The elusive etiology of autism: nature *and* nurture?

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Autism spectrum disorder (ASD) is a serious neurodevelopmental disorder encompassing severe deficits in social communication and language development, and associated with repetitive, stereotypic behaviors. It is estimated that as many as 1 in 150 children in the United States are affected (Centers for Disease Control and Prevention, 2007).

Over the past decade, we have witnessed remarkable scientific advancements in our ability to explore the origins and manifestations of autism, using tools such as genome-wide microarray analyses, functional neuroimaging and automated eye tracking. Yet, despite these innovations, we have failed to uncover a core psychobiological deficit for autism. Without such an understanding, treatment options are limited to various combinations of child-directed therapy, with minimal data supporting effectiveness (Ospina et al., 2008). With the dramatic rise in the number of children diagnosed with autism (Blaxill, 2004) comes an escalating burden for schools, governments and society to provide intensive and costly services. Clearly, understanding the etiology of autism is of paramount importance.

THE ETIOLOGY OF AUTISM – NATURE VS. NURTURE

Over the past 60 years, the pendulum of public and scientific opinion on the etiology of autism has swung between two extreme positions: (1) that autism is caused by some specific genetic abnormality, spawning a search for the "autism gene", and (2) that autism is the result of some specific environmental factor or condition, including a "lack of maternal warmth" (Kanner, 1949). Although the etiology of autism has remained elusive, the evidence to date has strongly refuted both of these extreme positions.

As one of the first to systematically examine and describe a cohort of children with autism, Kanner hypothesized that these children were both genetically predisposed to develop autism, but also affected by parenting behavior. In his original 1943 paper, he stated that they "come into the world with innate inability to form the usual, biologically provided affective contact with people", while he questioned "whether or to what extent [parenting behaviors and characteristics] contributed to the condition of the children" (Kanner, 1943). Based on his observations of the families of children with autism, he later suggested that autism may be caused by a "genuine lack of maternal warmth" (Kanner, 1949). However, this idea was directly confronted by a psychologist named Bernard Rimland (who was also the parent of an ASD child) in his book, "*Infantile Autism: The Syndrome and its Implications for a Neural Theory of Behavior*" (Rimland, 1964). Herein he proposed a purely biological mechanism for the etiology of autism.

NATURE: THE CONTRIBUTION OF GENETICS

Over subsequent years, epidemiological studies have pointed to a genetic etiology of autism, with up to 60% concordance in monozygotic twins compared with ~5% for dizygotic pairs (Bailey et al., 1995). Nevertheless, affected monozygotic twins did not exhibit similar autistic characteristics, any more so than dizygotic twins (Le et al., 1996), implying that non-genetic or epigenetic factors were also likely to be important.

Today, with the availability of genome-wide array analyses, multiple genetic markers of autism susceptibility have been identified, such as genes encoding for neuronal cell-adhesion molecules (Wang et al., 2009) and copy number variations in surrounding regions (Glessner et al., 2009). However, these factors appear to explain only a small degree of variance (Geschwind, 2008; Sutcliffe, 2008). Other rare genetic disorders, such as Fragile X syndrome and tuberous sclerosis, have been associated with a higher rate of autism, although each possesses fundamentally different genetic abnormalities (Levitt and Campbell, 2009). One recently discovered functional class of autism-associated genes is regulated by neuronal activity, suggesting that both genetic variation and experience may contribute to the development of autism (Morrow et al., 2008). Thus, current models propose that multiple genetic, epigenetic and environmental factors may contribute to the etiology of autism (Geschwind, 2008).

