

RUNNING HEAD: Commentary on Kung et al. (2016)

Are we expecting too much from the extreme male brain theory of autism? A commentary on
Kung et al. (2016)

Andrew J.O. Whitehouse

Telethon Kids Institute
The University of Western Australia
100 Roberts Road
Subiaco 6008
Western Australia, Australia

Author correspondence:

Prof Andrew Whitehouse

Telethon Kids Institute

University of Western Australia

100 Roberts Road, Subiaco

Western Australia 6008

Email: Andrew.Whitehouse@telethonkids.org.au

Phone: +61 8 9489 7770

Abstract

Kung et al. (2016) contribute further evidence demonstrating no clear link between prenatal androgen exposure and the autism phenotype. Do these findings represent a nail in the coffin for the extreme male brain (EMB) theory of autism, or are we simply asking too much of the hypothesis? This commentary highlights the inconsistent findings that have appeared to undermine the EMB theory, but presents an argument that that the data may not present an adequate test of the hypothesis. A research agenda is then outlined – the investigation of simple behavioural traits rather than the full combination of ASD behaviours - which may provide greater clarity as to how prenatal androgen exposure relates to developmental psychopathology.

Keywords: Autism Spectrum Disorders; Androgens; Testosterone; Language; Research design.

Abbreviations: ASD = Autism Spectrum Disorder, CAH = congenital adrenal hyperplasia, EMB = Extreme Male Brain.

The 'extreme male brain' theory was among the first prominent hypotheses that sought to explain the male preponderance of Autism Spectrum Disorders (ASD). Based on observations from animal studies that manipulation of hormone levels prenatally can lead to behavioural changes in offspring, the theory proposed that exposure to increased levels of androgens during critical windows of prenatal development may be a contributing factor to the development of ASD (Baron-Cohen, 2002). The empirical testing of this hypothesis has been a challenging exercise not just due to the ethical preclusion of manipulating prenatal hormone levels in humans, but also because of the difficulties associated with accurately measuring human biology several years prior to the development of ASD behaviours.

The study by Kung et al. (2016) contributes another set of null findings to a research literature already clouded by inconsistent results. The prevailing thought is that methodological differences between studies may account for discrepant findings. It is not ethically defensible to sample fetal blood for research purposes, and so human studies have relied on surrogate measures of prenatal androgen exposure, each of which have methodological strengths and weaknesses. The measurement of androgen concentrations from umbilical cord blood is an inexpensive methodology that facilitates data collection on a large number of normal pregnancies. Studies that have used this measurement technique have typically observed no link between perinatal androgen concentrations and the ASD phenotype (Whitehouse et al., 2012). However, a limitation of this approach is that cord blood androgen levels may not reflect concentrations during the first and second trimester, which is traditionally thought to be a critical period during which prenatal hormone exposure has its most pronounced effect on neurodevelopment.

Two methodologies that allow for the examination of androgen concentrations during early- and mid-pregnancy are the sampling of amniotic fluid from second trimester amniocenteses, and the study of individual exposed to unusual prenatal hormone environments, such as those with congenital adrenal hyperplasia (CAH). However, a drawback of these approaches is the questionable extent to which findings from these clinical populations – amniocenteses can only ethically be performed in high-risk pregnancies - can be generalised to the broader population. Previous studies using these methodologies have found elevated steroidogenic activity in amniotic fluid sampled from pregnancies that led to a male with ASD (Baron-Cohen et al., 2015), and increased levels of autistic-like traits among females with CAH (for a review, see Gore, Martien, Gagnidze, & Pfaff, 2014). However, these findings, which support the EMB hypothesis of ASD, are challenged by the data presented by Kung et al. (2016) that found no link between amniotic fluid androgen concentrations and ASD traits later in life, nor evidence for increase ASD traits in females with CAH. While Kung et al. (2016) acknowledge several methodological limitations of their studies – small sample sizes and the lack of measurement of amniotic fluid from foetuses who were later diagnosed ASD - the data provide further evidence that any link between prenatal androgen levels and the ASD phenotype is not clear cut.

Any observer of ASD science over the past three decades could not be surprised with the mixed finding; all hypotheses seeking to describe the aetiological pathways to ASD have endured similar inconsistent data. While any neurodevelopmental condition is likely to incorporate a degree of heterogeneity, the aetiological variability observed in ASD is thought to exceed that of other disorders (Whitehouse & Stanley, 2013). The scientific response has been to reduce the emphasis on categorical diagnostic boundaries, and instead focus on understanding the aetiological pathways underpinning behavioural/cognitive traits. One such

framework, the Research Domain Criteria (RDoC), highlights core biobehavioural dimensions that cut across diagnostic categories of psychiatric disorders (Casey, Oliveri, & Insel, 2014). Particularly relevant to ASD are difficulties with cognitive systems, such as attention and cognitive control, and differences in systems for social processes, such as social communication. The hope is that the investigation of dimensional measures may provide greater insight into biological-behavioural associations than the use of (what may prove to be) artificial diagnostic categories.

