The case for investment in early intervention for neurodevelopmental disorders

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Around 1% of UK children have Autism Spectrum Disorder (ASD), a condition that fundamentally affects their ability to understand other people[1]. Children with autism struggle to communicate with others, can have difficulty with change, and may be overwhelmed by new sights and sounds. Many adults with ASD experience a reduced quality of life[2]. Financial costs are also high: supporting an individual with ASD across their lifespan is estimated to cost £1.5 million for those with intellectual disability, and almost £1 million for those without an intellectual disability[3]. In this article we will argue that the time is right for a significant increase in investment in early intervention for children with ASD and other neurodevelopmental disorders. Using ASD as an example, we will illustrate how recent research identifies revolutionary new avenues for developing and targeting interventions in early development. We will also highlight how this is applicable beyond ASD by discussing the example of another common childhood-onset disorder, Attention Deficit Hyperactivity Disorder (ADHD). We suggest that new approaches may transform current debates on the ethics of early screening and early intervention. Finally, we consider how such approaches may narrow the gap between research and practice. Taken together, we believe that we are poised to make transformational changes in detection and treatment for early emerging neurodevelopmental disorders.

Early intervention and early identification

Early intervention offers the greatest potential for optimal outcomes for children with ASD. In a groundbreaking study, Pickles and colleagues studied language development in 192 children with autism followed longitudinally from age two to age 19[4]. Between age two and six years, there was substantial variability in language trajectories. Some children made substantial gains and ended with language in the typical range, whilst others remained significantly delayed. After age six, trajectories remained remarkably stable such that children with poor language skills at the age of 6 still had poor language skills 13 years later. This data indicates that the effects of a supportive environment may be maximal in the first years of life, providing a powerful illustration of early neurodevelopmental plasticity.

Randomized controlled trials have indeed shown significant benefits of early intervention for toddlers with ASD[5–7]. The success of such interventions is greater when started at a younger age[8]. Early intervention is economically beneficial: a recent Dutch study estimated the potential lifetime savings as 1.1 million euros per person[9]. However, current intervention models are intensive (often 20 to 40 hours per week), placing a significant burden on individuals and families. A further major challenge is that access to existing interventions typically requires early diagnosis (see Box 1). Jeremy Parr and colleagues recently investigated the experienced age of diagnosis for 2,134 families in the ASD-UK national database. Strikingly, this work showed that the average age of diagnosis in the UK has remained stable at 55 months for the last decade. Even within children diagnosed under age 3, the average age of diagnosis was 30 months. Since parents first show concerns at 10 to 16 months[10], this diagnostic gap is a substantial challenge to the provision of early intervention for children with emerging ASD.

We propose that there is a common solution to the twin challenges of developing better early identification and intervention approaches. Traditional approaches to mental health focus on identifying and targeting the surface symptoms that are used in diagnostic classification systems. Diagnosis is often required before treatment can commence, because the ‘disorder’ has to be identified in order to provide relevant treatments. We contend that we require a revolution in this approach

to mental health conditions. Instead of focusing on surface features of the condition, we should be targeting the neurodevelopmental mechanisms that produce troubling symptoms in early development[11]. This approach is comparable to the prescription of statins for those *at risk* of heart disease (NICE, 2014a), a drastic change in the management of this condition. Such a mechanistic approach would allow infants at heightened risk for particular symptom clusters to be identified prior to emergence of a recognizable clinical syndrome. Intervention could be provided based on the presence of the mechanism, and need not wait for clinical diagnosis. This would significantly reduce the troubling delays experienced by children in accessing intervention services. Early mechanistic interventions may in the long-term ameliorate or even prevent the emergence of troubling symptoms (e.g. lack of language), whilst leaving potential strengths (such as creativity or memory) untouched. Finally, mechanistic approaches are not limited to particular diagnostic categories and may more faithfully 'carve nature at its joints'. For example, in the latter part of the article, we discuss how attention difficulties may be relevant to both ASD and ADHD risk in early development[12]. These revolutionary changes will be made possible through a radical new approach to the study of neurodevelopmental disorders: prospective longitudinal studies of infants at heightened risk.

