direction of the effect (i.e., vocal > non-vocal red and blue, non-vocal > vocal magenta and cyan for HbO and HbR respectively). B) Average haemodynamic responses on each experimental group for vocal and non-vocal.

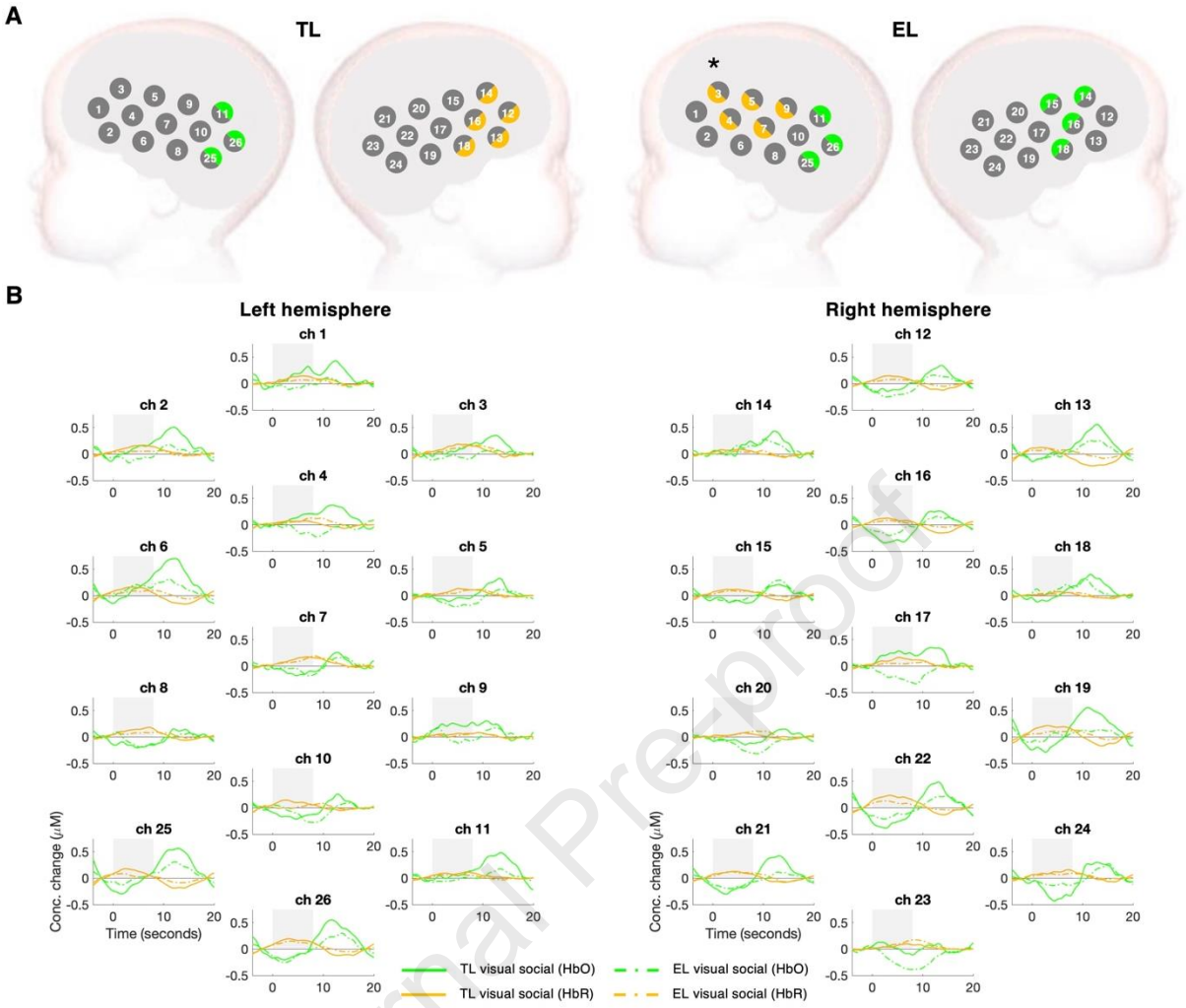

Figure 4. A) Clusters where significant activation changes were observed within each experimental group for the visual social condition (HbO and HbR shown in green and orange respectively) represented in a diagram of the infant head. * Denotes regions where inverted responses (i.e., positive HbR) were observed. B) Average haemodynamic responses on each experimental group for the visual social condition.

