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Review

Social visual engagement in infants and toddlers with autism: Early developmental transitions and a model of pathogenesis

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ABSTRACT

Efforts to determine and understand the causes of autism are currently hampered by a large disconnect between recent molecular genetics findings that are associated with the condition and the core behavioral symptoms that define the condition. In this perspective piece, we propose a systems biology framework to bridge that gap between genes and symptoms. The framework focuses on basic mechanisms of socialization that are highly-conserved in evolution and are early-emerging in development. By conceiving of these basic mechanisms of socialization as quantitative endophenotypes, we hope to connect genes and behavior in autism through integrative studies of neurodevelopmental, behavioral, and epigenetic changes. These changes both lead to and are led by the accomplishment of specific social adaptive tasks in a typical infant's life. However, based on recent research that indicates that infants later diagnosed with autism fail to accomplish at least some of these tasks, we suggest that a narrow developmental period, spanning critical transitions from reflexive, subcortically-controlled visual behavior to interactional, cortically-controlled *and social* visual behavior be prioritized for future study. Mapping epigenetic, neural, and behavioral changes that both drive and are driven by these early transitions may shed a bright light on the pathogenesis of autism.

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1. Introduction: From an array of lights and sounds to reciprocal social interaction, to hypotheses on autism pathogenesis

Were we to trace the evolutionary steps of a species whose brain specialization is shaped primarily by sociality – as is the case with primates (Ghazanfar and Santos, 2004) – the first hurdle would be to solve a pressing problem of initial conditions. Human neonates enter the world in a state of utter fragility. They are immersed in a complex array of lights and sounds and changing sensations. They will only survive and thrive through the intervention of another being—a caregiver. Given these initial conditions, what mechanisms would increase the odds of that neonate surviving? How, in that sea of sensations, would a newborn's perceptually-guided actions be successfully canalized toward the critical interactions with another being (the being who offers the greatest probability of helping that infant to continue)? Ample research already indicates that reciprocal social interaction becomes the platform for future

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development of social and communicative competence (Klin et al., 2003). This process, in turn, results in fast-paced and iterative social brain specialization (Johnson, 2001). But apart from cataloging certain physical features of the stimulus, we still know very little as to how that distal figure, the caregiver, initially attracts and then further maintains the attention of an infant. We know that that interaction typically succeeds, beginning in the first hours and days of life, and that it then becomes an almost inexhaustible source of reinforcement in later weeks and months, leading the infant through what will be its period of greatest post-natal change in structure and function of brain and body. But beyond those descriptions of typical success, we know very little about the biological mechanisms that make those steps possible.

In no other human condition is this initial problem more pressing than in the case of autism. A highly prevalent neurodevelopmental condition of genetic origins, autism is characterized primarily by early-onset, lifelong, and potentially devastating disabilities in social and communicative function (Volkmar et al., 2004). Hundreds of genetic variants associated with autism have been identified, but none has yet accounted for any more than a very small percentage of cases (Geschwind, 2011). Linking specific genetic findings to causal mechanisms has been particularly challenging because autism is defined behaviorally, by a cluster of symptoms – impairments in social communication and restricted patterns of interests and behavior (APA, DSM-5, 2013) – which only become visible, and can therefore serve as the basis for conventional clinical diagnosis, toward the end of the second year of life (Chawarska et al., 2008). These symptoms are likely the complex and heterogeneous outcomes or end results of genetically-based disruptions of the child's ongoing development, and therefore cannot be mapped directly onto genetic processes (Meyer-Lindenberg and Weinberger, 2006; Jones and Klin, 2009). To leverage genetic discoveries in pursuit of causes of autism, we need successful systems biology approaches, leading the field from gene to protein to cellular function to neuronal circuitry to behavior impacted in pathogenesis (State and Sestan, 2012). Clearly, tractable model systems are crucial to the study of autism, but creation of appropriate systems has, to date, been modest (Crawley, 2007). Once a system is developed, one of the greatest challenges in this field is the development of behavioral assays that hold adaptive relevance (as evolutionary adaptations) to the human syndrome (or to a mediating phenotype; Gould and Gottesman, 2006) and to the species used as a model system (Lederhendler and Schulkin, 2000; Moy et al., 2006). Here, we argue that the gene-symptom gap may be narrowed through a focus on adaptive skills that (1) are known to be more proximal to genetic expression (and thus relatively less complicated by later learning and compensatory mechanisms); (2) are central to the expression of the syndrome (and thus relate directly to the development of social interaction and communication); and (3) are equally relevant to species-specific adaptive survival in model systems that may be used to elucidate molecular mechanisms (Insel and Fernald, 2004; Jones and Klin, 2009). Such adaptive skills are likely to be the solutions to our initial problem: how infant and caregiver action become successfully connected to form adaptive, reinforcement-driven interaction.