Developmental paths to autism: Baby sibs studies

In 2005, Dr. Lonnie Zwaigenbaum and colleagues published a seminal study of infants with older siblings with ASD[13]. Because ASD runs in families, about 20% of such infants are diagnosed with autism by their third birthday[14]. For the first time, researchers could study the emergence of ASD in real time. Dr Zwaigenbaum's team showed that babies diagnosed with ASD at 24 months showed subtle developmental problems by 12 months of age. These included unusual eye contact, poor imitation, poor visual tracking, lack of smiling and laughter, and being slow to shift attention between two toys. This groundbreaking study has inspired more than a decade of 'baby sib' research that in turn has revolutionalised our understanding of the earliest signs and symptoms of autism.

Baby sibs research has shown that by the second year of life, clear behavioural warning signs emerge in infants with later autism. These include failure to respond to name, poor eye contact and slowed language development. Any loss of skills such as walking or talking is of substantial concern. These 'red flags' are now widely publicized by charities and other organisations (Box 2). But what mechanisms underlie these early symptoms? In infants under 12 months, there are few clear behavioural signs of autism that could be used to identify individual children at risk. However, there are subtle differences between groups of infants with later autism and those who develop typically. For example, at 6 months infants with later autism often struggle to hold their head steady when pulled to sit[15], and other early motor delays have been observed when large groups are studied[16]. Brain growth may also be subtly different, with faster expansion of head circumference and brain size in the first year[17]. These changes suggest that broad changes in brain development precede the emergence of specific autism symptoms.

Contrary to expectations, researchers have identified very few changes in overt social behavior in young infants with later autism. For example, infants with later autism look at people just as much as typically developing infants in the first year of life[18]. However, developmental trajectories may be critical in detecting changes that are not apparent at a single time-point. For example, infant boys with later autism show declining patterns of gaze to eyes between 2 and 6 months that can be detected with eye-tracking technology[19]. There may also be differences in how the infant's brain is responding to the incoming social information. Using EEG (Box 3), Mayada Elsabbagh and colleagues showed that 6-month-old infants with later ASD show a reduced ability to detect changes in eye gaze direction [20]. Neural responses to faces are also slower and less prolonged in 6-month-old infants with

later ASD[21], suggesting reduced engagement of attention to social stimuli. As a group, infants at heightened risk for ASD also show markedly reduced social brain activity in response to social videos[22]. Taken together, these results suggest an alteration of social brain specialization in the early development of infants with ASD.

Implications for early intervention

The infant brain becomes socially specialized through a complex interaction between innate programming and experience of the early environment[23]. If early social brain development is altered in ASD, interventions that support the early social environment may be powerful. In 2015, Green and colleagues reported the results of the first randomized controlled trial of a parent-mediated intervention for infants with older siblings with ASD. The 12-week intervention helped to enrich the child's social environment by teaching parents to boost their responsivity to their infant's bids for attention. Results showed that at 14 months, infants who received the treatment tended to show increased attentiveness to their parent. Promising effects were found on other potential early markers for later ASD, such as better attention shifting between two objects on a screen. An independent study using a similar intervention approach identified significant improvements in neurocognitive markers of social attention (Jones et al. in review). The small size of both studies means that further work is needed, but these results are highly promising in suggesting that relatively low-cost interventions could be used to target the mechanisms that underpin symptom emergence in infants with ASD.

Moving beyond autism

Mechanistic approaches to early intervention may not be restricted to particular diagnostically-defined disorders. For example, a wide range of infants can show early social communication vulnerabilities and thus may benefit from early intervention that could support their development. In a large study of typically developing infants, parents with higher levels of social anxiety had infants who showed poorer social attention on a range of neurocognitive measures similar to those used with infants at risk for ASD[21]. Long-term follow-up will indicate whether these infants (who are currently developing typically) are more vulnerable to shyness or social anxiety in later development, and whether they may benefit from brief parent-mediated interventions designed to support their social engagement. Such low-cost interventions may have broad positive impacts for children across the spectrum of social difficulties.