Comparisons between experimental groups: Vocal – Non-vocal contrast

A similar approach based on cluster permutation analysis was used to identify three-channel cluster candidates showing differences between TL and EL groups for the vocal – non-vocal contrast. In this initial step the EL group included all participants across EL subgroups (i.e., ASD, ADHD, ASD+ADHD). This analysis was conducted to identify ROIs where comparisons between likelihood subgroups (i.e., TL, ASD, ADHD or ASD+ADHD) could be performed. The main contrast of interest assessing vocal selectivity (i.e., vocal – non-vocal contrast) revealed a ROI formed by two overlapping clusters located in left MTG/STG where infants in the TL group showed stronger vocal selectivity than infants in the EL group (**Figure 5**). An ANOVA within this cluster assessing the effect of likelihood subgroup (i.e., TL, ASD, ADHD and ASD+ADHD) revealed a significant main effect of ASD ($F_{1,77}$ = 4.08, p = 0.047, η_p^2 = 0.050), a significant main effect of ADHD ($F_{1,77}$ = 9.39, p = 0.003, η_p^2 = 0.109),

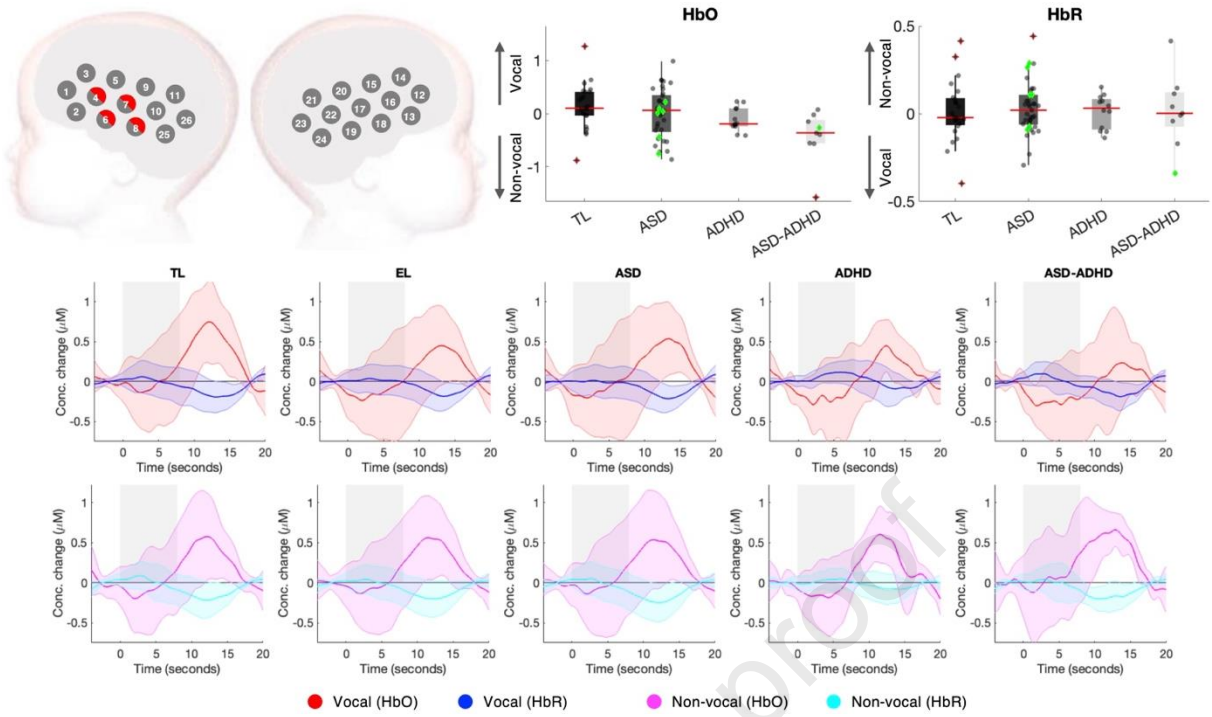

Figure 5. Haemodynamic responses and boxplots for each likelihood subgroup on the significant cluster observed in the vocal – non-vocal contrast. In boxplots the green diamonds represent infants who received ASD diagnosis at 36 months. Note that in boxplots vocal and non-vocal selectivity responses are reversed on the y-axis to account for the fact that, following the operational definition, activation responses in fNIRS are positive in HbO and negative in HbR. In the hemodynamic responses the solid line represents the group mean and the shaded area represents the standard deviation.

and a non-significant ASD*ADHD interaction ($F_{1,77}$ = 0.63, p = 0.429, η_p^2 = 0.008). No significant clusters were identified that exhibited differences in non-vocal selectivity between groups.

