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MINI REVIEW

Imbalanced genomic imprinting in brain development: an evolutionary basis for the aetiology of autism

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Abstract

We describe a new hypothesis for the development of autism, that it is driven by imbalances in brain development involving enhanced effects of paternally expressed imprinted genes, deficits of effects from maternally expressed genes, or both. This hypothesis is supported by: (1) the strong genomic-imprinting component to the genetic and developmental mechanisms of autism, Angelman syndrome, Rett syndrome and Turner syndrome; (2) the core behavioural features of autism, such as self-focused behaviour, altered social interactions and language, and enhanced spatial and mechanistic cognition and abilities, and (3) the degree to which relevant brain functions and structures are altered in autism and related disorders. The imprinted brain theory of autism has important implications for understanding the genetic, epigenetic, neurological and cognitive bases of autism, as ultimately due to imbalances in the outcomes of intragenomic conflict between effects of maternally vs. paternally expressed genes.

> So the goblins came. They pushed their way in and pulled baby out, leaving another all made of ice. (Maurice Sendak, Outside over there. Puffin Books, Middlesex, UK, 1981)

Introduction

Inclusive fitness theory predicts phenotypic conflicts between the effects of genes that differ in their means of increased replication. Such conflicts may involve distinct modes of inheritance or different likelihoods of genes identical by descent being present in interacting individuals, such as for autosomal genes in various classes of relative. Autosomal genes in offspring may also differ in the probabilities of identity by descent whenever a female produces offspring sired by more than one male. In this situation, a females' offspring are more closely related for maternally inherited genes than for paternally inherited ones (Haig, 2000a,b, 2004a; Goos & Silverman, 2001; Úbeda & Haig, 2003). Paternally expressed genes are thus expected to be selected for effects that extract higher levels of limiting resources from the mother, but these effects should be countered by selection on the effects of maternally expressed genes. Such intragenomic conflict has favoured the evolution of genomic imprinting, whereby genes are selected to be expressed or silenced, often in particular tissues at particular times in development, according to their parent of origin and their effects on the fitness of mothers and offspring (Haig, 1997a, 2000a,b, 2004a,b; de la Casa-Esperon & Sapienza, 2003; Day & Bonduriansky, 2004; Wilkins, 2005). For a gene that enhances offspring fitness at a fitness-reducing cost to mothers and broodmates, the paternally inherited gene should be expressed but the maternal copy is silenced (Haig, 2000a,b). Conversely, maternally inherited genes that restrain such effects should be expressed, whereas paternally expressed ones are silenced.

The conflict theory of genomic imprinting has been supported by a considerable body of genetic and physiological evidence, such as the direct interaction between insulin-like growth factor II production vs. degradation by paternal vs. maternal genes (Haig & Graham, 1991), the GNAS system with clear, conflicting effects of paternally and maternally expressed genes (Haig,

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2004b; Plagge *et al.*, 2004; Weinstein *et al.*, 2004; Chen *et al.*, 2005), and complex multigenic *cis*- and *trans*-interacting systems expressed during the embryonic development of mice (Cattanach *et al.*, 2004). Although some effects of imprinted genes have yet to be explained, such as growth in some uniparental disomies (Hurst & McVean, 1997), and development of white adipose tissue (Haig, 2004b), the conflict theory provides the only comprehensive, empirically supported explanation for the diverse effects of imprinted genes on growth and development (Haig, 1996, 2000a,b; Tycko & Morison, 2002; Burt & Trivers, 2006).

Thus far, most studies of genomic imprinting have focused on genes expressed during placental and embryonic development, where most known imprinted genes are expressed, and many are known to promote foetal growth enhancement or suppression (Goos & Silverman, 2001; Miozzo & Simoni, 2002). The dynamically balanced, 'tug-of-war' nature of genomically imprinted systems in placentation creates conditions where disruption of imprinted genes may result in disorders of pregnancy. Indeed, four of the most common disorders of human gestation, preeclampsia, miscarriage, foetal growth restriction and gestational diabetes, are mediated in part by effects of imprinted genes (e.g. Moore & Haig, 1991; Chilosi *et al.* 1998; Graves, 1998; Tsai *et al.*, 1998; Haig, 1999; Reik *et al.*, 2003; Oudejans *et al.*, 2004; McMinn *et al.*, 2006).

The placenta has evolved as a nexus of genomic-imprinting conflict because of its central role in the transfer of limiting resources between individuals that bear genes with divergent interests (Haig, 1993, 1996, 1999; Goos & Silverman, 2001; Crespi & Semeniuk, 2004). The other main tissue where genes are imprinted is the brain (Keverne, 1997; Davies *et al.*, 2001, 2005a). In this context, transfer of resources between relatives, including from mothers to offspring, is arbitrated by the behaviour of parents, offspring and potentially other relatives (Haig, 2000a,b). For example, in mice the paternally expressed imprinted gene Peg3 enhances suckling, lactation and maternal care, fostering mother–offspring coadaptation (Li *et al.*, 1999; Keverne, 2001a; Curley *et al.*, 2004; Isles & Holland, 2005). In humans, brain-expressed imprinted genes have been shown to affect diverse behavioural traits (Davies *et al.*, 2001, 2005a). As in placentation, disruption of brain-imprinted systems via mutation or epigenetic alteration can lead to major disorders, such as the single-locus Angelman and Prader-Willi syndromes, which involve behavioural changes apparently consistent with how the maternally vs. paternally expressed genes have been disrupted (Badcock, 2000; Nicholls, 2000; Haig & Wharton, 2003). Such disruptions can be hypothesized as due to loss of balance in physiological and developmental tugs-of-war, which may result in specific forms of disorder depending upon the direction of the phenotypic shifts.

A pervasive role for genomic imprinting in brain development has been demonstrated by Keverne and colleagues (Allen *et al.*, 1995; Keverne *et al.*, 1996a), who showed experimentally that in chimeric mouse brains, cells with exclusively paternal gene expression differentially contribute to development of the limbic system (the hypothalamus, amygdala and other structures of the 'emotional brain' that mediates basic drives such as hunger, fear and aggression), whereas cells with exclusively maternal gene expression differentially proliferate in the cortex (the 'executive brain' involved in language, social reciprocity, planning and behavioural inhibition). These findings imply that the brain is partitioned along a major axis of cognition that is characterized by imprinted-gene effects on behaviour (Keverne, 1997, 2001a,b; Davies *et al.*, 2005a). Here we refer to the regions of the brain in which paternally expressed genes differentially affect development (i.e. the limbic system) as the *paternal brain*, and those regions in which maternally expressed genes differentially guide development are called the *maternal brain* (the neo-cortex).

In this paper we describe and evaluate the hypothesis that autism, a major polygenic condition leading to altered human perception, cognition and behaviour, is driven by effects of imbalanced genomic imprinting in the brain. We first describe salient aspects of autism and related conditions, and we then explain and assess previous theory for the aetiology of autism with a focus on the 'extreme male brain theory' of Baron-Cohen (2002, 2003). We then present our 'imprinted brain' theory of autism, discuss relevant data from genetic, epigenetic, neurological and behavioural studies, and describe the implications of our theory for analysing the causes of autism.

Autism and autistic conditions

Autistic disorders are characterized by three main classes of features: (1) impairments in social interactions, (2) impairment in verbal and nonverbal communication, and (3) restricted, repetitive and stereotyped behaviour (American Psychiatric Association, 2000; Frith, 2003). Behaviourally, these traits are highly variable among individuals, but they often manifest as social withdrawal, insistence on sameness, attempts to control others, tantrums and social-emotional difficulties (Kanner, 1949; Asperger, 1991; Frith, 1991a; Wing, 1991; Grandin, 1995). Autism usually involves mental retardation (quantified via IQ), often severe, and a high incidence of seizures (Folstein & Rosen-Sheidley, 2001; Muhle *et al.*, 2004; Veenstra-VanderWeele *et al.*, 2004). It may develop gradually between birth and age 3, or by rapid developmental regression (Rogers, 2004), characterized in folklore as children 'stolen' from their parents by supernatural creatures (Leask *et al.*, 2005).

The incidence of autism is five cases per 10 000 individuals, with reported rates ranging from 2 to

20 cases per 10 000 (American Psychiatric Association, 2000). Nevertheless, a recent study of 788 pairs of twins investigating autistic tendencies suggested that autistic traits are continuously distributed in the population (Constantino & Todd, 2003). Diagnosed autism thus appears to be the extreme point on a much wider spectrum that shades into normality (Spiker *et al.*, 2002; Constantino & Todd, 2005). Today the term Asperger's syndrome is usually applied to so-called 'high-functioning autism': that is, subjects with IQ in the normal range or above and intact language ability (Asperger, 1991; Frith, 1991a; Wing, 1991; Rinehart *et al.*, 2002a). Autistic symptoms are also relatively common in a number of other disorders, notably Turner syndrome, Angelman syndrome, Rett syndrome, fragile X syndrome and tuberous sclerosis (Cohen *et al.*, 2005).

