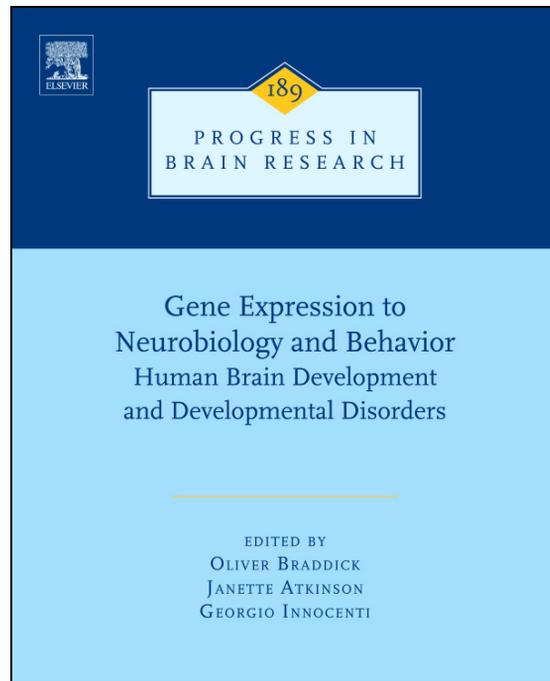


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CHAPTER 11

Social and attention factors during infancy and the later emergence of autism characteristics

Mayada Elsabbagh^{†,*}, Karla Holmboe^{†,‡}, Teodora Gliga[†], Evelyne Mercure[†],
 Kristelle Hudry[§], Tony Charman[§], Simon Baron-Cohen[¶], Patrick Bolton[‡],
 Mark H. Johnson^{†,*} and The BASIS Team¹

[†] *Centre for Brain and Cognitive Development, Birkbeck, University of London, London, UK*

[‡] *Institute of Psychiatry, King's College, London, UK*

[§] *Centre for Research in Autism and Education, Institute of Education, London, UK*

[¶] *Autism Research Centre, University of Cambridge, UK*

¹*The BASIS team in alphabetical order: Rachael Bedford, Susie Chandler, Sally Clifford, Janice Fernandes, Holly Garwood, Hayley Leonard, Leslie Tucker, and Agnes Volein.*

Abstract: Characteristic features of autism include atypical social perception and social–communication skills, and atypical visual attention, alongside rigid and repetitive thinking and behavior. Debate has focused on whether the later emergence of atypical social skills is a consequence of attention problems early in life, or, conversely, whether early social deficits have knock-on consequences for the later development of attention skills. We investigated this question based on evidence from infants at familial risk for a later diagnosis of autism by virtue of being younger siblings of children with a diagnosis. Around 9 months, at-risk siblings differed as a group from controls, both in measures of social perception and inhibitory control. We present preliminary data from an ongoing longitudinal research program, suggesting clear associations between some of these infant measures and autism-related characteristics at 3 years. We discuss the findings in terms of the emergent nature of autism as a result of complex developmental interactions among brain networks.

Keywords: autism; development; visual attention; face processing.

Modeling interactions in the developing brain

The human brain is a dynamic and self-organizing system. In the course of development, interactions among multiple systems give rise to highly specialized networks in adults. Among various strategies, the study of atypical development has

*Corresponding authors.

Tel.: +44 207 631 6231; Fax: +44 207 631 6258

E-mail: m.elsabbagh@bbk.ac.uk; mark.johnson@bbk.ac.uk

been used to illuminate the typical pathways through which the brain becomes wired. A key challenge for understanding both typical and atypical development is to model complex interactions among systems and over time (Johnson, 2011). In view of probabilistic epigenesis, where development is the result of bidirectional interactions among brain structure and function, a wide range of individual differences is to be expected. In addition, although much progress has been made in describing the resulting typical and atypical adult phenotypes, very little is understood about the developmental processes that give rise to variability in manifestations, and why certain domains of functioning in some conditions are more profoundly affected than others. These considerations stress the importance of studying the ontogeny of atypical development from the earliest possible stages (Karmiloff-Smith, 1998). Such approaches provide the opportunity to study the emergence of perturbations in brain and cognitive development, the interactions between systems as they develop, and the effects of compensatory mechanisms.

