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An evolutionary theory of schizophrenia: Cortical connectivity, metarepresentation, and the social brain

Jonathan Kenneth Burns
Department of Psychiatry, Nelson Mandela School of Medicine, University of KwaZulu-Natal, Durban, 4000, South Africa
jonny.eliza@3i.co.za

Abstract: Schizophrenia is a worldwide, prevalent disorder with a multifactorial but highly genetic aetiology. A constant prevalence rate in the face of reduced fecundity has caused some to argue that an evolutionary advantage exists in unaffected relatives. Here, I critique this adaptationist approach, and review – and find wanting – Crow's "speciation" hypothesis. In keeping with available biological and psychological evidence, I propose an alternative theory of the origins of this disorder. Schizophrenia is a disorder of the social brain, and it exists as a costly trade-off in the evolution of complex social cognition. Paleoanthropological and comparative primate research suggests that hominids evolved complex cortical interconnectivity (in particular, frontotemporal and frontoparietal circuits) to regulate social cognition and the intellectual demands of group living. I suggest that the ontogenetic mechanism underlying this cerebral adaptation was sequential hypermorphosis and that it rendered the hominid brain vulnerable to genetic and environmental insults. I argue that changes in genes regulating the timing of neurodevelopment occurred prior to the migration of *Homo sapiens* out of Africa 100,000–150,000 years ago, giving rise to the schizotypal spectrum. While some individuals within this spectrum may have exhibited unusual creativity and iconoclasm, this phenotype was not necessarily adaptive in reproductive terms. However, because the disorder shared a common genetic basis with the evolving circuitry of the social brain, it persisted. Thus schizophrenia emerged as a costly trade-off in the evolution of complex social cognition.

Keywords: cortical connectivity; evolution; heterochrony; metarepresentation; primates; psychiatry; schizophrenia; social brain; social cognition

Reasonable people adapt themselves to the world. Unreasonable people attempt to adapt the world to themselves. All progress, therefore, depends on unreasonable people.
—George Bernard Shaw

1. Introduction

Schizophrenia is a complex and widespread disorder, giving rise to a great burden of suffering and impairment in both patients and their families. It is human nature to seek meaning behind experiences, and indeed patients with schizophrenia seek meaning in the bizarre and perplexing phenomena of their psychoses. So too, in our scientific endeavour to understand this complex disorder, it is important to undertake a search for the meaning of the existence of schizophrenia in the human species.

In recent years, a number of researchers have sought to adopt an evolutionary perspective to explain the continued persistence of clearly maladaptive psychiatric disorders. In the field of schizophrenia research, Crow and others have pioneered an evolutionary approach to understanding the meaning of this distressing illness. They have asked questions about the evolutionary origins of schizophrenia and about why it is maintained in the human genome.

Jonathan Kenneth Burns is a Consultant Psychiatrist at the Department of Psychiatry of Nelson Mandela School of Medicine of the University of KwaZulu in Natal, South Africa, and is in private practice part time. He was trained in Medicine and Psychiatry at the University of Cape Town, South Africa, and is a Fellow of the College of Psychiatry of South Africa. From 2001 to 2003, he was a Research Fellow in the Department of Psychiatry at the University of Edinburgh in Scotland. Burns has done research on brain imaging in schizophrenia under the auspices of Professor Eve Johnstone and, in 2003, obtained an M.Sc. degree at the University of Edinburgh for this research. He is the co-author (with David Semple, Roger Smyth, Rajan Darjee, and Andrew McIntosh) of *The Oxford Handbook of Psychiatry,* to be published in January 2005 by Oxford University Press. He is currently writing *The Descent of Madness: Evolutionary Origins of Psychosis and the Social Brain,* which will be published by Brunner-Routledge. Burns is the winner of the 2002 Aaron Beck Award of the Across Species Comparisons of Psychopathology Society.

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This paper critically assesses these models drawing on evidence from various fields including psychiatry, psychology, paleoanthropology, and primatology; finds them wanting; and proposes an alternative and more integrated theory of the origins of schizophrenia that is in keeping with all the available evidence. The central argument I propose here is that schizophrenia reflects the severe end of a spectrum of disordered frontotemporal (FT) and frontoparietal (FP) connectivity, which is related to the evolution of metarepresentation and the "social brain" in the human line. I argue that schizophrenia exists as a costly trade-off at two stages of cognitive evolution.

I suggest that the first trade-off occurred between 16 and 2 million years ago (mya), when human ancestors evolved complex cerebral interconnectivity and specialised neural circuits to regulate social cognition and the intellectual demands of group living. Owing to anatomical constraints on foetal brain size, these changes evolved by a heterochronic process that prolonged brain maturation. This meant that the human brain, with its complex and recently evolved circuitry, became increasingly susceptible to complex gene interactions and/or genetic insults. This susceptibility was the trade-off for the advantages gained in social cognition.

The second trade-off occurred approximately 100,000–150,000 years ago, when genetic changes in some individuals resulted in aberrant connectivity in these cortical circuits. The exact mechanisms responsible at both the genotypic and phenotypic level is debateable and will be discussed in this paper. I argue that the expression of this genetic change is variable in different individuals and that, in some cases, milder expression may have manifested as extraordinary creativity and iconoclastic thinking. While this milder phenotype may have featured significantly in the emergence of human culture, there is little evidence that it conferred a reproductive advantage. Therefore, in contrast to authors who argue for a heterozygous or schizotypal advantage, I suggest a different genetic mechanism that may account for the persistence of schizophrenia. If the genes for schizophrenia were in some way intimately associated with genes regulating the development of complex cortical connectivity, and if these regulatory genes were advantageous during hominid evolution, then the genes for the disorder would persist by virtue of their association with the adaptive genes. Thus, schizophrenia would represent a trade-off in the evolution of the highly organised brain of modern *Homo sapiens.*

2. Evolutionary origins of the schizophrenic genotype

There is a need to integrate recent biological findings from schizophrenia research into an evolutionary framework based on current insights into the evolution of the human brain. The rationale for using evolutionary theory as an explanatory paradigm for the schizophrenic spectrum of disorders comes from attempts to reconcile several seemingly contradictory epidemiological observations. First, from the International Pilot Study of Schizophrenia conducted in nine countries (World Health Organization 1973), it appears that globally, schizophrenia has an incidence of approximately 1% and there is remarkable consistency cross-culturally in the core symptoms of the disorder. One of the "first-rank" findings of this study was that the evidence points to a significant genetic component in the transmission of schizophrenia (Jablensky 1988; Sartorius et al. 1986). Other evidence suggests that this is a polygenetic disorder (Kendler et al. 2000). Second, it is widely accepted that schizophrenia is associated with lower fecundity (Larson & Nyman 1973) and increased early mortality (Brown 1997). Third, as many authors have noted, there is evidence that some highly gifted and creative individuals either manifest schizotypal traits themselves or have a first-degree relative with schizophrenia (Karlsson 2001; Post 1994).

2.1. A critique of the case for heterozygous advantage

These observations have led some writers to speculate on why a clearly maladaptive disorder such as schizophrenia should have remained in the human genome at a constant prevalence rate (Allen & Sarich 1988; Crow 1995c; Farley 1976; Stevens & Price 2000). Importantly, such speculations assume the prevalence of schizophrenia has remained constant for millennia. According to a strict interpretation of Darwin's theory of natural selection (Darwin 1859), a phenotype that exhibits reduced fertility and earlier mortality should be subject to negative selection and disappear over a number of generations. That it persists has caused some to suggest that the disorder must have some inherent adaptive value to survive the process of natural selection. Furthermore, the well-founded notion of a spectrum in the expression of the genotype has provided a suitable model for considering just where the adaptive value might reside. Crow has proposed that psychotic illness should be viewed as lying on a "continuum of variation" (Crow 1995b; 1998a). It seems that there may be at least two dimensions to this spectrum – one stretching from schizophrenia to the affective psychoses and the other from disorder to trait to "normality." Evidence from neuroimaging and neuropsychology studies suggests that schizotypal people have milder but similar deficits to patients with schizophrenia (Buchsbaum et al. 1997a; 1997b; Cadenhead et al. 1999; Dickey et al. 2002a; 2002b). That these deficits are also found in relatives of patients with schizophrenia suggests a genetic cause (Byrne et al. 1999; Lawrie et al. 2001). This supports the idea of a genetic continuum. So, instead of vainly attempting to conjure up some aspect of this disabling disorder that might be considered "adaptive," it is legitimate to focus on individuals in the schizotypal spectrum and seek to identify adaptive traits in this population that may compensate for the former group's lack of fitness. Therefore, a popular assumption among evolutionary psychiatrists is that unaffected individuals in the schizotypal spectrum may be at some kind of reproductive advantage, thus compensating for the apparent disadvantage of the schizophrenic phenotype.

This argument has resulted in links being drawn between schizotypy and genius, and between divergent thinking and creativity, as if these associations automatically imply that these individuals have a selective advantage. And herein may lie the error. The evidence is not convincing that schizotypal individuals have a *reproductive* advantage. In fact, the studies of relative fertility in schizotypal disorder are contradictory and most fail to demonstrate an advantage (Avila et al. 2001; Haukka et al. 2003; Kendler et al. 1998). The recent study by Haukka and colleagues is large enough and has sufficient power to confirm this position (Haukka et al. 2003). An exception is a study by Avila and colleagues

that demonstrates an increased number of children in first-degree relatives of people with schizophrenia (Avila et al. 2001) and thereby supports the notion of enhanced fitness in carriers. However, most authors who favour this concept of enhanced fitness in unaffected individuals typically rely on anecdotes regarding a handful of historical figures. For example, Stevens and Price cite case histories of paranoid and almost certainly schizotypal "gurus" such as David Koresh and Jim Jones as examples of reproductively successful individuals within the spectrum (Stevens & Price 2000). They propose that these individuals performed an essential function in ancestral groups, splitting populations as they outgrew resources. This particular "group selection" model is problematic, not least because group-splitting has been observed in wild chimpanzees (Goodall 1990), suggesting that this is by no means a human-specific phenomenon. Similarly, Karlsson has demonstrated an increased incidence of psychotic illnesses, including schizophrenia, in a cohort of particularly gifted artists, philosophers, and politicians, and while it is not explicitly stated, Karlsson implies that this association might explain the persistence of schizophrenia (Karlsson 1973; 2001). While these data are intriguing, the assumption that social, political, or creative advantage automatically translates into reproductive advantage is erroneous. The constant prevalence of schizophrenia does not necessarily imply that the schizotypal genotype is adaptive; there are other mechanisms that could account for this. It is worth noting that several other brain disorders, for example learning disability and idiopathic epilepsy, also exhibit constant prevalence rates.