Autism is one of the most strongly heritable of all psychiatric conditions, with concordance (co-expression) rates of 60–92% for monozygotic twins and 0–10% for dizygotic twins (Folstein & Rosen-Sheidley, 2001; Muhle *et al.*, 2004; Veenstra-VanderWeele *et al.*, 2004; Veenstra-VanderWeele & Cook, 2004). The genetic models most compatible with inheritance data invoke many loci (>10) of weak to moderate effect, with three to six epistatic loci being the simplest scenario (Risch *et al.*, 1999; Folstein & Rosen-Sheidley, 2001; Jiang *et al.*, 2004a; Bonora *et al.*, 2005; Santangelo & Tsatsanis, 2005). However, conflicting evidence from eight independent full-genome scans suggests that genetic heterogeneity is common, such that multiple more or less overlapping sets of alleles at different loci apparently contribute to autism (Jiang *et al.*, 2004a; Cantor *et al.*, 2005). The genetic basis of autism is thus notably unclear, despite its high heritability.

The extreme male brain theory of autism

In his original 1944 report, Asperger (1991) suggested that 'the autistic personality is an extreme variant of male intelligence'. Baron-Cohen has developed this idea into the extreme male brain theory of autism (Baron-Cohen, 2002, 2003; Baron-Cohen *et al.*, 2005). By his theory, females tend generally to be more empathic, and males normally more systematic in their cognitive style. Here *empathy* 'comprises two major elements: (a) attribution of mental states to oneself and others, as a natural way to make sense of the actions of agents … and (b) emotional reactions that are appropriate to others' mental states' (see also Preston & de Waal, 2002). By contrast, *systemizing* is described as 'the drive to analyse objects and events to understand their structure and to predict their future behaviour. Systems are ubiquitous in the environment: technical systems (such as machines and tools), natural systems (such as biological and geographical phenomena), and abstract systems (such as mathematics or computer programs)' (Baron-Cohen & Belmonte, 2005). Independently, Badcock (2004) made a similar distinction in the broader terms of *mentalistic cognition* understood as an adaptation to the human, social environment and *mechanistic cognition* seen as an adaptation to the physical world.

According to the extreme male brain theory, 'the triad of behavioural abnormalities in social function, communication, and restricted and repetitive behaviours and interests can be explained psychologically by an impaired capacity for empathizing, or modelling the mental states governing the behaviour of people, along with a superior capacity for systemizing, or inferring the rules governing the behaviour of objects' (Baron-Cohen, 2002; Baron-Cohen *et al.*, 2005). The extreme male brain theory is consistent with a wide range of evidence, including:

1. cognitive and behavioural differences between girls and boys, such that girls exhibit increased ability to predict thoughts and feelings of others, enhanced empathy, better ability to detect emotions from eyes and faces, and faster language development, whereas boys show increased ability and interests in activities related to systematizing, such as mathematics, mechanics, rule-based systems, and collecting (Baron-Cohen, 2002; Baron-Cohen *et al.*, 2005).
2. the finding that prenatal exposure to male sex hormones is associated with two cognitive characteristics commonly found in autism: poorer quality of social relationships and more restricted interests, particularly in boys (Lutchmaya *et al.*, 2002a,b; Knickmeyer *et al.*, 2004), and two developmental traits, extreme finger-length ratios and precocious puberty, that have been reported to be characteristic of autistic males (Baron-Cohen, 2002); and
3. higher scores for males on the Autism Spectrum Quotient test (Baron-Cohen *et al.*, 2001).

The extreme male brain theory of autism matches mentalistic deficits of autism (along with the occasional mechanistic compensations) to normal sex differences, and helps in explaining the striking male sex ratio bias in autism, about 4 : 1 overall (Veenstra-VanderWeele *et al.*, 2004). The result is a view of autistic disorders stretching along a spectrum from severe impairment in classical autism at one extreme, to normal male mentality at the other, with the average female mind even further displaced away from the autistic extreme (Baron-Cohen, 2002, 2003). This theory has provided the first theoretical framework for understanding the evolutionary basis of autism, in terms of the extreme development of natural male–female differences, driven by genetic variants at many loci and perturbations of early brain development.

Despite the compelling evidence for the extreme male brain theory, several observations stand in contrast to its core predictions. First, the male bias in incidence of autism increases not towards the autistic extreme as might be expected, but towards the normal end of the spectrum. Thus, it is among so-called 'high-functioning' (i.e. more normal) Asperger's cases that the sex ratio of incidence is most heavily tipped towards males, with sex

ratios up to 10 : 1 male biased or higher (Wing, 1988; Gillberg, 1989; Ehlers & Gillberg, 1993; Volkmar *et al.*, 1993; Ehlers *et al.*, 1997; Ingram *et al.*, 2000a). If autism were purely a disorder of the extreme male brain, the opposite situation might be expected, with the greatest number of males being affected by the most severe symptoms. Indeed, seeing autism as an extreme male brain disorder makes any female cases problematic, unless Asperger syndrome is conceived as 'pure' autism (Baron-Cohen, 2002).

Second, autism-typical savant skills can be induced by fronto-temporal dementia or brain injury that sometimes devastate other functions (Miller *et al.*, 1998). Moreover, experiments in which magnetic stimulation is used to block frontal lobe functions in the brains of normal people suggest that they begin to function more 'autistically', and show better perception of detail as measured by a proof-reading test. The authors conclude that, 'these proof-reading results provide nonsubjective evidence of the ability to switch on savant-like skill by turning off part of the brain in healthy individuals' (Snyder *et al.*, 2003). These findings are not easily consistent with the extreme male brain theory, as such perturbations would not be expected to make a brain 'more male', especially as neurodevelopment has already been completed by late adolescence.

Third, although foetal testosterone levels are negatively related to quality of social relationships, and positively correlated with restricted interests (Knickmeyer *et al.*, 2004), there is no direct evidence as yet relevant to the hypothesis that prenatal (or postnatal) testosterone is associated with higher risk of autism in males or females (Skuse, 2000; Baron-Cohen *et al.* 2004).

Finally, autism is a highly convergent disorder, in that a fundamentally similar phenotype can result from a multiplicity of disparate genetic and environmental effects (Gillberg, 1992; Herbert, 2005). Thus, autism is common in single-locus genetic disorders such as Rett syndrome, fragile X syndrome, tuberous sclerosis and Angelman syndrome, and it can be environmentally induced by prenatal valproic acid, thalidomide or viral infection (Cohen *et al.*, 2005; Libbey *et al.*, 2005; Miyazaki *et al.*, 2005). None of these diverse causative agents have been linked to hormonal influences on brain development along the male–female axis of cognition, which suggests that autism is driven by alterations in more fundamental mechanisms of cognitive development.

The imprinted brain theory of autism

We suggest a new theory for the evolutionary underpinnings of autism, that it is a disorder of the extreme *imprinted* brain. By this hypothesis, the mechanisms that cause autism are those that impinge upon the evolved balance between the cognitive effects of the paternal brain and maternal brain, which are driven by genomic imprinting of brain-expressed genes. In particular, autism is caused by imbalances that involve increased genetic, neurological and behavioural effects of the paternal brain relative to the maternal brain. The imprinted brain theory of autism makes many similar predictions as the extreme male brain theory, and it is thus consistent with Baron-Cohen's body of evidence. However, our theory also elucidates the pattern of sex ratio bias and other observations that are otherwise inexplicable, and it provides novel predictions for understanding both the genetic basis and phenotypic features of autism.

Imprinted genes have profound and pervasive effects on body size, brain size and brain organization (Allen *et al.*, 1995; Keverne *et al.*, 1996a,b; Keverne, 1997; Badcock, 2000). In mice, paternal-cell chimeras (androgenetic, with a diploid paternal genotype) have relatively large bodies and small heads, whereas maternal-cell chimeras (parthenogenetic, with a diploid maternal genotype) show the reverse pattern (Allen *et al.*, 1995). In the brain, maternal cells are found in large numbers in the neocortex and forebrain but very few are found in the lower, limbic brain, especially the hypothalamus. This is true both of mature, fully grown maternal-cell chimeras but even more so of maternal cell chimera foetuses, where there is a complete absence of maternal cells from the hypothalamus. Maternal chimera cells are found to be particularly clustered in the frontal lobes of the cortex; by contrast, paternal cells are found in the hypothalamus and limbic brain, but not in the neocortex. The few that are found in the forebrain tissue of embryos do not proliferate and are subsequently eliminated.

These patterns indicate that brain relative size and structure are strongly affected by imprinting. Indeed, Keverne also shows an evolutionary trend among primates for a relatively larger forebrain relative to limbic system, and he suggests that intragenomic conflict, driven by imprinting effects in the brain, has been a major factor in the tripling of brain size along the human lineage (Keverne *et al.*, 1996b). As expected given their effects on brain development and structure, imprinted genes also exhibit diverse effects on behaviour such as parent–offspring interactions, inbreeding avoidance, novelty-seeking and dispersal (Haig, 1997b, 1999, 2000a; Li *et al.*, 1999; Davies *et al.*, 2001, 2005a; Isles *et al.*, 2002; Haig & Wharton, 2003; Plagge *et al.*, 2005).