Several research approaches have exploited the fact that typical and atypical development are mutually informative and are most beneficially studied hand-in-hand (Karmiloff-Smith, 1998). For example, there is growing interest in the study of autism, a developmental condition characterized primarily by impairments in social and communication skills, as a model for the development of the “social brain” (Johnson et al., 2005; Senju and Johnson, 2009). In typical adults, regions such as the orbitofrontal cortex, the amygdala, temporal lobe face-sensitive regions, temporo-parietal junction, and the superior temporal sulcus (STS) are among those primarily involved in the processing of socially relevant information (Adolphs, 2003). Multiple sources of evidence have suggested atypical functioning of the social brain network in autistic adults (Pelphrey and Carter, 2008). The study of older children and adults with autism may therefore contribute toward understanding the default pattern of specialization in the typical brain.

Beyond those models concerned with characterizing the adult phenotype, developmental models have taken different views on the emergence of autism, highlighting complex interactions between brain networks subserving social cognition and those related to nonsocial skills. Often debated is the relative contribution of potential infant precursors, that is, infant capacities mediating the later-emerging characteristic symptoms of the condition. It has been suggested that a failure, or abnormality, in one or more of the underlying mechanisms that bias infants to orient toward and attend to socially relevant information from early in life, disrupts the typical emergence of the social brain network (Dawson et al., 2005; Johnson et al., 2005; Schultz, 2005). For example, atypical neural responses to face and/or eye contact may interfere with the emergence of critical developmental milestones relevant for social cognition, such as joint attention. These cascading influences may eventually preclude the typical development of socio-communicative skills.

One challenge to this specificity view is that autism is also associated with a range of nonsocial impairments. For example, problems in executive functions (i.e., those mechanisms that guide actions in an endogenous goal-driven way, despite conflicting demands from the immediate environment) are often affected in autism. In typical adults, multiple distributed neuroanatomical systems, primarily associated with the prefrontal cortex, mediate such functions (Kramer and Quitania, 2007; Stuss, 2007). Some researchers have proposed that impairment in the prefrontal cortex is secondary to those found in social-communicative systems in the medial temporal lobe (Dawson et al., 2002; Griffith et al., 1999). An alternative account suggests that key characteristics of autism have their origins in early nonsocial abilities. Specifically, problems in executive functions may give rise to later emerging social impairments characteristic of autism such as those observed in theory of mind (Russell et al., 1999). Yet another view is that both

social-orienting deficits and executive dysfunction originate from early impairments in other systems critical for both domains, for example, those found in disengagement of visual attention (Landry and Bryson, 2004). According to the latter view, the infant's inability to flexibly switch the locus of attention leads to problems in self-regulation as well as a decrease in social orienting. By late childhood or adulthood, atypical disengagement is commonly reported in autism (Kawakubo et al., 2007; Landry and Bryson, 2004; van der Geest et al., 2001).

An intermediate perspective between those outlined above is that the social brain emerges as a result of "interactive specialization," in which the adult pattern of cortical specialization arises through a process of increasing functional specialization (or tuning) in response to interactions between cortical (and subcortical) regions during postnatal development (Johnson, 2001). According to the interactive specialization view, biases in attention and processing in early infancy are reinforced by differential patterns of experience, subsequently resulting in the patterns of specialization observed in adults. In autism, disruption in the typical emergence of the social brain network emerges as a function of an atypical early trajectory, which becomes compounded by atypical interactions with the environment, leading to the well-established pattern of symptoms becoming embedded and observable by the age of diagnosis (Johnson et al., 2005).

Converging lines of evidence from studying very young children, diagnosed with autism around 2–3 years of age, indicate that general deficits as well as specific precursors to some symptoms are present early on in autism (Elsabbagh and Johnson, 2010). By the time of diagnosis, several co-occurring impairments are clear, and encompass both social and nonsocial domains. After the onset of these symptoms in the early years, different sets of abilities show varying trajectories of development. Some social abilities, such as face processing, are seriously impaired, but over time, compensatory strategies and atypical neural systems may restore

behavioral performance to within the typical range. Other deficits, such as executive dysfunction, may not be evident at younger ages but become evident over development. In all cases, substantial variability is seen in the resulting phenotype (Elsabbagh and Johnson, 2010).

Testing competing theoretical alternatives for developmental interactions in autism has been challenging so far because nearly all research on the condition and its neural basis has been conducted on children and adults well after the full spectrum of symptoms has emerged. In fact, a key challenge for developmental accounts of autism is that the condition is currently defined and diagnosed on the basis of behavioral features that are not reliably observed before 2 and 3 years of age. However, insights into the nature of such developmental interactions in infancy have recently emerged from the study of infants at risk for autism.