Comparisons between experimental groups: Visual social condition

The analysis for the visual social condition followed the same approach as for the vocal – non-vocal contrast. In this condition, four ROIs were identified showing significant differences between experimental groups and spanning multiple cortical regions (**Figure 6**). In the four ROIs, infants in the TL group showed stronger activation than infants in the EL group. In ROIs 1, 2 and 3 the effects were observed in HbO, whereas in ROI 4 the effects were observed in HbR. Group-averaged haemodynamic responses for each condition are presented in the main text for ROI 2 only, as both groups displayed significant responses in this ROI, denoting its relevance for task performance (**Figure 4**). Due to their high similarity with the outcomes observed in ROI 2, figures for ROIs 1, 3 and 4 are presented in **supplementary materials**. Statistical comparisons between likelihood subgroups (i.e., TL, ASD, ADHD and ASD+ADHD) where performed on each ROI. First, an ANOVA in ROI 1 (HbO) assessing the effect of likelihood did not reveal a significant main effect of ASD ($F_{1,77}$ = 0.91, p = 0.343) or ADHD ($F_{1,77}$ = 0.17, p = 0.723), nor a significant ASD*ADHD interaction effect ($F_{1,77}$ = 3.5, p = 0.065). ROI 2 (HbO) did not show a significant main effect of ASD ($F_{1,77}$ = 0.54, p = 0.465) or ADHD ($F_{1,77}$ = 0.08,

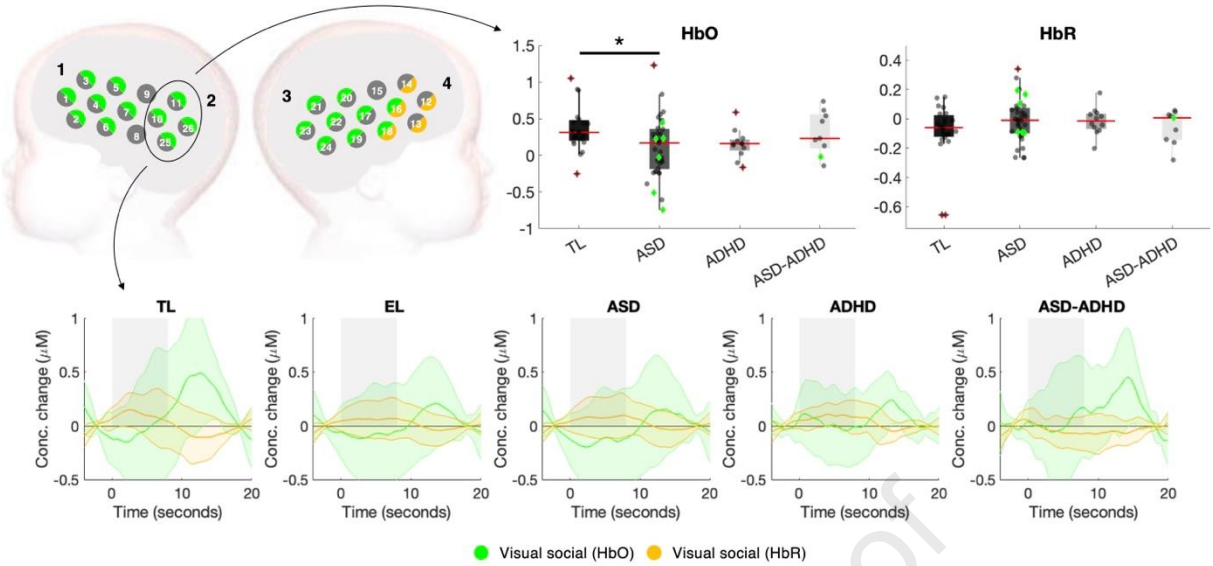

Figure 6. Haemodynamic responses and boxplots for each likelihood subgroup on a representative significant ROI observed in the visual social condition (ROI 2). In the hemodynamic responses the solid line represents the group mean and the shaded area represents the standard deviation. Green diamonds represent infants who received ASD diagnosis at 36 months.