Disparities in function and effects between paternally expressed and maternally expressed genes involved in cognition are ultimately driven by variation in genetic relatedness (here, identity by descent for paternally and maternally inherited genes) coupled with the extensive maternal investment typical of mammals. Thus, the mammalian father's only obligatory biological contribution to his offspring is a single sperm and any further parental investment on his part is entirely supernumerary, particularly if another male is already providing whatever additional paternal resources a woman's

children may require. Consequently, the father can only rely on his genes – and more specifically, the parts of the brain they build – to help his offspring behave in ways which will further his biological interest invested in it. As a result, the father's genes can be expected to motivate self-interested behaviour and use of the mother's resources at her expense and that of sibs lacking his paternally expressed genes. This might explain why paternal genes are preferentially expressed in the hypothalamus, amygdala and other parts of the limbic system, concerned as it is with expression of basic drives, appetites and emotions. But the same logic might also explain why a less empathic, more mechanistic, bottom-up, and less centrally coherent (Happé, 1999, 2000; Frith, 2003) cognitive style is associated with the paternal brain. As we describe below, it might also explain the notable social deficits at the core of autism – apparent manifestations of the cognitive style of truly selfish genes.

The contrary applies to maternally expressed genes. Here the important factor is that every child definitely carries half of its mother's genes, irrespective of who the father may have been. Furthermore, the mother is the sole provider of resources to the foetus before birth and to the baby afterwards by way of breast-milk. Universally, she is also likely to be considerably more involved with child-care than the father – particularly in early childhood when the child's demands are at their greatest (Browne, 2002, pp. 21–22). As a consequence, the mother has a strategic advantage in exploiting her role as a nurturer that the father seldom has. Because she is likely to be the most important person in the child's environment and the decisive influence on its development in early childhood, she can exploit her role as teacher, guardian, and provider of first resort (Brown, 2001). Her maternally active genes will be expressed in all her children and should further the mother's interests by building a cortical brain capable of integrating mental activity in the greater interests of her whole family. Her genes will control the parts of the child's brain that can be educated by verbal instruction and practical example. She will be able to use the speech centres of the cortex to teach her child its mother tongue and the inhibitory and prioritizing functions of the frontal lobes to control behaviour in accordance with her commands and instructions. Here a top-down, contextual, holistic and empathic cognitive style might be particularly useful in influencing a child's social interaction with its siblings, peers and parents. This would make a child much more likely to see things from its mother's point of view and perhaps less likely to act impulsively on the promptings of its paternal brain. According to the view described here, autism is the consequence of the failure of the maternal brain in this respect, and the impulsiveness, compulsiveness and contrariness of autistics the inevitable result of the paternal brain's corresponding success.

One of the major functions of what we call the maternal brain is the co-ordination, integration and inhibition of outputs from all over the nervous system, especially the paternal brain. Here it is significant that frontal brain volumes may be relatively larger in women, and that reduced frontal volume is associated with antisocial behaviour and psychopathy (Gur *et al.*, 2002). A review of the scientific findings regarding an ability to inhibit and control aggression concluded that humans' apparently increased emotional control relative to other primates is not likely due to a reduction in the role of the limbic system in human behaviour; we remain highly emotional animals. A more likely cause is inhibition from the prefrontal cortex' (Björklund & Harnishfeger, 1995).

The main predictions of the imprinted brain theory are threefold. First, and most importantly, the primary causes of autism should be alterations in imprinted genes, genes regulated by imprinted genes, and genes associated with the regulation of imprints, via their application and removal (Burt & Trivers, 1998; Wilkins & Haig 2002; Wilkins, 2005). Such mutations or alterations may be inherited or *de novo*, due to environmental or stochastic effects during development. Nonimprinted gene effects may also lead to autism, but primarily to the extent that they disrupt the evolved balance between the maternal and paternal brains.

Second, autism may be caused by diverse genetic, epigenetic and environmental factors that cause paternal–maternal brain imbalance (Eigsti & Shapiro, 2003; Lee *et al.*, 2003; Rubenstein & Merzenich, 2003; Cohen *et al.*, 2005; Herbert, 2005). Such causes may involve changes in brain structure or systems of neurotransmission that favour the paternal brain, via enhancement of paternal–brain influences, reductions in the role of maternal brain effects, or effects on how the paternal and maternal brains function jointly. Thus, no single axis of pathology (such as sexually dimorphic effects) is expected, although alterations of early development should be especially strong because they amplify during growth.

Third, the behavioural changes involved in autism should reflect extreme manifestations of general, evolved mechanisms for mother–offspring and among-sibling competition over resources. Thus, autism should be thought of as a disorder of kinship interactions, which grade into social reciprocity during childhood via evolved mechanisms for interactions with both kin and nonkin (Alexander, 1990).

We evaluate our predictions and hypothesis via consideration of syndromes involving autism that have a well-understood genetic basis, and by considering autism itself, for which the genetic basis is still the subject of intense scrutiny. Readers less specialized in genetics and neurobiology may wish to focus their reading on the sections below concerning the behavioural and sex-ratio correlates of autism, before considering our synthesis in the Discussion.

The imprinted brain in single-locus autistic syndromes

Angelman and Prader-Willi syndromes

Prader-Willi syndrome in infants involves lack of appetite, poor suckling ability, a weak cry, inactivity and sleepiness, high pain threshold, and reduced tendency to vomit (Franke *et al.*, 1995) – features which could be seen as benefiting the mother by making the baby less demanding on her resources (Haig, 1997a, 1999, 2000b; Haig & Wharton, 2003). By contrast, symptoms of Angelman syndrome in early childhood include prolonged suckling, hyperactivity, frequent waking, and temper tantrums – every mother's worst fear (Badcock, 2000; Cohen *et al.*, 2005). Although both Prader-Willi and Angelman children are mentally retarded, Angelman retardation is usually much more severe, and, as in the most severe cases of autism, speech is absent (Holm *et al.*, 1993). Whereas Prader-Willi children tend to be diagnosed as obsessive–compulsive or exhibit psychoses after adolescence, Angelman children commonly exhibit autism or autistic behaviours that include loss of language, intolerance to change, stereotyped behaviours, and seizures (Schroer *et al.*, 1998; Peters *et al.*, 2004; Cohen *et al.*, 2005; Sahoo *et al.*, 2006). Although Prader-Willi syndrome due to maternal duplications of chromosome 15 (rather than paternal deletions) involves impaired social behaviour in childhood, which is sometimes diagnosed as autism (Cook *et al.*, 1997b; Schroer *et al.*, 1998; Gurrieri *et al.*, 1999), such cases do not involve autism-typical deficits in theory of mind (Sullivan & Tager-Flusberg, 1999).

Angelman and Prader-Willi syndromes are caused by alterations in gene dosage of imprinted genes on chromosome 15, with the primary causative gene for Angelman syndrome being the ubiquitin protein ligase gene UBE3A, which is maternally expressed in the brain (Nawaz *et al.*, 1999; Herzing *et al.*, 2001; Nicholls & Knepper, 2001; Dan & Boyd, 2003; Yamasaki *et al.*, 2003). Dysregulation of UBE3A is also considered as a strong risk factor for autism (Nurmi *et al.*, 2003a,b; Jiang *et al.*, 2004a; Peters *et al.*, 2004), and mouse knockouts for this gene show changes in brain morphology and behaviour that resemble those found in human subjects with autism (Jiang *et al.*, 1998). In particular, loss of expression of UBE3A in Purkinje cells of the cerebellum is known to disrupt levels of the apoptosis-regulating gene p53 during neuronal development (Jiang *et al.*, 1998; Nawaz *et al.*, 1999; Fatemi & Halt, 2001). Abnormalities of the Purkinje cells are one of the most consistent patterns of human brain abnormality found in autism (Bauman & Kemper, 2005) and we hypothesize that alterations in this component of the paternal brain contribute to autistic behaviour in both Angelman syndrome and autism. Reduced UBE3A in Angelman syndrome may also cause cortical and thalamo-cortical dysfunction resulting from dysregulation of GABAergic neurotransmission, via deficiencies in expression of GABRB3 (Dan & Boyd, 2003), a gene with strong paternal bias in expression (Bittel *et al.*, 2003, 2005).

Rett syndrome

Rett syndrome is a neurological disorder characterized by autistic-like behaviour, impairment of language, mental retardation, seizures, changes of head growth, loss of gross motor skills, and repetitive hand movements, with a developmental onset, and regression, starting at age 1 or 2 (Glaze, 2004; Weaving *et al.*, 2005). This condition thus overlaps closely with autism in its core features (Olsson & Rett, 1990; Neul & Zoghbi, 2004; Rogers, 2004; Weaving *et al.*, 2005). The most notable difference between autism and Rett syndrome is its near-restriction to females, which is associated with its primary cause, male germline mutations in the X-linked gene MECP2, which codes for methyl-CpG binding protein (Weaving *et al.*, 2005).