Infants at risk for autism as a model for studying developmental interactions

In the hope of discovering early markers of the condition, attention has recently turned to the study of infant siblings of children with autism, pioneered by our group (Baron-Cohen et al., 2002) and now widely studied (Elsabbagh and Johnson, 2010; Yirmiya and Charman, 2010; Zwaigenbaum et al., 2007). Since the condition is highly heritable, later-born siblings of diagnosed children are at substantially higher risk for developing the condition than the general population (Bolton et al., 1998). Several studies have attempted to retrospectively differentiate the at-risk infants who subsequently receive a clinical diagnosis (the "affected" group) from those who do not (the "unaffected group"), as well as from low-risk infants with no family history of autism. Current evidence indicates that infants who subsequently receive a diagnosis as toddlers begin to be identified from around 12 months of age, on the basis of atypical social

and nonsocial behaviors such as unusual eye contact, lack of orientation to name, and reduced flexibility in switching attention. There is growing consensus that the behavioral manifestations of autism in the first year of infancy are subtle and that symptoms emerge gradually during development (reviewed in [Elsabbagh and Johnson, 2010](#)).

In addition to its clinical significance, the potential of this approach in informing theoretical models of typical and atypical development has been readily recognized. While the search for early diagnostic markers continues, we have suggested that studying development of infants at risk as a group may provide a viable model for developmental interactions among brain systems ([Elsabbagh and Johnson, 2010](#)). Such a model would, in turn, have significant implications for developing earlier and more reliable markers of the condition. Several findings suggest that at-risk infants, as a group, share some characteristics related to the condition known as the broader autism phenotype (BAP), thus blurring the boundary between those with and without a diagnosis. In adults, the BAP refers to behavioral and brain characteristics associated with autism found not only in affected individuals but also in their relatives ([Belmonte et al., 2010](#); [Bolton et al., 1994](#); [Dawson et al., 2005](#)). As such, several characteristics of autism might not be atypical, but their co-occurrence and severity within an individual determine whether they manifest as subclinical normative differences, as opposed to diagnosable symptoms.

While overt behavioral signs of autism in everyday interactions are rarely observable in the first year, cognitive neuroscience methods have recently differentiated groups of infant siblings at risk from low-risk control groups of infants. Putative BAP effects have been reported in visual processing ([McCleery et al., 2007](#)), flexibility of switching attention ([Elsabbagh et al., 2009b](#)), and inhibitory control ([Holmboe et al., 2010a](#)). Direct measurement of brain activity has also revealed early differences in response to face stimuli ([McCleery et al., 2009](#)) and in sensitivity to the direction of eye gaze ([Elsabbagh et al., 2009a](#)).

Studying the development of infants at risk can therefore provide a valuable strategy for understanding how early vulnerability gives rise to variable outcomes over time. The assumption here is that diagnosed forms of autism, which are themselves highly variable, are extremes of what is otherwise typical variation.

This “quantitative” approach toward assessing the characteristics of autism in those who are diagnosed, as well as in their biological relatives, has been strongly advocated in recent years. Increasingly, researchers in genetics, in particular, have turned to dimensional intermediate or endophenotypes, viewed as closer to the genotype than complex clinical characterization. Such measures of quantitative traits associated with autism and overlapping with other disorders are viewed as better candidates for gene mapping than diagnostic classification ([Abrahams and Geschwind, 2008](#); [Newbury et al., 2005](#); [Skuse, 2001](#)). Hence, apart from elucidating interactions among brain systems over development, such infant intermediate phenotypes based on experimental methods are likely to significantly advance research across these various disciplines.

While using this at-risk group to model developmental interactions may be appealing, it does pose significant methodological challenges. The success of this approach rests on our ability to complement group data with the validation of dimensional (individual difference) measures for assessing both risk and outcome, also allowing for testing of developmental interactions. The goal of this chapter is to provide preliminary findings to establish the feasibility and utility of infant laboratory measures of brain function and cognition for predicting the variation in key characteristics of autism in toddlerhood.

Infant precursors for autism characteristics: An overview

Data in the current study were made available through the British Autism Study of Infant

Siblings (BASIS; [Appendix](#)). BASIS families enroll in a longitudinal research program when their infants at risk for autism are below 1 year of age and they are followed up over time until toddlerhood. The current analysis was based on data from the first (pilot) BASIS cohort. Thirty-one families were seen for the first visit at the Babylab, Centre for Brain and Cognitive Development at Birkbeck, when the infants were around 10:0 months of age ($SD=49.6$ days). Subsequently, 27 families returned for a research assessment when the children were between the ages of 3 and 4 years (mean = 40.4 months, $SD=3$ months). All participating families had an older child with a community clinical diagnosis of an autism spectrum disorder (see [Appendix](#) for further details).