2.2. Evolutionary modes of selection

Dubrovsky has critiqued the "adaptationist programme" of many contemporary evolutionary psychologists and psychiatrists (Dubrovsky 2002). He observes that too often there is a focus on explaining variants in human behaviour and experience in terms of their potential adaptive qualities in the ancestral environment. In some cases this has resulted in the construction of so-called Just So stories as substitutes for objective scientific theories on the origins of behaviour.

There may be more plausible evolutionary genetic models for schizophrenia (Bailey 2000). For example, genes for the disorder may be expressed phenotypically as a spectrum, and some in the spectrum may have special cognitive abilities, but the schizotypal genotype does not, in itself, confer a reproductive advantage. However, if schizotypal genes are associated in some way with genes that code for some faculty essential to the human condition, then the disorder may persist by virtue of this association. In other words, maladaptive traits survive into the next generation because they are associated, at a genetic level, with traits that are highly adaptive and which confer a reproductive advantage on the individual. I will argue that these "adaptive genes" are genes that are involved in regulating the evolution and development of the social brain in humans.

There are several mechanisms that can be considered to explain this association between maladaptive and adaptive genes. The first is that the loci for schizotypal genes may be close on the chromosome(s) to the loci for the adaptive genes, and that they are "dragged" in selection. Sober makes the distinction between *selection for* a trait and *selection of* a trait (Sober 1993), and the distinction may be useful in clarifying this mechanism. *Selection for* a trait describes the process of discriminating between phenotypes, but this process is not entirely "clean," and linked traits that do not necessarily increase fitness may be "dragged" along in the inheritance process (i.e., *selection of* a trait). Therefore, while there may be *selection for* the social brain, there may in conjunction be *selection of* schizophrenia. A second possibility is that schizotypal genes are defective alleles of the adaptive genes, but the problem with this scenario is that one would expect defective alleles to have been selected against during evolution. A third possibility is that genes (subsequently responsible for schizophrenia) were already embedded in the genome before the social brain evolved in all its complexity in modern humans. In this scenario, the emergence of novel neural architecture may have served to activate the schizotypal genes. In other words, the genes responsible for schizophrenia existed prior to modern *Homo sapiens* (perhaps with neutral or even adaptive functions). With the emergence of a novel brain environment, characterised by a host of novel gene functions, the previously benign schizotypal genes changed (either through mutation or altered expression or gene interaction) and became the malignant genes responsible for schizophrenia.

For want of a better term, I will call this model (in which maladaptive genes are associated with adaptive genes) the "pleiotropic model" of selection and will draw on it in constructing an evolutionary theory of schizophrenia. But first I should briefly consider two other possibilities.

It is possible that the genes for schizophrenia represent random mutations or "neutral genes" and are not subject to natural selection. In 1968, Kimura put forward a revolutionary thesis that shook the biological community, for he suggested that most mutations responsible for molecular variability in populations are neutral (rather than advantageous) and became fixed as a result of random genetic drift (Kimura 1968). Given that human ancestors experienced several significant "bottlenecks" during evolution, with dramatic reductions in population size, it is possible that the mutations responsible for the schizotypal spectrum were neutral and were fixed in the human genome by random genetic drift.

It is also possible that care-giving behaviour by a family or group may have allowed individuals with less adaptive schizotypal traits to survive. There is some evidence that Neanderthals and early *Homo sapiens* cared for those with disabilities. For example, burial sites have been discovered where individuals have lived to a fair age with deformities, with which they could not have survived without care (Stringer & Gamble 1993; Trinkaus & Shipman 1993). Furthermore, observations of caring behaviour by chimpanzees towards sick or disabled group members (Aureli & de Waal 2000; Goodall 1990) suggest that care-giving behaviour has ancient origins.

As I have said, in terms of schizophrenia, I prefer the notion of the pleiotropy model. It follows, therefore, that we need to ask: Are there unique human faculties that might be associated with the origins and persistence of schizophrenia in *Homo sapiens*? Crow has suggested that there are – language and laterality (Crow 1995b; 1997a). He has suggested that a speciation event gave rise to the human capacity for language, and that this evolutionary change in the brain provided the neural and cognitive substrate for a disorder such as schizophrenia. He suggests that this speciation event occurred approximately 100,000–150,000 years

ago, prior to the migration of *Homo sapiens* out of Africa (Stringer & Andrews 1988; Stringer & McKie 1996). Crow links the origins of schizophrenia to the evolution of cerebral asymmetry and specialisation of the language area on the left side. The proposed schizophrenia gene (protocadherin) is said to be XY-linked and propagated by sexual selection (Crow 2002). I disagree with Crow on several points that I will address in the course of this paper, but before proceeding I think it is important to address the important question of speciation, since it bears heavily on this topic.

2.3. Speciation or gradualism in hominid evolution?

In making his case, Crow is continuing a long tradition of sometimes heated debate over the exact nature of our descent. Darwinists, faithful to the principle of gradualist change by natural selection, have, for more than a century, come up against sceptics (from Alfred Russel Wallace – the codiscoverer of the theory – to Stephen Jay Gould) who cite the discontinuities in the fossil and archaeological record, as well as the emergence of complex symbolic art and human-specific language, as evidence for *saltational* or sudden change (Gould 1982; Schwartz 1999; Wallace 1858).

I do not find it necessary to invoke a saltational explanation for the emergence of psychosis in humans. Crow's theory depends on two assumptions for which I believe there is insufficient evidence thus far. The first is that other species do not have a capacity for psychosis – to date, this is neither proven nor disproven. Secondly, he relies on discontinuity in evolution to explain the emergence of language. While speech itself is unique to humans, there is increasing evidence (Deacon 1998; Pinker 1994) supporting a gradualist model of language development within a number of higher mammalian species, for example, anthropoid primates and cetaceans (whales and dolphins). In *The Descent of Man,* Darwin committed himself to a gradualist theory of language evolution and a century later, this idea retains wide support:

> Nor, as we have seen, does the faculty of articulate speech in itself offer any insuperable objection to the belief that man has been developed from some lower form. . . . The lower animals differ from man solely in his almost infinitely larger power of associating together the most diversified sounds and ideas; and this obviously depends on the high development of his mental powers. (Darwin 1871)

Thus, articulate speech emerges from a gradual process of evolving communication in higher mammals and, as Darwin predicted, the unique properties of human thought and language relate not to a speciation event but to increasing cognitive complexity and specialisation of phylogenetically old neural networks for communication. I suggest that the social brain, as represented by prefrontal cortical connectivity, became highly developed within the human line, providing a substrate for consciousness and articulate speech, but that this reflected a continuation of a phylogenetically ancient process, as evidenced by immature forms of social cognition and communication in some extant primates (Baron-Cohen 1999; Byrne 2001) and cetaceans (Marino 2002).

2.4. A neuroevolutionary theory of schizophrenia

With respect for Crow's ongoing work on the "Speciation Hypothesis" (Crow 2002), I propose an alternative – but not necessarily incompatible – evolutionary model of schizophrenia. A sound evolutionary theory of schizophrenia must integrate current biological evidence about the disorder with insights from contemporary primate research, evolutionary genomics, and palaeontology. Across-species comparisons are the only way one can determine what is truly different about the human brain, and what the unique cognitive structure is that allows an illness such as schizophrenia to exist.

Schizophrenia is primarily a disorder of consciousness and in particular of the social brain. I suggest that schizophrenia exists in our species as a costly trade-off in the evolution of the prefrontal cortex and its connectivity with temporal and parietal cortices – these regions constituting the social brain. Under the selective pressures of increasingly complex social living, these interregional systems began to evolve gradually in the common ancestors of apes and humans 16–5 mya (Dunbar 2001). Subsequently, ontogenetic changes in the hominid brain, facilitating their further development, rendered these neural systems particularly vulnerable to insult. Specifically, the recently evolved neurodevelopmental processes, giving rise to cortical connectivity, exhibited the greatest vulnerability. With respect to the origins of schizophrenia, it is not clear whether gene changes giving rise to the disorder affected neurogenesis, neuronal migration, arborisation, synaptogenesis, or apoptosis. We know that schizophrenia is a neurodevelopmental disorder and that all these stages have been implicated. Given the heterogeneous nature of molecular and pathological findings in schizophrenia, it is likely that a number of these stages were subject to genetic change in the genesis of the notoriously amorphic schizophrenic phenotype.

As Crow argues, the origins of the schizotypal genotype, must predate the emergence of *Homo sapiens* out of Africa, approximately 100,000–150,000 years ago (as determined from mitochondrial DNA analyses [Cann et al. 1987]). This is the only feasible explanation (barring a random mutation explanation) for constant worldwide prevalence rates. A less parsimonious theory would have to argue that there was parallel evolution in geographically separate populations. This is unlikely. There are at least some historical references to schizophrenia-like illnesses in early Islamic, Ayurvedic, and Classic societies (Gottesman 1991; Youssef & Youssef 1996) but these obviously postdate the development of written records.

While agreeing with Crow that an evolutionary perspective is essential in trying to understand this most human of disorders, I would suggest that the phenotypic outcome of this genetic change was that neurodevelopmental processes giving rise to frontal circuits were disturbed, resulting in aberrant connectivity in these systems. Since these circuits contribute significantly to the regulation of normal social behaviour and therefore constitute a large part of what is termed the *social brain* (Brothers 1990; Brüne 2001), I believe that it is appropriate to conceptualise schizophrenia as a disorder of the social brain. In the next section, I will review evidence in support of this statement, drawing on both psychological and biological research in both healthy individuals and patients with schizophrenia.

3. Schizophrenia is a disorder of the social brain

3.1. Definition of terms

Brothers described the social brain as the higher cognitive and affective systems in the brain that evolved as a result of

increasingly complex social selective pressures (Brothers 1990; Brothers et al. 1990). These systems underlie our ability to function as highly social animals and provide the substrate for intact social cognition, social behaviour, and affective responsiveness. Brothers defines *social cognition* as "information processing that contributes to the correct perception of dispositions and intentions of other individuals" (Brothers 1990). Therefore, to "mindread" (Whiten 1991) successfully (i.e., to infer the mental states of others), an individual requires both an evolved perceptual system in order to detect social signals, as well as an information processing "module" that draws on stored emotions and memories in interpreting the mental state of conspecifics. Grady and Keightley include the following functions within social cognition: face perception, emotional processing (including both perception of emotional information in the environment and regulation of mood), "theory of mind" (see below), self-reference, and working memory (Grady & Keightley 2002). It is important to recognise these functionally separate aspects of social cognition, for most terms used in relation to it encompass all aspects as an integrated unit. Indeed, I would argue that, when social cognition is described in modular terms, there is the risk of viewing the social brain as a single anatomical region, rather than as a distributed network of interconnected systems that include both cortical and subcortical structures.