p = 0.776). A significant ASD*ADHD interaction effect ($F_{1,77}$ = 5.67, p = 0.02 *uncorrected*) was observed in this ROI. Post-hoc tests adjusted for multiple comparisons using Tukey's method revealed that this effect was driven by infants in the TL group showing stronger responses than infants in the ASD likelihood group (t = 3.02, p = 0.018 *corrected*, 95% CI [0.038, 0.548]), but not the ADHD group (t = 1.93, p = 0.225). In ROI 3 (HbO) we did not observe any significant main effects of ASD ($F_{1,77}$ = 0.43, p = 0.515) or ADHD ($F_{1,77}$ = 0.41, p = 0.521). A significant ASD*ADHD interaction effect ($F_{1,77}$ = 8.139, p = 0.006 *uncorrected*) was observed in this ROI. Post-hoc tests adjusted for multiple comparisons using Tukey's method revealed that this effect was driven by infants in the TL group showing stronger responses than infants in the ASD likelihood group (t = 3.4, p = 0.006 *corrected*, 95% CI [0.052, 0.404]), but not the ADHD group (t = 2.53, p = 0.064). Lastly, in ROI 4 (HbR) there were no significant main effects of ASD ($F_{1,77}$ = 0.25, p = 0.618) or ADHD ($F_{1,77}$ = 0.03, p = 0.866). A significant ASD*ADHD interaction effect ($F_{1,77}$ = 4.04, p = 0.048 *uncorrected*) was observed in this ROI. Post-hoc tests did not reveal any significant difference between likelihood subgroups.

Association between functional responses and behavioural outcomes

Following up on our previous study (Lloyd-Fox et al., 2017), we also investigated the association between the observed functional brain responses on each ROI where significant between-group differences were observed (vocal – non-vocal contrast and visual social condition), and measures of phenotypic outcome at 36 months of age. Due to the characteristics of our sample including infants at EL of ASD and ADHD, we used the total score from SRS-2 and raw scores from the ADHD sub-scale of the CBCL. The values representing individual brain responses were obtained by averaging the haemodynamic responses across channels within each of the ROIs within the 10-16 seconds time

window. We assessed the association between the scores obtained in the behavioural scales and the individual brain responses observed in each significant ROI using Spearman's correlation coefficient. Note that due to the impact of the COVID-19 pandemic, some participants with fNIRS data from the first visit did not complete behavioural measures at a later visit (n=22), and therefore the sample size is reduced for this analysis.

Figure 7 shows examples of the observed associations between the SRS-2 score and the amplitude of brain responses for the visual social condition in ROIs 2 and 4. For the visual social condition, ROI 2 showed a significant negative correlation between the SRS-2 score and the amplitude of the HbO visual social response (HbO, r_{57} = -0.272, p = 0.037), while ROI 4 displayed a positive correlation between the SRS-2 score and the HbR response amplitude (HbR, r_{57} = 0.301, p = 0.02). The interpretation of these results is equivalent across ROIs, as the operational definition of brain activation in fNIRS involves an increase in HbO and a decrease in HbR (Obrig & Villringer, 2003). This indicates that reduced cortical responses to the visual social condition at 4- to 6- months of age, are associated with higher levels of ASD behavioural traits as measured by the SRS-2 at 36 months of age across participants. To account for a potential effect of infants with ASD outcome on these results, we ran a partial correlation analysis controlling for ASD diagnosis. With this analysis, none of the previously observed associations in ROI 2 (HbO, r_{56} = -0.188, p = 0.158) and ROI 4 (HbR, r_{56} = 0.247, p = 0.061) remained significant, suggesting that diagnosis outcome was having a significant influence on the observed effects. We observed non-significant associations between SRS-2 scores and individual brain responses for the vocal – non-vocal contrast (HbO, r_{57} = 0.049, p = 0.714), as well as in ROI 1 (HbO, r_{57} = -0.112, p = 0.4) and ROI 3 (HbO, r_{57} = -0.99, p = 0.455) for the visual social condition. None of the studied associations between individual brain responses and the scores on CBCL ADHD sub-scale displayed a significant effect. Complete results for all the ROIs are provided in **supplementary materials.**