MECP2 is a transcriptional silencer that regulates the expression of other genes via binding to CpG islands (Bapat & Galande, 2005; Horike *et al.*, 2005; Pescucci *et al.*, 2005; see also Young *et al.*, 2005). It is highly expressed in the brain, where its expression is associated with maturation of neurones (Horike *et al.*, 2005). Horike *et al.* (2005) identified an imprinted gene as a primary target of MECP2 in the brain: reduced MECP2 function causes loss of imprinting in the maternally expressed homebox gene DLX5, which increases its expression. DLX5 plays a crucial role in forebrain development, where it induces maturation and differentiation of GABAergic neurones (Stuhmer *et al.*, 2002; Kishi & Macklis, 2004; Perera *et al.*, 2004; Cobos *et al.*, 2005). Disruption of the development of such neurones, and in GABAergic neurotransmission, have been strongly implicated in Angelman syndrome (Lalande *et al.*, 1999) and autism (Hussman, 2001; Fatemi *et al.*, 2002; McCauley *et al.*, 2004a). As described below, DLX5, and another imprinted gene that regulates its expression, DLX1, have also been potentially linked to autism in genome scans, at 7q and 2q respectively (IMGSAC 2001a,b).

The genetic basis and phenotypes of Rett syndrome provide evidence for loss of imprinting in DLX5 leading to disruption of maternal-brain development. The mechanisms linking gene-dosage effects of DLX5 with the cognitive and behavioural features of Rett syndrome have yet to be explored. MECP2 also regulates other genes, such as BDNF, that play important roles in brain development (Martinowich *et al.*, 2003; Wade, 2004; Tsai, 2005), and its altered expression in the cerebellum has also been proposed as crucial to the development of Rett syndrome (Naidu *et al.*, 2003). Rett syndrome also involves lower birth weight (Huppke *et al.*, 2003), which is consistent with stronger effects from maternally expressed genes. Moreover, one mouse model of MECP2 dysregulation, which exhibited doubled expression of the gene, showed enhanced motor and contextual learning

and increased synaptic plasticity in the hippocampus before 20 weeks of age, after which they developed seizures (Collins *et al.*, 2004). MECP2-deficient mice also exhibit dysregulation of the imprinted gene UBE3A (Makedonski *et al.*, 2005; Samaco *et al.*, 2005); UBE3A gene expression was also found to be altered in multiple brain samples from human Rett, Angelman and autism subjects (Samaco *et al.*, 2005). Taken together, these findings suggest that MECP2 functions as an 'imprinter' gene (Burt & Trivers, 1998; Fan & Hutnick, 2005; Wilkins, 2005), whose altered expression leads via multiple mechanisms to the development of autism and autism-spectrum disorders (Samaco *et al.*, 2004; Thatcher *et al.*, 2005).

Turner syndrome

Turner syndrome is due to X chromosome monosomy, with phenotypic effects due to haploinsufficiency of genes that normally escape X inactivation (Good *et al.*, 2003). Some phenotypic features of Turner syndrome depend upon whether the single inherited X chromosome is of paternal or maternal origin. Thus, females with a paternal X exhibit well-developed verbal and social skills, whereas females with a maternal X (the only X chromosome present in males) are less well-adjusted socially, less communicative, and demonstrate poor recognition of fear from faces, all features that are found disproportionately in both normal males and in autism (Skuse *et al.*, 1997; Creswell & Skuse, 1999; Bishop *et al.*, 2000; Donnelly *et al.*, 2000; Skuse, 2000; Good *et al.*, 2003). Turner females with paternal vs. maternal X chromosomes also differ in aspects of amygdala, cerebellum, and superior temporal gyrus morphology that are consistent with their behavioural divergence in social cognition (Brown *et al.*, 2002; Kesler *et al.*, 2003, 2004). Overall, there were no cases of autism in a sample of 65 Turner subjects with a paternal X, whereas 10 of 165 with a maternal X were autistic, an increase of over 100-fold above the expected norm (Creswell & Skuse, 1999; Skuse, 2000, 2005).

These observations of cognitive heterogeneity in Turner syndrome, according to the parent of origin of the X chromosome, indicate that an imprinted X-linked gene exerts a strong effect on expression of social behaviour and liability to autism, making maternal-X Turner females cognitively more like males (Skuse *et al.*, 1997; Donnelly *et al.*, 2000; Skuse, 2000, 2005). An imprinted, maternally expressed gene, Xlr3b, has recently been discovered using a mouse model for Turner syndrome (Davies *et al.*, 2005b; Raefski & O'Neill, 2005). This gene exhibits behavioural effects in mice comparable with those in humans, mediating a tendency for inflexible reversal learning, and microdeletions of its human homologue, FAM9B, have been linked to both autism and schizophrenia (Davies *et al.*, 2005b). Raefski & O'Neill (2005) suggest that expression levels of this gene may be critical in lowering the threshold for social impairment, and autism, in both males and Turner's females with a maternal X. These findings provide a clear link between genomic imprinting and autism, and provide a simple genetic mechanism helping to explain its strong male bias in expression (Skuse, 2000).

The imprinted brain in autism

Behavioural aspects of autism

Our hypothesis predicts that the behavioural changes associated with autism should reflect reduced maternal-brain functions, and a relatively intact or more-developed paternal brain. The mental retardation and loss of language characteristic of classic autism fit with this prediction, but they also necessarily engender a profound loss of phenotypic traits, making further evaluation difficult in this context.

By contrast, intact verbal ability and normal or above-average IQ are characteristic of Asperger syndrome, sometimes considered as so-called 'high-functioning autism' (Asperger, 1991; Frith, 1991a; Wing, 1991; Hippler & Klicpera, 2004). Such individuals, however, do not show a coincident amelioration in social adjustment. Asperger himself commented that 'this disturbance results in severe and characteristic difficulties of social integration', adding that 'in many cases the social problems are so profound that they overshadow everything else' (Asperger, 1991). In particular, he noted seemingly malicious and spiteful behaviour (Frith, 1991b, p. 7), ill-discipline, and resistance to formal instruction in school (Hippler & Klicpera, 2004). In Asperger's cases lack of social reciprocity is more typically manifested by one-sided interaction and less-cooperative behaviour (Soderstrom *et al.*, 2002) rather than by the complete indifference to others that is often seen in classical autism (American Psychiatric Association, 2000, p. 80). Moreover, so-called Asperger's savants (Fitzgerald, 2005) are typically found to be loners, despite the fame and appreciation their achievements may bring them, and those with artistic talent typically show no interest in others' reactions to their work (Hermelin, 2001, p. 137).

These findings suggest that in Asperger's syndrome an ability to empathize is damaged or absent, and that cognitive deficits are predominantly mentalistic. Such a pattern of selective dysfunction fits with our contention that in autism spectrum disorders social adaptations that would benefit maternal genetic self-interest are notably absent, but that behaviour focused on self-interest is intact or exaggerated, just as a preponderance of paternal genetic influence would suggest. Indeed, we expect that kin-selected and reciprocal altruistic behaviour should be specifically lacking, or at least not develop naturally, in Asperger's syndrome or high functioning autism (McGuire *et al.*, 1994; Grandin, 1995). As children, such individuals may often impose and elicit especially high costs on their parents, although in a pathological rather than adaptive context.

Sex ratio

By our hypothesis, the key to explaining sex ratio variation in autism is that both sexes exhibit maternal and paternal brains, and that autism can involve either impairment of the maternal brain (with a normal or enhanced paternal brain), or increased effects of the paternal brain (with a normal maternal brain). Impairment of the maternal brain is expected to result in more severe, 'classic' autism involving mental retardation and loss of language, whereas a normal maternal brain, with increased paternal-brain effects on cognition and behaviour, may give rise to 'higher-functioning' autism or Asperger's syndrome.

In accordance with Baron-Cohen's extensive evidence for sex differences in cognition (Baron-Cohen *et al.*, 2005), and Skuse's (2000) evidence for X-chromosome effects, males normally exhibit a skew towards stronger effects of the paternal brain, which predisposes them to autism. One might thus expect mainly males to be affected by increased paternal-brain effects, leading to the strong male sex ratio bias in high-functioning autism and Asperger's syndrome. By contrast, both sexes may be affected more or less equally, or females may be affected more, by the intrinsically more-severe deficits of a disrupted maternal brain, such as mirror neuron dysfunction (Dapretto *et al.*, 2006) or tuberous sclerosis (Wiznitzer, 2004), leading to the equal sex ratio in severe autism. This hypothesis can be evaluated via quantification of paternal–maternal brain imbalances in males and females, by linking specific epigenetic perturbations to the magnitude of autistic phenotypes in the two sexes, and by searching for neurological mechanisms of X-linked or hormonal female 'protection' against mild autistic impairment (Skuse, 2000).

Genetics of autism

One of the main predictions of the imprinted brain hypothesis is that the development of autism should be strongly influenced by the expression patterns and effects of imprinted genes. Evaluating this prediction requires consideration of the unique characteristic of genes subject to imprinting. First, imprinted genes may be imprinted only in particular tissues or brain regions at particular stages during development, imprint status may be polymorphic within populations, and the expression of paternal vs. maternal alleles need not be an all or none phenomenon (Weinstein, 2001; de la Casa-Esperon & Sapienza, 2003; Buettner *et al.*, 2004; Naumova & Croteau, 2004; Croteau *et al.*, 2005). For most such genes, spatial and temporal expression patterns have yet to be comprehensively explored. Second, most imprinted genes are highly pleiotropic and epistatic in their effects (Morison *et al.*, 2005). Their expression vs. silencing may be driven by regulatory effects of nonimprinted genes, and imprinter genes (Wilkins, 2005), and their downstream effects may cause nonimprinted genes to act imprinted, as for IGF-I (Cattanach *et al.*, 2004). Third, imprinting patterns are inherited but with a high mutation rate, where mutation refers to epigenetic modification of CpG island methylation or histone acetylation effects (Wilkins, 2005). These considerations, and the expectation that fewer than half of the imprinted genes in humans have yet been discovered or characterized (Nikaido *et al.*, 2004), imply that robust genetic tests of the imprinted gene theory of autism must await studies that target its predictions.

