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Infant development, Autism and ADHD: Early pathways to emerging disorders

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Extended Abstract: Autism spectrum disorders (ASDs) and attention deficit hyperactivity disorder (ADHD) are two common neurodevelopmental disorders, affecting around 1 to 2% of UK 7-year-olds with a high degree of co-occurrence (Russell, Rodgers, Ukoumunne, & Ford, 2014). For both of these disorders, diagnosis is often only possible during childhood. ASD can be diagnosed in some cases from as early as 2 years of age but diagnosis in many communities often occurs considerably later (Daniels & Mandell, 2013; Steiner, Goldsmith, Snow, & Chawarska, 2012) and ADHD is usually not diagnosed until school age (Hodgkins et al., 2013). Following long recognition that the two disorders commonly co-occur (Simonoff et al., 2008), the recent revision to the classification system now allows independent diagnosis of ASD and ADHD, according to the behavioural criteria of each disorder (DSM-5; APA, 2013). To move towards earlier diagnosis and more effective intervention for ASD and ADHD, we need to better understand the causal developmental pathways to these conditions. This requires longitudinal prospective studies of infants who later meet criteria for ASD or ADHD. Such studies of younger siblings of children with autism have recently revealed a range of infant markers for this disorder. Research on the early development of ADHD is currently less developed, but emerging evidence reveals a number of infant markers for later symptoms of inattention and hyperactivity. Here, we review current findings from longitudinal studies that have examined infant markers of later ASD and ADHD-related outcomes, across different domains of behaviour, perception, cognition, and brain structure and function. These emerging results allow us to address critical issues about the extent to which ASD and ADHD share developmental causal paths, and to what extent selected infancy measures associate with specific diagnostic outcomes.

Introduction

ASD and ADHD are two of the most common neurodevelopmental disorders, each with an estimated prevalence of approximately 1% to 2% of the population (Baird et al., 2006; Baron-Cohen et al., 2009; Erskine et al., 2013; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). The vast majority of all research on these disorders takes place after diagnosis. However, symptoms of both ADHD and ASD likely emerge from a complex interaction between emerging neurodevelopmental vulnerabilities, and aspects of the child's pre-natal and post-natal environment. Whilst some symptoms may therefore be primary reflections of genetic or environmental risk factors, others will be manifestations of compensatory processes or secondary 'cascading' effects following atypical interaction with the environment (Johnson, Jones & Gliga, in press; Dennis et al., 2013). From a basic science perspective, after the clear emergence of symptoms and diagnosis it becomes very hard to untangle these different factors. From a clinical point of view this means that we may be restricted to treating symptoms, rather than the primary pathological processes that cause the disorder. Bearing in mind these considerations, mapping how these common disorders unfold from birth is critical for understanding the chain of causal mechanisms leading to symptom emergence.

Over the past decade there has been increasing interest in prospective studies of infants at high risk for ASD. The majority of these studies have focused on infants who have an older sibling with a diagnosis and over 40 publications have now described early markers of later diagnosis of ASD in this population (for review, Jones, Gliga, Bedford, Charman, & Johnson, 2013). Research on infant markers of later ADHD is currently less developed. The high co-occurrence rates between these two disorders (approximately 20% of UK 7-year-old children with ASD meet criteria for ADHD, and vice versa; Russell et al., 2014[1]) has raised the intriguing possibility that ASD and ADHD may share developmental pathways and risk factors. A range of emerging evidence for common ASD and ADHD endophenotypes (Rommelse et al., 2011), genetic (Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008; Smoller, 2013) and environmental risk factors (Ronald, Pennell, & Whitehouse, 2011), and for moderate co-heritability (Rommelse, Franke, Geurts, Hartman, & Buitelaar, 2010

[1] These rates may be underestimates since many children would receive a diagnosis of ADHD beyond 7 years of age and also because clinicians often refrain from giving a dual diagnosis.

Ronald et al., 2008) has led some to suggest that the two conditions represent different manifestations of a common underlying disorder (van der Meer et al., 2012). Differential expression of the common endophenotypes/genes in different neural systems or at different time points in development could potentially lead to a combination of overlapping and distinct clinical symptoms.

Examining brain development prior to symptom emergence offers a new opportunity to investigate common or independent causal paths to ASD and ADHD symptomatology. Here, we review the literature on the emergence of ASD and ADHD in infancy, in order to identify shared or unique variance in causal paths to symptomatology. We focus our review on markers apparent in the infancy period (prior to age 2 years), in order to identify the earliest expressions of risk. Because infancy work in ASD is considerably more advanced, within each domain we begin by discussing work on ASD, and then move on to ADHD and comparative studies. We include information from a range of different developmental populations including infants at familial risk, population cohort studies, and premature infants. While we structure our review of early markers by clinical outcome (ASD, ADHD), in light of the importance of considering the dimensional nature of childhood psychopathology (Coghill & Sonuga-Barke, 2012; Plomin, Haworth, & Davis, 2009) we will extend the review to predictors of dimensional measures associated with ADHD or ASD traits. We note that studies in young children at risk for ASD have typically focused on predictors of categorical clinical outcomes, usually using expert 'clinical best estimate' diagnosis including information from the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) and Autism Diagnostic Observational Scale (ADOS; Lord et al., 2000). By contrast, studies of markers for ADHD have commonly used cut-points or clinical thresholds on dimensional measures of ADHD traits on population-normed screening scales such as the Child Behavior Checklist (CBCL; Achenbach, McConaughy, & Howell, 1987), the Conners Rating Scales (CRS; e.g. Arffa, in press) and the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997), sometimes also combined with more direct clinical assessment and judgment. We return to the potential implications of this pattern in our conclusions.

After summarizing the literature, we draw several methodological and conceptual conclusions. We review the merits and challenges of studying developmental mechanisms in infants who develop common developmental disorders,

and compare familial risk study designs to other study designs (e.g. large cohort studies; very pre-term infants). In our conclusions we will argue for the importance of considering different models of the relation between infant markers and ASD and ADHD outcome (Figure 1). We also note the theoretical importance of taking a more nuanced approach to the classification of particular markers; whilst some may represent precursors of later symptoms, others may reflect stable endophenotypes, and still others may relate to the activation of adaptive responses (see Box 1). Identifying the underlying processes that particular markers represent is critical to building models of the causal paths to behavioral symptoms in these conditions.

Review of the literature

Brain size and structure

Estimates of brain size during early development are deemed to be of interest as they may indicate delayed (or advanced) developmental trajectories. Data come from retrospective studies of head circumference measurements taken at birth or in the following months, often as part of regular health checks. More recently, direct measurements of brain volumes and structure have been taken using cerebral ultrasound or MRI.

Early ASD. Although no absolute differences in head circumference (HC) are found at birth (Courchesne, Carper, & Akshoomoff, 2003; Hazlett et al., 2005; Whitehouse, Hickey, Stanley, Newnham, & Pennell, 2011), there are reports of both higher rates of relative macrocephaly and relative microcephaly (HC related to body length), in newborns who later go on to autism (Grandgeorge, Lemonnier, & Jallot, 2013). Further, Rommelse and colleagues (2011) documented a subtle trend of children with ASD to have increased head circumference relative to height from birth to 2 months (Rommelse et al., 2011). However, in a sample of prospectively characterized children, Chawarska and colleagues (2011) found that one factor explained most of the variance in head size, weight and length, and it was overgrowth in this factor that predicted later autism (Chawarska et al., 2011). Larger HC than in control populations have been more consistently reported from 6 months of age (Elder, Dawson, Toth, Fein, & Munson, 2008; Fukumoto et al., 2008; Hazlett et al., 2005). However, a recent meta-analysis suggests that use of national norms as a comparison group for

clinical samples of children with autism significantly skews results, and that overgrowth is less apparent when comparisons are made to matched controls (Raznahan et al., 2013). When selection strategies are matched across groups (via population samples), results may be weaker. For example, a recent study of the Norwegian Mother and Child Cohort of 106,082 children found no evidence of general increases in rate of head circumference growth from birth to 12 months in children later diagnosed with ASD. However, variability was greater and 8.7% of boys with ASD had macrocephaly (Surén et al., 2013). Thus, data from head circumference presents a mixed view on brain growth and its relation to somatic growth in autism.

Interestingly, a recent prospective neuroimaging study of infants at high familial risk did observe increased HC from 6 months of age and corroborated these findings with MRI measures of cerebral volumes. At both 12–15 and 18–24 months of age infants who later received a diagnosis of ASD had larger brain volumes even when differences in body size were taken into account. Results also indicated that infants with later autism had greater volumes of extra-axial fluid at 6–9 months, which remained elevated at 12–15 and 18–24 months (Shen et al., 2013). Recent work indicates that ASD is associated with *deviance* in fetal growth, rather than specifically with over- or under-growth (Abel et al., 2013), and one recent study did identify greater variance in head circumference in infants with later ASD (Surén et al., 2013). Possibly, population studies of other growth parameters such as head circumference that fail to test for such U-shaped relationships may produce misleading results. Prospective studies of infants at high familial risk that apply a birth-weight or gestational-age based inclusion criteria (e.g. Elder et al., 2008; Shen et al., 2013) may thus be more likely to identify linear relations between later autism and increased head circumference, and this may have intriguing implications for the degree to which these groups experience distinct causal paths to autism. Increased brain volume could reflect delayed pruning of excess connections. Consistent with this hypothesis, Wolff and colleagues (Wolff et al., 2012) found increased connectivity (i.e. increased fractional anisotropy of white matter tracts) within projection pathways connecting frontal and parietal areas to posterior cortical areas in 6-month-old infants that developed autism symptoms by 24 months of age.