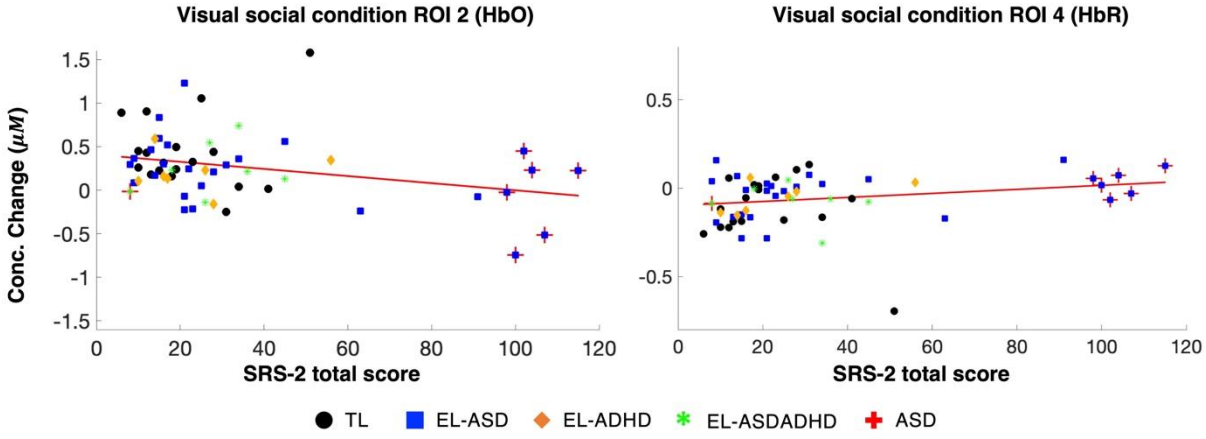

Figure 7. Individual responses condition in ROI 2 (left middle – posterior temporal regions – left panel) and in ROI 4 (right inferior frontal regions – right panel) for the visual social condition compared with individual SRS-2 total scores.

Discussion

In this study, we used fNIRS to assess early cortical specialization to social stimuli in a sample of 4- to 6-month-old infants at typical and elevated likelihood (TL and EL) of ASD and/or ADHD. We hypothesised that comparisons of the brain responses to visual and auditory social stimuli will reveal differences between infants at EL of ASD and/or ADHD and infants in the TL group. With regard to the auditory contrast, we expected higher vocal selectivity (vocal > non-vocal responses) in TL infants in the MTG and STG regions, as opposed to a higher non-vocal selectivity (non-vocal > vocal responses) elsewhere in the EL group. Observations from the current study confirmed this hypothesis and showed that infants in the TL group showed vocal selectivity in the left MTG/STG region, while no regions displayed vocal selectivity in the EL group. In the TL group, non-vocal selectivity was observed in one region in the left pITG/pMTG. Non-vocal selectivity was predominant in the EL group, with several regions in the left MTG and pITG/pMTG and right IFG/STG hemisphere showing stronger responses for non-vocal as compared to vocal condition. Participants across likelihood subgroups (i.e., TL, ASD, ADHD and ASD+ADHD) displayed similar response patterns in these non-vocal selectivity regions. Statistical comparisons between likelihood subgroups (i.e., TL, ASD, ADHD and ASD+ADHD) demonstrated that a region located in the left MTG/STG showed stronger responses to vocal relative to non-vocal sounds in TL infants as compared to infants in both the ASD and ADHD groups. Group differences between TL infants and EL infants without later phenotypic outcome have been reported previously (Jones et al., 2014). We conclude that reduced brain selectivity to vocal sounds in EL infants is not specific to EL of ASD and therefore could be a general marker of EL across ASD and ADHD.