There are two lines of genomic evidence relating imprinted genes to autism: genome scans that localize chromosomal regions linked to autism, and gene association studies, that relate autism to variants of specific genes. Both types of study have often been subject to inconsistency of replication in the study of autism, due at least in part to genetic and clinical heterogeneity of this disorder (Tager-Flusberg & Joseph, 2003; Veenstra-VanderWeele *et al.*, 2004; Bartlett *et al.*, 2005a). Imprinting effects can be indicated or implicated by either direct identification of a role for imprinted genes or gene regions, or by parent of origin effects, where the phenotype is genetically associated with inheritance from only one sex of parent. We note, however, that many genome scan and association studies have not included tests for parent of origin effects. Known imprinted genes are catalogued by Morison *et al.* (2005), and candidate imprinted genes from microarray studies, some of which are found in the regions discussed below, have been compiled by Nikaido *et al.* (2004).

Genome scans

The chromosomal regions most consistently linked to autism include 2q32, 7q21–q22, 7q32 and 15q11–q13 (IMGSAC 1998, 2001a,b; Ashley-Koch *et al.*, 1999; Barrett *et al.*, 1999; Bass *et al.*, 1999; Philippe *et al.*, 1999; Risch *et al.*, 1999; Bradford *et al.*, 2001; Buxbaum *et al.*, 2001; Liu *et al.*, 2001; Auranen *et al.*, 2002; Shao *et al.*, 2002a,b; Nurmi *et al.*, 2003a,b; Yonan *et al.*, 2003; Alarcón *et al.*, 2005; Cantor *et al.*, 2005; Lamb *et al.*, 2005; Vorstman *et al.*, 2006). All of these regions contain either imprinted genes, regions identified as subject to parent of origin effects, genes that are known to interact with imprinted genes, or genes involved in neurological systems strongly impacted by imprinted genes.

The linkage peak at 2q32 contains the genes DLX1 and DLX2, homeobox genes that interact with one of their paralogs, the imprinted gene DLX5 at 7q22 (IMGSAC 2001b). These genes are fundamental to early brain development, where they selectively regulate development of GABAergic interneurones (Merlo *et al.*, 2000; Stuhmer *et al.*, 2002; Cobos *et al.*, 2005). Dysregulation of DLX5 has been associated with Rett syndrome, as described above. DLX genes also regulate the Arista-less homeobox gene ARX (Rubenstein & Merzenich, 2003; Cobos *et al.*, 2005), and mutations in this

gene lead to mental retardation, seizures and autism (Turner *et al.*, 2002; Sherr, 2003). One association study that included DLX1 and DLX2 did not find evidence for a major role in autism (Bacchelli *et al.*, 2003). However, 2q21–q33 also contains a gene, subject to parent of origin effects, that is associated with bipolar disorder (Cichon *et al.*, 2001), which suggests a role for imprinting in this region.

The region 7q21–q22 contains the imprinted DLX5 gene, as well as the imprinted, paternally expressed genes PEG10, PON1, PON2 and PON3. This region also shows parent of origin effect in its linkage to autism, with paternal sharing (Ashley-Koch *et al.*, 1999; IMGSAC 2001b; Lamb *et al.*, 2005). PON1 gene variants have been linked to autism in a recent association study (D'Amelio *et al.*, 2005); this gene may be functionally linked to autism because it is responsible for detoxification of organophosphates, which cause defective methylation, and cognitive changes, in animal models (e.g. Ray & Richards, 2001). Another gene of notable interest at this locus is reelin at 7q22, a nonimprinted gene linked with autism via some association studies and analyses of function (Persico *et al.*, 2001; Zhang *et al.*, 2002; Bonora *et al.*, 2003; Devlin *et al.*, 2004). Reelin is an extracellular matrix protein, secreted by GABAergic interneurones, whose expression is regulated via promotor methylation by Dnmt1, a methyltransferase 'imprinter' gene (Wilkins, 2005). This gene is dysregulated in both autism and schizophrenia, apparently via changes in methylation status (Dong *et al.*, 2005; Fatemi, 2005; Fatemi *et al.*, 2005; Grayson *et al.*, 2005).

The linkage peak at 7q31–q32 contains a cluster of imprinted genes including PEG1/MEST (Yamada *et al.*, 2004), but one association study did not find evidence for linkage of these genes to autism (Bonora *et al.*, 2002). However, Lamb *et al.* (2005) found that linkage to this region increased when only male sibs were considered, which suggests a role for imprinting. This region also contains two genes that have been supported as candidate genes for autism in some (though not all) association studies: UBE2H (Vourc'h *et al.*, 2003) and WNT2 (Wassink *et al.*, 2001; McCoy *et al.*, 2002; Li *et al.*, 2004). Neither of these genes is known to be imprinted. However, the imprinted gene PEG12/FRAT3 is a regulator of the WNT signalling pathway of which WNT2 is an important component (Kobayashi *et al.*, 2002), and mice deficient in the Dvl1 gene, a crucial component of this pathway, show abnormal social behaviour and sensorimotor gating defects (Lijam *et al.*, 1997), two important autistic phenotypes.

The regions 15q11–q13 contains a large cluster of imprinted genes, and cytological abnormalities in this region have consistently been linked to autism (Clayton-Smith *et al.*, 1993; Flejter *et al.*, 1996; Browne *et al.*, 1997; Cook *et al.*, 1997a; Schroer *et al.*, 1998; Mohandas *et al.*, 1999; Roberts *et al.*, 2002; Battaglia, 2005; Vorstman *et al.*, 2006). Imprinted genes in this region that are linked to autism by association studies include UBE3A (Nurmi *et al.*, 2001), ATP10C (Nurmi *et al.*, 2003a,b) and GABRB3 (Cook *et al.* 1998; Martin *et al.*, 2000; Menold *et al.*, 2001; Bittel *et al.*, 2003, 2005; Nurmi *et al.*, 2003a,b, provide evidence for imprinting at this locus). This region thus provides strong evidence of a role for imprinted genes in autism, in addition to its links with Angelman and Prader-Willi syndromes.

Additional evidence for imprinting effects on autism comes from chromosomes 3, 5, 9, 10, 16, 17 and X. Shao *et al.* (2002b) found a strong linkage peak on chromosome 3 centred on the oxytocin receptor gene OXTR. OXTR is not known to be imprinted, but regulation of the oxytocin–vasopressin system is strongly influenced by imprinted genes in rodents (Li *et al.*, 1999; Glasgow *et al.*, 2005) and humans (Muscatelli *et al.*, 2000).

Parent of origin effects on linkage to autism have been reported for chromosomes 9 (Lamb *et al.*, 2005), 10 (IMGSAC 2001a), 16 and 17 (IMGSAC 2001a; Bartlett *et al.*, 2005b). Liu *et al.* (2001) also found notable parent of origin effects, and strong epistatic effects, for markers on chromosomes 5, 19 and X. They suggest that 'some interaction between loci on the X and autosomal chromosomes may help to explain the skewed sex ratio in autism'. As described above, a role for an imprinted X locus in cognitive function and autism has recently been described by Davies *et al.* (2005b). Such complex, *trans*-acting interactive effects of imprinted genes have recently been described in mice in the context of pre-natal and post-natal growth, where they provide strong evidence for the conflict hypothesis (Cattanach *et al.*, 2004). The parent of origin effects at chromosomes 5, 7 and 19 also each involves pairs of nearby genes (Liu *et al.*, 2001; Lamb *et al.*, 2005), which is consistent with the common presence of imprinted genes in clusters (Morison *et al.*, 2005).

Finally, the most recent genome scans for autism susceptibility loci emphasize the role of parent of origin effects in autism (Bartlett *et al.*, 2005b; Lamb *et al.*, 2005), and the most recent comprehensive genetic model for the inheritance of autism posits combined effects of imprinted and nonimprinted genes, with a notable role for the imprinted gene UBE3A (Jiang *et al.*, 2004a). Taken together, these genome-level findings suggest that genomic imprinting effects are fundamentally involved in the development of autism.

Association and functional studies

Autism has been closely linked with alterations in neurodevelopment and neurotransmission of both the serotoninergic and glutamate/GABAergic pathways. Indeed, these systems are closely associated and their interactions may also play an important part in the development of autism. We describe the evidence that imprinted genes are involved in the dysregulation of these systems, from studies of gene function and studies that associate genetic variants with autism.

