Developmental Review 34 (2014) 189–207

Contents lists available at ScienceDirect

Developmental Review

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

From early markers to neuro-developmental mechanisms of autism

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ARTICLE INFO

Article history:
Received 14 July 2013
Revised 19 May 2014
Available online 11 June 2014

Keywords:
Infants
Autism
The "social brain"
Sensory processing

ABSTRACT

A fast growing field, the study of infants at risk because of having an older sibling with autism (i.e. infant sibs) aims to identify the earliest signs of this disorder, which would allow for earlier diagnosis and intervention. More importantly, we argue, these studies offer the opportunity to validate existing neuro-developmental models of autism against experimental evidence. Although autism is mainly seen as a disorder of social interaction and communication, emerging early markers do not exclusively reflect impairments of the "social brain". Evidence for atypical development of sensory and attentional systems highlight the need to move away from localized deficits to models suggesting brain-wide involvement in autism pathology. We discuss the implications infant sibs findings have for future work into the biology of autism and the development of interventions.

Introduction

Autism is a disorder of social interaction and communication skills, accompanied by a restricted repertoire of interests and behaviors and by atypical sensory reactivity (DSM-5, American Psychiatric Association, 2013). In terms of behavioral signs, autism emerges over the first few years

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http://dx.doi.org/10.1016/j.dr.2014.05.003
0273-2297/

of life but robust clinical diagnosis is not typically achieved before 3 years of age (Steiner, Goldsmith, & Snow, 2012). It is therefore highly likely that, by the age of diagnosis, the symptoms presenting will be a result not only of early neurodevelopmental atypicalities, but also of adaptations and compounded effects that result from a child developing atypically within their social and physical environment for several years. A child's decreased responsivity or seeking of social interaction, for example, could discourage others from offering the right amount and quality of social input and thus further decrease social learning. Alternatively, social isolation may act as a protective mechanism (an adaptation) for an organism overwhelmed with the richness of the input one is exposed to in social interaction (Johnson, Jones, & Gliga, in press). Interactions between neural systems during development will also make it difficult to isolate primary and secondary causes. Decreased cortical specialization for face processing, for example, could result from decreased specialization of cortical circuitry, or alternatively, from downstream disturbance in subcortical structures driving environmental exposure to faces, early in life. Moreover, primary impairments could be transitory, and thus impossible to measure later in life, whilst still having knock-on effects on later development.

While some attempts are being made to differentiate compensations and compounded effects from the primary deficit using neuroimaging (Kaiser et al., 2010), it is evident that such effects cloud our understanding of genotype–phenotype associations. In considering these factors, some have proposed that we need an approach based on the prospective longitudinal study of infants at high-risk of developing autism (most commonly infant siblings in families with an older child already diagnosed with autism). Here the aim is to identify and study the early manifestations of the condition, less affected by atypical interactions with the social and physical environment. Studies of younger siblings of children with autism are motivated by the twentyfold increase in autism incidence in these groups with respect to the general population (Baird, Simonoff, Pickles, Chandler, & Loucas, 2006; Ozonoff, Young, Carter, & Messinger, 2011), making prospective studies feasible (Zwaigenbaum et al., 2007). Infants tend to be recruited in the first months of life and followed initially until 3 years of age, when a diagnosis can be made. A low-risk control group, composed of children that have no family history of autism, is typically followed in parallel. As simply having older siblings can affect development, control participants also have an older sibling. Around 20% of high-risk infants receive an autism diagnosis by their third birthday (Ozonoff et al., 2011). At-risk designs also allow the investigation of the broader autism phenotype (BAP, Bolton et al., 1994); sub-clinical traits or characteristics that are present at an elevated rate in families containing individuals with autism, with about 10–20% of high-risk infants developing sub-clinical ASD symptoms or other developmental problems (Messinger et al., 2013). The fast growing field of infant siblings (sibs) studies has been greatly motivated by the need to identify early reliable markers for this disorder, which would make possible earlier interventions. However, while markers are essential for early detection, a mechanistic understanding of autism emergence is crucial for designing efficient interventions. In addition, infant sibs studies offer the unique opportunity to tease apart different accounts about the origin of autism.

Like others before us (Pelphrey, Shultz, Hudac, & Vander Wyk, 2011), when discussing causes of autism, we choose to focus not on the genetic factors associated with this disorder but on the consequences they have on brain function. This is the level which best allows, for the time being, a mapping onto the spectrum of behavioral symptoms that are used to define and diagnose autism. A substantial number of neurobiological causes for autism have been proposed over the years, which can be roughly described as belonging to four lines of thought. Since autism is described as a disorder of social interaction and communication, some place the origin of autism within the category 'disorders of the "social brain"' (Adolphs, 2009). This set of hypotheses, one of the most widely accepted, branches out to focus on different components of the "social brain" (e.g., social orienting and sub-cortical structures, social motivation and reward networks or the processing of biological movement within the superior temporal sulcus). A second group of hypotheses proposes a domain-general developmental origin of autism. Many of these hypotheses still focus on circumscribed brain structures, for example the sensory cortices (Mottron, Dawson, Soulieres, Hubert, & Burack, 2006) or the frontal lobe (Hill, 2004). Another line of thought proposes that social and domain-general atypicalities influence additively the risk of developing autism symptoms (Happe, Ronald, & Plomin, 2006). Finally, inspired by increasing understanding of the genetic and molecular mechanisms involved in autism etiology, some autism researchers have suggested brain-wide neural impairments in factors such as long-distance