In two previous studies, we reported differences between groups of infants at risk for autism and control groups with no family history of autism on two measures: target tasks of saccadic inhibitory control ([Holmboe et al., 2010a](#)), and sensitivity to eye gaze ([Elsabbagh et al., 2009a](#)). Selection of these measures was based on theoretical considerations discussed earlier. First, both tasks have been previously validated with groups of typical infants ([Farroni et al., 2002](#); [Holmboe et al., 2008](#)). Second, atypicality in both areas has been previously associated with autism in those who are diagnosed ([Grice et al., 2005](#); [Hill, 2004](#)) and in unaffected siblings ([Belmonte et al., 2010](#); [Dalton et al., 2007](#)) in childhood and/or adulthood. Finally, the two target domains have been previously hypothesized to be precursors of later emerging characteristics of autism ([Elsabbagh et al., 2009a](#); [Holmboe et al., 2010a](#)).

The aim of the current analysis was to ascertain the extent to which individual differences among infants at risk measured using the two tasks of gaze sensitivity and inhibitory control map dimensionally onto characteristics of autism in the same individuals in early childhood. To measure the severity of autism-related characteristics, we used the Autism Observation Diagnostic Schedule-Generic (ADOS-G; [Lord et al., 2000](#)) with the children between their third and fourth birthdays.

The ADOS assessment measures the extent of atypicality in target items such as engagement in joint attention and use of eye contact, facial expression, and gesture for social communication, as well as the presence of unusual sensory-motor behaviors and repetitive/stereotyped interests. Higher overall scores indicate greater impairment across the range of target measures. Three ADOS dimensions (see [Appendix](#) for further details) were used in the current analysis: atypical communication ($M=2.9$, $SD=2.1$, possible range: 0–10), atypical social interaction ($M=4.2$, $SD=3.2$, possible range: 0–14), and presence of stereotyped behaviors/restricted interests ($M=1.1$, $SD=1.3$, possible range: 0–6).

Both theoretical and methodological considerations motivated use of the ADOS as a dimensional measure of the characteristics of autism. First, while the ADOS has not been tested in relation to brain functions, target measures in the instrument are likely to recruit multiple circuits in the social brain. Second, the measure is particularly valid for use with a group of infants at risk for autism (as opposed to a general population sample) because it taps key characteristics reliably associated with the condition. Third, the ADOS is an observer-rated measure of autism characteristics and was conducted more than 2 years after the experimental task, thus minimizing spurious associations due to measurement confounds. Finally, the assessment provides an adequate measure of individual differences, particularly in relation to functional impairment in social and communication abilities, permitting mapping of these outcome scores onto scores derived from infant laboratory measures.

To assess the correspondence between precursor infant measures and the later emerging characteristics of autism, similar statistical models as in the previous publications were used, but the three ADOS dimensions were entered as variables in the model. Of key interest were the interaction terms between the main factors tested in each task and the ADOS dimensions. Given the relatively small sample sizes, the primary

aim was to consider preliminary findings that can be used in refining future hypotheses to be tested with larger samples. The latter would permit modeling of the relationship among multiple predictors and outcome measures. Analyses and findings from each task are detailed below.

Sensitivity to eye contact: Event-related potentials in response to static gaze direction

Typically developing infants display very early sensitivity to gaze (Batki et al., 2000; Farroni et al., 2002), which develops rapidly in the first few years in the form of social referencing, joint attention, and communication more generally. Qualitatively unusual patterns of eye contact may reflect, or indeed precede, the more widespread deficits in communication and social interaction observed in autism (for a review see Senju and Johnson, 2009). Behavioral studies of children and adults with autism have demonstrated that the use of gaze cues in social contexts such as joint attention (Baron-Cohen, 1989; Leekam et al., 1998) or in inferring mental states (Baron-Cohen and Hammer, 1997) is an area often impaired in autism. Electrophysiological and neuroimaging studies have documented atypical neural correlates of gaze processing in autism. Using high-density Event Related Potentials (ERP) recording, passive viewing of faces with direct gaze on static faces elicited larger occipito-parietal negativity than averted gaze in 4- to 7-year olds with autism, a pattern not seen in typically developing children of the same age (Grice et al., 2005). Also, adult siblings of individuals with autism, who do not themselves have a diagnosis, show diminished fusiform activation correlated with reduced gaze fixation, similar to that seen in their affected siblings. Even at the neuroanatomical level, amygdala volume in siblings has been found to be significantly reduced (Dalton et al., 2007).