Glutamate – GABAergic system

Glutamate plays a crucial role in the formation of brain architecture, and it is the primary excitatory neurotransmitter in brain, directly involved in learning, memory, emotional behaviour and seizures (Carlsson, 1998; Purcell *et al.*, 2001; Jamain *et al.*, 2002; Owens & Kriegstein, 2002). Conversely, GABA is the main inhibitory neurotransmitter, whose effects are mediated by GABA receptors, most notably GABRB3, which is apparently present in every GABA receptor complex (Sinkkonen *et al.*, 2003), and is the only receptor subtype present early in life (Dan *et al.*, 2004). A central role for dysregulated glutamate and GABA systems in autism is indicated by three sets of findings: (1) abnormalities in glutamate and GABA in blood and brain of autistic subjects, (2) reduced GABA(A) receptors in autistic brains, and (3) pharmacological studies showing that some symptoms of autism are alleviated by therapeutic agents that target these systems (Hussman, 2001; Fatemi *et al.*, 2002; McCauley *et al.*, 2004a). These observations have led to the hypothesis that autism is fundamentally a hypoglutamatergic disorder (Carlsson, 1998), driven by altered synaptic excitation/inhibition ratios in crucial neural systems that underlie sensation and behaviour (Cline, 2005; Levinson & El-Husseini, 2005), with dysregulation primarily a function of deficits in inhibition of behaviour by the cortex (Casanova *et al.*, 2003).

Several lines of evidence implicate imprinted genes in glutamate and GABAergic systems. First, the GABA(A) receptor subunit GABRB3, which exhibits strong paternal bias in expression (Knoll *et al.*, 1994; Meguro *et al.*, 1997; Bittel *et al.*, 2003, 2005; see also Song *et al.*, 2003), has been linked to autism via numerous association and cytological studies (Cook *et al.*, 1998; Martin *et al.*, 2000; Menold *et al.*, 2001; Buxbaum *et al.*, 2002; Sinkkonen *et al.*, 2003; McCauley *et al.*, 2004a; Curran *et al.*, 2005). This gene also exhibits significantly reduced expression in autism, Rett, and Angelman subjects, and in MeCP2-deficient mice (Samaco *et al.*, 2005), and mice show male-limited parent of origin effects in GABRB3 regulation (Liljelund *et al.*, 2005).

Second, the GABAergic system is subject to regulation by two imprinted genes: DLX5, which induces GABA expression in GABAergic neurones (Horike *et al.*, 2005; Pescucci *et al.*, 2005), and UBE3A, which interacts with ubiquitin-like PLIC proteins that selectively bind to GABRB3 receptors and regulate their synaptic density (Dan & Boyd, 2003; Dan *et al.*, 2004).

Third, the glutamate receptor GluR7 is apparently imprinted in the human brain (Schiffer *et al.*, 2000). Genetic and functional studies of this gene has yet to be investigated for autism, but GluR7 does show increased expression in the prefrontal cortex in schizophrenia (Meador-Woodruff *et al.*, 2001).

Fourth, additional genes involved in the glutamate-GABAergic system that have been associated with autism include glutamate receptor 6 (GluR6, also known as GRIK2) (Jamain *et al.*, 2002; Shuang *et al.*, 2004), and glutamate receptor 8 (GRM8) (Serajee *et al.*, 2003). Jamain *et al.* (2002) found evidence for enhanced maternal transmission (a parent of origin effect) in the inheritance of GluR6 with autism, and a similar maternal transmission effect was noted independently by Bah *et al.* (2004), who linked this gene with susceptibility to schizophrenia. Serajee *et al.* (2003) also described significant parent of origin effects for language and repetitive-behaviour phenotypes, for alleles of GRM8. Confirmation that these parent of origin effects are driven by imprinting would provide evidence for pervasive effects of imprinted genes in the development and regulation of glutamate and GABA neurotransmission.

The gluamate-GABAergic system may be especially salient to the development and evolution of autism because GABAergic interneurones connect the limbic system with the neocortex, and disruption of their development and function has been suggested as an important cause of autism and other disorders such as schizophrenia (Keverne, 1999; Casanova *et al.*, 2003; Coyle, 2004; Dykens *et al.*, 2004; Levitt *et al.*, 2004). These observations are consistent with the idea that disrupted interactions between the limbic paternal brain, and the maternal-brain neocortex, drive the development of autism.

Serotonin system

Serotonin plays a crucial role in neurodevelopment and neurotransmission (Anderson, 2002; Scott & Deneris, 2005; Whitaker-Azmitia, 2005). Alterations of the serotonergic system have been implicated in autism based on diverse data, including: (1) highly elevated serotonin in about 30% of autism cases, and in unaffected first-degree relatives, (2) evidence that drugs targeting serotonin metabolism help alleviate some symptoms of autism, (3) functional imaging studies of serotonin metabolism in the brain, (4) a central role for serotonin in some behavioural features of autism, such as repetitive behaviours, and (5) genetic association studies and genome scans (Cook & Leventhal, 1996; McCauley *et al.*, 2004b; Bartlett *et al.*, 2005a; Coon *et al.*, 2005; Croonenberghs *et al.*, 2005; Janusonis, 2005; Scott & Deneris, 2005; Sutcliffe *et al.*, 2005; Whitaker-Azmitia, 2005).

Several imprinted genes are known or believed to impact the serotoninergic system. Elevated levels of serotonin in some patients are considered to be due to some combination of altered serotonin receptors and transporters, notably 5HTT (Coon *et al.*, 2005; Janusonis, 2005). The serotonin receptor 2A (HTR2A) is polymorphically imprinted in human brain (Bunzel *et al.*, 1998), and its location at 13q has been implicated in some genome scans. An association study did not find linkage of HTR2A polymorphisms to autism, although statistical power was admittedly low (Veenstra-VanderWeele *et al.*, 2002). However, variants of this gene have been linked with ADHD (Quist *et al.*, 2000), and panic disorder (Inada *et al.*, 2003), and HTR2A antagonists may be useful in ameliorating

some symptoms associated with autism (Marek *et al.*, 2003). The serotonin receptor 2C (5HTR2C) is apparently regulated by imprinted, brain-specific snoRNAs (Cavaillé *et al.*, 2000). Alterations of this receptor have been implicated in various psychiatric disorders including schizophrenia, anxiety disorder and depression (Sodhi *et al.*, 2001; Schmauss, 2003; Giorgetti & Tecott, 2004).

The imprinted genes NESP55 and CALCR also influence serotonin metabolism. NESP55 codes for a peptide that inhibits serotonergic 1B receptors (Ischia *et al.*, 1997; Kim *et al.*, 2000), and mouse knockouts for this gene show altered reactivity to novel environments (Plagge *et al.*, 2005). However, Kim *et al.* (2000) did not find an association of this gene with obsessive–compulsive disorder or autism. The calcitonin receptor CALCR is maternally expressed only in the brain (Hoshiya *et al.*, 2003; Okita *et al.*, 2003), and its mRNA product co-localizes with serotonin transporter mRNA (Nakamoto *et al.*, 2000). This gene is at 7q21, in a region linked to autism by genome scans, but association studies have yet to be conducted.

Four nonimprinted genes in the serotoninergic system have been linked with autism both genetically and functionally. Variant long and short alleles of SLC6A4, coding for the serotonin transporter 5HTT, have been associated with autism via genome scans and in seven of 12 association studies (see Stone *et al.*, 2004; Bartlett *et al.*, 2005a; Weiss *et al.*, 2005); these variants differ functionally in their activation in the amygdala (Hariri *et al.*, 2002), and in their effects on stereotypical and compulsive behaviour (Sutcliffe *et al.*, 2005). TPH2, a brain-specific tryptophan hydroxylase that mediates the rate-limiting step in serotonin synthesis, has been linked to autism, especially with repetitive behaviours (Coon *et al.*, 2005), and its variants also differ in their effects on amygdala function (Brown *et al.*, 2005). Finally, a functional polymorphism in monoamine oxidase A (MAOA), an X-linked gene involved in oxidative deamination of serotonin, has been associated with the severity of autism (Yirmiya *et al.*, 2002; Cohen *et al.*, 2003), and its paralog, MAOB, may be involved in the development of sex differences in amygdala development, and social-cognition deficits found in autism and Turner syndrome (Good *et al.*, 2003).

The precise role of serotonin dysregulation in autism has been difficult to demonstrate, and it probably involves effects on early foetal brain development (Chandana *et al.*, 2005; Whitaker-Azmitia, 2005), secondary effects on oxytocin production in the hypothalamus (Whitaker-Azmitia, 2005), and pleiotropic effects of serotonergic pathways on release of serotonin from the gut and signalling in the brain, mediating the expression of HTR2A or HTR1A (Janusonis, 2005). Moreover, brain development and function are also modulated by intimate interactions between the serotonergic system and the glutamate-GABAergic system (Aghajanian & Marek, 1999; Keverne, 1999; Scruggs *et al.*, 2000; Shutoh *et al.*, 2000; Licata *et al.*, 2001; Martin-Ruiz *et al.*, 2001; Regina *et al.*, 2004; Serrats *et al.*, 2005). We hypothesize that effects of imprinted genes are central to the roles of serotonin, glutamate and GABA in the development of autism, with nonimprinted genes shifting thresholds and levels of expression for autistic phenotypes.

