Getting answers from babies about autism

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Because autism is rarely diagnosed before two years of age, little is known about its early symptoms and causes. In order to determine the earliest manifestations of the condition, recent interest has focused on infants at genetic risk for autism. Current evidence indicates that overt behavioural symptoms emerge around the end of the first year. However, studies using laboratory brain function measures have reported differences in groups of infants at-risk compared with low-risk controls during their first year. Some infants displaying such early differences, however, do not subsequently receive a diagnosis. As the search for early markers continues, infants at-risk present a persuasive model for gene by environment interactions leading to variable developmental pathways.

What can babies tell us about autism?
Autism Spectrum Disorders (ASD) affect 1 in 100 to 150 children [1]. The annual societal cost of ASD in the UK exceeds £27 billion [2]. Our current knowledge of the early neural, behavioural and cognitive profile is very poor, and little is known about the underlying causes of ASD or the process through which symptoms emerge. Because a confirmed diagnosis of ASD can only be made from around two or three years of age (Box 1) researchers, until recently, have relied on limited retrospective data on infants younger than two years of age prior to diagnosis [3,4]. It is against this background of scientific and clinical challenges that investigators have recently turned to the prospective study of younger siblings of children already diagnosed with ASD (often referred to as ‘infant siblings’). Although community-based studies are needed to determine recurrence risk in these infants, some studies report that around 20 per cent of younger siblings go on to a diagnosis. Studies with this risk group have only recently begun in earnest, in part due to the large number of infants that are required to be studied over a period of several years before revealing the minority who receive a diagnosis.

Another motivation for research in this area is that infants at-risk, by virtue of being genetic relatives of children with autism, might share some characteristics with affected individuals, even if they do not themselves go on to receive a diagnosis. In adults the Broader Autism Phenotype (BAP) refers to behavioural and brain characteristics associated with ASD found not only in affected individuals, but also in their relatives [5–7]. As such, several characteristics of ASD might not be atypical, but their co-occurrence and severity within an individual determine whether they manifest as normative differences, as opposed to diagnosable symptoms. The BAP includes overlapping clinical characteristics [7] as well as differences in face processing [6,8], theory of mind [9], executive function [10,11] and central coherence [12].

Further interest in studying infant siblings comes from the field of developmental cognitive neuroscience, where studying atypical developmental trajectories is thought to illuminate basic mechanisms that underlie the emergence of typical social and cognitive skills and their associated brain functions. This would in turn help address challenging questions regarding the development of the ‘social brain’ [13]. Recently, several new methods have been developed for studying behaviour, cognition and brain function in very young infants (Figure 1; Box 2). Our goal in this article is to present an overview of current infant siblings research within a broader context of developmental cognitive neuroscience, and to explore the potential implications that studies of infant siblings have on our basic understanding of gene and environment interactions in early functional brain development.

Does ASD emerge over time?
Early signs
Despite recent advances in our understanding of the genetic and neurobiological basis of ASD, the condition is currently diagnosed on the basis of behavioural characteristics that can take qualitatively different forms in infancy. Tools currently used for screening and diagnosis, relating to the three areas affected in ASD (social abilities, communication and repetitive behaviours), have been validated for children of 18 months and older but not for younger infants (Box 1). Thus, most approaches to studying infant siblings aim to identify risk markers through precursors of later developing symptoms. Because ASD is a complex condition that encompasses characteristics outside the social domain (e.g. motor coordination and visual attention), some investigators view these as equally important candidate risk markers, despite the fact that such characteristics are not specific to, or universal in ASD [4,14,15].

Emerging findings indicate that during their first year many infants who go on to a later diagnosis show surprisingly few overt behavioural signs of atypicality. As a group, these infants might interact well with their caregivers and show the expected level of social reciprocity for their age [15–17]. However, during their second year they begin to
show differences across a range of measures, summarised in Table 1. These early signs of ASD, that can first appear around 12 months, include several precursors to later developing symptoms in social and communicative behaviours. Other studies indicate that early signs might include behaviours that fall outside the range used in diagnosing ASD in children, for example motor and temperamental characteristics. The nature of early behavioural signs seems to vary between infants and can also change over time. Even by 18 months, diagnosis is at best tentative and its stability is poor. However, differences in the affected group do become increasingly clear after this age.