Based on these converging lines of evidence, we previously hypothesized that atypical sensitivity to eye gaze may be an early precursor of a

variety of social and communication difficulties observed in children with autism and, to a lesser degree, in at-risk siblings (Elsabbagh et al., 2009a). We tested this hypothesis by examining the neural correlates of the direction of eye gaze displayed on static face images. The brain's spontaneous electrical activity (EEG) was recorded while infants viewed photographs of females displaying direct or averted gaze. From the initial group, 16 at-risk siblings (8 boys and 8 girls, mean age = 9:3 months) completed sufficient trials to permit inclusion in the analysis and were followed up in toddlerhood.

Measures of interest were the mean amplitude and latency of face-sensitive ERP components in infancy: P1, N290, and P400. The P1 is observed in both infants and adults in response to visual stimuli including faces. It has been suggested that the P1 reflects an early stage of visual information on faces (de Haan et al., 2003). By contrast, the latter two components are thought to be precursors to the N170 in adults, a face-sensitive component (de Haan et al., 2003) reported to be atypical in individuals with autism as well as their genetic relatives (Dawson et al., 2005). In our previous study with this pilot cohort, we found that infants at risk as a group showed a slower P400 response to direct gaze relative to the control group (Elsabbagh et al., 2009a).

For the current analysis, we focused on variability within the at-risk group. Key variables from the ERP task were the amplitude and latency of the P1, N290, and P400 in response to either direct or averted gaze displayed on static images of faces. Four general linear models (GLMs) were used for the amplitude and latency of the three components. Factors included were condition as a repeated measures factor (direct vs. averted gaze) and the three ADOS dimensions (social interaction, communication, and stereotyped behaviors) as continuous variables. We also controlled for age (in days) at the first visit in infancy as a continuous variable.

A significant condition \times ADOS Communication was observed for the P1 amplitude ($F(1,$

11)=5.5, $p=0.03$, $\eta^2p=0.33$) and condition \times ADOS stereotyped behaviors for the P400 amplitude ($F(1, 11)=5.6$, $p=0.03$, $\eta^2p=.34$). Communication scores at the age of 3 years were strongly associated with the infancy P1 response to averted gaze ($r=-0.70$, $p=0.001$) but not to direct gaze ($r=0.23$, $p=0.34$). Moreover, those infants who had a more positive P400 response to direct relative to averted gaze tended to exhibit less stereotyped behaviors and restricted interests at 3 years ($r=-0.48$, $p=0.05$). None of the condition \times ADOS dimensions interactions reached significance for the latency of the three components. In addition to these interaction effects, a main effect of the ADOS social interaction dimension approached significance for the N290 ($F(1, 11)=3.9$, $p=0.07$, $\eta^2p=0.26$). Greater functional impairment at 3 years was associated with a less negative N290 ($r=0.48$, $p=0.05$) averaged across direct and averted gaze.

Inhibitory control: The Freeze-Frame task

Executive functions, frequently associated with the prefrontal cortex (Kramer and Quitania, 2007; Stuss, 2007), include abilities such as planning, monitoring, working memory, and inhibition. So-called executive dysfunction in autism is commonly manifested in terms of rigidity and preference for sameness, repetitive and restricted interests, and behaviors. These manifestations fall under the diagnostic characterization of stereotyped behaviors and restricted interests. Difficulties in executive function tend not to be as universal as those found in social communication (Hill, 2004). Moreover, similar deficits tend to be present in various developmental conditions including attention deficit/hyperactivity disorder and Tourette syndrome, although some argue that a specific profile of executive dysfunction can be found in individuals with autism (Ozonoff and Jensen, 1999). Uncertainty arises, in part, due to the wide range of tasks and the different levels of complexity assessed by these tasks.

However, the performance of individuals with autism on tasks of planning and mental flexibility is consistently impaired (Hill, 2004). Atypical frontal cortex functioning has been associated not only with people with autism but also with their genetic relatives. An fMRI study found that unaffected siblings showed atypical fronto-cerebellar activation in a visual divided attention task (Belmonte et al., 2010).