Early ADHD. In accord with evidence that adults with ADHD have smaller brain volumes (Krain & Castellanos, 2006), a slower increase in head circumference (HC) has been observed in a retrospective study of infants who later developed ADHD. Smaller head circumferences were apparent from 3 month of age and persisted as far as 18 months of age (Gurevitz, Geva, Varon, & Leitner, 2012; Heinonen et al., 2011). Some report that head circumference is related to the severity of ADHD symptom scores (Heinonen et al., 2011), but this finding is not universally observed (e.g. Stathis, O'Callaghan, Harvey, & Rogers, 1999). No anatomical abnormalities were observed in cranial ultrasound measures carried out on extremely low birth weight infants that later developed ADHD (O'Callaghan & Harvey, 1997), but a large scale prospective study of infants with no birth complications did show a relationship between a shorter corpus callosum at 6 weeks of age and greater deficits in executive functioning at 4 years (Ghassabian et al., 2013). However, corpus callosum length did not relate to later Attention Deficit/Hyperactivity Problem Scores (Ghassabian et al., 2013). More recently, using structural MRI in a population of very pre-term infants, Bora and colleagues (Bora, Pritchard, Chen, Inder, & Woodward, 2014) document a relationship between reduced total cerebral tissue, particularly in the dorsal prefrontal region, and later persistent attention/hyperactivity problems. No association was found with white matter abnormalities. Although comparison across studies could thus be interpreted as consistent with overgrowth in ASD, and undergrowth in ADHD, comparative studies have not supported this conclusion. Gillberg & de Souza (2002) found no significant differences in head circumference at birth between children with ASD and ADHD. Rommelse and colleagues (2011) compared early head circumference, height and weight over 9 time-points between birth and 18 months in 129 children with ASD and 59 children with non-ASD psychiatric disorders (ADHD, ODD, LD, regulation problems, developmental delay). No significant differences between groups were observed. Both groups showed increased growth in height that was not matched by head circumference with reference to population norms, such that by age 2 children were somewhat taller, thinner and with proportionally smaller heads than in the general population.

General Issues. Work thus indicates that atypicalities in estimated and actual brain volumes are potentially present in both ASD and ADHD. Although these emergent findings require confirmation, there is also some limited evidence that where

differences do exist in comparison to control samples, ASD is more often associated with increased HC or brain volumes and ADHD with decreased HC or volumes of particular structures, though this has not been supported in comparative studies. A variety of factors, such as neuronal or glial cell number or size, number of synapses, white matter fascicule size or the size of the ventricles, can contribute to differences in brain volumes. Histological post-mortem studies of brains belonging to individuals with ASD have pointed to difference in both cellular number and size, sometimes specific to particular structures (e.g. more and larger prefrontal neurons; Bauman & Kemper, 2005). Genetic and histological studies suggest difference in synaptic morphology and function in ASD (Parikshak et al., 2013; but also in other disorders like schizophrenia and Alzheimers, Kenny et al., 2013; Penzes, Cahill, Jones, VanLeeuwen, & Woolfrey, 2011). Differences in ASD and ADHD brain development trajectories could be related to different genetic causal factors. Alternatively, there may be common genetic risk factors that due to modulation by other genetic or environmental risk factors differ in the timing of their expression, which can lead to different trajectories of growth (Cox, Jackson, Bond, & Woods, 2006; Parikshak et al., 2013; Pletikos et al., 2014).

Understanding the molecular pathways involved in brain growth, differentiation and connectivity has relevance beyond ASD and ADHD, since early brain size differences have been documented in other disorders. For example, a meta-analysis of head circumference data suggests a marginal association between reduced HC and later schizophrenia (Cannon, Jones, & Murray, 2002), and smaller head circumference at birth and reduced HC to length ratio is associated with increased risk for hospitalization for personality disorder in men (Lahti et al., 2011). It is interesting to note though that the majority of psychiatric conditions have been associated with decreased HC or brain volumes, autism being the exception. It is therefore possible that decreased synaptic production or cellular size is a general risk factor predisposing to functional difficulties. Interestingly, some work has suggested a degree of specificity of increases in HC within particular diagnosis categories; as for example in regressive autism (Nordahl et al., 2011), boys with autism (Fukumoto et al., 2011), or autism in relation to children with developmental disabilities (Webb et al., 2007).

Given the variety of different factors that collectively contribute to total brain volume, and the further factors that then determine HC, it is important to always consider potential confounding variables. First, it is critical to take other areas of

growth into account (Chawarska et al., 2011; Fukumoto et al., 2008; Ghassabian et al., 2013; Grandgeorge et al., 2011). Second, the choice of comparison sample is critical (Raznahan et al., 2013). Finally, prenatal/perinatal or post-natal factors have to be taken into account as they may explain discrepancies between studies. This may be the case with the discrepancy in finding HC or brain volumes as predictors of later ADHD/executive functions impairments in full term infants (Ghassabian et al., 2012; Heinonen et al., 2011) but not in extremely low birth weight infants (ELBW, O'Callaghan & Harvey, 1997; Stathis et al, 1999). This could be due to either a floor effect in the ELBW infants or to different developmental mechanisms leading to disorders like ASD/ADHD in full term versus very premature infants.

Motor skills:

The typical development of motor skills is often assessed through the attainment of particular 'milestones' like sitting up, crawling and walking independently. Achievement of such milestones within a particular time-window is taken as a general indication that development is on target. Significant delays in motor development are often 'red flags' for the presence of other disorders. Attainment of motor milestones also appears to have consequences for the development of skills in other domains. For example, the transition to independent locomotion (usually crawling) is associated with improvements in spatial memory (Clearfield, 2004), and memory generalization (Herbert, Gross, & Hayne, 2007); expert locomotors make fewer perseverative errors than novice locomotors (Berger, 2010), suggesting that fragile motor skills reduce cognitive resources for other tasks. Reaching experience leads to greater understanding of goal-directed action (Sommerville, Woodward, & Needham, 2005), and fine motor skill is correlated with neural responses to watching other people's hand movements (Lloyd-Fox, Wu, Richards, Elwell, & Johnson, 2013). Thus, it is possible that early motor delays could form part of the causal path to disruptions in other domains. In addition, it is important to consider more subtle aspects of motor development that may also be sensitive to developmental problems and have consequences for the development of other skills, such as visual tracking and muscle tone.

Although gross motor development can often be an area of relative strength for children with ASD, atypicalities have been noted in postural control (e.g. Minshew, Sung, Jones, & Furman, 2004), and in gross and fine motor coordination,

movement patterns during locomotion and goal-directed motion (for review, Bhat, Landa, & Galloway, 2011; Fournier, Hass, Naik, Lodha, & Cauraugh, 2010). Of note, these deficits are not only restricted to children with poor cognitive skills (Jansiewicz et al., 2006). Similarly, children with ADHD also show significantly poorer motor skills than children with typical development, such as in manual dexterity and balance (Pick, Halperin, Schwartz, & Newcorn, 1999); reaching speed and accuracy in the absence of visual feedback (Eliasson, Rösblad, & Forssberg, 2004) and precision and stability of figure tracing, particularly with the left hand (Rommelse et al., 2007). There is a high degree of comorbidity between ASD and ADHD and Developmental Coordination Disorder, which occurs in 30 to 50% of children with ADHD (e.g. Fliers et al., 2008) and 30 to 80% of children with ASD (Kopp, Beckung, & Gillberg, 2010). Further, Developmental Coordination Disorder is associated with deficits in attention and social skills (Lingam et al., 2010). Interestingly, children with ADHD who also have parent-reported motor coordination deficits also have elevated ASD-like symptoms, suggesting that motor deficits may be associated with shared risk for ASD and ADHD (Reiersen, Constantino, & Todd, 2008). Direct comparisons of children with ASD and ADHD suggest similar levels of motor impairment (Dewey, Cantell, & Crawford, 2007), and similar deficits in visual-motor integration (Englund, Decker, Allen, & Roberts, 2013). Thus, there is significant evidence for the presence of motor atypicalities in both ASD and ADHD.

Early ASD. Transient delays in motor milestones have been widely reported in ASD. For example, displaying significant head lag when pulled to sit at 6 months is associated with later ASD diagnosis (Flanagan, Landa, Bhat, & Bauman, 2012). During free play sessions conducted 6-, 9-, 12- and 14-months, four infants with later ASD diagnoses showed substantial delays in the emergence of new postures, spent more time in less developmentally advanced postures (e.g. lying, sitting) and shifted posture less often (Nickel, Thatcher, Keller, Wozniak, & Iverson, 2013). Delays in performance on measures of fine and gross motor abilities are observed by the second year in infants who go on to autism from high-risk families (Landa & Garrett-Mayer, 2006; LeBarton & Iverson, 2013; Ozonoff et al., 2010); similar delays were seen from 6 months in the ALSPAC longitudinal cohort (Bolton, Golding, Emond, & Steer, 2012). These delays in skill acquisition may subtly disrupt developmental pathways through reducing an infant's opportunities for other types of learning. Indeed,

decreases in fine motor skill in high-risk infants are correlated with later language development (LeBarton & Iverson, 2013), and infant oral and manual motor skills have been associated with teenage speech fluency in autism (Gernsbacher, Sauer, Geye, Schweigert, & Hill Goldsmith, 2008).

Atypicalities in other aspects of motor development have also been noted in early ASD. Studies of home videos taken in infancy also indicate atypicalities in early posture and tone (Adrien et al., 1993), asymmetric and unusual movements and reduced movement maturity at 6 to 9 months (Teitelbaum, Teitelbaum, Nye, Fryman, & Maurer, 1998; though see Ozonoff et al., (2008) for a critique of methodology and failure to replicate these findings); and atypical foot, arm and global movements and less symmetric lying and walking postures as toddlers (Esposito, Venuti, Maestro, & Muratori, 2009). Prospective studies have also revealed differences in motor control; for example, a higher percentage of infants later diagnosed with ASD who spent time in neonatal intensive care showed abnormal upper extremity tone and asymmetric visual tracking at one month old (Karmel et al., 2010). Interestingly, similar problems with visual tracking have been observed at 12 to 15 months in a case series of infants who later developed ASD (Bryson et al., 2007). This could potentially be related to recent observations of higher volumes of extra-axial fluid in infants with later autism from 6 through 24 months (Shen et al., 2013), since atypicalities in oculomotor control are a common consequence of increased cranial pressure.

Early ADHD. Delays in gross motor milestones have also been measured from 3 months in infants who developed ADHD traits (Gurevitz et al., 2012); however, the ADHD group appeared to perform at the extremes, with some infants showing particularly *early* achievement of milestones (also see Jaspers et al., 2013). Although overall activity level was thought to be a potential early marker of ADHD, a recent study found no relation between activity level coded from videotape at 12 months and ADHD at 7 years (Johnson et al., 2014).