Different pathways towards an ASD diagnosis?
The lack of uniformity in the nature and timing of early markers among infants, and their probabilistic nature in terms of predicting diagnosis, has generated interest in the notion that there are multiple pathways to ASD. Traditionally, two subgroups have been hypothesised based on their trajectory of symptoms [24]. The first trajectory characterises infants whose symptoms appear early in development and become clearer with age. The second trajectory involves typical initial stages of development followed by a phase of ‘regression’. Prospective studies of infant siblings have lent support to the first of these trajectories in which early subtle signs first appear around the end of the first year then develop into clearer symptoms by two years. Notwithstanding this pattern, the evidence also indicates significant variation in the rate of change over time among infant siblings [25–27]. In some cases of ASD, delays or atypicality can begin later and appear more gradually, leading to a plateau in typical skills. The regression pathway hypothesised to occur in a minority of children

### Table 1. Characteristics of ASD emerging between 12 and 24 months. Early signs are variable and initially have low predictive value that then increases with age

<table>
<thead>
<tr>
<th>Deficits and delays in emerging joint attention [17,18]</th>
<th>Decreased response to name [19]</th>
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<tr>
<td>Motor delay [17]</td>
<td>Elevated frequency of repetitive behaviours, e.g. hand waving [21]</td>
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<tr>
<td>Atypical visuo-motor exploration of objects [22]</td>
<td>Extremes of temperament [23]</td>
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<tr>
<td>Decreased flexibility in disengaging visual attention [15]</td>
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diagnosed with ASD has yet to be established in infant siblings studies. These hypothetical trajectories (Figure 2) are based on findings from behavioural studies, and it remains possible that clearer or more consistent trajectories will become apparent when underlying functional brain development is understood.

Getting beneath behaviour

Whereas the majority of infant siblings studies to date have searched for atypicalities in social behaviour, a few laboratories have recently used methods from developmental cognitive neuroscience with this risk group. The motivation is that more direct measurements of brain function or cognition might reveal indicators of atypical development before these become evident in the overt social behaviour of the infant. Because work with such methods is relatively new, there is little current data on the predictive value of the measures in relation to diagnostic outcome at three years or beyond. However, in contrast to the behavioural studies described above, such methods have already documented differences during the first year between groups of infant siblings and low-risk control groups. For example, measurement of saccadic reaction time in tasks targeting developing brain attention networks have shown reduced flexibility in disengaging from a central stimulus to orient towards a peripheral one [28], a finding parallel to that observed in older children diagnosed with ASD [29]. Furthermore, the study of contrast thresholds in infants at-risk highlighted differences in neural systems mediating early visual processing [30]. More direct electrophysiological measurement of brain activity using Event Related Potentials (ERP) has found early group differences in response to face stimuli [31] and in sensitivity to the direction of eye gaze, a developmental precursor to joint attention [32]. Other emerging findings indicate differences in the risk group in resting state spontaneous EEG activity at the gamma frequency [32].

There are at least three reasons for differences in the overall pattern of results from measures of overt social behaviour and measures of underlying brain functions. First, as mentioned above, it might be that methods from developmental cognitive neuroscience are simply more sensitive at indicating risk in individual infants earlier in development. Until studies using these methods have followed up large cohorts of infants at-risk to the point of diagnosis this issue will remain unresolved. A second

Figure 2. Siblings studies have highlighted variation in the nature and rate of change in behaviour in infants at risk. This has led to proposals of hypothetical variable trajectories as illustrated. Available findings support variability in onset of clear behavioural symptoms whereas the regression trajectory has not been established in infant siblings.
account builds on the view of some authors that their findings constitute group-level differences that are not attributable to the small number of infants going on to receive an ASD diagnosis (Box 2), and thus that they represent an early form of the BAP. This account might help explain some of the current inconsistencies in describing the behavioural phenotype in ‘unaffected’ siblings (those who do not go on to receive a later diagnosis). When considering behaviour, unaffected siblings appear to muddy the waters in terms of finding early markers for ASD. Behavioural differences between this group, affected siblings and low-risk control infants are difficult to detect at six months of age [16,33,34]. Between 12 and 24 months, groups inconsistently overlap in some early signs [35–37]. At least in some studies, affected and unaffected siblings continue to be indistinguishable early in this developmental period but diverge in their trajectories over time [37]. Interestingly, by school age, unaffected siblings reach typical levels of functioning with very few residual delays or deficits [38]. In summary, according to this view variability in the expression of behavioural risk within the first years might reflect an infant BAP revealed more clearly through measurement of underlying brain and cognitive functions.