Genetic research that focused on behavioural dimensions relevant to ASD have started yielding informative results. For example, St Pourcain et al. (2013) conducted a genome-wide association study of 6948 children from the general population and found links between two single nucleotide polymorphisms and social communication skills that had not previously been identified through analyses of individuals with the full ASD syndrome. While the role of these common genetic variants in clinical ASD remains to be determined, the key point is that the study of behavioural dimensions was able to identify new biological candidates that may not have been identified through the investigation of aetiologically heterogeneous ASD samples. A similar principal may apply in the investigation between prenatal androgens and the ASD phenotype. While findings are inconsistent when examination the relationship with the measures reflecting the full collection of ASD behaviours (either in clinical or general population samples), greater clarity may be observed when investigating individual behavioural traits.

Evidence from existing studies suggests that one area for future investigation that may be particularly fruitful is the link between prenatal androgen exposure and language development. The link between increased prenatal androgen exposure and language

difficulties are remarkably consistent, having been observed when androgen concentrations are measured from amniotic fluid and from umbilical cord blood, as well as when observing the development of individuals with CAH (for a review, see Whitehouse et al., 2012). Early language delays are often present in individuals later diagnosed with ASD, but are also observed in children who do not develop ASD. A research focus that first seeks to understand how increased prenatal androgen exposure relates to language development more generally, is likely to provide greater clarity on the mechanisms underpinning this biological-behavioural association, and also how this biological mechanism may contribute to the aetiological pathways for ASD.

The investigation by Kung et al. is an important milestone in the study of the EMB theory of ASD. The data contribute to the now substantial body of evidence demonstrating no clear link between prenatal androgen exposure and the full ASD behavioural profile. To advance beyond this stalemate, future research must first understand how the prenatal hormone environment relates to individual behavioural dimensions, and then incorporate this knowledge into the investigation of links with the more aetiologically and phenotypically complex profile of ASD.

Acknowledgments

Andrew Whitehouse is supported by a Senior Research Fellowship from the National Health and Medical Research Council (APP1077966).

References

- Baron-Cohen, S. (2002). The extreme male brain theory of autism. *Trends in Cognitive Sciences*, 6(6), 248-254. doi: [http://dx.doi.org/10.1016/S1364-6613\(02\)01904-6](http://dx.doi.org/10.1016/S1364-6613(02)01904-6)
- Casey, B. J., Oliveri, M. E., & Insel, T. (2014). A neurodevelopmental perspective on the Research Domain Criteria (RDoC) framework. *Biological Psychiatry*, 76(5), 350-353. doi: 10.1016/j.biopsych.2014.01.006
- Gore, A. C., Martien, K. M., Gagnidze, K., & Pfaff, D. (2014). Implications of prenatal steroid perturbations for neurodevelopment, behavior, and autism. *Endocrine Reviews*, 35(6), 961-991. doi: doi:10.1210/er.2013-1122
- Kung, K. T. F., Spencer, D., Pasterski, V., Neufeld, S., Glover, V., O'Connor ... Hines, M. (in press). No relationship between prenatal androgen exposure and autistic traits: Convergent evidence from studies of children with congenital adrenal hyperplasia and of amniotic testosterone concentrations in typically developing children. *Journal of Child Psychology and Psychiatry*.
- St Pourcain, B., Whitehouse, A. O., Ang, W. Q., Warrington, N. M., Glessner, J. T., Wang, K., . . . Smith, G. D. (2013). Common variation contributes to the genetic architecture of social communication traits. *Molecular Autism*, 4(1), 1-12. doi: 10.1186/2040-2392-4-34
- Whitehouse, A. J. O., Mattes, E., Maybery, M. T., Sawyer, M. G., Jacoby, P., Keelan, J. A., & Hickey, M. (2012). Sex-specific associations between umbilical cord blood testosterone levels and language delay in early childhood. *Journal of Child Psychology and Psychiatry*, 53(7), 726-734. doi: 10.1111/j.1469-7610.2011.02523.x
- Whitehouse, A. J., Mattes, E., Maybery, M. T., Dissanayake, C., Sawyer, M., Jones, R. M., . . . Hickey, M. (2012). Perinatal testosterone exposure and autistic-like traits in the general

population: a longitudinal pregnancy-cohort study. *Journal of Neurodevelopmental Disorders*, 4(1), 1-12. doi: 10.1186/1866-1955-4-25

Whitehouse, A.J.O., & Stanley, F.J. (2013). Is autism one or multiple disorders? *Medical Journal of Australia*, 198, 302-303.