Atypicalities have also been found in more subtle aspects of motor development in ADHD. For example, Robertson and colleagues have demonstrated that movement and visual attention are robustly coupled in typically developing young infants (e.g. Robertson, Bacher, & Huntington, 2001). As infants look at an object, ongoing motor activity decreases below baseline, before rebounding and later surging above baseline as the gaze shifts away from the object. Movement

suppression is likely coupled with increased activation of the parasympathetic nervous system, facilitating focused attention and detailed processing of the stimulus. Increases in motor activity may release tonic inhibition of saccades exerted by the basal ganglia, increasing vulnerability to distraction and facilitating eventual disengagement (Robertson et al., 2001). Friedman, Watamura, & Robertson (2005) examined the relation between motion-attention coupling at 1 and 3 months, and parent-report of inattentiveness and hyperactivity at age 8 years. Inattentiveness at age 8 years was associated with less suppression of body movement at look onset, and greater rebound of movement following initial suppression at 3 months. The authors suggest that these patterns may reflect individual differences in the vulnerability of attention to disruption.

Other measurements of the complexity of movement during periods of quiet activity in very young infants have suggested atypicalities that may be related to later psychopathology. "General Movements" refer to the complex movements of trunk, head, arms and legs that show different characteristic patterns during fetal life ('preterm'), at birth ('writhing') and at around 3 to 4 months ('fidgety'; Einspieler & Prechtl, 2005). General Movements can be characterised for fluency, complexity and variation, and have been linked to the integrity of the cortical subplate and its motor efferent connections in the periventricular white matter (Hadders-Algra, 2007). For example, complete absence of 'fidgety' General Movements is associated with a high risk of cerebral palsy (Hadders-Algra, Klip-Van den Nieuwendijk, Martijn, & van Eykern, 1997). In a group of low (healthy children born at term) and high-risk infants (children with severe perinatal asphyxia or preterm infants), Hadders-Algra & Groothuis (1999) found that infants with mildly abnormal fidgety movements showed higher levels of externalizing problems, distractibility and aggression at 4 to 9 years. Notably, a follow-up study of the same children at 9 to 12 years indicated that atypical fidgety movements were related to ADHD with psychiatric comorbidity (n=4), but not to isolated ADHD (n=3), and were correlated with parent report of hyperactivity/impulsivity. The authors suggest that mildly abnormal fidgety movements indicate compromised neurological functioning, and thus present a general risk factor for the later development of psychopathology. Indeed, Phagava et al., (2008) found reduced general movement optimality in home videos of infants later diagnosed with ASD. This work needs replication given the small participant

numbers, but adds to other evidence suggesting that risk for later psychopathology may be expressed in suboptimal motor functioning early in development.

General issues. Evidence suggests that delays in motor milestones may be a common feature of early ASD (e.g. Bolton et al., 2012) and ADHD (e.g. Gurevitz et al, 2012), though evidence in the latter case is more limited. What significance might delays in the attainment of early milestones have? Subtle disruptions to the timing of the achievement of particular core abilities may have negative consequences for development in other domains or may be a marker of more general developmental delay (see Discussion). For example, retrospective parent report of fine and gross motor skill in the early development of children with ASD is associated with later language skills in childhood (Gernsbacher et al., 2008), and motor skills and language skill are correlated in typical development by both parent report and direct observation (Alcock & Krawczyk, 2010; Cheng, Chen, Tsai, Chen, & Cherng, 2009), though this is likely confounded by the use of the same instrument to measure the two domains. However, relations between early milestones and continuous measures of outcome such as IQ in typical populations are generally very small and often clinically insignificant (e.g. Hamadani et al., 2011, Hamadani, Tofail, Cole, & Grantham-McGregor, 2013; Roze et al., 2010), indicating that any direct effect of variation in motor milestone attainment on other domains is likely very small. Further, delayed milestones have been observed across a wide range of conditions, suggesting they have limited specificity for any particular domain of atypicality (e.g. schizophrenia - Isohanni et al., 2001; Jones, Rodgers, Murray, & Marmot, 1994). Rather, current evidence is more consistent with the proposal that early transient motoric delays (or accelerations) are indicators of a nervous system that is operating less than optimally, and thus may represent a general risk indicator for a range of conditions. This may account for the general presence of a range of common motor atypicalities across infants with later ASD and ADHD. However, more detailed investigation of a range of early motor skills conducted with both populations is required to validate this conclusion. Further, the observation that some infants with later ADHD show particularly early achievement of motor milestones (Gurevitz et al., 2012) is intriguing and should be further explored.

Sensory processing and perception

Although over 90% of children with ASD present with sensory atypicalities (Kern et al., 2006; Susan R. Leekam, Nieto, Libby, Wing, & Gould, 2007; Tomchek & Dunn, 2007) and sensory over-reactivity has also been reported in ADHD (Lane, Reynolds, & Thacker, 2010; Yochman, Parush, & Ornoy, 2004), sensory processing and perception remain understudied as early markers for these disorders. Sensory difficulties, either as hypo- or hyper- sensitivities, can be documented through parental report using questionnaires like the Infant Behaviour Questionnaire (Gartstein & Rothbart, 2003) or Dunn's Sensory Profile (Dunn, 1997). Direct measurements of brain responsiveness to sensory stimulation can be made using EEG. In one example of this approach, the sensory gating paradigm measures event related potentials to pairs of stimuli. Pairs of clicks separated by short within-pair interstimulus intervals (ISIs) are presented with much longer inter-pair ISIs. A reduction in the amplitude of a mid-latency component, the P50, evoked by the second stimulus, is thought to reflect the brain's ability to inhibit irrelevant sensory input (e.g. Grunwald et al., 2003),

Early ASD. Overall performance on developmental measures of visual reception is reported to be typical at 6 months in infants that later develop ASD (e.g Ozonoff et al., 2010). However, atypicalities in object exploration (i.e. using the peripheral visual field during object manipulation) have been documented (Ozonoff et al., 2008). Parental reports indicate that, from 6 months onwards, infants who later develop symptoms of ASD appear more reactive to sensory stimulation (Clifford, Hudry, Elsabbagh, Charman, & Johnson, 2013). In another study, including sensory-regulatory markers improved the accuracy of ASD screening at 12 months (Ben-Sasson, Soto, Martínez-Pedraza, & Carter, 2013).

Early ADHD. Diminished P50 sensory gating measured at 2.5 months was related to ADHD symptoms (externalizing behaviour, attentional problems) in addition to symptoms of anxiety and depression at 40 months (Hutchinson, Luca, Doyle, Roberts, & Anderson, 2013).

General Issues. There is some evidence that both disorders may be characterised by early sensory issues, which makes this domain a promising area for future work. One

question that future studies will have to address is whether sensory hyper- or hypo-sensitivities reflect atypicalities of sensory processing (e.g. in the tuning curves of sensory neurons or their thresholds), learning (e.g. to predict incoming stimulation), attention (e.g. selective attention) or regulation (e.g. of the response to incoming sensory stimulation). Again, surface similarities in the ASD and ADHD phenotypes could be the result of different underlying mechanisms. Attempts to tease apart between putative mechanisms in studies of older children and adults with ASD have had only partial success. For example, in the visual modality, initial reports of enhanced visual acuity (Ashwin, Ashwin, Rhydderch, Howells, & Baron-Cohen, 2009) have not been confirmed (Bolte et al., 2012), but many report better visual search abilities (Plaisted, O'Riordan, & Baron-Cohen, 1998; Joseph, Keehn, Connolly, Wolfe, & Horowitz, 2009) which may reflect different attentional styles, as for example a wider attentional spot (Kaldy, Giserman, Carter, & Blaser, 2013) but also perceptual differences (Plaisted et al., 1998). In a sensory gating paradigm, it is the first (less predictable stimulus) that differentiated participants with ASD and controls (Orekhova et al., 2008), suggesting that sustained monitoring of incoming stimulation may also be atypical. Since sustained attention is expected to be poor in ADHD, this could be a common source of sensory difficulties in ASD and ADHD. However, in a sensory gating paradigm ADHD participants showed a lesser reduction in the P50 response to the second, more predictable stimulus, suggesting decreased gating of incoming sensory input (Holstein et al., 2013).

Attention

The two domain-general components of attention that have been most commonly studied in ASD and ADHD are orienting and reflexive attention-shifting (reliant on the posterior attention system, including the pulvinar, parietal lobe and superior colliculus), and sustained attention (associated with frontal areas such as the anterior cingulate, frontal eye fields and dorsolateral prefrontal cortex; for review Petersen & Posner, 2012). In early development, orienting and attention-shifting are typically assessed in paradigms in which stimuli are presented to the infant's peripheral visual field; reaction time for gaze to shift to the target is taken as a measure of orienting/shifting speed. For example, in the 'gap-overlap' task individuals shift their visual attention from a central to a peripheral stimulus; in different trial types, the

central stimulus either disappears concurrent with (baseline), slightly before (gap – assessment of facilitation), or overlaps with peripheral stimulus onset (overlap – assessment of disengagement) (Johnson, Posner, & Rothbart, 1991). Work with such paradigms indicates that reflexive orienting is present from birth (Richards and Hunter, 1998), though there is substantial improvement in the speed and accuracy of orienting over the first months of life (Dannemiller, 2000) that is likely related to the maturation of subcortico-cortical and cortico-cortical pathways (Johnson, 1990). Disengagement shows significant improvements over the first year of life in typically developing infants (Johnson et al., 1991).

Atypicalities in attention-shifting have been well characterised in ASD. Several studies have indicated that children with ASD show relatively specific problems in disengaging and shifting attention under competition conditions (e.g. Landry & Bryson, 2004). A recent meta-analysis found generally slowed orienting in ASD that was not modulated by the presence of a central stimulus and that increased in magnitude with age (Landry & Parker, 2013), but this may be because the social versus non-social nature of the central stimulus was not considered (Chawarska, Volkmar, & Klin, 2010). More naturalistic measures of orienting and attention-shifting (for example, examining whether children orient to sounds or voices when playing with toys) provide converging evidence of attention-shifting difficulties in ASD (Dawson et al., 2004; Swettenham et al., 1998). In contrast, children with ADHD show generally slowed reaction times to respond to a peripheral stimulus but this difficulty is not increased in competition conditions (Klein, Raschke, & Brandenbusch, 2003; Munoz, Armstrong, Hampton, & Moore, 2003; Tajik-Parvinchi & Sandor, 2013). Thus, current literature indicates that disengagement is particularly problematic for children with ASD, whilst children with ADHD may show a more general slowing of orienting. A recent preliminary comparison of children with ASD and ADHD on the gap-overlap task did not reveal group differences, but subject numbers were low (Azadi et al., 2010).

