

Original Article

Testing the imprinted brain: parent-of-origin effects on empathy and systemizing

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Abstract

Genomic imprinting is a violation of Mendel's laws that enables selection to act on genes, depending on parent of origin, but, even more controversially, on the sex of the offspring. This study tested whether there are parent-of-origin effects on the heritability of empathy and systemizing in the general population as part of a larger question concerning the role of imprinted genes in the evolution of human cognition and behaviour. The measures tested were the Empathy and Systemizing Quotients as proxies for the related terms mentalistic and mechanistic cognition in the imprinted brain theory. To test genomic imprinting hypotheses, correlations in behavioural scores between pairs of full, maternal and paternal siblings were compared. Where scores are influenced by imprinted genes, the actual correlations between pairs of siblings will differ from those expected following classical Mendelian inheritance in a predictable way depending on what kind of imprinting is influencing the trait. These theoretical predictions were used to test the fit of the data against Mendelian and imprinting models using structural equation modeling. The imprinted brain theory proposes a trade-off between maternally influenced mentalistic cognition and paternally influenced mechanistic cognition. However, the results of this study support a model of contrasting maternal and paternal influences on strong and weak empathizing and a maternal influence on systemizing. Although the sample size was insufficient to comprehensively analyse sex-limitation models, there is some evidence that heritability of systemizing is stronger in females than in males.

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1. Introduction

When gene expression is reduced, partly or entirely, depending on whether that gene is maternally or paternally derived, the gene is said to be imprinted. This violates Mendel's law of independent assortment: imprinted genes are effectively only (or mostly) inherited from one parent.

The first imprinted genes identified were the paternally expressed mouse insulin-like growth factor II, *Igf2* (DeChiara, Robertson, & Efstratiadis, 1991), and the maternally expressed *Igf2* receptor, *Igf2r* (Barlow, Stoger, Herrmann, Saito, & Schweifer, 1991), and *H19* (Bartolomei, Zemel, & Tilghman, 1991). These genes are all involved in

regulating fetal growth, fuelling speculation that imprinting was a consequence of a 'parental tug-of-war' over the developing fetus culminating in the conflict theory of genomic imprinting (Moore & Haig, 1991). This explanation proposed that there was a conflict of interest between the mother restraining the growth of her fetus in order to conserve her resources for herself and future offspring, and the father, whose only concern was the quality of the immediate offspring.

Mouse studies showed that imprinted genes also influenced brain development and behaviour. In particular, maternal gene expression is associated with the cortex, striatum and hippocampus, and paternal gene expression with the hypothalamus (Keverne, Fundele, Narasimha, Barton, & Surani, 1996). A role for imprinting in human brain development was suggested by behavioural traits and psychopathologies showing parent-of-origin effects, such as alcoholism (Durcan and Goldman, 1993; Paterson & Petronis, 1999), Angelman syndrome (Clayton-Smith & Laan, 2003;

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Lalande & Calciano, 2007), autism spectrum condition (ASC) (Arking et al., 2008; Ashley-Koch et al., 1999; Cook et al., 1997; Lamb et al., 2005; Repetto, White, Bader, Johnson, & Knoll, 1998), bipolar disorder (Dick et al., 2003; McInnis et al., 2003; Schultze et al., 2004), Prader–Willi syndrome (Gallagher, Pils, Albalwi, & Francke, 2002; Glenn, Driscoll, Yang, & Nicholls, 1997; Runte, Varon, Horn, Horsthemke, & Buiting, 2005; Sahoo et al., 2008) and schizophrenia (DeLisi et al., 2002; Francks et al., 2003; Seal et al., 2006).

There have been many theories regarding the evolution of imprinting, but as more imprinted genes are discovered and their function becomes better understood, few theories have retained any credibility as they struggle to accommodate the data (Day & Bonduriansky, 2004; Moore & Mills, 2008; Weisstein, Feldman, & Spencer, 2002; Weisstein & Spencer, 2003). Theories drawing on intragenomic conflict and/or sexual dimorphism remain relevant to the present discussion.