Although executive functioning is not usually measured in infancy, one such task has recently been developed (The “Freeze-Frame task”; Holmboe et al., 2008), which maps onto established measures of this aspect of cognition in toddlerhood, and is associated with genes regulating dopaminergic neurotransmission in the frontal cortex (Holmboe et al., 2010a,b). The Freeze-Frame task measures attentional flexibility and regulation of looking behavior in response to changes in the visual environment. Specifically, the task examines whether the value of a centrally presented fixation target modulates automatic orienting responses to briefly presented peripheral distractors. The task is similar to the “fixation shifts” paradigm used previously in typically developing infants and infants with perinatal brain damage (e.g. Atkinson et al., 1992; Braddick et al., 1992; Hood and Atkinson, 1990). On each trial in the Freeze-Frame task, the infant is presented with dynamic cartoon stimuli in the center. Once the infant fixates the central target, a distractor appears either on the right or the left of the target. The value of the fixation target is manipulated: In half the trials, the infant is presented with varying and interesting cartoon animations (interesting trials), and in the other half, the infant is presented with the same animation of a rotating orange star (boring trials). To measure and control for differences in the ability to disengage visual attention, the duration of the distractors is individually calibrated for each infant. This is achieved by fixing the duration of the distractor once the infant reaches the calibration criterion of looking away from the fixation toward the distractor on two consecutive trials.

Data for 22 infants ($M=302$ days, $SD=47$) were available for the current analysis. Similar to previous analyses (Holmboe et al., 2008, 2010a,b), postcalibration data (defined as all trials from two trials before calibration) were analyzed using GLM. Trial type (two levels, boring and interesting) and phase (3 levels, 16 trials in each phase) were the within-subjects factors. In the present analysis, the three ADOS dimension scores were entered as continuous variable. Potential effects of age during the infancy period were controlled for by entering this as a continuous variable in the GLM.

Results of this analysis in the present sample showed the same main effects of trial type and phase as reported previously. Freeze-Frame performance at 10 months was significantly associated with the ADOS social interaction dimension in toddlerhood ($F(1, 10)=9.99$, $p=0.010$, $\eta^2p=0.50$). Specifically, a significant interaction of trial type \times ADOS social interaction score was observed ($F(1, 10)=7.38$, $p=0.022$, $\eta^2p=0.43$). Controlling for infant age, the proportion of looks to the distractors in the boring Freeze-Frame trials strongly predicted ADOS social interaction scores later in childhood ($r=-0.638$, $p=0.002$). At-risk infants who looked less to the distractors in the boring trials therefore had a higher level of impairment in social skills in early childhood. In contrast, there was no such effect in the interesting trials ($r=-0.107$, $p=0.635$).

Infants at risk for autism: Implications for typical and atypical development

Recent insights into the emergent nature of autism have given rise to a perplexing puzzle: on one hand, the human brain undergoes substantial and rapid development prenatally and in the early postnatal years, with the clear emergence of precursors of many adult skills. Autism, however, frequently associated with atypical brain and behavioral functioning in childhood onward

appears to confer only subtle overt behavioral manifestations very early in life, with the core symptoms appearing gradually over development. By contrast, more recent studies tapping brain function more directly have suggested that infants at risk, as a group, can be distinguished in the first year from those with no family history of autism. At least some have argued that these findings reflect a broader phenotype in infancy. Yet, an alternative possibility is that group differences are driven by a subset of infants who go on to a diagnosis of autism in toddlerhood. In the current study, we tested the sensitivity of brain function measures in the first year as predictors of the severity of emerging characteristics of autism in toddlerhood. Our findings suggest that at least some infant measures appear to map dimensionally onto autism characteristics in toddlerhood, irrespective of specific diagnostic status of individuals in the group.

Variability observed in infants at risk is likely to be the result of dynamic and probabilistic interactions over development, and the systematic study of these variations can offer important clues toward understanding the emergent nature of autism. While the current findings require replication with a larger sample allowing for appropriate statistical modeling, our key findings provide some initial insights. In the group at risk, the P1 and N290 ERP response to static faces displaying direct or averted gaze was associated with emerging difficulties in the social and communication domains at 3 years. Moreover, differential P400 response to direct relative to averted gaze displayed on faces was associated with later emerging nonsocial characteristics. Hence, response characteristics in this task were associated with later emerging social and nonsocial characteristics of autism, suggesting some interdependence of social and nonsocial circuits early in development. This pattern is broadly consistent with the suggestion that while the P1 and N290 are sensitive to the visual analysis of face and gaze information, the P400 is associated with top-down processing of gaze information (Elsabbagh et al., 2009a; Senju

et al., 2006). In other words, it is both the overall response to faces together with functional interpretation of gaze information in infancy which map onto the variability in autism-related characteristics in toddlerhood.