Measures of sustained attention in infancy typically include peak look duration during object viewing (e.g. Kannass & Oakes, 2008) or during screen-based presentation of static stimuli (e.g. Courage, Reynolds, & Richards, 2006). Combining information about visual attention with measures of motion (e.g. Robertson, Bacher, & Huntington, 2001), coding of expression (e.g. Lawson & Ruff, 2004b) or heart rate (Richards & Casey, 1991) can provide a more detailed assessment of attention states.

Other paradigms that have been used with infants include the 'freeze-frame' task (Holmboe, Fearon, Csibra, Tucker, & Johnson, 2008), in which infants are required to suppress saccades to peripheral stimuli in order to continue viewing a repetitive or variable central stimulus. Ruff and colleagues (Ruff, Capozzoli, Dubiner, & Parrinello, 1990) have also developed a measure of vigilance for infants, in which an interesting event occurs at a particular place that is repeated after brief but variable time intervals. Taken together, work with such tasks indicates that there are significant improvements in sustained attention throughout infancy and toddlerhood (for review, Colombo, 2001).

Children with ADHD show well-documented deficits in sustained attention across a variety of contexts (e.g. Loo et al., 2009; Schoechlin & Engel, 2005). Slower reaction times are often accompanied by increased intra-individual variability, which is generally assumed to reflect occasional lapses of attention (for review Tamm et al., 2012). The literature on sustained attention is ASD is less clear. Direct comparisons of sustained attention in ASD and ADHD have variously indicated greater impairments in ADHD (e.g. Johnson et al., 2007); similar impairments but with a greater decrease in vigilance in ADHD over time (Swaab-Barneveld et al., 2000); similar deficits but more impulsive behaviour in ASD (Riccio & Reynolds, 2001); or broadly similar deficits across ASD, ADHD and comorbid groups (Nydén et al., 2010). Recent evidence suggests that one important factor may be variability in language skill of the ASD group (Kelly, Walker, & Norbury, 2013). Increased variability has also been reported in individuals with ASD (e.g. Geurts et al., 2008; Verté, Geurts, Roeyers, Oosterlaan, & Sergeant, 2006). Again, evidence from direct comparisons is mixed, with some studies showing that deficits are more marked in the presence of ADHD symptoms (Adamo et al., 2012; Johnson et al., 2007; Lundervold et al., 2012) and others suggesting that deficits are similar (Nyden et al., 2010) or more marked in ASD (Geurts et al., 2008). Taken together, current evidence suggests there is no clear evidence for differential impairment in sustained attention in ASD or ADHD (Rommelse et al., 2011).

Early ASD. Consistent with evidence from older children with ASD, slowed disengagement from a central to a peripheral stimulus appears to be a hallmark of infants who go on to later ASD by 12 to 14 months (Elison et al., 2013; Elsabbagh, Fernandes, et al., 2013; Zwaigenbaum et al., 2005). Similar behaviours are also seen

during object exploration (Sacrey, Bryson, & Zwaigenbaum, 2013), and in response to social stimuli such as a name call (Nadig et al., 2007). Such effects are typically absent at 6 months (Elsabbagh, Fernandes et al., 2013; Sacrey et al., 2013; Zwaigenbaum et al., 2005; Nadig et al., 2007; though see Elison et al., 2013), suggesting that they emerge on a similar timescale to other early behavioural symptoms of autism. Concerns about vision and hearing, which emerged as the predictors of later ASD in the first year of life in the ALSPAC cohort study (Bolton et al., 2012), may also reflect difficulty in shifting attention from the focus of interest to respond to a peripheral cue. Overall, slowed disengagement appears to be a robust candidate for an early autism endophenotype.

Fewer prospective studies have focused on aspects of sustained attention or attentional control, and results are mixed. In one study, *lower* distractibility from repetitive stimuli at 9 months was related to later variation in social and communication symptoms of ASD (Elsabbagh et al., 2011). In contrast, during toy exploration Sacrey et al (2013) report that breaks in visual fixation prior to grasp are *more* common in infants who go on to ASD at 6 months than infants who go on to other outcomes; this effect declined with age. Chawarska and colleagues (Chawarska, Macari, & Shic, 2013) report that 6-month-old infants look less at a screen-based video with social content than other infants; this may reflect sustained attention difficulties, but could also reflect decreased interest in social events. Finally, parents prospectively judge their infants who went on to ASD as being less good at waiting at 9 and 18 months than other infants (Feldman et al., 2012). Taken together, this work suggests there may be subtle disruptions to sustained attention in early ASD, but there is a clear need for more systematic investigation.

*Early ADHD***.** There is surprisingly little data on orienting and attention-shifting in infants with later ADHD symptoms. However, some preliminary evidence suggests that this may be an important avenue to explore. In a group of typically developing infants, greater disengagement from a variable stimulus was related to common polymorphisms associated with increased risk of ADHD (Holmboe et al., 2010). Further, a greater difference in distractibility between repetitive and variable stimuli at 9 months was related to better spatial conflict resolution but *worse* effortful control at age 2 years (Holmboe et al., 2010) . Thus, one hypothesis may be that infants who later develop ADHD will show *reduced* disengagement latencies or an altered ability

to modulate disengagement, in contrast to the longer disengagement latencies seen in ASD. Longitudinal prospective studies of both conditions will be necessary to validate this conclusion. Further, examining intra-individual variability in reaction time will be important, given that increased variability is a more robust marker of ADHD in childhood than changes in mean reaction time (Kofler et al., 2013).

As might be expected from work with older children, greater sustained attention in in infancy is typically associated with reduced risk for later ADHD symptoms. Kochanska & colleagues (Kochanska, Murray, & Harlan, 2000) found that more focused attention during an observational task at 9 months was related to better effortful control, more regulated anger and joy and stronger restraint at 22 and 33 months. Qualitative ratings of attention on a 1 to 3 scale (very attentive, moderately attentive, very inattentive) at 1 and 2 years together predict observed attention and inattention, cognitive performance and maternal ratings of hyperactivity and behavioural problems at 3.5 years (Lawson & Ruff, 2004a) . Outcomes were particularly poor for low attentive children who also had higher negativity, suggesting that examining combinations of risk factors will be important. Further, less focused attention (manipulation with an interested expression) in very low birth-weight infants at 7 months predicts more hyperactivity and inattention at 4 to 5 years, and poorer cognitive skills (Lawson & Ruff, 2004b). This range of evidence suggests that lack of focused attention during toy play in infancy is related to ADHD-type symptoms in the preschool years. However, these studies have typically examined children with high levels of inattention and hyperactivity who nonetheless fall within the typical range; future work will be required to establish whether similar effects are seen in children with clinical outcomes.

General issues. The literatures on early ASD and early ADHD have generally focused on different components of attention, making direct comparisons difficult. Studies of early ASD have focused on examining disengagement and social features of attention, since these are prominent aspects of the clinical phenotype (e.g. Elsabbagh, Fernandes et al., 2013; Nadig et al., 2007). Although current work shows a clear pattern of early emerging disengagement atypicalities in ASD (e.g. Elsabbagh, Fernandes et al., 2013), similar phenotypes have not been studied in infants with later ADHD. Similarly, longitudinal studies examining later ADHD symptoms have commonly focused on early, sustained attention, since this is a robust hallmark of later ADHD

(e.g. Lawson & Ruff, 2004). The few studies of related measures in ASD have yielded mixed results, but suggest that subtle atypicalities may also be present early in the development of this disorder.

It should not be assumed that the very early manifestations of attention deficits in infants who later develop ASD or ADHD will necessarily resemble the deficits seen in older children. Rather, even subtle and transient impairments may have significant developmental consequences. Further, it will be important to assess the relation between infant attentional measures and later comorbidities. For example, prospective studies of infants with older siblings with ASD have yet to report on comorbid ADHD symptoms in ASD outcome groups. This poses a significant challenge to interpretation of apparently shared early risk factors, and could potentially account for the mixed evidence on sustained attention in infants with later ASD. Long-term follow-up of such cohorts at ages at which ADHD can be more readily diagnosed will be critical to answering such questions. Finally, incorporating other psychophysiological or imaging measures (such as heart-rate, motion or EEG) into assessments of attention in at-risk groups may identify more subtle underlying atypicalities that precede or underlie behavioural changes in attention, and may indicate whether apparently similar deficits have distinct underlying causes.

Temperament and regulation

Temperament has been defined as "constitutionally-based individual differences in reactivity and self-regulation, as observed in the domains of emotionality, motor activity, and attention" (Rothbart, Posner, & Kieras, 2008). Rothbart's widely influential model divides temperament into effortful control/self-regulation, extraversion/surgency, and reactivity/negative affectivity (Rothbart, Ahadi, & Evans, 2000). Self-regulation involves effortful control of attention and emotion, and in early infancy may be related to regulation of basic activities like feeding and sleeping (Geva & Feldman, 2008); surgency involves the degree to which the infant tends to approach or withdraw from novel situations or people; and reactivity includes expression of negative emotions such as anger, sadness or fear. Particular subdomains may also be of interest, including activity level, approach, or orienting behaviours. Typically, temperament dimensions are assessed through parent-report questionnaires or through observations made during semi-standardised laboratory batteries.

Individual differences in temperamental factors are typically somewhat stable across early development, with correlations of around .2 to .5. Observational assessments typically produce lower stability than parent-report questionnaire assessments (Rothbart et al., 2000), suggesting either that parent-report assessments are confounded by parental biases about personality, or that parent reports are less affected by day-to-day variation in state and thus more accurately capture trait variables. Heritability of temperament is also moderate, with a range of around .3 to .6 in early to middle childhood (Nigg & Goldsmith, 1998; Saudino, 2005). This suggests that commonly used temperament measures have reasonable validity as measures of constitutionally-based individual differences.

Average scores on core temperament domains vary in children diagnosed with ASD or ADHD. For example, children with ASD often exhibit reduced effortful control and higher negativity (e.g. Konstantareas & Stewart, 2006); and similar patterns are seen in children with ADHD (e.g. De Pauw & Mervielde, 2011; Nigg, Goldsmith, & Sachek, 2004; though see Martel & Nigg (2006) for discussion of the relation between negativity and comorbid ODD). The temperamental profiles of children with diagnoses of ASD and ADHD thus appear broadly similar in these domains. Where direct comparisons of effortful control and negativity have been made, few differences between ADHD and ASD groups are observed (e.g. Anckarsäter et al., 2006; Samyn, Roeyers, & Bijttebier, 2011). Rommelse and colleagues (2011) review temperament/character as one of the domains that may represent a shared endophenotype between ASD and ADHD. However, reduced levels of approach or surgency may be relatively specific to children with ASD (Schwartz et al., 2009), since ADHD is more often associated with higher levels of approach or surgency that are potentially related to impulsivity (Martel & Nigg, 2006). Further, a recent comparative study found that group differences in temperament and character only overlapped on two of seven domains in groups with ASD and ADHD (Sizoo, Gaag, & Brink, 2014), challenging the hypothesis that this represents a common endophenotype. Thus, the three overarching factors may have different degrees of specificity to a later ASD or ADHD diagnosis in prospective longitudinal studies.