In this perspective piece, we describe two important means to this social-adaptive end. As such, each is a basic mechanism of social engagement. Each one is also a mechanism of social *visual* engagement: preferential attention to biological motion (the movements of vertebrate animals), and preferential attention to others' eyes. Both are evident in the earliest expression of behavior in human infants and in infants of several other species whose survival depends upon the care of an adult conspecific. Of course, neither of these is the only such means to social engagement (in visual or non-visual domains), but new research indicates that both of these mechanisms are compromised in infants and toddlers with autism. They are not a cause of autism, rather they are signs of the unfolding of autism: evidence of the derailment of typical development that almost assuredly adds to the ongoing disruption of subsequent social and communicative growth. However promising these findings may be, they are currently descriptive in nature. Insights into their biology await lessons from model systems that can generate hypotheses about gene–brain–behavior relationships. Nature is parsimonious in its solutions (Thompson, 1942). Whether we see the same functions appear via evolutionary conservation (a solution inherited from a common ancestor), or via convergent evolution (a solution evolving independently in different species as a result of similar selective pressures), there may be lessons to learn from well-studied model systems.

This issue of *Neuroscience & Biobehavioral Reviews* is celebrating the work of Gabriel Horn. Over several decades of advances in research of visual imprinting in the domestic chick (Horn, 2004), Horn and colleagues painstakingly documented a cascade of genetic, epigenetic, cellular, and brain transformations resulting from this event—the preferential movement toward and subsequent recognition of the mother hen. Interestingly, young chicks and human infants share a very similar adaptive task (the same that formed the basis of our initial value problem): both species need to detect and orient to the caregiver, and both species need to learn the characteristics of the caregiver, as the caregiver becomes the anchor of infants' experiences and guarantees their survival. In the chick, visual recognition of the natural parent happens within hours from hatching (Horn, 2004). In the human infant, visual recognition of mother is well established by three months of age (Mash et al., 2013). Many studies have drawn parallels between chicks and human infants in the evolution of social orienting (e.g., Hoffman and Ratner, 1973; Horn and Johnson, 1989; Rosa Salva et al., 2011). This model system suggests a hypothesis to explain a new finding from our laboratory (Jones and Klin, 2013) by focusing on a narrow set of early neurodevelopmental transitions that infants later diagnosed with autism fail to make. Elucidating the biological bases of these transitions could shed a bright light on the pathogenesis of autism.

2. Social orienting in autism spectrum disorders (ASD), Part 1: Perception of biological motion

For human infants, engagement with the caregiver is the initial task upon which survival depends. Given their fragility at birth, success in this task is of immediate survival value and is of fundamental evolutionary significance. A central skill facilitating this adaptive task is preferential attention to biological motion—a form of perceptual "life detector" (Troje and Westhoff, 2006). Biological motion refers to the movement of vertebrate species; in humans, it corresponds to actions that range from gait and bodily gestures, to facial expressions and change in gaze direction. Special sensitivity and preferential orientation to forms of biological motion are widely present across species – from humans (Johansson, 1973; Fox and McDaniel, 1982) to monkeys (Oram and Perrett, 1996) to cats (Blake, 1993) to birds (Omori and Watanabe, 1996) – and are developmentally very early-emerging. Signs can be found in newly-hatched chicks (Vallortigara et al., 2005) and in human infants as young as 2 days of age (Simion et al., 2008). These abilities are believed to be critical for filial attachment and for detection of predators in many species (Johnson, 2006). In addition, in humans, this ability has been postulated to be the forerunner of the capacity for attributing intentions to others, a cardinal social cognitive skill (Frith and Frith, 1999).

The evidence pointing to the key role of biological motion perception in social brain networks is impressive:

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