Similarly, results from the Freeze-Frame task indicated that at-risk infants' propensity to be engaged by a repetitive nonsocial stimulus predicted later social functioning. The best predictor of later autism-related social characteristics was the overall rate of looking to the distractors in the boring trials (suggesting an increased preference for the central "boring" stimulus), not the initial response to the two trial types or changes across the session. Together, the findings of the present and previous study suggest that interest in a nonsocial repetitive visual stimulus (perhaps akin to the restricted interests associated with autism), and conversely, the lack of interest in a more dynamic and social stimulus, can be observed in at-risk infants of 9–10 months of age and appears to predict later development. The follow-up study indicates that the more at-risk infants display this tendency, the more functionally impaired their performance within the core autism domain of social functioning at the time where symptoms start to become apparent.

It is critical to emphasize that these preliminary findings require confirmation and extension with a larger sample. The modest sample size in the current study provided sufficient power to perform longitudinal analyses among a few variables; future success will depend on multifactorial longitudinal modeling that can be achieved with larger data sets. With the accumulation of more data from infants at risk, the testing of such cumulative effects will become feasible. Moreover, it is likely that developmental change may be a better predictor of later outcome than measures taken at any single point in time. For example, one previous study reported that while clinical outcomes could not be predicted by attentional skills at 6 months, those infants who showed little change or became worse between 6 and 12 months were more likely to receive a

diagnosis of autism as toddlers (Zwaigenbaum et al., 2005). Hence, examining developmental change in the target precursors is potentially valuable in predicting later outcomes.

Another alternative (not mutually exclusive) is that while some of the precursors examined here mapped onto later emerging atypical characteristics of autism, others may be more strongly associated with performance in relevant domains, which are not measured on the ADOS, such as face/emotion processing or executive functions in toddlerhood. Given that a wealth of studies have revealed a BAP effect using laboratory measures of social (Baron-Cohen and Hammer, 1997; Dalton et al., 2007) and nonsocial functions (Baron-Cohen and Hammer, 1997; Belmonte et al., 2010), mapping these subclinical characteristics onto their precursors in infancy will help elucidate why severe symptoms emerge in some cases but not in others.

The current findings, combined with others emerging from research on infants at risk, have raised further questions regarding the nature of complex interactions among the developing brain networks and factors situated within the external environment. The study of infants at risk for autism may provide valuable clues regarding the nature of such interactions in typical development and how they may be altered in atypical development. Studies with infants at risk have not so far identified compelling evidence for a single factor driving the emergence of autism. A range of atypical social and nonsocial characteristics have been observed in the subgroup which goes on to develop autism as well in the group of infants at risk as a whole. It is possible that these functions, which later become core deficits, arise from widespread albeit subtle impairments in several systems where the typical developmental constraints are altered (Karmiloff-Smith, 1998). We suggest that the development of autism in infancy is best understood in terms of multiple risk factors, where the presence and the severity of each risk factor, as well as the interaction between these, can explain the resulting phenotype.

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Appendix

Participants

Recruitment, ethical approval (NHS NRES London REC 08/H0718/76), informed consent, as well as anonymized data were made available through The BASIS, a UK collaborative network facilitating research with infants at risk for autism (www.basisnetwork.org). Data in the current study were those collected from the first (pilot) cohort of BASIS. Some of the measures collected are anonymized and shared among scientists to maximize collaborative value and to minimize assessment burden on the families. A clinical advisory team of senior consultants works closely together with the research teams, and if necessary with the family's local health services, to ensure that any concerns about the child arising during the study are adequately addressed.

At the time of enrolment, none of the infants had been diagnosed with any medical or developmental condition. All had an older sibling with a community clinical diagnosis of an autism spectrum disorder (hereafter, proband), diagnosis of whom was confirmed by two expert clinicians (co-authors Patrick Bolton and Tony Charman) using the development and wellbeing assessment (Goodman et al., 2000) and the parent report social-communication questionnaire (SCQ; Rutter et al., 2003). Most probands met criteria for an autism spectrum disorder on both the DAWBA and SCQ. One child scored below threshold on the SCQ but was not excluded due

to meeting threshold on the other instrument. For two probands, neither DAWBA nor SCQ data were available. Parent-reported family medical histories were taken, with no exclusions made on the basis of significant medical conditions in the proband or immediate family members.