Early ASD. Several studies have examined parent reports of temperament in infants with a later diagnosis of ASD. By age 24 months, children with later ASD show

greater negative affect than other toddlers; this is less apparent at younger ages (e.g. Clifford et al., 2013; Zwaigenbaum et al., 2005). Positivity appears reduced by 12 months (Clifford et al., 2013; Zwaigenbaum et al., 2005) and remains low at 24 months (Del Rosario, Gillespie-Lynch, Johnson, Sigman, & Hutman, 2014; Garon et al., 2009) in infants with later ASD. These general patterns are consistent with those seen in older, diagnosed children. Effects seem to broadly increase in severity and scope with age, possibly suggesting that these temperament changes relate to the emergence of other behavioural symptoms. Indeed, del Rosario and colleagues (2013) examined trajectories of temperamental variables in infants at high familial risk with a later ASD diagnosis. Infants with later ASD showed initially higher levels of approach and adaptability, and lower activity level, at 6 and 12 months than controls. However, by age 2 years these children were showing *lower* approach and adaptability, and no differences in activity level, broadly consistent with work with clinically referred samples. Although these effects should be treated with caution since they have not been reported in other cohorts, they suggest that the temperament patterns that are most likely to represent causal or early risk factors do not necessarily resemble those seen in older, diagnosed children.

Self-regulation/effortful control also appears generally reduced in the second year of life in infants who go on to ASD (Clifford et al., 2013; Zwaigenbaum et al., 2005; Garon et al., 2008; del Rosario et al., 2013). Across studies, this effect was not apparent earlier in development. Similarly, temperamental differences did not emerge as significant predictors of later ASD until 2 years of life in the ALSPAC longitudinal cohort (Bolton et al., 2012). Possibly, the increasing contribution of frontal executive systems to self-regulatory behaviours across the early years drives the emergence of group differences in children with later ASD. Indeed, reduced fronto-posterior connectivity has been reported to emerge between 12 and 24 months in toddlers with ASD (Wolff et al., 2012).

Alternatively, examining earlier precursors of regulatory control may reveal important group differences. Indeed, atypical neonatal auditory brainstem responses and atypical patterns of arousal-modulated attention at 4-months predict later autism in preterm infants (Cohen et al., 2013; Karmel et al., 2010); these behaviours have been linked to later self-regulatory capacity (Geva & Feldman, 2008). Other basic early regulatory behaviours that may be related to later effortful control difficulties are feeding and sleeping; disruptions to both have been reported in early ASD (Bolton

et al., 2012; though see Jaspers et al., 2013). Mapping the longitudinal relations between early brainstem-related physiological regulation, frontal cortex development and effortful control of attention and emotion will provide insight into the roots of effortful control deficits in children with ASD.

Early ADHD. Temperament atypicalities are apparent from 6 months in infants with high levels of ADHD symptoms in preschool (Arnett, Macdonald, & Pennington, 2013); specifically, infants with later ADHD symptoms were characterised as showing higher activity level, less adaptability, reduced approach, negative mood and high intensity. A retrospective chart review of children with ADHD or ASD indicated that later ADHD was predicted by early attention and hyperactivity problems, and absence of parent-reported positive behaviours in toddlerhood; conversely, ASD was predicted by social problems in toddlerhood (Jaspers et al., 2013). In another population cohort, difficult temperament was more commonly reported by parents of 9- and 18-month-old infants who later developed ADHD, with only 62% and 47% characterised as 'easy' (versus 90%/81% of the control group; Gurevitz et al., 2012). Taken together, this work suggests that temperament profiles in infants who go on to ADHD may be different to those in infants who go on to ASD. In the two studies that used very similar measures (del Rosario et al., 2013; Arnett et al., 2013), 6-month-olds with later ASD showed better adaptability and more approach (del Rosario et al., 2013), whilst 6-month-olds with later ADHD showed lower adaptability and lower approach (Arnett et al., 2013). This raises the intriguing possibility that temperamental risk factors for ASD and ADHD are different in very early development. However, direct comparison within the same sample is necessary to confirm these findings.

Atypicalities in physiological regulatory processes may also be apparent in early ADHD. For example, sleep difficulties predict later diagnosis of ADHD (O'Callaghan et al., 2010; Thunström, 2002; though there is less evidence to support this for ASD - Jaspers et al., 2013). Gurevitz and colleagues (2012) also found an increased prevalence of feeding issues (e.g. reflux) and poorer sleep regulation at 3 months in infants later diagnosed with ADHD, and Geva and colleagues (Geva, Yaron, & Kuint, 2013) found that poor neonatal sleep predicts later attention orienting and

distractibility. Interestingly, increased prevalence of 'regulatory disorder' (excessive crying with feeding and sleeping problems) in infancy is associated with ADHD, but only in the presence of the DRD4 -7 risk allele (Becker et al., 2010). Consistency of such markers across ASD and ADHD raises the possibility that physiological regulatory difficulties represent general risk factors for later psychopathology.

*General issues***.** Current evidence indicates that there are early-emerging subtle temperamental differences in infants who later develop symptoms of ASD or ADHD. By toddlerhood, these differences appear to be similar to temperament differences observed in children with a diagnosis. One key open question is the degree to which temperament differences in infants with later ASD or ADHD are simply the earliest manifestation of behavioural symptoms of the disorder; or whether different temperamental profiles represent specific or general risk, or differential susceptibility factors. These (not necessarily mutually exclusive) possibilities make differing predictions about the specificity and onset of temperamental differences. First, if temperamental differences merely reflect emerging symptoms, temperamental differences would be expected to be condition-specific, resemble those seen in older children with a diagnosis, and emerge over development. The work reviewed above provides evidence consistent with a certain degree of condition specificity, with distinct variables related to the two conditions in early infancy (Arnett et al., 2013; del Rosario et al., 2013) and toddlerhood (Jaspers et al., 2013). Temperament patterns seen in toddlers with later ASD or ADHD also seem to broadly resemble those seen in children with a diagnosis, although this is not necessarily the case in infancy (e.g. infants with later ASD show *reduced* approach in toddlerhood, but *greater* approach in infancy; del Rosario et al., 2013; Arnett et al., 2013). Longitudinal datasets from infants who later develop ASD suggest that differences from typically developing controls are more widespread and more pronounced in older infants (e.g. Clifford et al, 2013; Zwaigenbaum et al., 2005; del Rosario et al., 2013), a finding that has not been explicitly tested for ADHD. Further work should also explore the stability and reliability of temperament constructs in infants with later ASD or ADHD, because this should be reduced if temperament changes reflect the emergence of behavioural symptoms. Thus, there is some evidence that temperament may be influenced by the emergence of behavioural symptoms of ASD or ADHD, but the observation of temperament differences at 6 months (del Rosario et al., 2013; Arnett et al., 2013)

suggests that some temperamental differences precede behavioural symptom emergence.

If temperamental styles represent general risk or differential susceptibility factors, they should be present from very early in development, may not be condition specific, and should remain stable over time. For example, longitudinal studies have suggested that high negativity (as seen in infants with later ADHD; Becker et al., 2010 and those with later ASD; Clifford et al., 2013) represents a differential susceptibility factor, such that infants who are highly negative have particularly positive outcomes in some circumstances, and particularly negative outcomes in others (e.g. Poehlmann et al., 2011). Such research has typically focused on susceptibility to early social environments. For example, highly negative infants who experience supportive mother-child relationships show better self-regulation at age 2 years, but worse self-regulation if they experience unresponsive relationships (Kim & Kochanska, 2012). However, differential susceptibility factors may also interact with other internal factors, so infants with other risk factors for neurodevelopmental disorders, and who are also fussy, have particularly negative outcomes (the 'modifier' model; Mundy, Henderson, Inge, & Coman, 2007). This would be consistent with work showing that the presence of the DRD4-7 risk allele moderates the association between regulatory disorder in infancy and ADHD in childhood (Becker et al., 2010).

In addition, particular temperamental characteristics may not represent susceptibility or risk factors, but may rather reflect variation in resilience, adaptability or the ability to exploit positive situations ("vantage sensitivity"; Pluess & Belsky, 2013). For example, Johnson (2012) suggests that executive functioning may act as a general protective factor against the emergence of neurodevelopmental conditions. In early childhood, there are relations between effortful control and aspects of executive functioning (such as executive attention; Chang & Burns, 2005; Gerardi-Caulton, 2000; Rueda et al., 2004), and it has been suggested that the two rely on similar brain networks (Rothbart & Rosario, 2005). Infants who display early risk factors for developing ASD or ADHD but who have good self-regulatory capacity may thus be more likely to go on to develop typically. Reductions in effortful control observed in toddlers with later ASD (e.g. Clifford et al., 2012) and ADHD (Jaspers et al., 2013) are consistent with this possibility, but more sophisticated statistical analyses of the relation between different risk and potential resilience factors will be important in

untangling such effects. Identifying characteristics that predict variation in ASD or ADHD severity may also highlight important potential targets for intervention.