Attention is another critical neurocognitive domain in infancy. Attention difficulties are common in children with ASD, but are also a diagnostic feature of Attention Deficit Hyperactivity Disorder (ADHD). Attention difficulties in the two conditions may share developmental roots. First, the two conditions have substantial overlap in genetic risk factors[24]. Second, ASD and ADHD commonly co-occur within individuals and their families[24,25]. Third, patterns of performance on many neurocognitive tasks are similar in the two conditions[26]. Fourth, poor attention skills in infancy (such as difficulty sustaining attention) are apparent prior to both ASD and ADHD diagnosis[27,28]. Early alterations in attention may thus be a common treatment target for infants at risk of ASD and ADHD. To test this hypothesis, we are currently conducting the first large longitudinal study of infants with older siblings with ASD and/or ADHD. Within this study (see Box 3) we will examine attention and other domains in very early development to identify distinct and similar causal paths.

We are currently testing new interventions previously demonstrated to improve attention in low-risk young infants. In 2011, Wass and colleagues reported that attentional control (the ability to move attention at will) can be improved in typically developing infants by playing a series of innovative gaze-contingent games over a short period[29]. In these games, infants watch objects on a screen and can control them by moving their gaze. This can now be achieved with relatively low-cost

eye-tracking systems that use infrared light to detect where an infant is looking on the screen. We are currently using these games with infants at high familial risk for ADHD to test whether helping infants to improve their attentional control skills provides significant benefits for learning and development (www.interstaars.org). In an exciting new collaboration, we are also working with Zwaigenbaum and colleagues at the University of Alberta to test whether this intervention is also beneficial for infants at risk for ASD. This approach will allow us to test the hypothesis that such potentially low-cost interventions could be applicable to a range of risk groups.

Ethics of early intervention

Although early detection and intervention can be effective, concerns remain about widespread implementation of screening and treatment programs (Box 1). Overdiagnosis is a concern, particularly for ADHD where reports indicate far higher rates of diagnosis and prescription amongst children who are young for their school year. Children who are relatively young for their school year may be judged to have difficulty[30] with attention and concentration skills because of their relative immaturity in comparison to their peers, not because they have a neurodevelopmental disorder. Developing more objective tools that do not rely on subjective comparisons made by teachers or parents may be one way to tackle this issue.

The autism and ADHD communities also stress the need to consider whether intervention is desirable. The 'neurodiversity' movement argues that neurodevelopmental 'disorders' like ASD and ADHD should instead be seen as being on the spectrum of individual differences; applying a disease model to these conditions is inappropriate. The neurodiversity movement is sometimes misrepresented as being against any form of treatment – rather, the goal is generally to move away from 'curing' and towards options that might enable individuals with ASD or ADHD to reach their full potential (e.g. http://www.psychologytoday.com/blog/my-life-aspergers/201310/what-is-neurodiversity). Not all individuals with ASD or ADHD will want to access treatment or intervention options, since not all individuals will feel that they have difficulties with which they need help. However, the needs of those individuals (particularly with ASD) who cannot communicate and thus cannot contribute to debates in this area must also be considered. Many individuals with ASD or ADHD have significant strengths, like artistic ability, creativity, detail-orientation or skill with computers. We must ensure that intervention techniques support improved quality of life but do not diminish these skills. If mechanisms that produce challenging symptoms can be disentangled from those that produce strengths, we may be able to develop more targeted treatment options.

This question is particularly problematic when applied to intervention in the early years, because infants and young children cannot themselves choose whether to receive it. Led by Sue-Fletcher Watson at the University of Edinburgh, we recently asked 2,317 stakeholders across Europe about their views on early autism research[31]. Respondents included parents of children with autism, clinicians working with families with autism, and autistic adults. Whilst respondents were generally very positive about early autism research, adults with autism were less likely to want to prioritise research on early diagnosis than other groups. However, adults with autism were significantly *more* likely to prioritise intervention designs. We need interventions targeted to the mechanisms that produce unwelcome symptoms, rather than efforts to diagnose and treat the full syndrome at younger ages. Moving forward, it is critical to engage adults with autism and their family members in the research design process to ensure that all views are represented when designing intervention studies. However, ensuring that the views of individuals with more significant communication problems are recognized remains a significant challenge.