We also predicted higher activation to visual social condition in the TL as compared to the EL group in IFG and STS-TPJ areas. This prediction was confirmed as the TL group showed stronger responses than infants in the EL group over a widespread set of cortical regions in the left and right hemispheres. Specifically, statistical comparisons between likelihood subgroups (i.e., TL, ASD, ADHD and ASD+ADHD) showed significant effects in ROI 2 (left ITG/STG) and ROI 3 (right pITG/pMTG) demonstrating reduced activation to visual social stimuli in infants at EL of ASD as compared to infants in the TL group. These findings are consistent with our previous reports (Lloyd-Fox et al., 2013) where TL infants exhibited increased activity in the left posterior STS during the visual social condition, whereas this response was not present in infants at EL of ASD. Additionally, the spatial distribution of the current results is consistent with our previous findings (Lloyd-Fox et al., 2017) in which differences were observed between TL infants and infants with a later ASD diagnosis. We conclude at this point that an attenuated response to visual social stimuli is observed in infants at EL of ASD.

Differences were not observed between EL-ASD and EL-ADHD subgroups either in vocal specificity or in their responses to visual social stimuli. One explanation for the lack of differences is that early in development these neurodevelopmental conditions might be less clearly discriminable,

with infants showing heterogeneous profiles across multiple areas with common markers across conditions (Gillberg, 2010). Indeed, mixed evidence for the specificity of particular deficits has been observed in other cognitive domains such as atypical sustained attention, or early language delays (Johnson et al., 2015; Miller et al., 2020; Rommelse et al., 2011). Thus, cross-condition approaches to neurodevelopment, such as the one presented in this study, have the potential to improve our understanding of the developmental trajectories and the heterogeneous profiles characterizing neurodevelopmental conditions.

Next, we assessed the extent to which these differences are associated with phenotypic outcomes at 36 months. Based on previous work we predicted that differences in early patterns of brain activation to social stimuli will associate with later social abilities, with reduced activation to social stimuli in infancy relating to later ASD traits. Our results show associations between individual brain responses to visual social stimuli and measures of behavioural outcome collected at 36 months. Specifically, we observed associations between the amplitude of brain responses for the visual social condition in ROIs 2 and 4 in EL infants and ASD trait scores (on the SRS-2), similarly to what was reported in our previous study with a subset of the participants presented in the current sample (Lloyd-Fox et al. 2017). However, we extended these previous results in finding no associations between individual infant brain responses and later ADHD trait scores (on the CBCL ADHD sub-scale). These results suggest that infant brain activation to visual social stimuli associates with later social abilities and autism traits in a selective manner. Nonetheless, caution should be exercised when interpreting these findings as they have not been corrected for multiple comparisons and, as described below, this analysis was conducted on a reduced sample.

A number of factors may have influenced our results in comparison to our previous studies. First, while our current results with an extended sample size shows high overlap with the results from our previous reports (Lloyd-Fox et al., 2013, 2017), a limitation was that the acquisition of behavioural measures at 36 months of age was affected by the COVID-19 pandemic with around 25% of infants included in the fNIRS analysis having missed this study visit. However, we plan to follow these children at later time points in mid childhood, which might provide further opportunities to gather additional information on behavioural outcomes. This will be crucial in complementing the results obtained thus far and enhance our understanding of developmental trajectories in neurodevelopmental conditions. The limited number of infants diagnosed with ASD in our sample restricts our ability to draw conclusions regarding the influence of this group. Future studies including a larger sample of infants with ASD and/or an ADHD diagnosis should provide a better understanding of typical and atypical cortical activation for socially relevant stimuli.

A second consideration when comparing this study to our previously published work (Lloyd-Fox et al., 2013, 2017) is the difference in the preprocessing and analysis pipelines. Our current processing pipeline included stricter criteria for channel rejection (Pollonini et al., 2016) and motion artifact detection, as well as a step for motion artifact correction (Di Lorenzo et al., 2019). The goal of

this modified pipeline was to reduce the potential impact of motion artifacts, while maximizing the number of channels and trials included per participant. Another difference between the current study and our previous works is the time window of interest employed for data analysis of the hemodynamic responses (i.e., 10-16 seconds vs. 8-12 and 12-16 seconds). fNIRS studies following a block-averaging approach have generally considered a time window comprising a few seconds around the expected or estimated peak response (Lloyd-Fox et al., 2019; Luke et al., 2021). However, peak latencies might differ across brain regions and between task conditions, and they also vary across HbO and HbR and potentially across participants (Pinti et al., 2020). Here, we used an improved data-driven approach to combine information across conditions, brain regions, and across HbO and HbR in order to empirically determine a more representative time window of the effects elicited by the task. For these reasons, results across the published studies are not directly comparable.