Social Interaction & Communication:

The time course of social and communication development in typical development has been extensively studied and it is widely accepted that a chain of cascading events lead to typical social integration and social learning. For example, the acquisition of language depends on learning the use of various ostensive and referential cues that adults use when teaching new words (e.g. gaze direction, emotional expressions), and learning about these cues depends on children's ability and motivation to engage in social interaction. Since ASD is mainly defined as a disorder of social interaction and communication, the great majority of studies of early markers of ASD focus on investigating these developmental cascades leading to the social interaction and language difficulties documented in older children with ASD (e.g. Charman et al., 1997; Groen, Zwiers, van der Gaag, & Buitelaar, 2008; Klin, Jones, Schultz, Volkmar, & Cohen, 2002). Extensive reviews of this field have recently been published (e.g. Jones, Gliga, Bedford, Charman, & Johnson, 2013), therefore we will only focus on highlighting representative findings from studies of infants at risk for ASD. Social cognition and linguistic skills have often been described as atypical or delayed in children with ADHD. ADHD was associated with social cognition impairments involving facial emotion and prosody perception (Ibáñez et al., 2011; Uekermann et al., 2010). One important question in this field is whether these difficulties are there from the onset or a consequence of atypical social interaction resulting from frequent conduct problems. Relevant to this question and to our review, automatic facial mimicry in response to emotional expressions was typical in 6-7 year olds with ADHD (Deschamps, Munsters, Kenemans, Schutter, & Matthys, 2014). Intriguingly, after many studies failed to establish impairments in establishing secure attachment in ASD (Rutgers, Bakermans-Kranenburg, van Ijzendoorn, & van Berckelaer-Onnes, 2004), insecure attachment has been frequently associated with ADHD (Storebo, Rasmussen, & Simonsen, 2013). Language delay has been described in children with ADHD or ADHD symptoms (Helland, Posserud, Helland, Heimann, & Lundervold, 2012; Rohrer-Baumgartner et al., 2013), although some difficulties do not match those seen in children with specific language impairment (Redmond,

Thompson, & Goldstein, 2011). In a comparative study, pragmatic language difficulties were documented in both children with ASD and with ADHD (Geurts & Embrechts, 2008). Interestingly, a relationship between characteristics of impulsivity and language abilities was found in the ADHD group, suggesting a possible different developmental origin of language impairment in ASD and ADHD. Another study found general pragmatic abilities as measured by parent ratings, to mediate the relation between ADHD and poor social skills, in this population (Staikova, Gomes, Tartter, McCabe, & Halperin, 2013). Understanding social interaction and communication difficulties in ADHD will benefit from better developmental models and therefore from developmental studies of ADHD.

Early ASD. Orienting to faces and eyes is commonly reported to be typical during the first year of life (Elsabbagh, Bedford, et al., 2013; Elsabbagh, Gliga, et al., 2013; Ozonoff et al., 2010; Young, Merin, Rogers, & Ozonoff, 2009) but decreases subsequently (Jones & Klin, 2013; Ozonoff et al., 2010). In a recent, densely sampled longitudinal eye-tracking study infants that later developed autism looked significantly more towards the eyes when they were 2 month old but this preference decreased steadily from 2 months on, becoming significantly less prominent than in controls around 24 months (Jones & Klin, 2013). One eye-tracking study of 6-month old infants did measure decreased proportional time spent watching an actress's face but also less looking at the screen, in general (Chawarska et al., 2013). Responses to the 'still face' – which may index early social motivation, are also typical at 6 months of age (Rozga et al., 2011; Young et al., 2009). However, low infant positive affect and infant attentiveness to parent, recorded at 12 months during parent-child interaction, predict 3-year autism outcome (Wan et al., 2013). Before social orienting and social motivation become atypical, event-related potentials (ERP) show atypical gaze processing. Unlike controls, 6- to 9-month-olds that later develop ASD did not differentiate faces that shifted gaze away, from faces that shifted gaze towards, the viewer (Elsabbagh et al., 2012). Impairments in behavioural measures of gaze following become apparent at the beginning of the second year (Bedford et al., 2012; Landa, Holman, & Garrett-Mayer, 2007) and correlate with measures of autism symptom severity (Bedford et al., 2012).

Several studies have identified delays in receptive and expressive language by

12 months of age in infants later diagnosed with ASD (Landa & Garrett-Mayer, 2006; Mitchell et al., 2006; Zwaigenbaum et al., 2005); but see Hudry et al., 2014; Talbott, Nelson, & Tager-Flusberg, 2014 for no differences). Suggesting that atypicalities may be present even earlier in development, Paul, Fuerst, Ramsay, Chawarska, & Klin (2011) observed lower expressive language scores on the MSEL at 6 months in infants who showed high levels of ASD symptoms on the ADOS-T at 24 months. Expressive language skills tested by the MSEL at 6 months include sounds like coos and laughs, vocalizations like 'ah' or 'ah-goo', imitation of sounds and production of consonants. These infants also produced more immature vocalizations (e.g. fewer 'middle' consonant types at 6 months, fewer 'late' consonant types at 9 months, and a lower total number of different consonant types at 12 months). In a study of infant cry samples, Sheinkopf, Iverson, Rinaldi, & Lester, (2012) found that three high-risk 6-month-old infants diagnosed with ASD at 36 months produced cries that were more poorly phonated than those of infants with typical outcomes. Whether these atypicalities indicate general compromised motor development or are an early expression of problems with learning language specific phonological or prosodic information is unknown.

Early ADHD. Very few studies have examined early social skills in infants with later ADHD. However, disorganised attachment in infants next-born after stillbirth predicts teacher ratings of ADHD in preschool (Pinto, Turton, Hughes, White, & Gillberg, 2006). Speech and language delays have been documented at 9 and 18 months in a retrospective chart review of children with ADHD relative to typically developing controls (Gurevitz et al., 2012). One third of children with later ADHD showed delays in speech development at 9 months, and two-thirds by 18 months. One large population cohort prospective study only measured language skills at 36 months of age and found boys with more severe ADHD to be delayed in receptive language (Arnett et al., 2013). Interestingly, a longitudinal study of low-birth weight pre-term infants found a relationship between maternal ratings of attention, at 18 months, and maternal rates of language abilities at 36 months (Ribeiro et al, 2011).

General Issues. There is strong evidence that language delays are detectable from 12 months in at least some infants with later ASD (e.g. Zwaigenbaum et al., 2005), and some preliminary evidence that delays may also be apparent in up to two thirds of

infants with later ADHD (Gurevitz et al., 2012). Since language acquisition draws on a great variety of skills, different developmental trajectories could explain language difficulties in ASD and ADHD. Early difficulties with gaze following and joint attention have been proposed to explain the slow rate of word acquisition in ASD (Gliga et al., 2012). Difficulties with word production could also negatively impact on word memory, in this population (Barona et al, submitted). However, general attention and memory are also limiting factors in word learning (Samuelson & Smith, 1998; Smith, Colunga, & Yoshida, 2010). Moreover, establishing joint attention itself might depend on the ability to flexibly switch attention (Schietecatte, Roeyers, & Warreyn, 2012; although see Leekam, López, & Moore (2000)for a dissociation, in children with ASD) and indirectly impact on language acquisition (Kelly et al., 2013). Thus, attentional difficulties associated with later ADHD symptoms may be responsible for language delays in these individuals (as suggested by Ribeiro et al, 2011). Diminished social reward is another source of impaired social learning. The motivation to engage in social interaction seems to be typical initially, in those infants that develop ASD, and to diminish only later, possibly as a secondary consequence of earlier difficulties with social interaction (Johnson, 2012). Interestingly, both children and adolescents with ADHD show diminished responsiveness to social rewards, as compared to monetary rewards (Demurie, Roeyers, Baeyens, & Sonuga-Barke, 2012). It remains to be determined whether in both populations this is a secondary effect of earlier difficulties with social interaction (e.g. a common adaptive response, Johnson, Jones & Gliga, in press), or whether it reflects general difficulties with reward learning, in ADHD (Dichter, Damiano, & Allen, 2012). Studying precursors to later language difficulties in both ASD and ADHD, as well as in other developmental disorders (Downs syndrome, Williams Syndrome), will help us to understand the contribution of overlapping or distinct developmental pathways to social interaction and language development (Karmiloff-Smith et al., 2012) .

Discussion

We have reviewed several domains in which evidence indicates early markers for later ASD and/or ADHD. Leaving aside, for the moment, any differences between diagnostic categorical outcomes and trait dimension associations, we have reported

atypicalities in all domains reviewed for both disorders. The following section will discuss the implications of these findings for existing developmental models of ASD and ADHD.

Are there syndrome-specific infant markers?

One of the motivating questions for this review is whether infant markers are specific to later diagnostic or dimensional outcome. While most studies we report have involved an association between selected infant markers and specific later outcomes, including diagnosis of ASD or ADHD, there is currently no strong evidence for a syndrome-specific predictor. However, we note that the standard of evidence required for such a claim would be high, as it requires studies that involve infants at-risk both for ASD, ADHD, and co-morbid outcomes, receiving a common battery of infant and outcome measures. Even with such a study, further evidence would be required to demonstrate specificity with regard to other commonly co-morbid conditions such as anxiety. Nevertheless, our review highlighted a few candidate specific predictors worthy of further investigation: at least some children with ADHD show particularly early attainment of motor milestones (Gurevitz et al., 2012), whilst motor delays are more commonly reported in ASD (Ozonoff et al., 2010; Landa & Garrett-Mayer, 2006; LeBarton & Iverson, 2013); there are reports of reduced head circumference in ADHD versus early overgrowth in ASD (but see Rommelse et al., 2011); early temperament ratings suggest better adaptability and more approach in 6-month-olds with later ASD (del Rosario et al., 2013), but lower adaptability and lower approach in 6-month-olds with later ADHD (Arnett et al., 2013); and disengagement of attention is problematic in ASD (e.g. Elsabbagh et al., 2013), while difficulties in maintaining attention may predict later ADHD symptomatology (e.g. Lawson & Ruff, 2004). However, usually assessment of behavioural skills have been made under conditions that are not directly comparable (e.g. computerised automated coding of saccadic reaction times in Elsabbagh et al. 2013, versus qualitative coding of attentional style in Lawson & Ruff, 2004). In order to better establish these candidates for specific markers, future prospective studies of infants that later develop ASD and/or ADHD symptoms will require us to use identical experimental paradigms.

Are there common markers across different syndromes?

While the criteria for establishing common infant markers are less stringent than those described above (as only one instance of a common predictor need be observed in the two conditions), establishing that this is true across multiple measures will require considerable further evidence. Reviewing the current body of evidence from studies of early ASD and ADHD suggests that some commonalities can be established, such as similarities in the time-course of language milestones (often reported as delayed in both ASD and ADHD). However, cross-study comparisons relying on different measures do not allow us to determine whether there may be differences in the degree or nature of the delay experienced by infants who go on to ASD or ADHD. This is critical to evaluating models in which ASD and ADHD represent different aspects of an underlying continuum of impairment (van der Meer et al., 2012). In addition, since no studies have yet examined predictors of comorbidity, it may be that early language delays appear to be a common predictor but in fact relate to later symptoms of autism in children with ADHD diagnoses (Figure 1 A). Further, global assessments of development may not be sufficiently sensitive to inform us about common underlying mechanisms. As we have discussed previously within the section on social interaction and language development, many factors, some of which could be syndrome specific, can lead to similar alterations in language development trajectories. Moreover, those domains that show atypicalities in both ASD and ADHD may also be atypical in some other neurodevelopmental disorders. For example early motoric delays (or accelerations) could be indicators of a trajectory of brain development that is generally accelerated or slowed (Johnson et al., in press).