As is common in the behavioural sciences, a vast nosology has emerged in relation to the concept of social cognition. For example, in relation to apes' capacity to recognise or infer mental states in other individuals, Byrne and Whiten have used the term *metarepresentation* (Byrne & Whiten 1991). As Brüne puts it, one has "metarepresentations about the social world" and this in turn indicates the possession of *social metacognition.* And drawing on the social machinations of Machiavelli's *The Prince,* de Waal introduced the term *Machiavellian Intelligence* to describe the social and political behaviour of chimpanzees (de Waal 1982). Others have referred to "mentalizing" (Morton 1980), "folk psychology" (Wellman 1991), and "the intentional stance" (Dennett 1987). Finally, within the psychiatric literature at least, theory of mind (ToM) is the concept most familiar to clinicians and researchers alike.

The term *theory of mind* was coined by Premack and Woodruff in 1978 in relation to chimpanzees' capacity for deception (Premack & Woodruff 1978) and has become increasingly popular in attempting to describe the cognitive deficits in schizophrenia. In essence it refers to the assumption one makes during communication that another individual possesses a mind just like one's own. It is the ability to attribute mental states to others and thus forms the very basis of social interaction and communication. This is because it is critical to understand the beliefs and intentions of others in social discourse. Having ToM ability enables individuals to engage cognitively in the social arena. It is therefore a core aspect of social cognition. In healthy children it is generally accepted that ToM ability is achieved by 4 years of age (Perner 1991; Wimmer & Perner 1983). Avis and Harris studied Baka pygmy children in Cameroon and concluded that this is reliable cross-culturally (Avis & Harris 1991). However, Lillard argues that in terms of the actual manifestation of ToM, cultural variations do exist (Lillard 1998).

In this discussion I will restrict myself to the use of the terms *theory of mind, metarepresentation,* and *social cognition;* and, in referring to the neural systems that regulate this faculty, I will use the term *social brain.*

3.2. Schizophrenia and theory of mind (ToM)

Functional imaging has demonstrated the neural basis of ToM ability. When healthy subjects perform a variety of ToM paradigms (including mental state attribution, eye gaze detection, and attribution of intentions), scans reveal that a number of cortical regions are activated. These most commonly include the left medial prefrontal cortex (PFC), the orbitofrontal cortex (OFC) and the left temporal cortex (Baron-Cohen et al. 1994; Fletcher et al. 1995; Goel et al. 1995; Levine et al. 1999; Vogeley et al. 2001). Of these anatomical regions, the medial PFC (and specifically the anterior cingulate cortex) has been most commonly identified in subsequent studies of this nature (Brunet et al. 2000; Calder et al. 2002; Castelli et al. 2000; Gallagher et al. 2000; Gusnard et al. 2001). Other structures that have only occasionally shown activation during similar experiments include the paracingulate sulcus, the posterior cingulate, the temporoparietal junction and the PFC (Fletcher et al. 1995; Gallagher et al. 2000; McCabe et al. 2001). The only experiment that showed PFC activation was an fMRI (functional magnetic resonance imaging) study using cooperation games in a "prisoners' dilemma"-type paradigm (McCabe et al. 2001).

Within psychiatry, the concept of ToM or metarepresentation is most commonly associated with autism. The seminal study was conducted by Baron-Cohen and colleagues in 1985; they demonstrated a specific difficulty with acknowledging false belief in autistic children (Baron-Cohen et al. 1985). Numerous subsequent studies employing a variety of novel tasks have confirmed this finding (Frith 1989; Leekam & Perner 1991; Leslie & Thaiss 1992; Perner et al. 1989). Baron-Cohen has examined the neural basis of autism and describes a circuit including the amygdala, OFC, and superior temporal sulcus (STS) that mediates ToM ability and is dysfunctional in the disorder (Baron-Cohen 1995; Baron-Cohen et al. 2000). Frith argues that impaired mentalising in autism probably relates to the failure of medial prefrontal–parietal attentional networks to effectively modulate connectivity in regions such as the extrastriate visual cortex and temporal lobes (Frith 2002).

It is interesting to note that the cardinal features of autism, (autistic aloneness, poor communication, and lack of pretend play [Wing & Gould 1979]), parallel some of the negative symptoms of schizophrenia, namely social withdrawal (or "autism," as termed by Bleuler), poverty of speech, and stereotyped rather than spontaneous behaviour. In addition, the language difficulties are similar in the two disorders, with pragmatic rather than syntactic or semantic aspects impaired (Frith & Allen 1988). Frith and Frith have argued that autism and schizophrenia may represent early and late acquired variations of a similar underlying process. They cite evidence presented by Murray and Lewis (1987) that there is a "neurodevelopmental" subgroup of schizophrenics who exhibit features that closely resemble childhood autism, namely: early onset illness; male predominance; and defects in premorbid IQ, behaviour and sociability. They suggest that there may be greater comorbidity between the two conditions than is acknowledged.

In terms of ToM impairment and the specific sympto-

matology of schizophrenia, Frith has proposed several mechanisms within a cognitive framework (Frith 1994). Negative symptoms such as flattening of affect and impoverishment of will are attributed to the individual's lack of awareness of his own mental and emotional states and a corresponding unawareness of personal goals and intentions. Incoherence of speech and language, Frith argues, is attributable to a failure to take account of the listener's lack of knowledge. Therefore, the ToM-impaired individual uses speech that lacks referents (Rochester & Martin 1979) and assumes the listener shares an understanding of his "logical" train of thought. Similarly, there is a failure in discourse planning, with the omission of explicit links between different topics in the discourse. Positive symptoms in schizophrenia, argues Frith (1994), result from attempts to infer the mental states of others, because, unlike the autistic patient, the person with schizophrenia has had an experience of using ToM abilities prior to onset of illness and knows that one must attempt to interpret the mental contents of others. However the illness impairs mind-reading ability, and errors result – this is the basis of some positive symptoms. False inferences about the intentions of others therefore lead to paranoid delusions, while referential delusions are a consequence of falsely inferring that others are communicating with one.

ToM abnormalities have been demonstrated in people with schizophrenia by using a range of experiments that seek to test their ability to attribute mental states and to detect deception and false beliefs. Using "hinting" and "false-belief" tasks, Corcoran and Frith have shown that patients with schizophrenia who have negative, disorganised, or paranoid symptoms struggle to infer intentions behind indirect speech (Corcoran et al. 1995; Frith & Corcoran 1996). Doody and colleagues have shown that, within the functional psychoses, ToM impairment is specific to schizophrenia (Doody et al. 1998). Subsequent studies have substantiated the specificity of ToM impairment to behaviourally disorganised patients with schizophrenia and have argued that it reflects disturbance of a particular cognitive module rather than general cognitive impairment (Mazza et al. 2001; Pickup & Frith 2001; Sarfati et al. 1999; Sarfati & Hardy-Baylé 1999). Pickup and Frith also reiterate earlier observations (Pilowsky et al. 2000) that ToM impairments in schizophrenia are less severe than in autism, probably as a result of earlier age of onset in the latter and some residual mind-reading skills in the former. The single functional imaging study to date examining ToM in schizophrenia correlated poor mentational ability with abnormal activity in the PFC and the temporal lobes (Russell et al. 2000).

3.3. The neural basis of social cognition

As stated earlier, there are functions besides ToM that contribute to social cognition. Grady and Keightley include face perception, emotional processing, self-reference, and working memory (Grady & Keightley 2002). I would add eye-gaze detection and interpretation, social decision-making, conflict-monitoring, and affiliative behaviour.

Adolphs has proposed a simple model that describes the various component processes of social cognition (Adolphs 2001). He describes three major stages in social cognition: "social perception," which is the detection of social stimuli; "central social cognition," which entails the recognition, evaluation, and interpretation of material; and "social behaviour," which is the effecting of the individual's response. In terms of social perception, Adolphs identifies the sensory and association cortices (including the fusiform gyrus and the superior temporal sulcus [STS]) as the primary sites involved. The central processes include the amygdala, the OFC, the anterior cingulate cortex (ACC) and the right somatosensory cortex. Finally, the areas implicated in social behaviour include the motor cortex, the basal ganglia, the hypothalamus, and the brain stem. Importantly, the central processes operate at multiple levels – cognitive, emotional, and motivational – and draw on memory systems for the recognition and evaluation of stimuli and the preparation of the organism's response. Adolphs' selection of brain structures involved in the central component is very similar to that of Brothers, who identifies the STS, the amygdala, and the OFC (Brothers 1990), while Brüne adds the dorsolateral PFC (DLPFC) and the ACC (Brüne 2001). Drawing on Adolphs' model, is there evidence that supports these regions as comprising the social brain?

Adolphs attributes "social perception" to the fusiform gyrus and the STS. This attribution is derived from both primate and human studies that have focussed on neuronal responses to socially important visual stimuli. Emery argues that eye gaze plays an important signalling role in conveying emotional and mental states between individuals (Emery 2000). In higher primates, the following and interpretation of gaze is an essential part of social cognition. In primates, a number of studies have identified neurones in the OFC, the amygdala, and the STS that respond selectively to facial expression, eye gaze, and intended action (Emery 2000; Perrett et al. 1985; 1992). Other primate studies have identified neurones responsive to eye gaze in the amygdala (Brothers et al 1990; Brothers & Ring 1993). Human studies have largely corroborated these findings. For example, electrophysiological studies in epileptic patients have found regions of the STS that respond to socially salient visual stimuli (especially facial motion) (Allison et al. 2000), while functional imaging studies have identified a "fusiform face area" on the lateral fusiform gyrus that is "specialized for face perception" (Haxby et al. 1994; Kanwisher et al. 1997; McCarthy et al. 1997). The STS has also been implicated, using functional imaging, in face perception (Haxby et al. 2001; Puce et al. 1998). Haxby and colleagues argue that "face perception is mediated by a distributed neural system in humans that consists of multiple bilateral regions" (Haxby et al. 2002). They describe a "core system," consisting of the fusiform gyrus and STS, that mediates the visual analysis of faces. The former, they argue, is responsive to invariant aspects of faces (i.e., identity), while the latter is responsive to changeable aspects (i.e., expression). The "core system" connects with a number of regions from other neural systems involved in other cognitive functions (e.g., amygdala) forming the so-called extended system. This interaction between core and extended systems allows for the extraction of meaning from faces. Of the amygdala, Haxby and colleagues say "it plays a central role in processing the social relevance of information gleaned from faces" (Haxby et al. 2002).

