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Title: Is this conjectural phenotypic dichotomy a plausible outcome of genomic imprinting?

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Abstract

What is the status of the dichotomy proposed and the nosological validity of the contrasting pathologies described? How plausibly can dysregulated imprinting explain the array of features described, compared with other genetic models? We believe that considering alternative models is more likely to lead in the long term to the correct classification and explanation of the component behaviours.

Main Text

At the conceptual core of Crespi and BadcockÕs case are two developmental syndromes in humans attributed to imprinted genes on chromosome 15q11-13: Angelman syndrome (AS), caused by mutations abolishing expression of the maternally transcribed *UBE3A* gene (Lalande and Calciano, 2007), and Prader-Willi syndrome (PWS), caused by deficits in expression of paternal genes in the same imprinting cluster (Bittel and Butler, 2005). Given this, and the dominance of the conflict theory for the evolution of imprinting (Haig and Westoby, 1989; Moore and Haig, 1991), the effects of intragenomic conflict have been inferred from several phenotypes manifested in these conditions (Haig and Wharton, 2003; Brown and Consedine, 2004). The genetic causes of ASD and schizophrenia are more complex than those of AS and PWS, and manifestly polygenic in nature. This should make one cautious of the authorsÕ proposal, but not dismissive.

Because of their complex epigenetic regulation, imprinted genes are vulnerable to dysregulation (section 3) though they are not unique in this respect (e.g. maternal behaviour regulates promoter methylation of the glucocorticoid receptor gene in rat pups: Weaver *et al.*, 2004). However, many imprinted genes are expressed in the mammalian brain (Davies *et al.*, 2005) thereby presenting a large mutational target and increasing the prior probability of imprinted gene involvement in ASD and schizophrenia. Classic work with mouse embryos chimeric for wildtype and androgenetic (Ag) or parthenogenetic (Pg) cells (Allen *et al.*, 1995; Keverne *et al.*, 1996) also suggests a role for imprinting in brain development, but some evidence presented by the authors seems contrary to neuroanatomical predictions one might derive from this work. For example, increased and decreased hippocampal size in autism and schizophrenia (section 6.1.2) is not consistent with Pg cell accumulation in the hippocampus (Allen *et al.*, 1995) and overall brain size is

decreased in chimeras with a high contribution of Ag cells (Keverne *et al.*, 1996) contrary to brain size increases in autism (section 6.1.1).

These concerns aside, the authorsÕ theory is impressive in terms of the wealth of phenomena it endeavours to embrace and several features described in table 1 are plausibly supportive. Even here, though, the authorsÕ exclusive reliance on the conflict theory may be misleading. For example, *in utero* growth restriction is associated with paternal over-expression in transient neonatal diabetes (Temple and Shield, 2002) against the predictions of this and some other theories for the evolution of imprinting. Comparisons with existing theories or data are *post hoc* and the authors know they need to propose falsifiable hypotheses. While they make some interesting predictions we do not believe their model sufficiently specifies how imprinted genes are involved and in what phenotypes.

The behavioural phenotypes of ASD and schizophrenia are complex. In ASD the trio of Òimpaired social interaction, impaired communication and restricted and repetitive interests and activitiesÓ are linked conceptually by jointly providing the inclusive definition of ASD rather than biologically by any strong associations in their occurrence in psychological tests of the general population (HappŽ *et al.*, 2006) or in genetic twin studies (Ronald *et al.*, 2006). Thus comparative studies between groups of ASD versus other individuals could produce artefactual associations between the separate components of this triad (HappŽ *et al.*, 2006). The same is likely to be true *a fortiori* for any umbrella concept of schizophrenia (Bentall, 2003) let alone for an opposing cluster of psychoticism which also includes bipolar disorder and major depression.

These considerations raise the question: what constitutes a continuum in biology? Is a nominal scale sufficient? We see this conspectus of phenotypic features as more idiographic than nomothetic. But even on a nominal scale there is the problem of co-morbidity. The authors cite evidence for co-morbidity of obsessive-compulsive disorder (OCD) and attention-deficit hyperactivity disorder (ADHD) with both autism and schizophrenia. From this they predict the existence of different types of OCD and ADHD in

autism and schizophrenia. But why do they not consider co-morbidity a major problem for their position? Are there any kinds of co-morbidity that would constitute a disconfirmation of the hypothesis?

In so far as Crespi and BadcockÕs thesis depends on conflict theory, we note the need for hypotheses to be developed regarding differential manipulation of parents in autism and schizophrenia. We remain to be persuaded that the mechanizing/mentalizing dichotomy will map onto more manipulation in autism and less in schizophrenia. It seems reasonable to suppose the existence of Machiavellian manipulators of maternal care possessed of good mentalizing abilities. We must wait for data to be collected to settle this question.

More generally, while we believe that conflict theory has considerable explanatory utility, an alternative model of imprinting evolution under sexually antagonistic selection might help the authors elucidate the links between parental gene effects and sexual differences (section 7). For example, a gene may tend to show expression limited to the paternal allele when alleles of that gene benefit males more than they cost females (Day and Bonduriansky, 2004). Such a mechanism could provide a specific explanation for why autism appears simultaneously to be caused by an excess of paternal gene expression and manifests as an Òextreme male brainÓ phenotype. In this context the authorsÕ observations about the relations between sex and severity in autism and schizophrenia (e.g. figure 6) seem to hint at such a selective regime.

Finally we emphasize the importance of considering alternative genetic models that explain the prevalence of ASD and schizophrenia or their components. We will mention just one here. Some alleles (of one or more genes) may show benefits when inherited alone, but cause mental dysfunction when inherited together such that selection maintains them in the population in a balanced polymorphism. For instance, Nettle and Clegg (2006) have noted that schizotypy is strongly related to creativity, which in turn has been linked to reproductive success (Miller, 2001), at least in terms of number of sexual partners over a lifetime. They confirmed this by showing that two out of four component dimensions of schizotypy were positively correlated with mating success in a large sample of British adults which included amateur and professional artists and poets.

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