A third account of the diverging results between measures of overt social behaviour and those of underlying brain and cognitive functions is more speculative in view of limited data on infant siblings. It is possible that in most infants, expression of risk is measurable in the form of subtle aspects of brain and cognitive function. It is only in a subset of these infants that initially subtle differences become compounded, leading into a developmental trajectory that results in an ASD outcome. In the majority of infants, however, well-described processes of brain adaptation and plasticity (discussed next) may restore the developmental trajectory to a typical course.

**Babies at-risk for ASD and gene-environment interaction**

Researchers in areas of genetics and developmental psychopathology have invoked gene by environment interaction to help explain why an early genetic or environmental perturbation affects some individuals and not others [39]. In Figure 3 we illustrate some of the underlying assumptions about how genetic or environmental risk factors operating within the infancy period give rise to later behavioural outcomes. Although our focus here are those factors leading to ASD, it is likely that similar factors might also contribute to other behavioural phenotypes such as those observed in language or attention disorders [28].

Since pioneering studies have estimated heritability for ASD to exceed 90% [40,41] much research has focused on genetic risk as contributing to the emergence of the condition. Once viewed as a realistic endeavour, the search for candidate genes as causal factors has been hampered by heterogeneity in DNA loci and variable penetrance and expression. Most geneticists have now abandoned the notion of susceptibility genes of major effect as accounting for a large number of ASD cases. Emerging consensus focuses on genetic heterogeneity, where at least some cases appear to result from de novo mutations in the form of rare copy number variants, leading to genomic imbalance and change in gene expression [42]. In such cases, genetic mutations might be the overriding risk factor giving rise to ASD (Figure 3a).

However, it is important to emphasise that such mutations, along with all of the other genetic factors discovered so far, account for no more than 20% of ASD cases, with no individual factor explaining more than 1 to 2%. Therefore, a ‘gene-dosage’ model is increasingly popular, in which susceptibility to ASD might be determined by cumulative genetic and non-genetic effects reaching a threshold [42–45]. According to the gene-dosage model, infant siblings’ outcome is determined by the nature, proportion, or combination of genetic and non-genetic ‘hits’ (Figure 3b).

In addition to considering genetic factors, some models also emphasise the role of the early environment in determining outcomes. For example, in some cases typical allelic variation determines children’s response to different early social or physical environments resulting in the emergence of developmental disorders [39]. In this context, environmental risk is viewed as additive to the ‘gene dose’, and thus influences the infant’s overall susceptibility to adverse outcome (Figure 3b). Thus, specific combinations

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Figure 3. Different models for how single or multiple genetic and/or environmental risk factors in infancy lead to ASD behavioural outcomes in childhood. In model c, risk factors predict outcomes through dynamic changes over the course of development. Alternatively, the developmental process might buffer initial vulnerability, canalising the impact of risk.
of genetic and environmental risk factors can determine the nature of the resulting phenotype, that is ASD or another developmental condition, as well as variability in expression ranging from severe diagnosable outcomes to milder normative characteristics. Consistent with this model, findings from infant siblings research indicate variability in the early expression of risk, but much work will be required in future studies to specify which combinations lead to which outcomes (also Box 3).

Although relatively simple Gene by Environment models might help explain the onset of some developmental disorders [39], in other cases the effects of their interaction seem to be more complex. For example, evidence from research on language, and literacy impairment [46,47], as well as conditions such as Williams Syndrome, where the genetic underpinnings are clearly understood [48], supports probabilistic and indirect mapping between genetic and/or environmental factors and developmental outcomes [49] (Figure 3c). In these cases the favoured view is that dynamic gene by environment interactions during the period of maximal brain plasticity lead to variable developmental trajectories, not readily predicted by a simple model of additive risk.

Computational models (neural networks) designed to illuminate non-linear interactions between genetic and environmental factors [50] have reaffirmed older ideas in the literature about the different effects of early perturbations on developmental trajectories [51]. In some cases, an early perturbation can reset a developmental trajectory along a different route, as a result of the compounding of atypical brain computations or behaviour eliciting or recruiting an atypical environment. In other cases, the typical developmental trajectory can be resilient in the face of genetic or early environmental ‘hits’ through canalisation, a process through which brain adaptation and plasticity maintains or restores the typical trajectory. Such trajectory differences, emerging from the dynamic interaction of multiple factors over time, are not easily decomposable into separate genetic and environmental contributions.