In terms of "central social cognition," which regulates recognition, evaluation, and interpretation of socially related material, Adolphs identifies a network of structures including the amygdala, the OFC, the ACC, and the right somatosensory cortex. Clearly these stimuli are presented

to the individual in predominantly the visual and auditory modalities, and the central processing entails integration of these stimuli with emotional, memory, and higher cognitive systems. According to Haxby, visual material from the perception of faces is distributed from the core system to a number of regions in the extended system where it is invested with meaning (Haxby et al. 2002). Specifically, information such as gaze direction and head position is processed within the neural systems for spatial attention and perception in the intraparietal sulcus and the frontal eye fields (Hoffman & Haxby 2000). Phonemic information from speech-related lip movements is processed within the neural system for auditory verbal comprehension in the superior temporal gyrus (STG) and STS (Calvert et al. 1997; Puce et al. 1998). Perception of identity and retrieval of semantic knowledge about a person recruits neural systems in the anterior temporal lobes (Gorno-Tempini et al. 1998; Nakamura et al. 2000). Finally, the emotional content of expression is processed in the amygdala, insula, and other parts of the limbic system (Breiter et al. 1990; Streit et al. 1999).

The amygdala forms an interface between the information processing activities of the neocortex and the autonomic and endocrine functions of subcortical structures such as the hypothalamus and brain stem. It is therefore well placed to perform its function as the brain's emotion-regulation system, integrating emotional, motivational, and cognitive processes (Le Doux 1994). The important array of connections the amygdala has with cortical and subcortical regions is critical to its task. In particular, two connections that are known to play a central role in processing social material are between the lateral nucleus of the amygdala, and the STS and OFC, respectively (Amaral et al. 1992).

Evidence from primate studies (Leonard et al. 1985; Nakamura et al. 1992), from human studies on patients with amygdala lesions (Adolphs et al. 1994; Jacobson 1986; Young et al. 1995; 1996), and from autism research (Baron-Cohen et al. 2000) supports the central role played by the amygdala in recognition and interpretation of facial expressions of emotion. In particular, the amygdala seems to play a role in detecting and responding to threat and danger and mediating the fear response. Amygdala lesions in macaques result in a loss of fear responses to threatening objects (Amaral 2002), while functional imaging in normal subjects has demonstrated amygdala activation when viewing facial expressions of fear (Morris et al. 1996). It appears that this structure is critical for vigilance and recognition or evaluation of potential threat and therefore, in evolutionary terms, the amygdala plays a vital adaptive role for the organism, and one can speculate that its origins are extremely ancient.

In addition to fear responses, there is a wealth of evidence for the key involvement of the amygdala and its anterior connections in more general affective and social responsiveness (Barbas 2000; Davis 1992; Le Doux 1994). Work with autism links the well-described abnormalities of this structure to a broad array of emotional and social deficits (Baron-Cohen et al. 2000). Its role in emotional memory is supported by functional imaging of normal individuals, where emotionally charged information is remembered better than neutral information, and this correlates with activation in the amygdala (Cahill et al. 1996; Hamann et al. 1999). In patients with amygdala lesions, this function is also impaired (Adolphs et al. 1997).

Finally, the amygdala and its connections with the OFC have been attributed a major role in establishing and maintaining social bonds. Studies in rodents have shown how oxytocin and vasopressin, two key peptides involved in affiliative behaviour, effect their action by modulating the amygdala and parts of the ventral striatum (Young 2002). Monkeys with lesions placed in the amygdala, the anterior temporal pole, or the OFC show varying degrees of social isolation and marked reductions in affiliative behaviours (Kling & Steklis 1976). Having said this, it is important to note that Amaral reports relatively normal affiliative behaviour (except for a loss of the fear response) in young monkeys following lesioning of bilateral amygdalae, suggesting that an intact OFC may be more important than intact amygdalae in mediating affiliative behaviour (Amaral 2002).

The classic case of Phineas Gage illustrates the central role of the OFC in regulating socially appropriate behaviour. This unfortunate railway construction foreman was blasting rock in the Vermont mountains in 1848 when an accidental explosion blew his tamping iron through his head, specifically his OFC. He was transformed from a socially responsible and polite man to an irreverent and grossly profane individual, so much so that his friends are recorded to have stated that he was "no longer Gage"! If Gage's case is deemed unreliable because of the diffuse frontal injury he sustained, then there are a number of case reports of surgically placed lesions in the OFC that confirm the selective social impairments resulting from OFC damage (Eslinger & Damasio 1985). In humans, damage to the OFC is notable for a diminished capacity to respond to punishment, stereotyped and sometimes inappropriate social manners, and an apparent lack of concern for other individuals, all in the face of otherwise normal intellectual functioning (Damasio 1994).

In primates, Perrett and colleagues have identified neurons sensitive to facial expression, not just in the amygdala and STS, but also in the OFC (Perrett et al. 1985; 1992). The human OFC appears to have cells similarly sensitive to socially and emotionally aversive visual stimuli (Kawasaki et al. 2001).

The OFC (as well as the ventral PFC) is implicated in Damasio's "somatic marker hypothesis," an adaptive mechanism by which we acquire, represent, and retrieve the values of our actions (Damasio 1994). These structures generate representations (or *somatic markers*) of emotional or somatic states that correspond to the anticipated future outcome of decisions, thus steering the decision-making process towards those social outcomes that are advantageous for the individual (Adolphs 1999). Studies using a gambling task have shown that subjects with damage to the OFC are unable to represent choice bias in the form of an emotional hunch or "gut feeling" (Bechara et al. 1997). Therefore, impairment of the OFC and its circuits may result in ambivalence and impulsivity rather than carefully considered decision-making in social situations. These difficulties are commonly observed in patients with schizophrenia and are likely to originate, in part at least, from the abnormalities I have described in the OFC.

As mentioned in the previous section on the amygdala, the OFC is ascribed an important role in affiliative behaviour. Lesions placed in the OFC in monkeys result in dramatic reductions in sociability as well as shifts in social ranking (Butter & Snyder 1972; Kling & Steklis 1976). Furthermore, the density of certain serotonin receptors in the

OFC correlates with a monkey's social status, and pharmacological manipulation of serotonergic neurotransmission results in changes in its social status and rank (Raleigh et al. 1996; Panksepp 1998). Other neuromodulatory compounds known to have an important role in maternal behaviour, such as oxytocin, oestrogen and prolactin, have high numbers of receptors in the OFC (Leckman & Herman 2002). Affiliative behaviour (the making and maintaining of social bonds) is vital for the individual's survival and sanity. Two components of affiliative behaviour, the ability to empathise and the ability to forgive others have been studied with fMRI in normal individuals. Farrow and colleagues used fMRI to demonstrate the role of the OFC and the anterior temporal lobe in the social phenomena of empathy and forgiveness (Farrow et al. 2001).

The ACC plays a key role in emotion and social behaviour (Devinsky et al. 1995; Maddock 1999). Damage to the ACC can result in a gross loss of motivation (akinetic mutism), and this region is activated in normal subjects by emotional versions of the Stroop task (Bush et al. 2000) supporting the idea that it helps to monitor errors and response-conflicts (Adolphs 2001). An fMRI study by MacDonald and colleagues identified the ACC as playing a central role in the monitoring of performance and conflict monitoring (in other words, the evaluating and selecting of choices and reactions to stimuli) (MacDonald et al. 2000). Allman has attributed to the ACC a role in adaptive response to changing conditions (Allman et al. 2001). Furthermore, the ACC, together with other connected regions, plays a prominent role in attention and working memory, and it goes without saying that these are centrally important cognitive processes in social cognition and behaviour.

As for the amygdala and OFC, the ACC has a role in affiliative behaviour. A neuroethological study using fMRI linked parental and infant separation to the ACC (Lorberbaum et al 1999). Mothers were scanned while listening to recorded infant cries, and the activity demonstrated in the ACC suggests that this structure plays a role in attachment and bonding, arguably the ontogenetic precursors to human sociability.

3.4. Schizophrenia and the social brain

In addition to the impairments of ToM ability described in section 3.2, patients with schizophrenia demonstrate a range of other impairments of social cognition. For example, judgement of the direction of eye gaze has been shown to be impaired in schizophrenia (Phillips & David 1997; Rosse et al. 1994). Furthermore, there is ample evidence that face processing is altered in the condition, both in the processing of neutral faces (Williams et al. 1999) and in the perception of emotional expressions on faces (Archer et al. 1994; Borod et al. 1993; Gaebel & Wölwer 1992; Kohler et al. 2000). Imaging experiments, using emotional faces as stimuli, have demonstrated reduced activity in the ventral lateral PFC for angry faces (Phillips et al. 1999) and reduced activity in the amygdala in response to fearful, happy, and sad faces (Phillips et al. 1999; Schneider et al. 1998), in patients compared with healthy controls. A recent fMRI study of facial emotion processing in schizophrenia demonstrated significantly reduced activation in the left amygdala and bilateral hippocampi (Gur et al. 2002).

Patients who are said to have prominent "negative symptoms" classically exhibit deficits in volition, motivation, and affect. As these are crucial components of social cognition and behaviour, it is useful to consider the evidence from imaging experiments involving these particular patients. The DLPFC has classically been implicated, with evidence of both structural (Chua et al. 1997; Sanfilipo et al. 2000) and functional abnormalities (Frith et al. 1991; Liddle et al. 1992; Tamminga et al. 1992) reported in the literature. In addition, the OFC and its connections have similarly been implicated in negative symptoms with various studies showing structural (Baare et al. 1999; Gur et al. 2000; Sigmundsson et al. 2001) and functional abnormalities (Tamminga et al. 1992). Other regions that may be involved in the generation of negative symptoms include the temporal lobes (especially left-side and limbic structures) (Sanfilipo et al. 2000; Sigmundsson et al. 2001), the ACC, and the inferior parietal cortex (IPC) (Kirkpatrick et al. 1999; Ross & Pearlson 1996; Sigmundsson et al. 2001).

When patients with schizophrenia are asked to induce sad moods during fMRI scanning, the amygdala fails to activate compared with controls (Schneider et al. 1998), implying a functional abnormality of this structure in addition to the structural abnormalities that have been observed (Lawrie & Abukmeil 1998). Finally, deficits in response and conflict-monitoring (Mathalon et al. 2002; Yucel et al. 2002), decision-making (Paulus et al. 2002), and affiliative behaviour (Kirkpatrick 1997) have been observed in schizophrenia. Neuroanatomical regions implicated include the ACC and DLPFC during response and conflict monitoring (Mathalon et al. 2002; Yucel et al. 2002) and the PFC and IPC during decision-making (Paulus et al. 2002).

In summarising this section on schizophrenia and the social brain, I think it is fair to state: (a) that *Homo sapiens* is characterised by a highly developed cognitive and emotional processing ability that enables individuals to engage successfully in social interaction – a faculty we term *social cognition;* (b) that the components of social cognition, including theory of mind, are based anatomically in a distributed network of neural circuits and regions we might call *the social brain,* and that this network includes the DLPFC, the OFC, the ACC, the superior-medial temporal cortex, the amygdala, the parietal association cortex and the visual association cortex (and both cortical-cortical and cortical-subcortical connections between/with these regions); (c) that people with schizophrenia exhibit deficits in several aspects of social cognition, and specifically in ToM ability, as evidenced by both psychological and neuroimaging experiments; and (d) that schizophrenia may therefore be considered a disorder of the social brain.