Additional imprinting effects

Additional suggestive evidence for effects of imprinting in the aetiology of autism comes from the homeobox genes HOXA1 and EN2, genes involved in the oxytocin–vasopressin system, some immune system genes, insulin-like growth factor II, and the LAMB1 gene, which codes for an extracellular glycoprotein.

The gene HOXA1 exhibits an important role in early brain development (Rodier *et al.*, 1996), truncating mutations of this gene contribute to autism (Tischfield *et al.*, 2005) and functional allelic variation at this locus has been associated with autism, although only in some studies (Ingram *et al.*, 2000a; Conciatori *et al.*, 2004). Ingram *et al.* (2000a) provide suggestive evidence for a parent of origin effect, and they note that the HOXA1 chromosomal region in mice harbours imprinted genes. Similarly, Bartlett *et al.* (2005a) describe suggestive evidence of imprinting for the homeobox gene EN2, which has been linked with autism and shows some evidence for sharing of paternal alleles (Zhong *et al.*, 2003; see also Gharani *et al.*, 2004).

The oxytocin–vasopressin system mediates aspects of social learning and bonding in humans and other mammals (Young & Wang, 2004; Curley & Keverne, 2005). This system has been implicated in autism in diverse ways, including: (1) lower levels of oxytocin in autistic humans (see Wu *et al.*, 2005), (2) a central role for reelin in the development of that GABAergic system, with GABA modulating the release of oxytocin (Liu *et al.*, 2005), (3) serotonergic regulation of oxytocin release (Whitaker-Azmitia, 2005), (4) the modulation of excitatory neurotransmission by both hormones in the amygdala and cortex (Huber *et al.*, 2005); and (5) association with autism of the oxytocin receptor OTXR (Wu *et al.*, 2005), the vasopressin receptor AVPR1a (Kim *et al.*, 2002; Wassink *et al.*, 2004), and the gene NCAM (Bonora *et al.*, 2005), which contributes to regulation of oxytocin release (Theodosis *et al.*, 2004). These genes are not known to exhibit imprinting effects in humans. However, two brain-imprinted genes, Peg3 and APeg3, strongly influence oxytocin and vasopressin production, and affiliative interactions, in rodents (Li *et al.*, 1999; Glasgow *et al.*, 2005; Isles & Holland, 2005), and Peg3 is also paternally expressed in humans (Murphy *et al.*, 2001). These data, and the expression of Peg3 in the limbic system of chimeric mice (Keverne, 2001a), strongly suggest that the oxytocin–vasopressin system is subject to regulation by imprinted gene effects in humans.

Immunological abnormalities imply a role for the neuroimmune system in the development of autism (Korvatska *et al.*, 2002; Torres *et al.*, 2002; Krause *et al.*,

2002). The immune system genes HLA-DR4 and HLA-DR13 have been linked to autism via an association study, and both genes exhibit notable parent of origin effects (Torres *et al.*, 2002). These HLA alleles may influence brain development via effects on glutamic acid decarboxylase, which converts glutamate to GABA (e.g. Larsson *et al.*, 2005; Mimura *et al.*, 2005), especially given that prenatal viral infection may also predispose to autism via effects on regulation of this enzyme (Fatemi *et al.*, 2004).

The adenosine deaminase gene ADA exerts effects on normal development and function of the immune and nervous systems; its enzyme levels are decreased in autism (Stubbs *et al.*, 1982), and association studies have linked functional variants with autism (Persico *et al.*, 2000; Bottini *et al.*, 2001; Lucarelli *et al.*, 2002). Persico *et al.* (2000) also reported possible parent of origin effects on transmission disequilibrium of ADA variants, although the ADA gene is apparently not imprinted.

Insulin-like growth factor II, transcribed from the imprinted promotor P3, is involved in the proliferation of neural precursor cells in the cerebellum (Hartmann *et al.*, 2005), and imprinting of IGF-II in this brain region involves notable lability (Albrecht *et al.*, 1996; Pham *et al.*, 1998). Links between IGF-II and autism have not been investigated thoroughly, but one association study showed near-significance ($0.10 < P < 0.05$) (Hérault *et al.*, 1994) and abnormal development of the cerebellum is one of the most consistent findings in neuroanatomical studies of autism (Carper & Courchesne, 2000; Kern, 2002, 2003; Bauman & Kemper, 2005).

Finally, a rare allelic variant of the gene LAMB1 showed preferential paternal transmission to autistic subjects in a recent study, in accordance with parent-of-origin effects noted at 7q from genome scans (Lamb *et al.*, 2005).

Environmental effects on development of autism

Several lines of evidence implicate dysregulated methylation, and imprinting effects, in environmental determinants on autism. First, valproic acid induces autism when administered in early foetal development (Ingram *et al.*, 2000b; Chudley, 2004; Schneider & Przewlocki, 2005), apparently via its role as a specific inhibitor of histone deacetylase activity, which reduces methylation of promotor regions (Detich *et al.*, 2003). Experiments with mice indicate that effects of valproic acid on genomically imprinted genes contribute to its neurological effects (Beck, 2001), which include abnormalities in serotoninergic neurone development and hyperserotonaemia (Miyazaki *et al.*, 2005). Thalidomide, which similarly leads to autism via perturbation of early brain development, exerts similar effects on the serotoninergic system (Narita *et al.*, 2002; Miyazaki *et al.*, 2005).

Second, impaired methionine metabolism, caused by heavy metals, thimerosal and other agents, and mediated by genetic factors such as propensity to autoimmune disease (Hornig *et al.*, 2004), abnormal metal metabolism (Serajee *et al.*, 2004), or adenosine deaminase activity, may cause dysregulated methylation and contribute to autism (Waly *et al.*, 2004).

Third, autism increases with paternal (and maternal) age (Gillberg, 1980), and assisted reproduction via intracytoplasmic sperm injection (ICSI) may increase the risk for syndromes of dysregulated imprinting, including Angelman and Beckwith-Weideman (Paoloni-Giacobino & Chaillet, 2004; Waterland & Jirtle, 2004; Maher, 2005). Both paternal age and ICSI are expected to contribute to methylated-gene defects, which may include effects on brain-imprinted genes (Waterland & Jirtle, 2004; Malaspina *et al.*, 2005).

Finally, James *et al.* (2004) demonstrated impaired methylation capacity in children with autism; altered methylation, and its effects on imprinted gene expression, can persist through development (Waterland & Jirtle, 2004). Monozygotic twins have also recently been demonstrated to diverge in their patterns of gene methylation starting in early development, which may contribute to their divergence in the expression of cognitive disorders (Petronis *et al.*, 2003; Fraga *et al.*, 2005; Wong *et al.*, 2005).

Further analysis of the links between environmental agents, gene–environment interactions, disrupted methylation, and imprinting may usefully focus on brain-region specific and stage-specific effects of genomic imprinting in early foetal development, and how perturbations during this time period can cause or potentiate autism (Rodier *et al.*, 1997; London & Etzel, 2000; Rodier, 2002; Skoyles, 2002).

Neurodevelopment and neuroanatomy of autism

Genetic and environmental influences in autism are apparently mediated by alterations in neural stem cell determination, timing and patterning of neuronal growth and differentiation, synaptic function, and apoptosis, which lead to altered brain development (Keverne *et al.*, 1996a; Howard *et al.*, 2000; Araghi-Niknam & Fatemi, 2003; Courchesne & Pierce, 2005a).

The imprinted brain theory predicts that abnormal brain development in autism involves imbalances in function between the cortical maternal brain regions and the limbic paternal brain, that result in increased influence on behaviour by the paternal brain. In accordance with this prediction, autism involves abnormal development of widely distributed brain regions, including the fronto-temporo-parietal corticies, limbic system and cerebellum, with notable differences in the anatomy of limbic-striatal 'social brain' systems (Carlsson, 1998; Baron-Cohen, 2000a; Hussman, 2001; McAlonan *et al.*, 2002, 2005; Lee *et al.*, 2003; Schumann *et al.*, 2004; Bauman & Kemper, 2005). Neurodevelopmental disruption in autism appears to result in functional 'underconnectivity' of brain circuitry, leading to increased local vs. global processing of information and

reduced 'central coherence' (Happé, 1999, 2000; Belmonte *et al.*, 2004; Just *et al.*, 2004; Baron-Cohen & Belmonte, 2005; Belmonte, 2005; Herbert, 2005). Such reduced integration includes the connections between the cerebral cortex and limbic systems, some of which 'appear to be unique neural connections between the areas of the brain to which the paternal genome contributes most, and those to which the maternal contribution is primary' (Goos & Silverman, 2001). Indeed, some authors have suggested that underdevelopment or other disruptions in the neural circuits connecting these brain regions underlie autism (Aylward *et al.*, 1999; McAlonan *et al.*, 2002, 2005; Skoyles 2002; Brambilla *et al.*, 2004; Baron-Cohen & Belmonte, 2005).