Procedure and data processing

Event-related-potentials in response to static gaze direction (Elsabbagh et al., 2009b)

The infants sat on their parent's lap at 60-cm distance from a 40 × 29 cm computer screen. Infants' behavior was monitored and recorded by video camera. Each trial block began with a static colorful fixation stimulus followed by a color image of one of four female faces, with gaze directed either toward or away from the infant. Faces were aligned with the center of the screen with the eyes appearing at the same location as the fixation stimuli. The faces subtended 21° × 14° of visual angle. Fixation stimuli subtended approximately 1.6° × 1.6° and were presented for a variable duration of 800–1200 ms. Each trial lasted for 1000 ms.

A 64-channel geodesic net was mounted on the infant's head, while the infant sat on their parent's lap in front of the stimulus screen. When the infant was attending toward the screen, trials were presented continuously for as long as the infant remained attentive, with brain electrical activity measured simultaneously, using the vertex as a reference (Cz in the conventional 10/20 system). EGI NetAmps 200 was used (gain = 1000); data were band-pass filtered between 0.1 and 100 Hz.

Participants' overall behavior was initially coded from videotape. Trials were retained only when infants were fixating on the center of the screen at stimulus onset, without any gaze shifts, blinking, or head movements occurring during the 800 ms segment following onset of the face or the gaze shift. Artifact rejection was then

performed by visual inspection of individual trials and data from any sensors were excluded if they contained artifacts. Missing data from 10% or fewer channels were interpolated; otherwise, the entire trial was rejected. Data were then referenced to the average.

The selection of regions for analysis was based on visual inspection of the grand average of the data as well as previous research showing that gaze-sensitive ERP and EEG components are found over occipito-central channels. Mean amplitude and latency of three gaze-sensitive components in infancy (P1: 100–199 ms, N290: 200–319 ms, and P400: 320–539 ms) were averaged for each of the channel groups.

Freeze-Frame task (Holmboe et al., 2010a)

Infants were presented with the stimuli on a 19-in. (48.3 cm) monitor, while seated on their parent's lap. Looking behavior was monitored and recorded from an adjacent room. Whenever needed, the infant's attention was drawn to the screen using sounds. Infants were encouraged to complete at least 60 trials, but the session was stopped if the infant became fussy. On each trial, the infant was presented with a moving stimulus in the center of the screen subtending between $10.5^\circ \times 10.5^\circ$ and $12.4^\circ \times 15.2^\circ$. Once the infant fixated the central target, a distractor appeared either to the right or to the left of the target at an eccentricity of 13.5° . The distractor was a white square subtending 3.2° . To examine the effect of varying the central stimulus, the apparent attractiveness of this stimulus was manipulated: on even numbered trials, the infant was presented with varying and dynamic cartoon animations ("interesting" trials) and on odd numbered trials the infant was presented with an animation of a simple rotating orange star ("boring" trials).

The beginning of the experiment was used as a calibration phase. Thus, the experimenter progressively increased the presentation duration of peripheral distractors online for each infant until

they reliably elicited saccades. At the beginning of the calibration phase, the duration of the distractor was set to 200 ms and increased trial by 40 ms steps whenever the infant did not look to the distractor. The duration of the distractor was fixed once the infant reached the calibration criterion, which consisted of two consecutive trials where the infant made a saccade to the distractor, or once a maximum distractor duration of 1200 ms was reached. This method was used to ensure that infants detected the distractors adequately.

Analyses were carried out using all trials from two trials prior to calibration. The postcalibration data were divided into three phases of 16 trials each (8 boring and 8 interesting trials). Subsequently, invalid trials were removed and the proportion of looks to the distractors in each phase and trial type was calculated. Infants had to have at least four valid trials in a trial type \times phase cell for the proportional measure to be calculated for that cell.

Video recordings of the infants' looking behavior were coded offline. Trials were only considered valid if the infant looked at the central stimulus throughout the trial or made a saccade to the distractor. Trials where the infant looked away from the screen during any part of distractor presentation were discarded. Intercoder reliability was excellent for both judgments in the at-risk group (based on data from 9 infants/520 trials): Look to distractor: $\kappa = 0.98$; trial validity: $\kappa = 0.93$.

ADOS assessment

Toddlers were administered the ADOS-G (Lord et al., 2000) by researchers trained to high reliability in administration and scoring, and blind to any data collected previously. Parents remained in the testing room during the assessment. All but one toddler completed module 2 (appropriate for children with flexible three-word phrases), while the remaining child completed module 1 (appropriate for nonverbal

children and those with single word speech or simple word combinations). ADOS algorithm domain scores were computed in the usual way, thereby yielding the outcome dimensional measures for social interaction, communication, and stereotyped behaviors/restricted interest, used in the current analyses.

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