4. A cognitive model of schizophrenia

If schizophrenia is a disorder of the social brain, then the obvious question that begs an answer is: How is social cognition disrupted in this disorder? At a psychological level, can we explain these impairments of mental state attribution, "mind-reading," and affective responsiveness in information-processing terms? And if we can, then would a cognitive model of schizophrenia serve to inform our understanding of what is happening at a neural level? In this section, I will draw upon the work of several authors in constructing a cognitive model of schizophrenia, and then, in section 5, I will attempt to integrate this with contemporary evidence regarding the brain in schizophrenia.

In my discussion of theory of mind in schizophrenia, I referred to Frith's model of impaired mental state attribution and faulty self-monitoring (Frith 1994). Frith conceptualises positive symptoms in terms of misattribution of intentions and beliefs of others, while negative symptoms result from a lack of awareness of one's own mental state. At the cognitive level, he has argued that this failure in mental state attribution results from a deficiency in the "central monitoring of action" (Mlakar et al. 1994). Therefore, symptoms such as delusions of control and thought insertion arise when "the monitor fails to receive information about intended actions generated by the patient on his own initiative. As a result, these actions are perceived as emanating from 'outside' or from an alien force" (Frith 1987). In a later elaboration of this model, Frith suggests that central monitoring deficiency results from the patient's inability to reflect on his own mental activity (Frith 1992). Subsequently, Frith has explored the neural basis of these impairments in a number of imaging studies that will be discussed in Section 5. It is important though, at this point, to refer to his conclusions of that work in terms of a cognitive model of schizophrenia. Frith (and others) have shown that the cognitive deficiencies exhibited by patients with schizophrenia can be linked to a breakdown in the functional integration of the PFC with the temporal and parietal cortices (Fletcher et al. 1998; Frith et al. 1995). This has led to the so-called *dysconnectivity hypothesis of schizophrenia* (see below).

It is useful to consider briefly a novel proposal by archaeologist, Steven Mithen, outlined in his book *The Prehistory of the Mind,* regarding the cognitive architecture of the modern mind (Mithen 1996). Mithen has critiqued the popular modular model of the mind (Fodor 1983) or "Swiss Army knife" model of evolutionary psychologists such as Cosmides and Tooby (Cosmides & Tooby 1992), in which the mind is conceived as a collection of independently evolved and independently used modules, each hardwired and adapted to the environment of the Pleistocene. Drawing on his impressive grasp of the archaeological record, Mithen suggests that, much like extant apes such as chimpanzees, early hominids possessed a brain that was organised around a number of module-like processing systems. Similar to Gardner's "multiple intelligences" (Gardner 1983), Mithen includes modules for "social intelligence," "technical intelligence," and so on. However, he argues that humans became the creative and imaginary species they are because of a gradual breakdown in this modularisation, producing increasing connections between modules and resulting in a "cognitive fluidity" that first became apparent in the symbolic and religious art of early *Homo sapiens* 60,000–30,000 years ago. I shall return to Mithen later, but what is extremely useful at this stage, I believe, is his conceptualisation of the modern mind as a fluid and connected entity that allows for integration of specialised information in the formation of abstract and symbolic thought. With respect to schizophrenia, one might surmise that intact mentational ability and self-monitoring relies on healthy connections and "cognitive fluidity," while impaired social cognition implies a breakdown in the normal integration of knowledge as a result of *cognitive mal-integration.*

Indeed, this is by no means a novel concept in the schizophrenia literature. Cleghorn and Albert argue that psychosis, and schizophrenia in particular, may be a problem in the integrated functioning of internal modular processing systems (Cleghorn & Albert 1990). They suggest that neural networks subserving cognitive and emotional modules are desynchronised in their activation and inactivation – a problem they term *cognitive disjunction* – and that this causes the symptoms of the disorder. They attribute both positive and negative symptoms to "desynchronisation of widely distributed neurocognitive systems."

In terms of specific symptoms, a number of authors have suggested that the specific cognitive error that underlies hallucinations is the misattribution of internal cognitive events to an external source (Bentall 1990; Hemsley 1987; Hoffman et al 1999; Morrison & Haddock 1997). For example, Bentall has argued that this misattribution may reflect a bias, rather than a primary deficit, in the monitoring of internal events and that this bias may be influenced by "top-down" processes such as a patient's beliefs and expectations about what events are likely to occur (Bentall 1990). And Morrison and Haddock have proposed that "metacognitive beliefs inconsistent with intrusive thoughts lead to their external attribution as auditory hallucinations" (Morrison & Haddock 1997).

The work of Paul Gilbert is helpful with respect to positive symptoms in schizophrenia. Gilbert has highlighted the importance of dialogical reasoning – the way in which people create dialogues within their own heads (Gilbert 2000). For some authors, he says, this inner dialogue is at the centre of the development and construction of the self and is based on the internalisation of social roles. For example, Mead eloquently explains, "There is a field, a sort of inner forum, in which we are the only spectators and the only actors. In that field each one of us confers with himself. We carry on something of a drama" (Mead 1913). Gilbert describes how various "selves" such as the aggressive, dominant, forgiving, and blaming "evolved to enact a plurality of social roles," and, at the cognitive level, he locates them in specialised modules for information-processing. With respect to schizophrenia, symptoms such as hostile, shaming voices represent the misinterpretation of signals from one's own dominant, blaming "self," such that these signals are experienced as external. Gilbert presents supporting empirical evidence (Gilbert et al. 2001) and attributes such symptoms to "problems in the integration of the modular processes underpinning self-other cognitions."

Finally, returning to ToM, it would be an omission not to cite Bering, who has questioned the suitability of domain-specific accounts of mind-reading (Bering 2002). As with Mithen, Bering has stressed the importance of emerging "cognitive fluidity," or integrated cognitive functions, in the genesis of what he calls the "existential ToM (EToM)." Bering defines EToM as "a biologically based, generic explanatory system that allows individuals to perceive meaning in certain life events." A meaningful life event is one that implies purpose or intention as the causal force. Therefore, natural events are interpreted as "symbolic of the communicative attempts of some nondescript or culturally elaborated (e.g., God) psychological agency." As he himself admits, Bering is not the first to suggest a link between ToM and theism (see Barrett & Keil 1996; Boyer 1994). Neither is he the first to propose that ToM becomes generalized to other domains (see Barrett & Keil 1996; Boyer 1994). However, his suggestion that EToM occupies a domain different from the one occupied by the "domain-specific" module of ToM proposed by these authors, is novel. He states:

> The notion of domain specificity crumbles, and the very idea that theory of mind is modular suffers a serious blow, when one considers that intentional explanations can be evoked by entirely different classes of input: behaviour and experience. (Bering 2002)

Bering is arguing that the case of flexible EToM shows us that a modular concept of ToM is inappropriate, in that this highly evolved aspect of mentational ability (EToM) is related to experiential rather than purely behavioural stimuli. Instead, he proposes that ToM ability as a whole has a cognitive architecture that is based on the integration of separate cognitive faculties related to intentionality. He goes on to suggest that ToM and EToM evolved in modern *Homo sapiens*, not as "exaptations" (Gould 1991) or useless by-products of a large brain, but rather as adaptive systems in their own right. Furthermore, he envisages a separate evolutionary history for EToM specifically, arguing that sometime after the human lineage split from the African apes, "the intentionality framework expanded to include those ambient life experiences that humans had little or no control over." EToM has thus been "co-opted from a broad intentional stance taken by our ancestors, the primary adaptation of which was to explain and predict behaviour" (Bering 2002).

This analysis is helpful, both in terms of understanding the concept of perceived intentionality as a part of ToM competency, and because it echoes Mithen's proposal that the modern conceptual mind represents a breakdown of phylogenetically older modularisation, allowing for integration of information. I certainly agree with Bering that ToM is the product of a gradual breakdown in cognitive modularity. As for an evolutionary time frame, it seems intuitively correct that EToM should have evolved later than ToM, given Bering's argument that chimpanzees may be capable of "secondary representation" (Suddendorf & Whiten 2001) (an immature aspect of ToM), whereas there is no convincing evidence that they are capable of representing intentionality (Heyes 1998). I shall return to phylogenetic aspects of ToM and EToM later. Finally and importantly, Bering's analysis is useful in terms of understanding the role of misattribution of agency in the genesis of symptoms in schizophrenia. As I stated in the opening paragraph of this paper, patients with schizophrenia seek meaning in the bizarre phenomena of their psychoses. Theistic and philosophical phenomena populate their hallucinations, while the frantic search for, and misattribution of, intentionality must lie at the heart of symptoms such as thought insertion, ideas of reference, and paranoid delusions.

The unifying theme, therefore, in all of these accounts of normal social cognition, and of ToM specifically, is one of integration of functionally distributed cognitive systems. Within the period between the divergence of hominid and chimpanzee lineages 5–6 mya and the emergence of modern *Homo sapiens* 60,000–30,000 years ago, a process has occurred involving the gradual breakdown in the modular construction of the mind. There is evidence that this process may have commenced prior to the last common ancestor, but if so, it was still in its infancy. In hominids, I argue, evolving changes in the brain provided a substrate for integration of previously modularised components of cognition, leading to "cognitive fluidity" and a capacity for increasingly complex social cognition. A cognitive model of schizophrenia must take this process into account. What we see in schizophrenia, in cognitive terms, is multiple deficits in the integration of information related to social behaviour, metarepresentation, and the attribution of intentionality. On the basis of the evidence I have presented thus far, I believe there are three hypotheses we can make regarding schizophrenia:

1. The origins of this disorder are closely related to the breakdown of the modular mind and the subsequent emergence of sophisticated social cognition in modern *Homo sapiens*.
2. The evidence regarding hominid brain evolution should tell a story of gradually increasing neural connectivity, specifically in the areas composing the social brain.
3. In studies of the brain in schizophrenia, the primary finding should be that of impairment in the function and possibly the structure of neural circuits comprising the social brain. Since I have argued that the cortical component of the social brain comprises FT and FP circuits, it is in these interconnected regions that these impairments should be sought.

5. The "dysconnectivity hypothesis" of schizophrenia

5.1. Background and definition of terms

There is a host of evidence from structural and functional imaging studies supporting the notion that schizophrenia is a disorder of cortical connectivity. This has given rise to the so-called *dysconnectivity hypothesis* (Friston & Frith 1995). This reflects a shift from the previously popular *hypofrontality hypothesis* (Weinberger & Berman 1988). Before elaborating on this recent change in thinking, I think it is important to draw attention to the fact that the concept of "dysconnectivity" is not new to psychiatry but merely resuscitated. The term refers to a disruption of interconnecting fibres that link spatially distributed regions in the brain. This idea has been variously entertained for more than 100 years, and by some very illustrious figures in the history of neuroscience.