There are a number of reasons why common markers across different outcomes may be observed: (1) ADHD and ASD are actually two manifestations of a common underlying disorder, and therefore the earliest emerging markers are common, (2) ASD and ADHD share a common endophenotype(s), in addition to factors specific to each condition, (3) common compensatory mechanisms of brain adaptation are evoked in both syndromes. We now consider each of these possibilities in the light of the evidence we have reviewed on early predictors, and discuss the extent to which they can potentially be teased apart by evidence from the infancy period.

(1) Are ASD and ADHD really a common underlying disorder?

As mentioned in the Introduction, despite the different diagnostic categories, some experts have proposed that these syndromes could be manifestations of a common underlying disorder (van der Meer et al., 2012). From this perspective, finding common early predictors would be expected, and we would predict little success in the search for syndrome-specific infant predictors. has suggested a pattern of early commonalities that then increasingly diverge with development. Another possibility is that ADHD may represent a milder form of the same underlying condition as ASD (van der Meer et al., 2012). From our review of existing evidence, differences in measures such as head circumference or motor skills seem incompatible with identical early profiles. However, the possibility remains that some underlying endophenotypes are shared.

(2) Do ASD and ADHD share a sub-set of common endophenotypes?

A second model proposes that while ASD and ADHD are distinct syndromes, they share one or more endophenotypes in common (Figure 1B). This was inspired by finding similar performance in, for example, measures of empathy, sensory responsiveness or emotion regulation (reviewed in Rommelse et al, 2011), but also by twin studies showing that that more children with one condition show *features* of the other condition than show complete comorbidity (Ronald et al, in press). Under this model, we predict longitudinal continuity for the specific domains that are underpinned by common endophenotypes. For example, early life motor milestones being delayed for some individuals who go on to both conditions could be interpreted as reflecting a common underlying endophenotype that is then shared between the two diagnostic categories in later life. Alternatively, delayed milestones could be a more general reflection of atypical developmental trajectories, and therefore will also be observed in other developmental disorders. Thus, whether endophenotypes that are *only* shared between ASD and ADHD exist will depend on similar investigations of other developmental disorders. Finding common endophenotypes will be helped by dimensional approaches to ASD and ADHD characterization where early markers for particular symptoms (e.g. inattention or poor joint attention) are assessed across disorders.

The level at which the investigation is carried out, molecular, neuronal function or behavioural, will also determine whether common endophenotypes are observed or

not. For example, it is possible that common genetic factors that act on brain growth are switched on at different time points in pre-natal development (by other genetic or environmental factors), leading to either accelerated or reduced growth. Later expression of particular genetic risk factors in post-natal life, could lead to delayed manifestations of a disease to adolescence. Lifespan transcriptome analysis has revealed a period of less cortical differential activity, during which the deviation from the ‘‘typical’’ neuronal development might not be obvious at the phenotypic level. Later in adolescence, even without additional insults, reorganization of neural networks (as indexed by increased transcriptome cortical differential activity) reveal the long-existing, hidden deficits, leading to establishment of such diagnoses as ADHD or schizophrenia (Korade & Mirnics, 2014).

(3) Brain adaptation and common compensatory factors

Under this third scenario (Figure 1C, D), common infant markers of outcome are observed because they reflect common mechanisms of brain adaptation or compensation, in the face of mild but widespread disturbances to early brain function (Johnson, 2012, Johnson et al. in press). As discussed earlier, Johnson (2012) argued good prefrontal EF skills may be a protective factor across several different development disorders (Figure 1D). Under this view, poor EF skills in infants at-risk will tend to be associated with later diagnoses. The reductions in “effortful control” observed in both toddlers who go on to later ASD and ADHD diagnoses are consistent with this proposal, but clearly further work is required. A more radical proposal is that key diagnostic features of ASD, and possibly also ADHD, are primarily manifestations of brain adaptation in the face of poor quality signal processing early in life (Johnson et al. in press; Figure 1C). Under this view, the diagnostic features of ADHD differ from those in ASD by virtue of the time in the life course when the adaption processes begin (happening in ASD before ADHD), and co-morbidity is a likely consequence of processes of adaptation being engaged over a longer period. This model presupposes that a variety of different initial underlying causes lead to common adaptive responses and therefore to common behavioural markers. A possible example of an adaptive response in ASD could be stereotypic behaviour. The child with emerging ASD has difficulties with processing the higher-level regularities of social interaction and chooses instead to create simpler and more predictable interactions and stimulation. Similarly, one could imagine that stereotypic

behaviour confers regularity to otherwise disorganised behaviour and attention in ADHD. Although stereotypic behaviour has not yet been documented during infancy, it is present in older children with ADHD (Hartley & Sikora, 2009).

Recommendations for future work

Causes or consequences: One of the benefits of studying the emergence of conditions such as ASD and ADHD is that the earliest emerging signs are assumed to be closer to the genetic and environmental causes of the atypical trajectory of development. Traditionally, when studying infants at high risk, investigators have typically chosen tasks in infants that are thought to be domain-relevant precursors. For example, social orienting is assumed to be a necessary precursor skill for more advanced social perception and cognition, and therefore has been a primary target for groups investigating infants at high risk for ASD. The work we have reviewed suggests the need for two other categories of infant measure; the first of these are putative markers that are stable from initial appearance through to the diagnosed syndrome. For example, repetitive behaviours in ASD could provide a continuous marker that precedes diagnosis but persists throughout an extended period of development. This would be indicative of an endophenotype that may have secondary consequences, but persists over the long-term. A second category of marker that has been less considered to date are those that reflect a temporary disturbance of functional brain development that may have little apparent surface similarity to its consequences. Johnson et al. (in press) discuss a number of examples of behavioural traits that may result from mechanisms of brain adaptation in the face of early disturbances to synaptic function. The resulting adaptations may bear little resemblance to the original atypicality as they represent a whole developing brain's attempts to select an environment that best suits its own capacities. For example, by this view withdrawal from social interactions in toddlers with emerging ASD is a consequence of their inefficient processing of complex spatial-temporal information. In this case, infant predictors of the efficiency of synaptic processing will be better candidate predictors than domain-relevant social responses.

The effect of risk group: Clearly, the work reviewed above indicates the critical importance of measuring both ASD and ADHD symptoms and examining their relation to infant markers within particular cohorts. For example, no study of infants

with older siblings with autism to date has reported whether putative autism markers relate to ADHD-type symptoms; this is a limitation of the field that should be addressed. However, examining whether markers represent endophenotypes for ASD or ADHD requires us to not only study infants at high risk for both outcomes, but to study infants who may be at high risk for different reasons within the same protocol (e.g. prematurity, early environmental exposure, familial risk, single gene mutations). This is particularly important in differentiating infant markers that represent common risk factors from those that represent common protective or compensatory factors. For example, if behavioural symptoms of ASD and ADHD represent common compensatory responses to a multitude of original risk factors (Johnson et al., in press), one would predict that infant markers that reflect compensatory responses should be observed across multiple risk groups, whilst infant markers of the original risk factor may be risk-group specific. Thus, we argue that it will be critical to examine which aspects of causal paths to developmental disorders are shared versus distinct in different risk groups.

In order to better unravel causal factors, studies of infants selected to be at familial or perinatal factor risk (such as prematurity) will also need to be supplemented by studies of infants with de-novo or single gene mutations. Single gene mutations have the obvious advantage that one of the original causal factors is known. However, since the prevalence of ASD and ADHD in children with single gene mutations is rarely 100% (e.g. c.25% ASD and c.50% ADHD in NF1; Garg et al., 2013, c.40% ASD and c. 50% ADHD in TSC; Bolton, Park, Higgins, Griffiths, & Pickles, 2002; Numis et al., 2011; Vries, Hunt, & Bolton, 2007), it is important to recognise that pathways to later behavioural traits of ASD or ADHD will be a complex one. As an example of the potential of studying single gene disorders, a recent study indicated that approximately 25% of individuals with the NF1 mutation meet criteria for ASD, and approximately 50% meet criteria for ADHD (Garg et al., 2013). However, the rate of ADHD was similar in the groups with and without ASD, indicating no statistical association between the two disorders. This raises the intriguing possibility that NF1 mutation impacts neurophysiological mechanisms that act as common risk/protective factors for both ASD and ADHD, revealing the base rate of risk for the two disorders. Mapping early causal paths to later ASD and ADHD symptoms in infants with NF1 versus infants with other risk factors (e.g. familial risk)

may thus allow us to tease out markers that represent the absence of protective factors from those that represent active risk factors for each condition.

Early intervention: A better understanding of common and different causal pathways to ASD/ADHD should allow for more targeted interventions (e.g. directed at social and communication skills, Wallace & Rogers, 2010; versus directed at attention skills, e.g. Wass, Porayska-Pomsta, & Johnson, 2011). Such interventions may also reveal causal mechanisms in developmental pathways (Green et al., 2013). Parent-mediated interventions may be particularly powerful in early infancy, since parental behaviour affects both social-communicative learning (Tamis-LeMonda, Song, Leavell, Kahana-Kalman, & Yoshikawa, 2012) and the development of executive functions (Cuevas et al., 2014). Identifying common protective factors may be particularly important, because interventions that target these factors would be applicable to a broad range of conditions. Further, identifying which early risk markers have cascading consequences and which are simply reflections of the disease process will be critical in determining the most critical intervention targets. For example, transient delays in achieving motor milestones could contribute to later socio-communicative delays because infants are not able to actively influence their social environment to the same extent; alternatively, motor delays may simply reflect an immature nervous system. In the former case, specifically treating early motor delays may bring benefits for social communication skills; this would not be true of the latter case.