Abnormal brain circuitry may translate into altered behaviour via its effects on perception and cognition through development, and via feedback from behaviour to brain development (Carper & Courchesne, 2000; Brambilla *et al.*, 2004; Schultz, 2005). Thus, autism involves reduced filtering of sensory input (Grandin, 1995; Vermeulen, 2001), and impaired ability to attach emotional significance to visual input such as facial expression (Baron-Cohen & Belmonte, 2005). Such perceptual changes may, in turn, affect the development of relevant cortical regions used in social interaction (Dunbar, 2003; Schultz, 2005), and circuitry between the maternal and paternal brains fails to develop and function normally. Increased local vs. global brain connectivity may also lead to reduced 'top-down' control of behaviour by the neocortex (Courchesne & Pierce, 2005b), and enhancement of some systems, such as spatial and mechanistic abilities (Grandin, 1998; O'Neill, 1999; Hermelin, 2001; Koenig *et al.*, 2001; Frith, 2003), in extreme cases leading to savant skills (Hermelin, 2001; Heaton & Wallace, 2004). We suggest that reduced functional integration and central coherence in the brain may also lead to a greater influence on behaviour from the paternal brain, as the neocortex is less able to inhibit 'inappropriate' self-focused behaviour (Minshew *et al.*, 1999; Baron-Cohen & Belmonte, 2005). Such impairments in functional integration may, in principle, be driven by any genetic and environmental factors that impact the development of limbic-neocortical circuitry, including impaired neuronal development (Carlsson, 1998; Skoyles, 2002; Courchesne & Pierce, 2005a,b; Levitt, 2005), lesions in the amygdala (Baron-Cohen *et al.*, 2000), cortical pathologies such as those seen in tuberous sclerosis (Wiznitzer, 2004), and developmental feedback (Schultz, 2005); this general mechanism of neuroanatomical, cognitive disordering in autism can thus account for its diverse causes.

Discussion

The imprinted brain hypothesis unifies data from genetics, neurobiology, psychology and behaviour, and provides a conceptual framework for the aetiology of autism grounded in evolutionary theory. This hypothesis complements and extends the extreme male brain theory of autism (Baron-Cohen, 2002) and generates novel predictions and recommendations for future work.

We consider the diverse evidence for the imprinted brain hypothesis to be compelling, especially as none of it was collected in the context of testing its predictions. Genome scans, association studies, and analyses of environmental factors demonstrate notable effects of imprinted genes in the development of autism, especially for genes involved in the glutamate/GABAergic and serotoninergic systems of development and neurotransmission. We hypothesize that genetically and environmentally dysregulated ontogeny and function of interneurones that connect paternal and maternal brain structures are especially important in autism, in that reduced efficacy of these neuronal pathways should lead to increased local vs. global brain connectivity, enhanced mechanistic cognition, and greater control over behaviour by the paternal brain. This hypothesis is speculative but consistent with diverse evidence, and it is directly testable through functional imaging in humans, neuroanatomical experiments with animal models (e.g. Hemby *et al.*, 2001), and studies that directly link genetic changes with altered brain structure and function (Thompson *et al.*, 2001). Eventually, analyses of the physiological and developmental effects of disrupted imprinted-gene expression, and mutations in imprinted genes, should allow the inference of causal connections between paternal vs. maternal gene dysregulation and their expected effects on cognition and behaviour.

The psychological and behavioural changes associated with autism fit with the imprinted brain hypothesis, in that the 'mild' end of the autism spectrum, characterized by Asperger's syndrome, involves selective disruption of social behaviour that makes individuals more self-focussed. Moreover, such variation in behaviour exhibits a high heritability, which implies a strong, specific genetic basis to reciprocal social interactions (Constantino & Todd, 2000; Constantino *et al.*, 2003; see also Ronald *et al.*, 2005). We suggest that the brain may usefully be considered as a 'social placenta', evolved to extract socially based resources via behavioural interactions in complex networks of social reciprocity and kinship (Alexander, 1990; Dunbar, 1993, 2003). Both placenta and brain involve mutual dependence between agents with partially divergent avenues of fitness maximizing, which generates complex, conflicting physiologically balanced systems vulnerable to disruption (Haig, 1993, 1999, 2000a; Davies *et al.*, 2001). By our hypothesis, autism is thus a direct result of disturbed balance between the paternal and maternal brain that results in behaviour more 'selfish' in a literal sense of the word.

The imprinted brain hypothesis implies that autism can be characterized along two dimensions, developmental

and evolutionary. Like dysregulated placentation and the development of cancer, both of which involve strong effects from imprinted genes that impact growth (Tycko & Morison, 2002; Hernandez *et al.*, 2003), autism involves disordered development (Schumann *et al.*, 2004; Bauman & Kemper, 2005; Courchesne & Pierce, 2005a,b; Herbert, 2005), in this context via alterations in the coevolved relationship between maternal and paternal brain regions. We predict that such ontogenetic, and perhaps heterochronic, shifts in growth, differentiation and apoptosis are driven primarily by changes in gene dosage due to altered expression of imprinted genes, mutations in imprinted genes themselves, and alterations in imprinter genes such as MeCP2, in a developmental system characterized by extensive pleiotropy, epistasis and gene–environment interaction. The imprinted brain theory can thus easily accommodate the diversity of convergent genetic and neurological causes in autism and autistic disorders (Gillberg, 1992; Eigsti & Shapiro, 2003; Lee *et al.*, 2003; Cohen *et al.*, 2005; Herbert, 2005), as perturbation in so many components can alter maternal–paternal brain interactions. Indeed, differential impairment of the maternal (vs. paternal) brain may lead to a specific subset of autistic symptoms (loss of language and mental retardation), whereas imbalance due to enhanced paternal-brain effects, with spared maternal-brain functions, may underlie Asperger syndrome and 'high-functioning' autism (see Rinehart *et al.*, 2002a,b).

An evolutionary dimension for autism is more speculative, but it neatly ties together Grandin's (Grandin & Johnson, 2005) view of autism as atavistic animal genius with the inferences from Kevene's work that the evolution of brain development has involved progressive enhancement of the maternal brain along the lineage leading to humans (Keverne *et al.*, 1996b; Curley & Keverne, 2005). Autism thus involves loss of several uniquely human features mediated by the neocortex, such as language, cognitive capacity and complex social interaction (Dunbar, 1993, 2003), but it often also entails concomitant gains in mechanistic and perceptual skills that Grandin describes as characteristic of hyper-specialized animal cognition (Grandin & Johnson, 2005). This hypothesis is also supported by the pattern of symptoms found in paranoid schizophrenia, which appear as diametric opposites to those of autism and apparently involve perceptual and cognitive imbalance towards increased effects of the maternal brain (Emery, 2000; Badcock, 2004; see also Horrobin, 1998, 2001).

The imprinted brain hypothesis has several implications for the approaches used to analyse the causes and nature of autism. First, this theory compels a focus on the discovery and characterization in imprinted brain-expressed genes, especially those active in early foetal development (Nikaido *et al.*, 2004; Davies *et al.*, 2005a; Morison *et al.*, 2005). Such an approach should also accelerate progress in understanding bipolar disorder and schizophrenia, which are also notably affected by imprinted genes (e.g. Nicholls, 2000; Davies *et al.*, 2001; Goos & Silverman, 2001; Petronis, 2003). Second, a central role for imprinting in autism implies that animal models of the disorder may be less applicable than currently believed, due to the uniqueness of extensive maternal-brain development in humans (Keverne *et al.*, 1996a,b; Curley & Keverne, 2005), and our unusually high levels of methylation in brain-expressed genes (Enard *et al.*, 2004). Third, developmental and neurophysiological studies may usefully focus on the systems of neurones that connect the paternal and maternal brains, to discern new mechanisms of dysregulation that generate autistic phenotypes. Indeed, considering the brain as a social system, predominantly cooperative (Haig, 2003; Just *et al.*, 2004) but with elements of competition for consciousness (Crick & Koch, 2003) and behavioural decisions (Hamilton, 1987; Haig, 2000b; Brito, 2002), should provide new insights into neurological function and cognition. Tinbergen & Tinbergen's (1983) ethological hypothesis of a central role for unresolved motivational and emotional conflicts in autism is also compatible with proximate (neural system) conflicts, and an ultimate basis in genetic conflict. Fourth, we suggest that the incipient autism genome project (Hu-Lince *et al.*, 2005) include an emphasis on characterizing genetic and epigenetic variants in brain-expressed imprinted genes, and their upstream and downstream regulatory interactions. Such a component to the project should complement results from genome scans and association studies, which have thus far yielded the complex, unreplicated results that are expected if effects of genomic imprinting play a central role in the development of autism and psychosis (Petronis, 2000; Jiang *et al.*, 2004b). Not goblins, but forces of conflict equally mysteriously and capricious, may otherwise continue to frustrate searches for the causes of autism.

Finally, in elucidating adaptive mechanisms that underlie autism, the imprinted brain hypothesis underscores the viewpoint that the autism spectrum represents human cognitive diversity rather than simply disorder or disability (Baron-Cohen, 2000b). Indeed, individuals at the highest-functioning end of this spectrum, not least among them Isaac Newton and William D. Hamilton, may have driven the development of science, engineering, and the arts, through mechanistic brilliance coupled with perseverant obsession (Grandin, 1995, 2004; Baron-Cohen *et al.*, 2001; Hamilton, 2001, xxvii; Fitzgerald, 2002, 2004, 2005; Badcock, 2004).

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