Carl Wernicke (1848–1905) attributed psychiatric diseases to disturbances of associative systems in the brain – these disruptions of continuity he termed *sejunctions* (Wernicke 1906). Likewise, Goltz argued that higher brain function involves cooperative interactions between anatomically separate brain regions (Goltz 1881). Eugen Bleuler, adopting a psychological view of psychiatric disorders, described schizophrenia in terms of a splitting of psychic functions (Bleuler 1911/1950). Finally, Camillo Golgi, in his Nobel Prize acceptance speech said:

> If one halts, to consider these connections, one becomes convinced that one single nerve fibre may have connections with an infinite number of nerve cells, as well as with completely different parts of nerve centres which may be a long way from each other. (Golgi 1906)

In recent years, largely as a result of PET studies of neural activity during verbal fluency tasks, researchers in the field have begun to think in terms of "functional dysconnectivity" in schizophrenia. Friston defines normal functional connectivity as "the temporal correlation between spatially remote neurophysiological events" (Friston et al. 1993). As I have discussed, this is in contrast to the classic theoretical framework informing concepts of higher brain function, namely "functional segregation." Functional segregation emphasises a modular system in which different cognitive

functions are localized to discrete anatomical regions. This classic framework has dominated much of neurology and also the early decades of brain imaging in psychiatry. However, with the recent re-emergence of interest in network models of the brain, functional connectivity is once again in vogue. Friston and colleagues have described two approaches to measuring connectivity in the brain. The first is, as I have described, termed *functional connectivity.* The second is *effective connectivity,* which is mechanistic and harder to measure, and refers to the effect on a brain region of one or more extrinsic inputs to that region (Friston et al. 1995). To date, the vast majority of research into connectivity in schizophrenia has relied on measures of functional connectivity.

5.2. FT and FP dysconnectivity

Recent studies demonstrate abnormal FT activations on verbal fluency and verbal memory tasks, especially in the presence of auditory hallucinations, lending support to the hypothesis that the core feature of schizophrenia is a disruption of normal FT integration (Frith et al. 1995; Hoffman & McGlashan 1998; Lawrie et al. 2002; McGuire & Frith 1996; McGuire et al. 1995; Yurgelun-Todd et al. 1996a). In normal subjects, Frith and colleagues demonstrated DLPFC activation during a verbal fluency task on PET scan (Frith et al. 1991). This activation is accompanied by a reduction of activity in the STG, with an inverse correlation between the prefrontal and temporal responses (Friston et al. 1991). Friston and colleagues concluded that the DLPFC modulates the responsivity of a neural system in the STG relating to willed action and intentional states. When the same analysis was applied to patients with chronic schizophrenia, it was found that this correlation between prefrontal and temporal activation was disturbed (Frith et al. 1995). Patients demonstrated the same DLPFC activation during the verbal fluency task, but failed to show the normal decrease in blood flow in the left superior temporal cortex. In a review of their findings, these authors argue that this loss of correlation represents "a profound disruption of large-scale prefrontotemporal interactions in schizophrenia" (Friston & Frith 1995). In other words, it reflects abnormal functional connectivity between frontal and temporal cortices. Of interest, this initial study also demonstrated these findings across three groups of patients with different symptoms, leading the authors to suggest that it might be a marker of the illness per se. Subsequently there have been many replications of these findings (Dolan et al. 1999; Lawrie et al. 2002; Yurgelun-Todd et al. 1996b). Novel methods of analysis, including electrophysiological techniques (Peled et al. 2001; Lee et al. 2003), have also provided confirmation (Sigmundsson et al. 2001; Woodruff et al. 1997; Wright et al. 1999).

Although the focus has undoubtedly been on connected DLPFC and temporal systems in schizophrenia, there is also evidence that other prefrontal and parietal circuits exhibit similar deficits. In particular, the ACC, the OFC, and the IPC and their interconnections are implicated. For example, in normal subjects, McIntosh used fMRI to demonstrate strong right hemisphere interactions between the ACC and the hippocampus during a working memory task, suggesting functional connectivity between these two regions (McIntosh 1999). A number of studies have highlighted the role played by the ACC in schizophrenia, both in terms of its own discrete functions as well as its role in modulating neural circuits. In Cambridge, researchers have demonstrated both a segregated abnormality of ACC function in that there was a relative failure of activation in the ACC with a verbal fluency task, and an integrative abnormality in that there was a relative failure of corresponding deactivation in the left STG and inferior parietal lobe (IPL) (Dolan et al. 1995; Fletcher et al. 1999). They have argued that schizophrenia is associated with a disruption of normal ACC modulation of FT integration. Abnormal ACC function has also been shown in schizophrenia in the resting state (Tamminga et al. 1992), during attentional tasks (Yucel et al. 2002), during self-monitoring tasks (Carter et al. 2001; Nordahl et al. 2001), and during working memory tasks (Artiges et al. 2000; Meyer-Lindenberg et al. 2001).

With respect to the OFC in schizophrenia, the majority of structural MRI studies correlate reduced OFC volume with negative symptoms (Baare et al. 1999; Gur et al. 2000) and some specifically correlate orbitofrontal white matter reductions with negative symptoms (Sanfilipo et al. 2000; Sigmundsson et al. 2001). Although the functional imaging literature on OFC function in schizophrenia is scarce, there are a few studies and they tend to show reduced metabolism in the OFC (Andreasen et al. 1997; Clark et al. 1989; Kawasaki et al. 1996). For example, Kawasaki and colleagues used SPECT and correlated reduced cerebral blood flow (rCBF) in the left OFC with increased rCBF in the right temporal lobe in schizophrenics with delusions and hallucinations, suggesting that functional dysconnectivity between these regions may account in part for positive symptoms of the disorder.

As for the ACC and the OFC, the IPC and its connections have been relatively neglected in the dysconnectivity hypothesis of schizophrenia. This is surprising, considering the prominent role of the parietal cortex, and the IPC in particular, in a variety of important cognitive functions; for example, attentional processes (Kastner & Ungerleider 2000; Mesulam & Geschwind 1978; Morecraft et al. 1993), working memory (McCarthy et al. 1997b), language processing (Aboitiz & Garcia 1997a), and the attribution of agency (Farrer & Frith 2002; Ruby & Decety 2001). Both structural abnormalities (Bilder et al. 1994; Frederikse et al. 2000; Schlaepfer et al. 1994; Tien et al. 1996) and functional abnormalities (Cleghorn et al. 1989a; 1989b; Honey et al. 2002; Paulus et al. 2002) of the IPC have been demonstrated in schizophrenia. For example, Cleghorn and colleagues reported results from a resting PET study in which they found significantly reduced glucose metabolism in the IPC that correlated with increased metabolism in frontal lobes in schizophrenia (Cleghorn et al. 1989a; 1989b). They state that this suggests "that the relation of frontal and parietal regions is altered in drug-naïve schizophrenics in episode" and suggest "that they may be reciprocally related." It is surprising then, in the light of these early findings, that the dysconnectivity hypothesis of schizophrenia focussed almost exclusively on FT interactions until very recently.

In summary, then, it appears that certain regions and structures in the brain are functionally interconnected, and that impairment of the functional relationship between these regions may well be the primary pathology in schizophrenia. These regions include: the DLPFC, OFC, ACC, amygdala, hippocampus, STG, anterior temporal pole, and the IPC.

5.3. Structural correlates of functional dysconnectivity

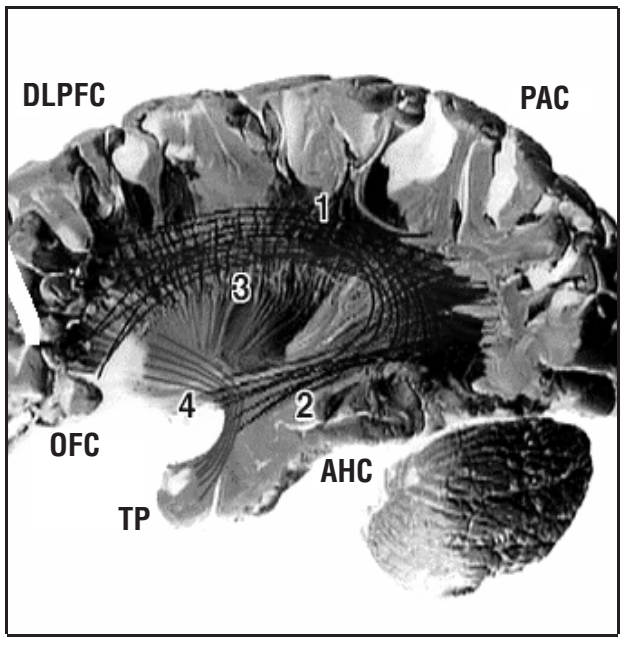
Given that there is evidence for abnormal functional connectivity between these regions in schizophrenia, it is logical to consider whether there might be a structural basis for this finding.

FT white matter tracts have been studied in nonhuman primates (using horseradish peroxidase or radioactively labelled compounds injected into tracts and then analysed autoradiographically) and inform our understanding of the likely comparable anatomy in humans. The OFC and ACC (Brodmann's area 24) have robust reciprocal connections with the medial and anterior temporal lobes via the uncinate fasciculus (UF), which constitutes much of the white matter of the anterior temporal stem. The UF carries reciprocal fibres from the OFC and the ACC via the anterior temporal stem to the rostral STG, the anterior temporal pole, the entorhinal cortex and the amygdala (Morris et al. 1999; Pandya & Yeterian 1996; Petrides & Pandya 1988; Seltzer & Pandya 1989).

In addition, the anterior cingulum bundle (AC) runs within the anterior cingulate gyrus and connects the DLPFC and the ACC with the parahippocampal gyrus (PHG) and hippocampal formation (Pandya et al. 1981; Petrides & Pandya 1999; Morris et al. 1999).

There are also connections via the arcuate fasciculus (AF) (or superior longitudinal fasciculus) between the DLPFC and the STG and temporal association cortex (Ban et al. 1991; Petrides & Pandya 1988; 1999).

Other smaller tracts that carry FT fibres include the extreme capsule and the external capsule (Petrides & Pandya 1988).



Key: 1 Arcuate fasciculus, 2 Inferior longitudinal fasciculus, 3 Fronto-occipital fasciculus, 4 Uncinate fasciculus.

Figure 1 (Burns). Left hemisphere dissected to reveal major association tracts including those implicated in the social brain. Relevant cortical regions are also labelled: dorsolateral prefrontal cortex (DLPFC); orbitofrontal cortex (OFC); parietal association cortex (PAC); amygdalo-hippocampal complex (AHC); temporal pole (TP).

