



*Commentary*

## **Embracing the challenge of bold theories of autism**

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This article is a commentary on 'Fetal testosterone and autistic traits' (Auyeung *et al.*, 2009).

Autism research needs bold ideas. The recent race of advanced molecular genetic studies (Gupta & State, 2007), the structural and functional neuroimaging studies of younger and younger children followed longitudinally (Courchesne *et al.*, 2007; Schultz, 2005), and the new social neuroscience of babies at greater genetic risk for autism (Chawarska *et al.*, 2008) have all moved this field to a higher plateau of knowledge. And yet, the translation of this research into tangible treatments targeting the very causes of the autism spectrum disorders (ASD) is still disappointing.

Valuable treatments that make a significant impact on the lives of children with ASD are available, but these are, to date, focused on increasing competence and decreasing impairing symptoms (National Research Council, 2001); they do not touch, as yet, the causes of this highly heterogeneous family of conditions nor do they appear to fundamentally change the natural course of the social disability. To be sure, educational and behavioural, and at times psychopharmacological treatments change lives and alleviate stressful challenges while optimizing outcome. But we do so despite of autism, and not, as yet, by addressing the risk factors leading to autism.

This state of affairs creates a dangerous void, which is often filled with empty promises and pseudo-science that preys on a vulnerable community by trading on hope (Hyman & Levy, 2005; Nature Neuroscience, 2005). Clearly, we need to redouble our resolve to advance new ideas and new methods for research of the social brain and of autism.

In this light, the work of Baron-Cohen's group on the prenatal androgen theory of autism has been unique in its scope, detail and comprehensiveness (Baron-Cohen, Knickmeyer, & Belmonte, 2005). The approach builds on the observation that central

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traits of autism appear to be extreme manifestations of typical male (as against female) traits: a predisposition to engage in mechanical or engineering activities contrasting with child rearing and family building – in fact activities focused on the minds and hearts of others. Various clues from autism led to Baron-Cohen's extreme male brain (EMB) theory of autism (Baron-Cohen, 2002) such as the male/female ratio of affected individuals – many more males than females; the focused learning of facts and rules of systems contrasting with severe challenges in empathy and 'mind reading' – the empathizing–systemizing (ES) spectrum of learning styles (Baron-Cohen, Wheelwright, *et al.*, 2005); and the familial link with professions such as engineering and physics in individuals with ASD (Baron-Cohen, Wheelwright, Stott, Bolton, & Goodyer, 1997). While all of these were at times dismissed as 'popular psychology' themes, building the ES argument on male/female stereotyped dichotomies better accounted for in terms of enculturation, what followed from these humble beginnings was indeed very impressive: a systematic, stepwise and prolific program of research transcending its forerunner themes of 'mindblindness' and 'folk physics versus folk psychology', which were now integrated into an overarching theoretical framework more easily translated into a neurobiological hypothesis of autism. The EMB hypothesis is now supported by a large series of neuropsychological, brain structure and function, and now, prospective neurobiological studies. They strengthen the hypothesis and place its etiologic origins in exposure of the fetal brain to excessive amounts of testosterone, which masculinise body, mind and brain. To date, no theory of autism has provided such a connecting thread linking etiology, neuropsychology and neural bases of autism.

To be sure, none of the elements of this theoretical edifice has gone unchallenged, though still only in a handful of studies or reviews (e.g. Ellis, 2005; Voracek & Dressler, 2006). For such a radical departure from the more common themes in autism research, this is surprising. For example, the Systemizing concept turns 60 years of autism research on its head. This concept poses a drive to understand how inanimate systems work, to derive rules, to learn concepts that account for isolated instances of physical events and predict their function, to infer the regularities and principles of rule-governed systems, and the like. Kanner (1943), and Golstein and colleagues (Scheerer, Rothmann, & Goldstein, 1945) in the 1940's and 1950's, Rimland in the 1960's (1964), Hermelin and O'Connor (1970) and Wing and Gould in the 1970's (Wing, Gould, Yeates, & Brierly, 1977), and many others subsequently proposed that children with autism learn facts and information in a rote fashion, failing to abstract rules, and in fact, failing to profit from meaning when performing say verbal memory or other learning tasks. It is clear that many intellectually intact individuals with autism are capable of learning rather intricate rules. Generalization, however, may be limited, not only across systems or settings but within the specific system of knowledge itself as well. And yet some can not only do that but in fact excel in professions that capitalize on more circumscribed talents in science or other rule-defined vocations. All of that notwithstanding, for a large number of individuals with autism the new concept of Systematizing feels more wishful than reality. For example, is a child who obsesses about electronics and builds radios . . . of cardboard really learning the principles of electronics? Or is a child who fixates on a class of objects such as bottles, and spends days looking at or manipulating bottles, really learning principles about bottles or light reflection on bottles? In some intriguing cases, like those of savants, it is indeed a fact that regularities and rules are learned to surprising levels of performance, such as the cases of children with calendar calculation skills (e.g. Thioux, Stark, Klaiman, & Schultz 2006). And yet, researchers have long isolated rote learning, rather than rule deriving, as one of the more fundamental forces

involved in savant skills and in the acquisition and display of circumscribed interests (Hermelin, 2001; Klin, Danovitch, Merz, Dohrmann, & Volkmar, 2007). Thus the Systemizing concept can be challenged on the basis of not accounting for at least some manifestations of unusual skills, stereotyped fixations, perceptual or language patterns displayed by individuals with autism. And alternative explanations for the typical profile of learning style exist (e.g. Klin, Jones, Schultz, & Volkmar, 2003; Mottron, Dawson, Soulieres, Hubert, & Burack, 2006).

In contrast to the Systemizing concept, the EMB and fetal testosterone (fT) elements of the theory remain virtually unexplored by researchers outside the Cambridge group. That hormonal regulation, particularly prenatal androgens, can have an impact on brain structure and function is an established fact (Becker *et al.*, 2008). That malfunction of this system, in the form of excessive prenatal exposure to testosterone may be a risk factor for autism is a bold new idea. In the present paper, Baron-Cohen's group makes, for the first time, a direct connection between elevated levels of fT and autistic symptoms. The far-reaching implications of this finding requires replication, expansion, and the scientific scrutiny of other research programs battling this idea into full corroboration or full falsification.

The fT hypothesis of autism was first formulated several years ago (Baron-Cohen, Lutchmaya, & Knickmeyer, 2004). That research from other groups has been slow in coming is puzzling, particularly since the concepts of this hypothesis fall squarely in an area of medicine that evolves in leaps and bounds. Prenatal hormonal influences on brain growth have been studied for many years. And no other theory of autism promises more immediate rewards for treatment since hormonal influences could, in principle, be targeted for intervention in, at least, high risk samples. Of course, before a clinical trial is justified, there is still quite a bit of groundwork to be covered. Most immediately, there is a need for replication of findings obtained in convenience samples of fT (as used in this study). Then, if warranted, there will be a need for prospective studies of fT relative to diagnostic outcome years later in large samples of high risk conceptions. With a recurrence rate of maybe 5 to 20% of autistic-like behaviours or developmental delays in siblings of children with autism, if findings such as the ones reported in this paper are independently validated, such a study would be justified.

Thus this important line of research has been orphaned by the research community so far, and critical evaluation of its premises and findings remains to be done. The Cambridge group has generated a large body of peer-reviewed studies. The bold ideas have been launched. The time has come for these ideas to be subjected to the grind of other laboratories.

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