Mind the Gap

Translation of new research findings to improvements for service users remains a significant issue across child psychiatry. Research on early autism and ADHD is in its infancy, and substantial progress is required before some of the newest findings can be translated into practice. For example, many 'biomarkers' for ASD actually represent group differences, and are not individually predictive. Although this is a challenge, predicting ASD as a diagnostic category with high accuracy is not the goal. Rather, identifying markers of symptoms of ASD that may be particularly problematic (such as social communication problems, or sensory sensitivities) is critical. Further, markers for screening are usually judged by their sensitivity (what percentage of children with the disorder are identified?) and their positive predictive value (of the children with the marker, what proportion are later diagnosed with the condition?). However, markers for mechanisms that may be sensitive to intervention may actually have a poor positive predictive value to later diagnosis, because the child's environment between assessment of the marker and eventual diagnosis would be expected to have a relatively greater effect. Such considerations are important and under-discussed in the field.

Reproducibility and generalizability are also critical challenges. There have been very few replication studies of neurocognitive markers of later ASD to date. Such efforts are underway – with a team of investigators we are currently running a multi-site study of infants with older siblings with ASD across Europe (www.eurosibs.eu). This study will attempt to replicate several key findings from the baby sib literature. Generalizability is also very important. For example, we recently showed that some early 'markers' for later ASD may only be related to later autism symptoms in boys and not girls[32]. In addition, findings from baby sibs research will need to be replicated in other populations. We are currently running such studies with infants with known genetic conditions linked to ASD and ADHD, such as tuberous sclerosis; other work should identify infants with early behavioral signs and examine whether neurocognitive markers could enhance individual prediction.

Despite the challenges, new mechanistic interventions hold significant translational potential. Parent-mediated interventions that appear efficacious in baby sibs[33] are based on existing programs that are low-cost, manualised and have been used in other populations in the community. Once sufficient evidence of their efficacy in the short and long-term accumulates, roll-out would be more straightforward. Other new interventions such as gaze-controlled eyetracking programs rely on equipment that is becoming significantly cheaper. In the medium-term, such training programmes could be operated remotely by parents, with less need for clinician input. Such advances improve the potential accessibility of interventions, and lower the bar in terms of the cost-benefit ratio of intervention provision.

Summary

Prospective longitudinal studies of infants at heightened risk of neurodevelopmental disorders provide the potential for developing new interventions that are targeted at the mechanisms that underlie symptom emergence. There is much work to do in improving the quality and replicability of early indicators, and testing new intervention approaches in rigorously controlled trials. However, this new mechanistic approach has significant potential to overcome some of the ethical and translational obstacles to the provision of early intervention to vulnerable children. As such, these advances could transform the outlook for infants at heightened risk for conditions like ASD and ADHD. The resources that need to be devoted to these efforts are not trivial, but the potential economic, societal and personal benefits vastly outweigh the possible costs.

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Box 1: Should we screen for autism?

In 2007, the American Academy of Pediatrics recommended continuous developmental surveillance and specific autism screening and 18 months, 24 months, and whenever a parent or provider expresses concern. These guidelines were based on the growing understanding of early red flags for the condition (see Box 1). Recent reports suggest that this recommendation has significantly reduced age of diagnosis in the US^. However, in February 2016 the US Preventative Services Task Force decided not to recommend universal screening in the US on the basis that there is insufficient evidence of benefit. The Task Force accepted that common screening tools (like the Modified Checklist for Autism in Toddlers questionnaire) were effective. Further, there is evidence that early intervention can produce significant gains for young children. However, this work on early intervention has been conducted with clinically-referred rather than screen-positive populations. The Task Force thus called for more research following children from screening to

diagnosis and treatment. This judgment echoes the findings of the UK National Screening Committee, who in 2012 concluded that there was no justification for universal screening for ASD. The UK panel also argued that there was a need for greater information about the long-term benefits of early intervention before the value of screening could be determined. Whilst the need for more research is widely accepted by the field, many prominent clinicians and researchers disagree with the Task Force's approach. Autism Speaks and other prominent charities have argued that the risk to benefit ratio 'strongly favours universal screening for autism'*. The debate on screening for autism requires full consideration of the scientific, ethical, economic and societal dimensions, and the urgent need for further research is clear.