Human anatomical studies confirm that these connections in nonhuman primates are paralleled in the human brain (Dejérine 1895; Makris et al. 1999) (see Figure 1). In particular, the UF in humans is the most substantial of the FT tracts, forming a tight bundle as it hooks around the temporal stem and fanning out at either end into the frontal and temporal lobes. In the temporal lobes some of its fibres become continuous with the fibres of the inferior longitudinal fasciculus.

There are a number of FP white matter tracts, but for the sake of brevity and relevance to this discussion, I will focus on the two major tracts. The arcuate fasciculus (AF), referred to above, is a highly connected structure, regarded as the principal association tract linking the DLPFC to cortical regions of the parietal, temporal, and occipital lobes. In particular, after tracking posteriorly as a well defined bundle parallel to the cingulum, it fans out with fibres connecting to the parietal association cortex in the region of the temporoparietal junction (Dejérine 1895; Makris et al. 1999). It also forms the main cortical connection between the language areas of Wernicke and Broca.

The anterior cingulum, also discussed in relation to FT tracts, connects the DLPFC and the ACC to parietal, temporal and occipital cortex. In particular, its parietal connections include the medial aspect of the parietal cortex (Dejérine 1895; Makris et al. 1999).

I have established that functional abnormalities of FT and FP neural networks underlie many of the predominant features of schizophrenia. I have also raised the question of whether "functional dysconnectivity" implies "structural dysconnectivity" in the disorder. In order to address this question I have argued that, in the first instance, white matter tracts that constitute these FT and FP connections need to be identified. Here, several such tracts have been identified. In terms of the pathology of schizophrenia, I believe that the following white matter tracts may be implicated in the disorder: the uncinate fasciculus, the anterior cingulum and the arcuate fasciculus. If there are indeed structural abnormalities in these tracts that correlate with functional dysconnectivity, is there a method for investigating their structural integrity?

5.4. Structural dysconnectivity of FT and FP tracts in schizophrenia

Examining the structure of human white matter tracts in vivo is a challenging task. This is because on standard structural brain imaging with MRI the resolution of white matter is poor and analysis is difficult. However, new MRI methodologies, such as diffusion tensor magnetic resonance imaging (DT-MRI), may have the potential to identify structural correlates of impaired FT and FP functional connectivity in schizophrenia. DT-MRI is a relatively new structural MRI technique that to date has been used mostly within the neurological and neurosurgical disciplines, with a fair degree of success. DT-MRI measures the mobility of brain water molecules in vivo (Basser et al. 1994; Jones et al. 1999). Most MR visible water is enclosed within axons. Structures such as myelin sheaths, axonal membranes, and micro-filaments cause the water diffusion to be slower perpendicular to axons than parallel to them. Within tissue with an orientated structure (such as white matter) the diffusion of water is therefore higher in the direction of the fibre tracts. This directional dependence of water diffusion

is called *diffusion anisotropy.* In this technique, the deviation from pure isotropic diffusion along axons is measured and described in terms of the *fractional anisotropy* (FA). This parameter is thought to provide a useful marker of white matter fibre integrity, with high levels of FA indicating healthy neurons (O'Sullivan et al. 2001).

In Edinburgh, we conducted a DT-MRI study to investigate the structural integrity of FT and FP white matter connections in a group of 30 schizophrenics and 30 matched controls (Burns et al. 2003). Using voxel-based morphometry with a small volume correction tool we compared FA values between groups in the UF, the AF, and the AC bilaterally. The results showed significantly reduced FA in the left UF (as it became continuous with the *inferior longitudinal fasciculus*) and left AF, suggesting that there are indeed structural correlates for functional dysconnectivity in schizophrenia and that these changes affect specifically FT and FP tracts. Furthermore, the fact that structural changes were lateralized to the left hemisphere, suggests that future work on connectivity must somehow incorporate Crow's cerebral asymmetry hypothesis into a cohesive theory that accounts for both the FT and FP and the asymmetry findings.

Two schizophrenia studies merit consideration in terms of our findings, and indeed in terms of the asymmetry hypothesis. The first is a DT-MRI study by Kubicki and colleagues (Kubicki et al. 2002) where the authors looked at diffusion anisotropy in the UF and found a group-by-side interaction in the patient group with reduced FA on the left side, supporting our finding. The second is a post-mortem study of the UF (Highley et al. 2002) where right-greater-than-left asymmetry was demonstrated in both patients and controls, with no significant differences in asymmetry between the two groups. A possible interpretation, in terms of our findings, is that the different techniques are examining different aspects of uncinate morphology. Highley and colleagues' study may yield information about fibre number and density, while our study is detecting differences in neuronal integrity as the uncinate tracts disperse near their termination in the temporal lobe.

In summary then, both functional and structural dysconnectivity has been demonstrated in white matter tracts linking the PFC to the temporal and parietal association cortices respectively. Schizophrenia is indeed a disorder of the neural circuits comprising the social brain. In Section 6, I will précis the well-supported evidence regarding the neuropathological basis for cortical dysconnectivity in schizophrenia.

6. Schizophrenia and neurodevelopment

What pathological process underlies the findings of abnormal connectivity in schizophrenia? And if we are arguing that schizophrenia lies on a genetic continuum with schizotypy and schizotaxia (an historical term describing the "preschizophrenic" phenotype which may include so-called schizophrenic-spectrum disorders) and entails a variation in normal white matter connectivity, how could this schizophrenic genetic spectrum translate into altered anatomy? Research indicates that schizophrenia is primarily a disorder of neurodevelopment (Weinberger 1987).

6.1. Normal ontogeny

First, we need to briefly consider the normal ontogeny of the brain. During the fifth week of gestation, the anterior end of the embryonic neural tube balloons outwards, forming the telencephalon, the precursor of the cerebral hemispheres. Progenitors of cortical neurons are confined to the ventricular zone (VZ) where they divide symmetrically during the process of neurogenesis (Rakic & Kornack 2001). Early pattern formation and neurogenesis are under the genetic control of homeobox genes such as *POU* (e.g., Brn, Oct-6 and SCIP), *Dlx, Emx, BF-1* and *-2,* and *MADS box* (e.g., MEF2 class genes) (Allman 2000). Asymmetric division occurs in cells originating in the VZ with migration in radial columns or units towards the pial surface. Postmitotic cells settle in an inside-out temporospatial gradient such that later "born" cells settle in more superficial layers. Radial migration is facilitated by glial cells that span the embryonic cerebral wall, and it is therefore *gliophilic* (Rakic 2000). Other cells are *neurophilic* and migrate tangentially along axons; for example, GABA interneurons from the basal ganglia. Migration is regulated by a host of *cell adhesion molecules* (CAMs, e.g. NCAM), *cadherins, Reelin,* and various chemoattractant molecules. Axonal arborisation follows with the outgrowth of axonal cones along pathways, mediated by molecules such as *limbic associated membrane protein (LAMP), GAP 43,* and *ephrins* (e.g., Eph-A5) (Rubenstein et al. 1999). Synaptogenesis involves the interaction of dendritic filipodia and axonal spinous processes in the formation of connections (Cohen-Cory 2002). A variety of CAMs and tyrosine kinases are involved in synaptogenesis and maintenance including *synaptophysin, cadherins,* and *neurotrophins* (e.g., BDNF, NGF, and NT-3). Both synapse formation and myelination continue well into adolescence in highly interconnected regions such as the association cortices. Simultaneously there is a normal process of pruning or apoptosis that results in fine-tuning of connections. This fine-tuning is necessary for specialisation of cognitive skills (Bock & Braun 1999; Casey 1999; Changeux & Danchin 1976; Chechik et al. 1998). Apoptosis involves a number of molecules including *Caspases 3* and *9, Jnk1* and *2,* and *BCL-2* gene family (Kuan et al. 2000; Kuida et al. 1998).

6.2. Neuropathology of schizophrenia

Regarding schizophrenia, one may speculate at which phase(s) of ontogeny the genetic defect becomes manifest. Does the schizophrenic genotype disturb normal neurogenesis, cell migration, arborisation, synaptogenesis, myelination (Randall 1983; 1998), or pruning (Feinberg 1983), or a combination of several phases? It is also possible that the disturbance involves either an increase or decrease in one or more of these processes. Therefore, abnormal connectivity may, for example, reflect either reduced pruning of abnormal connections or increased pruning of healthy connections or reduced dendritic arborisation in the "right" places or increased arborisation in the "wrong" places, and so on. There are numerous possibilities, and different processes may be implicated to varying extents in particular subpopulations of schizophrenics.

Harrison has reviewed the evidence regarding the neuropathology of schizophrenia (Harrison 1999), and the abnormalities for which he finds strong evidence are tabulated in Table 1.

Harrison concludes that the evidence points towards later processes in ontogeny, namely arborisation, synaptogenesis, and pruning. Conversely, the evidence for migra-

Table 1. *Neuropathology of schizophrenia*

Hippocampus/DLPFC	Hippocampus	DLPFC	ACC
Normal number neurons ↓ size of neurons ↑ packing density ↓ neuropil ↓ pre/postsynaptic markers ↓ arborisation ↓inhibitory neurons ↓ NAA ↑ synaptic pruning no gliosis	↓ synaptophysin ↓↓ SNAP 25 ↓↓ complexin II ↓↓ GAP 43 mRNA ↓/aberrant expression of MAP 2 (in dendrites)	↓ synaptophysin ↓ dendritic spines on layer III pyramidal neurons	↑ synaptophysin ↑ glutamatergic axons ↑ axospinous synapses ↓ inhibitory (GABA) neurons

tory processes (such as neuronal disarray, maldistribution, and dysplasia) is inconclusive and unsubstantiated (Harrison 1999). Abnormalities in *Reelin* protein and *Reelin* mRNA have been demonstrated in the PFC, temporal cortex, and hippocampi (Impagnatiello et al. 1998); however, this may relate more to *Reelin*'s role in synaptic function than in migration (Weeber et al. 2002). In terms of the timing of insults, Harrison argues that the evidence points to the second trimester. First trimester insults affecting neurogenesis are unlikely, as gross structural defects (such as schizencephaly and polymicrogyria) would be expected. However, the increased findings of abnormal dermatoglyphics, craniofacial dysplasias, and abnormal septum pellucida in people with schizophrenia do suggest early insults, and therefore the first trimester cannot be ignored.

A perennial problem for the neurodevelopmental hypothesis is the adolescent or early adult onset of the disorder. If schizophrenia is a disorder of neurodevelopment, why does the disorder typically not manifest earlier on? And how do we account for the obvious role played by psychosocial factors in its onset? The explanation favoured by most schizophrenia researchers is that genetic (and possibly foetal and perinatal) insults disturb neurodevelopmental processes resulting in abnormal cortical circuitry. This may manifest clinically as a spectrum of minor behavioural and psychological problems in childhood. However, with the hormonal and neurodevelopmental changes of adolescence (including late synaptogenesis and myelination in association cortices as well as the onset of pruning) and the possibility of multiple "hits," vulnerability to psychosis increases and, in some cases, the disorder manifests.