The conflict theory of imprinting postulates that genes will be imprinted such that those influencing traits that benefit the mother's interests over the father's will be maternally expressed and vice versa (Moore & Haig, 1991; Wilkins & Haig, 2003). Conflict theory was a particularly good fit to the early studies on imprinting that found genes that increased foetal growth (at a cost to the mother) were paternally expressed, while those that down-regulated foetal growth were maternally expressed. As the catalogue of imprinted genes and associated traits has expanded, it has been less obvious how the conflict theory might account for all patterns of imprinting. Behaviour, which is sometimes referred to as an extended phenotype, led to the extension of conflict theory to reflect not only parental interests but also those of matrilineal and patrilineal kin — the kinship theory of imprinting (Haig, 2004).

Studies on ASC and Turner's syndrome also indicate that sexual dimorphism in traits associated with these conditions may be due to X-linked imprinted genes (Skuse, 1999). The two theories are not mutually exclusive, depending on whether, and to what degree, the conflict in question is one between maternal/paternal or female/male interests. Gregg et al. found that imprinting status can depend not only on parent of origin but also on the sex of the offspring with the imprinting status of both autosomal and X-linked genes being sex-dependent (Gregg, Zhang, Butler, Haig, & Dulac, 2010a; Gregg et al., 2010b).

Evidence for a primary role of imprinted genes in the evolution and aetiology of ASC has been comprehensively reviewed by Badcock and Crespi (2006). They suggest that autism is the result of imbalanced imprinting in the brain resulting in dysfunction of the maternally influenced neocortex and/or the paternally influenced limbic system. Crespi and Badcock (2008) have comprehensively expanded their theory to encompass the relationship between imprinted genes and the full range of conditions associated with ASC and psychoses: a psychogenetic theory of everything. In this model, ASC lies at one extreme, predominantly influenced by paternally expressed genes, and the psychoses at the other

extreme, predominantly influenced by maternally expressed genes. More specifically, they propose that mental processes which can be termed 'mechanistic' lie at one pole of an axis from 'mentalist' processes. The term 'mentalist cognition' refers to the drive to understand human 'minds, motives and emotions', while 'mechanistic cognition' strives to understand the 'physical, non-human universe of inert objects' (Badcock, 2009, p. 15). In this context, mentalistic and mechanistic cognition are related but not synonymous with empathy and systemizing. Mentalism replaces the term 'theory of mind': the ability to infer another person's mental state (Premack & Woodruff, 1978). Theory of mind is generally viewed as contributing to empathy, and there is some evidence for a maternal influence on theory of mind as measured by the ability to read another person's mental state from the expression in the eyes (Ragsdale & Foley, 2011). Mechanistic is preferred to systemizing as a simpler, less abstract process.

Developing a methodology to test for the influence of imprinted genes requires reworking the basic assumptions that usually underpin research in human behavioural genetics, namely, Mendel's law of independent assortment which predicts that each offspring inherits traits randomly from its parents. In order to track parent-of-origin effects, the experimental design must be able to distinguish between maternal and paternal influences. In this study, parent-of-origin effects were tested by comparing pairs of full siblings with pairs of maternal and paternal half-siblings. Two tests developed to measure empathy and systemizing in the general population were given to each sibling: the Empathy Quotient (EQ) (Baron-Cohen & Wheelwright, 2004) and the Systemizing Quotient (SQ) (Wheelwright et al., 2006). The development of the EQ and SQ is part of a larger study on the traits associated with autistic spectrum condition (ASC). Individuals with ASC tend to have lower EQ and higher SQ scores.

ASC is characterized by language impairment, abnormal social interaction, unusually intense, restricted interests and repetitive behaviours (American Psychiatric Association, 2000). ASC is known to be highly heritable compared to other psychopathologies (Bailey et al., 1995; Freitag, 2007; Steffenburg et al., 1989). Many genes, probably with epistatic effects, appear to be involved, including imprinted loci on chromosomes 4, 7, 9, 11, 15, 20 and X (Fradin et al., 2010; The Autism Genome Project Consortium, 2007). It follows therefore that traits associated with ASC, such as empathy and systemizing, may also be influenced by imprinted genes.

The EQ was developed to measure 'the drive to identify another person's emotions and thoughts, and respond to these with an appropriate emotion' (Wakabayashi et al., 2006). This encompasses the ability to attribute agency to social behaviour, which has been termed 'folk psychology', and is a universal cognitive domain (Cosmides & Tooby, 1994). The questionnaire was developed to target 'empathy' more specifically than previous measures (Baron-Cohen &

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