However, bridging the gap to clinical applicability requires increasing the translational focus of infant experimental work. For example, showing that an intervention is effective requires the definition of primary outcome variables that are clearly understood to represent improvement in the targeted construct. Typically, these variables should be valid and reliable, and the expected change should be clearly positive for the child (e.g. improved language skills, reduced hyperactivity). However, there are very few infant measures that currently meet these criteria. Test-retest reliability of infant markers has rarely been reported, and the kind of robust replicated longitudinal associations between infant markers and later development that would be required to demonstrate which direction of change would be viewed as positive are still broadly lacking. Further, tackling ethical issues surrounding the application of intervention to infants who are at 'risk' will be important, since this entails providing a 'treatment' to infants who would not have necessarily developed

any behavioural symptoms. Since clinical provision has traditionally been targeted on the basis of experienced difficulties, this represents an important conceptual shift that raises significant ethical issues. One approach that has begun to emerge is for prodromal interventions to draw on generic developmental approaches that have been shown to support positive parenting or cognitive control rather than to target emergent, or not yet apparent, atypicality (Green et al., 2013; Wass et al., 2011).

Measurement issues: Coghill and Sonuga-Barke (2012) review evidence suggesting that ASD is qualitatively distinct from typical development, whilst ADHD symptoms represent the extreme of a continuous distribution. Evidence from infant precursors has the potential to inform this debate. However, most studies currently examine either categorical outcome of ASD, or dimensional measures of ADHD symptoms. In the ASD field this is despite increasing recognition that the behavioural elements that constitute the diagnostic triad/dyad (social and communication impairments; repetitive and restricted behaviours) are only moderate phenotypically and aetiologically associated . Examining whether predictors of categorical outcome also relate to continuous variation in individual dimensions of symptomology within the population will provide valuable information about the categorical vs. dimensional nature of diagnosis. Further, increasing the comparability of measures of ASD and ADHD symptoms will also be valuable. Finding that a marker relates to ADHD but not ASD symptoms can only be viewed as robust if those symptoms are measured with comparable power and accuracy. Variation in the use of parent-report versus observational assessments, or the psychometric properties of particular instruments could impact the degree to which an infant marker is related to ASD or ADHD symptoms at outcome. To date in the ASD familial at risk sibling studies, outcome has mostly been reported in terms of diagnosis of ASD at age 3 years despite considerable variability in the course of ASD from the toddler years into middle childhood and later life. Given the later age at which a clear diagnosis of ADHD can be confirmed, longitudinal studies of infants at risk for ASD and ADHD will be required to adopt a long-term approach to understand the developmental outcomes of early atypical development.

Another factor that need to be considered are the degree to which sex differences in risk factors, or the expression of risk factors, are involved. Both ASD and ADHD are more common in males than females and the mechanisms that lead to

this sexual dimorphism are only partly understood. Although there is clinical evidence that recognition and possibly expression of the phenotypes might differ in males vs. females (Dworzynski, Ronald, Bolton, & Happé, 2012; Lai et al., 2012; Mandy et al., 2012) it has yet to be determined that neurodevelopmental processes that lead to the ASD and ADHD phenotypes differ between sexes. The sample sizes that will be required in order to examine these factors with appropriate statistical power are a challenge for both scientists and funding agencies.

Conclusions

Our review of infant precursors for the later emergence of ASD or ADHD has overall revealed more evidence for commonalities than syndrome-specific early markers. However, in discussing these findings we note that the criteria for establishing that a marker is unique to a syndrome are challenging, and further that there are multiple possible explanations for why different diagnostic syndromes may share common early life predictors. We conclude that future work needs to examine the relation between infant predictors and ASD and ADHD symptomology in the same cohorts, with both categorical and dimensional outcome measures. Models should test whether apparently similar early symptoms reflect the same or different underlying causal mechanisms, and whether apparently different patterns of early atypicality (e.g. motor milestones, head circumference) support strong conclusions about qualitatively different causal paths. Examining these domains in children with different patterns of co-occurrence will also be critical. Finally, realizing the potential of this field to provide transformative clinical change requires an increased focus on laying the translational foundations for the development of new intervention paradigms.

Box 1: Relating infant features to later outcome: Terminology

There are several ways in which particular patterns of cognitive, biological or behavioral features in infancy may be related to later outcome of ASD or ADHD, each associated with different terminology. Different relations require different types of supporting evidence, as outlined below.

Markers/Predictors

'Marker' implies that the infant feature is significantly associated with later ASD or ADHD, but does not carry any further causal or mechanistic implications. Depending on the domain in which the marker is observed, it may also be more specifically termed a biomarker, cognitive marker or behavioral marker. Demonstrating that an infant feature is a marker for ASD or ADHD simply requires demonstration of a statistical association between the presence of the marker and the presence of the diagnosis.

Precursors

A precursor is a marker that precedes diagnosis of ASD or ADHD, and additionally indicates the approach of the disorder. Thus, we reserve the term 'precursor' for markers that are domain-relevant to the behavioral symptoms characteristic of ASD and ADHD. Demonstrating that an infant feature is a precursor for ASD or ADHD thus requires demonstration of a statistical association between the presence of the marker and the presence of the diagnosis; that the marker be present before the classic diagnostic symptoms of the disorder; and that the marker is relevant to core symptom domains. For example, early social communication delays may be precursors to later ASD at 12 months (Ozonoff et al., 2011).

Antecedent

An antecedent is a type of marker that precedes diagnosis of ASD or ADHD. Typically, use of the term 'antecedent' implies some degree of causal relation between the marker and the later outcome (something which 'logically precedes' another). Demonstrating that an infant feature is an antecedent for ASD or ADHD thus requires demonstration of a statistical association between the presence of the marker and the presence of the diagnosis; that the marker be present before the classic diagnostic symptoms of the disorder; and that there should be some evidence that the marker is at least logically causally related to the end phenotype. Antecedents will be needed to describe causal associations between atypical features in infancy that initiate specific adaptive responses, where these adaptive responses are behavioural features of developmental disorders. In this case, the infant marker need not appear to be domain relevant.

Endophenotypes

Endophenotypes are particular kinds of marker that fulfill five key criteria (Gottesman & Gould, 2003). Specifically, they should be associated with ASD /ADHD in the population; be heritable; be primarily state-independent; co-segregate with ASD/ADHD in families; and potentially also be found in unaffected family members of individuals with ASD/ADHD at a higher rate than in the general population. To date, there are no infant markers that fulfill all of these criteria. However, examining the infant manifestation of endophenotypes observed in work with diagnosed individuals (e.g. Rommelse et al., 2011) is an important step in understanding ASD/ADHD across the lifespan. Unlike precursors and antecedents that can be transient and occur at a single developmental time point, endophenotypes are assumed to be long-lasting or permanent features of the child's biology.

Protective factors or compensatory markers

A protective or compensatory marker would be a marker associated with neurotypical development within the context of increased risk. Identifying such markers would require demonstrating that within infants displaying early risk markers, the protective marker was associated with not developing ASD or ADHD. Within infants without early risk markers, the protective factor may exhibit no statistical association with later neurotypical development. Good executive functioning skills may be one example, although this is yet to be tested in longitudinal prospective studies (Johnson, 2013).

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Figure Legend

Figure 1 shows four possible models of the developmental emergence of behavioural symptoms of ASD and ADHD. For simplicity, bidirectional interactions between genetic and environmental risk factors, intermediate phenotypes and behavior over developmental time are not shown. A: ASD and ADHD are associated with condition-specific risk markers; in addition, there are risk factors that specifically lead to comorbid ASD and ADHD. Here, some children with comorbid ASD and ADHD would represent a separate clinical group, whilst others would represent children who presented with risk factors of both ASD and ADHD. Testing this model in infancy requires studying the relation between early markers and later symptoms of ASD, ADHD and their overlap. B: Here, ASD and ADHD are caused by a combination of general risk markers, and condition-specific risk markers. C: Here, common risk factors and adaptive processes are activated at condition-specific points in development. Comorbidity is created by a longer period of activation. Condition-specific genetic and environmental factors affect the timing of expression of common risk markers. To test such models, it is critical to collect repeated measures of the same markers over time. D: Risk factors for ASD and ADHD are condition-specific, but require the absence of condition-general protective factors to be expressed. Here, comorbidity simply results from the statistical overlap of the presence of risk factors for ASD and ADHD.

Key: RM = Risk Marker; PF = Protective Factor; A = ASD; D = ADHD; AD = Adaptive response. GE = genetic and/or environmental risk factors.

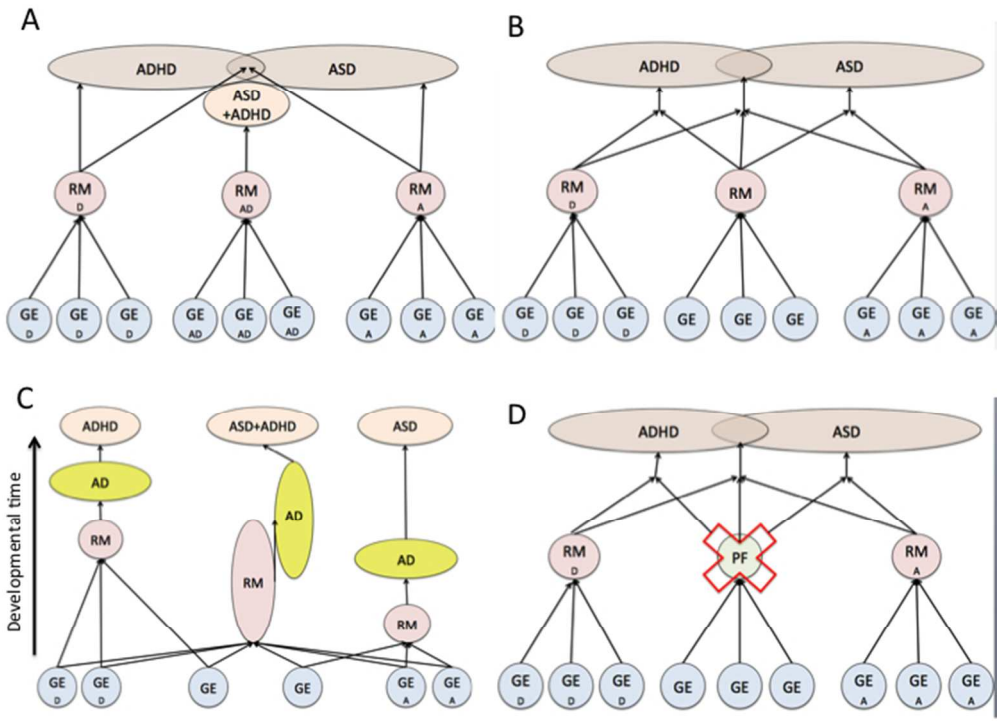

Figure 1.
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