Neuroscience and Biobehavioral Reviews 39 (2014) 1–33

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Developmental pathways to autism: A review of prospective studies of infants at risk☆

Emily J.H. Jones[a,*], Teodora Gliga[a], Rachael Bedford[c], Tony Charman[b], Mark H. Johnson[a]

[a] Centre for Brain and Cognitive Development, Birkbeck College, University of London, UK
[b] King's College London, Institute of Psychiatry, Department of Psychology, UK
[c] King's College London, Institute of Psychiatry, Department of Biostatistics, UK

ARTICLE INFO

Article history:
Received 7 May 2013
Received in revised form
18 November 2013
Accepted 2 December 2013

Keywords:
ASD
Autism
Infant sibling
High-risk
Causal path
Developmental mechanisms

ABSTRACT

Autism Spectrum Disorders (ASDs) are neurodevelopmental disorders characterized by impairments in social interaction and communication, and the presence of restrictive and repetitive behaviors. Symptoms of ASD likely emerge from a complex interaction between pre-existing neurodevelopmental vulnerabilities and the child's environment, modified by compensatory skills and protective factors. Prospective studies of infants at high familial risk for ASD (who have an older sibling with a diagnosis) are beginning to characterize these developmental pathways to the emergence of clinical symptoms. Here, we review the range of behavioral and neurocognitive markers for later ASD that have been identified in high-risk infants in the first years of life. We discuss theoretical implications of emerging patterns, and identify key directions for future work, including potential resolutions to several methodological challenges for the field. Mapping how ASD unfolds from birth is critical to our understanding of the developmental mechanisms underlying this disorder. A more nuanced understanding of developmental pathways to ASD will help us not only to identify children who need early intervention, but also to improve the range of interventions available to them.

Contents

* Corresponding author at: Centre for Brain and Cognitive Development, School of Psychology, Birkbeck College, Malet Street, WC1E 7HX, UK. Tel.: +44 020 7631 6258.
E-mail address: e.jones@bbk.ac.uk (E.J.H. Jones).

0149-7634/$ – see front matter © 2014 The Authors. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neubiorev.2013.12.001

1. Introduction

Autism Spectrum Disorders (ASDs) are neurodevelopmental disorders characterized by impairments in social interaction and communication, and the presence of restrictive and repetitive behaviors (DSM-5, APA, 2013; ICD-10, WHO, 1993). In addition, there is significant comorbidity between ASD and clinically significant difficulties in a number of neurodevelopmental domains, including attention (e.g. Hanson et al., 2012), mood (e.g. Kim et al., 2000), cognitive skills (e.g. Charman et al., 2011a,b), and adaptive skills (e.g. Perry et al., 2009). One of the diagnostic features of ASD is its early emergence; symptoms must begin in early childhood for a diagnosis to be given. Detailed work with retrospective parent report and home-videos of young children with ASD has consistently shown that children who are later diagnosed with ASD show impairments in a range of skills in the first years of life (for review, Barbaro and Dissanayake, 2009; Yirmiya and Charman, 2010). As a developmental disorder, symptoms of ASD likely emerge from a complex interaction between pre-existing vulnerabilities and the child's environment. Initial genetic and environmental risk factors interact to alter the development of brain structure and function, compromising the child's ability to learn from their environment (Johnson, 2011). Early emerging behavioral symptoms alter the child's self-directed patterns of attention, changing their experience of the environment and further restricting social learning opportunities. Compensatory skills and pre-existing protective factors are also likely to play a role in the dynamics of a clinical phenotype. Understanding how ASD unfolds from birth onwards is critical to beginning to understand these developmental mechanisms, for identifying children who require early intervention and to indicate appropriate intervention targets.

Retrospective work is valuable but has many limitations; for example, memory or videotaped events may be selective, and researchers are limited to the assessment of overt behaviors that have been captured on tape or that are memorable to parents. To overcome these challenges, researchers have recently turned to prospective longitudinal studies of infants at high familial risk for ASD. Recent estimates suggested that ASD is moderately heritable (Hallmayer et al., 2011), with recurrence rates within families in community samples estimated to be around 10% (Constantino et al., 2010) compared to a population prevalence of ~1% (Baird et al., 2006). Prospective studies of infants who later develop ASD are thus feasible within a familial high-risk design. Such studies of *high-risk infant siblings* follow younger siblings of children with the disorder from early infancy until 2–3 years of age, when a diagnosis of ASD can be made. A low-risk control group, composed of children with a typically developing older sibling and who have no family history of ASD, is typically followed in parallel. Around 20% of high-risk infant siblings meet criteria for ASD by their third birthday (Ozonoff et al., 2011); by comparing prospective data collected from infants who later do or do not meet diagnostic criteria for an ASD, researchers can identify early markers of later diagnosis. Of note, the lower sibling recurrence rate in community samples (c. 10%, Constantino et al., 2010) likely reflects a combination of "stoppage effects" (choosing not to have additional children if one child has a disability) and failure to detect milder forms of ASD in the community.

High-risk infant sibling designs also allow for the investigation of the broader autism phenotype (BAP, Bolton et al., 1994), subclinical traits or characteristics that are present at an elevated rate in family members of individuals with ASD. Around 10–20% of high-risk infants develop such sub-clinical ASD symptoms or other developmental problems (Messinger et al., 2013). Studying infants prospectively allows researchers to observe behavior in a more standardized context, and the use of a wider range of tools such as eye-tracking and neuroimaging allows inferences about underlying mechanisms. These rich datasets should enable both the development of new clinical screening tools for early behavioral signs of ASD, and new models of the developmental pathways leading to ASD and other related disorders.

Previous reviews in this area have identified several common themes (Elsabbagh and Johnson, 2010; Rogers, 2009; Yirmiya and Charman, 2010). Firstly, few behavioral markers have been identified in the first year of life. Rather, observable behavioral impairments appear to accumulate across the second year of life. Second, rather than observing clear early impairments in social behavior that precede impairments in other domains, early symptoms are apparent across multiple domains including sensory and repetitive behaviors as well as impairments in early social communicative behaviors. This review is motivated by the need to revisit and extend these conclusions based on the many subsequent studies that have emerged since the publication of these recent reviews.

We draw conclusions in two key areas. First, we consider the implications of reviewed findings for theoretical accounts of the development of ASD. For example, social orienting models of ASD suggest that an early emerging reduction in social attention compromises the child's opportunities to learn about their social environment, contributing to the development of symptoms of ASD. This account thus predicts that deficits in social orienting should emerge before other signs of ASD. Prospective work with infant siblings can prove a critical test of this hypothesis. However, early markers of ASD identified in prospective sibling studies span a broad range of domains that include both social (Chawarska et al., 2013; Elsabbagh et al., 2012), and non-social abilities (Elison et al., 2013; Elsabbagh et al., 2013b; Flanagan et al., 2012). We discuss the challenges this picture presents for models that place a strong emphasis on early social deficits. Secondly, we identify several methodological improvements that should be considered as the field moves forward, and that are equally relevant to longitudinal studies of any developmental disorder. These include: (i) strategies to deal with publication bias when evaluating evidence for and against particular theories of ASD development; (ii) the need to move away from identifying deficits on particular tasks and toward employing multiple measures of underlying core constructs; (iii)