Our current sample included infants collected in two different recruitment phases of the BASIS project (i.e., Phase 2 and Phase 3). Most of our infants at EL of ADHD belong to recruitment Phase 3. Infants in this phase of the overall program were, on average, around one month older than infants in Phase 2 at point of testing which could have been a potential confounding factor. However, including age or Phase as a covariate in our analyses did not substantially alter the results (**supplementary materials**). Dissimilar ages across participants might also imply potential differences in head size/circumference across Phases, and therefore in the underlying cortical structures measured by the fNIRS layout. Here, we used a cluster-based permutation approach for ROI selection, as opposed to looking at effects on individual channels. This approach aimed to improve our sensitivity to detect underlying activation by including response information of spatially adjacent channels, and it also helped mitigate the multiple comparisons problem. For completeness, channel-level results showing similar within-group effects and between-group differences are provided in **supplementary materials**.

The current study used fNIRS to characterize infants' brain responses to social stimuli. This optical imaging technique provides information about changes in the concentration of HbO and HbR, and therefore focuses on one aspect of the haemodynamic response (i.e., oxygen supply) during neurovascular coupling. Future research could consider utilizing multi-wavelength (i.e., broadband) fNIRS systems, which also provide information about cellular oxygen metabolism by measuring the enzyme cytochrome-c-oxidase (Siddiqui et al., 2017). This technology might help detect more subtle changes in the neurovascular response, which may in turn enable the identification of additional and potentially more sensitive biomarkers that could serve as indicators of neurodevelopmental conditions such as ASD and ADHD.

To further advance our understanding of the neurobiological mechanisms underlying ASD and ADHD conditions, it would be relevant to complement brain activity measures and behavioural outcomes with genetic information from these (and other) neurodevelopmental conditions. For instance, individuals with Neurofibromatosis Type 1, a genetic condition that affects the nervous system, have also been reported to have an EL for developing ASD (Chisholm et al., 2022). Investigating genotype–

phenotype relationships in a more homogenous genetic context such as Neurofibromatosis Type 1, can help identify markers of atypical early-stage processing contributing to later neurodevelopmental outcomes (Garg et al., 2022; Johnson et al., 2021; Kolesnik et al., 2017). These markers could then inform the characterization of other neurodevelopmental conditions with more complex genetic or environmental influences.

We have demonstrated group differences in brain responses to auditory and visual social stimuli between TL and EL infants. The current study shows that auditory differences are not selective to EL ASD but can also be observed in EL ADHD infants. The findings regarding visual social differences provide stronger evidence for specificity, as this effect was observed only in infants at EL of ASD. This visual selective effect was also associated to some extent with later measures of social abilities, which might indicate specificity for the prediction of later ASD phenotypic profiles. However, further research with a larger cohort of participants will be necessary to fully ascertain the strength or otherwise of this effect. These results highlight the importance of examining different experimental conditions to ascertain whether effects are specific to a particular condition or have broader transdiagnostic relevance.

Author contributions

Borja Blanco: Conceptualization, Formal analysis, Visualization, Writing – Original Draft, Writing – Review & Editing.
Sarah Lloyd-Fox: Conceptualization, Methodology, Investigation, Data Curation, Methodology, Writing – Review & Editing, Supervision.
Jannath Begum-Ali: Investigation, Data Curation, Project Administration.
Laura Pirazzoli: Investigation, Data Curation.
Amy Goodwin: Investigation.
Luke Mason: Software, Methodology.
Greg Pasco: Investigation, Data Curation.
Tony Charman: Conceptualization, Writing – Review & Editing, Supervision, Funding Acquisition.
Emily J.H. Jones: Conceptualization, Writing – Review & Editing, Supervision, Funding Acquisition.
Mark H. Johnson: Conceptualization, Methodology, Writing – Review & Editing, Supervision, Funding Acquisition.

Data sharing declaration

Data and research materials supporting the results in the article are stored in the British Autism Study of Infant Siblings (BASIS) Network Data Repository and are subject to the BASIS data sharing policies https://www.basisnetwork.org/.

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Declaration of competing interest

TC has served as a paid consultant to F. Hoffmann-La Roche Ltd. and Servier and has received royalties from Sage Publications and Guilford Publications. All other authors have no conflict of interest to disclose.

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Disclaimer

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