* https://www.autismspeaks.org/blog/2016/02/17/keeping-%E2%80%9Cgrade-a%E2%80%9D-universal-early-screening-autism

^ https://www.sciencedaily.com/releases/2016/04/160430100542.htm

Box 2: Red Flags and other internet resources

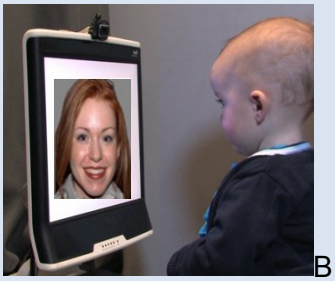
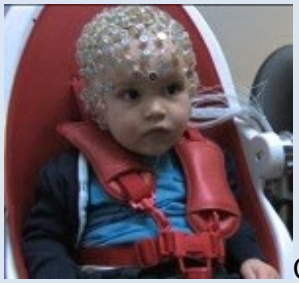
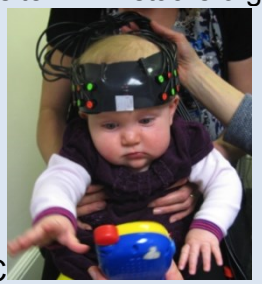
There are a variety of excellent resources for finding out more about early signs of ASD and ADHD, and support and treatment options in the UK.

- Autism Speaks (a US charity) offers a range of videos that illustrate atypical and typical development in domains related to ASD: http://www.autismspeaks.org/what-autism/video-glossary
- The US Center for Disease Control also offers a range of information about early red flags for ASD: http://www.cdc.gov/ncbddd/autism/signs.html
- Research Autism is a UK charity devoted to summarising research on autism for families. In particular, they provide excellent information on the evidence-base for a range of treatment options: http://www.researchautism.net/
- The National Autistic Society and Autistica are UK charities that provides a range of information and resources for families affected by ASD: http://www.autism.org.uk/; http://www.autistica.org.uk/
- NHS choices provides some information on signs of ADHD, although descriptions are mainly applicable to older children: http://www.nhs.uk/Conditions/Attention-deficit-hyperactivity-disorder/Pages/Symptoms.aspx
- ADDISS, UK ADHD and the ADHD Foundation are UK charities who provide a range of information about ADHD: http://www.addiss.co.uk/; http://www.adhdfoundation.org.uk/parent.php; http://www.ukadhd.com/index.htm.

Box 3: New studies of early ASD and ADHD

In the UK, the BASIS study (British Autism Study of Infant Siblings) is a UK-wide network dedicated to the study of infants with older siblings with ASD. The BASIS team, led by Professor Mark Johnson at Birkbeck College London and Professor Tony Charman at Kings College London have recently launched STAARS (Study of Attention and ADHD Risk in Siblings), which will follow both infants with older siblings with ASD and infants with older siblings with ADHD in the same protocol. Infants are studied at 5, 10, 14, 24 and 36 months. Methods used include eyetracking (A), electroencephalography (EEG; B) and Near InfraRed Spectroscopy

(NIRS; C), both noninvasive measures of brain activity (see pictures); eye-tracking, a way of studying what infants attend to; and measures of behavior, cognition and arousal. Following both groups of infants in the same protocol will allow us to compare and contrast the early developmental paths to the two disorders. We will be able to ask whether there may be similar or different early markers for ASD and ADHD, and whether there may be core paths that could be targeted by prodromal interventions. Further information can be found on our website: www.staars.org.

A  B  C 

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