NURTURE: THE CONTRIBUTION OF SOCIAL ENVIRONMENT

Even before the careful descriptions of ASD patients were published by Kanner and Asperger, isolated cases were reported of children exhibiting autistic features, who had been exposed to severe trauma or deprivation (Wolff, 2004). Harlow's studies of rhesus monkeys exposed to severe maternal deprivation also revealed behavioral characteristics resembling that of autism (Harlow and Harlow, 1972). In 1999, "quasi-autistic" traits were described in up to 12% of Romanian orphans exposed to severe deprivation, who were later adopted in the UK, with symptoms related to the age of adoption (Rutter et al., 1999). At age 4, these children were clinically indistinguishable from children with "typical" autism, although differences in behavior and response to treatment emerged over time (Rutter et al., 2007). Rutter and colleagues proposed that "social privation might also impair developmental programming for aspects of psychological functioning relevant to the genesis of autism".

Many congenitally blind children also exhibit characteristics of autism, to varying degrees. A spectrum of autistic features has been observed in visually impaired children (Hobson and Bishop, 2003), with autistic features significantly correlated with severity of blindness and mental retardation (Mukaddes et al., 2007). This leads to the question: are there mechanisms which may account for the observed relationship

between sensory deprivation, congenital blindness and autism?

FACE PROCESSING, OXYTOCIN AND AUTISM

Both Dawson (2008) and Schultz (2005) have hypothesized that basic deficits in social perception may underlie many of the other developmental and behavioral abnormalities seen in autism. They hypothesize that a set of defining experiences early in development may critically affect the development of multiple neural systems. Just as visual deprivation during a critical period of development may result in long-term visual impairment (Wiesel and Hubel, 1965), it is proposed that social deprivation – either externally or internally derived – may contribute to impairment in social development.

While face processing is a key factor in the development of social perception, it is severely impaired in autistic children. Numerous studies have noted face processing deficits using ERP (Dawson et al., 2005b), as well as an impaired ability to recognize faces (Klin et al., 1999) and to fixate on the eyes of others (Jones et al., 2008). Functional MRI studies have demonstrated reduced activation of the fusiform face area when viewing or discriminating faces of unknown adults (Pierce and Redcay, 2008; Schultz, 2005). While infants possess an innate perceptual bias for face-like shapes, the capacity to distinguish facial features develops during the first year of life (Cassia et al., 2006; Gliga and Csibra, 2007). It is proposed that some cases of ASD may result from a deficit in exposure to contingent, socially responsive facial expressions during a sensitive period of social development.

Oxytocin (OT), a neuropeptide associated with social memory and learning, enhances direct eye gaze and the ability to identify and remember faces, as seen in blinded placebo-controlled trials (Guastella et al., 2008; Savaskan et al., 2008). OT receptor expression also appears to be programmed by early life experience via epigenetic mechanisms (Champagne et al., 2001, 2006), with decreased expression seen in the brains of animals who received lower levels of contingent maternal care in infancy. OT deficits in humans have also been implicated in autism, with reduced peripheral OT levels observed in autistic subjects (Green et al.,

2001; Modahl et al., 1998). Furthermore, intravenous OT produces a reduction in stereotypic behaviors in adult ASD subjects (Hollander et al., 2003). Together, these studies suggest that OT may play an important role in promoting social perception, while deficits may be associated with the development of autism.

CONCLUSIONS: NATURE *AND* NURTURE?

As originally observed by Kanner, and confirmed in numerous recent studies, parents of autistic children often exhibit similar characteristics, including face processing deficits, aloofness, behavioral rigidities, and pragmatic language deficits (Dawson et al., 2005a; Piven et al., 1994, 1997). While these characteristics have generally been ascribed to a genetically based "broad autism phenotype", it is also possible, as Kanner first proposed, that "the patient, endowed with an innate disability to relate to people, is further influenced adversely by the parents' emotional detachment" (Kanner, 1965). Is it possible, for example, that the parents' face processing deficits may be causally linked to the deficits seen in their children? Furthermore, could "institutionalization" of infants, in the form of prolonged early non-parental care, be an additional risk factor for autism? As our understanding of epigenetics evolves, the answers may lie in how the social environment influences gene expression and social development.

Thus, despite detours along the way, we return to the original observations of Kanner to propose that the true etiology of autism may incorporate both nature and nurture – genetically determined predispositions and the cumulative effects of exposure to adverse or atypical social environments.

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