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.

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,

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)

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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 mediate 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 autisitic 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; Rinchet 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-Shidley, 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-Shidley, 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 systematizing, 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 compensation) 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., 1993; Keeverne et al., 1996a,b; Keeverne, 1997; Badcock, 2000). In mice, paternal-cell chimeras (andro-genetic, 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, Keeverne 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 paternally expressed genes are preferentially expressed in the hypothalamus, amygdala and other parts of the limbic system, considered 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 (Happeé, 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; Herzwing 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 (Olsion & 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 homeobox 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 subjects (Skuse et al., 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; 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).

**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 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 versus 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-1 (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; Nummi et al., 2003a,b; Yoon 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 interneurons, whose expression is regulated via promoter 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, transacting 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 serotonergic 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 glutamate-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 serotonergic 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 serotonergic 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-GABAAergic 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 A Peg3, 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.,
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 hyperserotonemia (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 (Ayward 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 (Minschew 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 (Wizinower, 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 interneurons 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 (Tyc\(\text{\textregistered}o\) \& Morison, 2002; Hernandez \textit{et al.}, 2003), autism involves disordered development (Schumann \textit{et al.}, 2004; Bauman \& Kemper, 2005; Courchesne \& Pierce, 2005\text{a,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, 1996\text{a,b}; Hernandez \textit{et al.}, 2004; Bauman \& Kemper, 2005; Courchesne \& Pierce, 2005\text{a,b}; Herbert, 2005), in this context via alterations 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 \textit{et al.}, 2003; Cohen \textit{et al.}, 2005; Herbert, 2005), as perturbation in so many components can alter material–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 \textit{et al.}, 2002\text{a,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 Keverne’s work that the evolution of brain development has involved progressive enhancement of the maternal brain along the lineage leading to humans (Keverne \textit{et al.}, 1996\text{b}; 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 \textit{et al.}, 2004; Davies \textit{et al.}, 2005\text{a}; Morison \textit{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 \textit{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 \textit{et al.}, 1996\text{a,b}; Curley \& Keverne, 2005), and our unusually high levels of methylation in brain-expressed genes (Enard \textit{et al.}, 2004). Third, developmental and neuro-physiological 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 \textit{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 \textit{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 \textit{et al.}, 2004\text{b}). 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 \textit{et al.}, 2001; Hamilton, 2001, xxvii; Fitzgerald, 2002, 2004, 2005; Badcock, 2004).

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