Examples of hypothetical developmental trajectories in infant siblings based on the latter account are illustrated in Figure 4. In the ‘affected’ group, early and widespread, albeit subtle differences, in multiple brain systems might become compounded over time as a result of atypical interactions between brain systems and the external environment. A second group show less initial sub-clinical characteristics and continue within the BAP profile over time. A third possibility is that although early manifestations of risk can be observed in infant siblings as a group, canalisation restores the trajectory of development back to its typical path. Such dynamic pathways within the early developmental period might arise as a consequence of compensatory plasticity in the developing brain. However, it has been recently proposed that even some older children, who already exhibit a clear profile of autistic symptoms, may reach optimal outcomes [52]. The precise factors involved in this adaptation in infancy or in childhood have yet to be verified.

### Box 3. Taking individual differences seriously: infant intermediate phenotypes?

There is currently growing interest in using laboratory methods as biomarkers of risk for a diagnosis of ASD later in life. Biomarkers are defined as measurable factors specifically associated with a particular condition, which can be used to ascertain an individual’s susceptibility for that condition [63]. Although developing such biomarkers is a long-term aim of research on infant siblings, findings have already highlighted that individual differences need to be considered seriously as these can reflect different developmental pathways to outcome.

A standard approach in infant siblings research focuses on identifying group differences in early behaviours as defined by clinical outcomes, for example ASD vs. unaffected. These category groups are defined through cut-off scores across a number of instruments such as the ADOS and the ADI and in combination with expert clinical judgment. One disadvantage of this approach is that potentially meaningful variability in the data might be lost. Increasingly, researchers in areas of genetics have advocated the use of dimensional intermediate or endo-phenotypes, viewed as closer to the genotype than complex clinical characterisation [64,65]. Specifically, measures of quantitative traits associated with ASD and overlapping with other disorders are viewed as better candidates for gene mapping than diagnostic classification [45,46]. The assumption here is that diagnosed forms of ASD, which are themselves highly variable, are extremes of what is otherwise typical variation. Even in clinical circles, once viewed as essential for screening specificity, access to services, treatment design, and reducing heterogeneity of participants in research, categorical approaches are gradually being complemented by dimensional ones in ASD [66] and in other developmental disorders [46,67]. It is probable that the development of such infant intermediate phenotypes based on experimental methods will significantly advance research across these various disciplines. A further implication of recent findings from infant siblings is that such intermediate phenotypes need not be static over development. In other words, understanding the impact of dynamic gene by environment interactions in how these characteristics change over time will be essential.

Infant siblings research has introduced new challenges for infancy science, which traditionally tests group performance on single measures. Group studies on infant siblings have demonstrated success in improving our understanding of the early ASD phenotype and have allowed comparisons with existing research. However, future success rests on our ability to complement group data with validation of dimensional and longitudinal measures for assessing both risk and outcome.
Different models for gene by environment interactions provide exciting opportunities for future research on infant siblings (Box 4). Genotyping of participating families has already begun in some projects. By contrast, there is currently less focus on environmental factors. In this regard, most researchers are rightly cautious in view of the recent past, where an influential theory attributed the cause of ASD to parenting style [53]. This idea has been dismissed by converging evidence including some of the findings reviewed here. However, models that incorporate environmental influence raise the possibility that modulating the early social environment might help infants overcome the adverse impact of genetic vulnerability. It is against this background that some scientists are beginning to pilot behavioural interventions based on modifying the early social environment for the prodromal period of the condition, modelled after those designed for very young affected children. The success or otherwise of such interventions will help determine the extent to which early environmental factors can influence outcome in infants at-risk [54,55].

Concluding remarks

Attempting to understand the ways in which genes, brains and the environment operate and interact is an enormous challenge. Owing to the fruitful integration of theories from different disciplines, innovative methodologies, and a successful alliance of scientists, babies and their families, we are at the cusp of very exciting discoveries. Studies of infant siblings of children affected by ASD are beginning to reveal how genetic risk for developing the condition takes them through diverging routes in their development. In addition to advancing basic and clinical research, science with infant siblings provides promising opportunities for exploring whether early interventions are successful in reducing the impact of the adverse symptoms in at least some cases.

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