As we have seen, there is pathological evidence for disturbances of neurogenesis, arborisation, synaptogenesis, and pruning in schizophrenia. One scenario that integrates these findings is the following: Abnormal neurogenesis results in small cortical neurons with reduced axospinous processes and arborisation; abnormal synapses result; finally, pruning in adolescence results in mass loss of synapses, loss of neuropil, denser packing of neurons, and a decrease in synaptic marker proteins. Reduced and dysfunctional synapses would also account for the disturbed neurotransmitter levels described in schizophrenia. Of course, it is also possible that neurogenesis is normal and that the primary gene effects disrupt arborisation or synaptogenesis, leading to a similar array of neuropathological findings. Regardless of the exact mechanisms, it seems that these disturbances predominate in regions composing the social brain and result in functional and structural abnormalities of neuronal connectivity.

Finally, in terms of the pathological basis for the notion of a schizotypal spectrum, McGlashan and Hoffman have used computer-simulated pruning to demonstrate enhanced cognition by means of pruning and refinement (Hoffman & McGlashan 1997; McGlashan & Hoffman 2000). They hypothesise that with excess pruning (beyond normal apoptosis), certain cognitive skills might be further refined, giving rise to creative genius in, for example, the schizotypal individual – and to possible select genius in the autistic savant – and that schizophrenia may represent an overshoot of the pruning process, resulting in severely abnormal connectivity. This is certainly a useful model, since one might envisage a mild degree of dysconnectivity in the schizotype and more severe dysconnectivity in the person with schizophrenia, relating to the respective "dose" of the genotype.

Having described a theory of the genotype and anatomical phenotype of the schizotypal/schizophrenic continuum, I believe it is instructive to consider the evolution of the human brain. By examining both phylogenetic and ontogenetic aspects of brain evolution, I propose to provide further important evidence for the central argument of this paper – that schizophrenia is a disorder of primarily FT and FP connectivity, and that it constitutes a trade-off in the evolution of a highly complex social brain in our species.

7. Evolution of metarepresentation

Does current theory about how the brain evolved in *Homo sapiens* and his ancestors lend any support to the hypothesis that schizophrenia is a disorder of predominantly cortical connectivity? We have evidence from neuropathology, neuroimaging, and neuropsychology. But does evidence from paleoanthropology, paleoanatomy, and primatology add any supporting evidence? And does this evidence support Crow's hypothesis of cerebral asymmetry and language?

Humans are genetically very close to the African apes

(98.5% of the genome is identical (Allen & Sarich 1988)) and especially close to the two species of chimpanzees (Waddell & Penny 1996). Therefore, human cognitive advances are only 5–6 million years old, the date of our last common ancestor, which is very young by evolutionary standards. Mesulam argues that increased brain size alone could not accommodate and explain adequately the enormous cognitive advances that occurred during this short period (Mesulam 2000). He argues that it was the evolution of cerebral connectivity that allowed for the huge leaps forward.

An increase in brain size commenced in the common ancestor of Old and New World monkeys and hominoids approximately 35–40 mya (Fig. 2). Cladistic analysis suggests that this volume increase occurred under the selective pressures of increased social complexity as a result of group living (Byrne & Whiten 1988; Chance & Mead 1953). Jerison used the *encephalization quotient* (EQ) as a measure of progressive encephalization, but this does not correlate with group size or increased intelligence (Jerison 1973). Dunbar showed a constant relationship between *neocortex ratio* (NR) (i.e., neocortex:rest of the brain) and group size – the former representing the selective increase in neocortex size that marked the clade and the latter being a crude measure of social complexity (i.e., the number of relationships the animal has to keep track of) (Dunbar 2001). Monkeys share social skills and increased memory (especially visuospatial) for finding fruit and remembering allies (Mackinnon 1978). The first stage in the evolution of intelligence therefore commenced approximately 35–40 mya, with an increase in brain size (Byrne 1999).

However, it is not just brain size that determines cognitive ability. Holloway has critiqued Dunbar's model (Holloway 1993), while Byrne has pointed out that apes do not have an increase in NR relative to monkeys, yet apes show increased cognitive abilities (Byrne 2001). He also notes the smaller group size in some apes (e.g., single or mother-child pair in orangutans) and argues against the extrapolation of Dunbar's hypothesis to the hominoid superfamily.

Various authors have argued for the existence of a ToM or elements of ToM in the great apes (Premack & Woodruff 1978; Russon 1999; van Schaik et al. 1996). Byrne argues that apes demonstrate the ability to represent "thoughts" in mind in the absence of a direct stimulus, an ability not found in other primates (Byrne 1999). He terms this *representational intelligence* and cites complex tool use by chimps (McGrew 1992) and orangutans (van Schaik & Van Hoof 1996), their ability to perform false belief tasks (Byrne & Whiten 1991), their complex political dynamics (de Waal 1982; 2000), and their ability to attribute causality (Limongelli et al. 1995) as examples of representational intelligence. He estimates that the origin of this further step in the evolution of mind dates from approximately 16–13 mya when orangutan ancestors (such as Sivapithecus) split off from the African apes, and was complete by 5 mya when human ancestors split from those of the chimpanzees. He suggests that the biological basis for this cognitive step was an organizational change in the brain, allowing for increased flexibility. He also suggests that the selective pressure for such change in the apes was the need to evolve complex new strategies for food acquisition to compete with monkeys, which were better adapted for tree climbing. These new strategies include use of tools to extract embedded foods (Parker 1996; Parker & Gibson 1977) and novel ways of manipulating nutritious plant foods, for example, nut cracking (Byrne & Russon 1998).

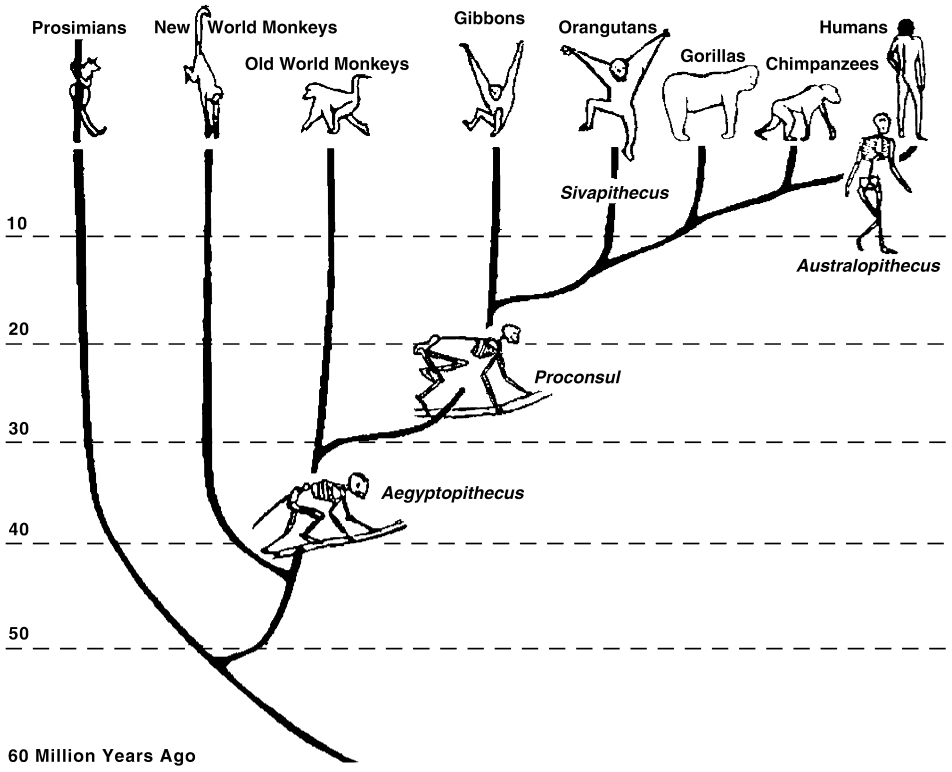


Figure 2 (Burns). Simplified model of primate evolution (reproduced from Mithen [1996] with kind permission).

Baron-Cohen argues that our last common ancestor with chimps, 5 mya, could have possessed only immature elements of a ToM (Baron-Cohen 1999). His evidence comes from ToM tests in apes that showed only a limited ability to attribute mental states and intentionality to others (Povinelli & Eddy 1996; Premack 1988). He suggests that our common ancestor may have possessed an "intentionality detector module" and an "eye detector module," both of which are apparent in chimps. He puts the time frame for the evolution of a full ToM at approx. 150,000–40,000 years ago, supported by archaeological records which show the earliest fictional art and symbolic adornments dating from that period (Henshilwood et al. 2002; Mithen 1996).

Suddendorf agrees, putting the emergence of the "metamind," which is first evident during a child's fourth year, at approximately 2 million to 100,000 years ago, as evidenced by the complex Acheulian tool culture of *Homo ergaster/ Homo erectus* (Suddendorf 1999; Suddendorf & Corballis 1997). Unlike the Oldowan tradition of *Homo habilis*, which predated this epoch and was within the scope of modern chimpanzee tool culture, the Acheulian tools required planning, precision, and a concept of the future; they implied cultural learning.

Whiten (1999) argues that hominids evolved a "deep social mind" as a "cognitive niche" (Tooby & de Vore 1987) to compete for food with better-adapted monkeys in the trees and carnivores on the savannah during the Pleistocene period. This cognitive advance, which is probably synonymous with Byrne's ToM and Suddendorf's metamind, resulted from social interdependence and involved the refinement of cooperative behaviour, cultural and social learning and transmission, and mind-reading ability.

In summary, all commentators argue for: (a) an initial increase in brain and neocortex size under pressures of social living, roughly 40–16 mya; and (b) an acceleration of evolving cerebral reorganization and connectivity from approximately 16 mya onwards (Table 2). This subserved the beginnings of the evolution of metarepresentation in hominoid ancestors between 16 and 5 mya, and the later further acceleration leading to a full ToM in the human line between 150,000 and 40,000 years ago.

I would argue that it was only with the recent evolution of cerebral connectivity and a capacity for a full ToM and complex social cognition, that a disorder of cortical connectivity such as schizophrenia was possible. Conversely, the lack of evidence, to my knowledge, of psychotic disorders in other animals – including our nearest relatives, the chimps – implies that it is precisely what sets us apart from them in terms of brain structure and psychology, that also underlies our capacity for this specifically human malady. It is our possession of complex cerebral connectivity that allows for full metarepresentation.

8. Evidence from comparative primate anatomy

Recent comparative studies of primate brain anatomy add further support to the thesis of this paper – that schizophrenia represents a disorder of cortical connectivity that evolved late in hominid ancestry. I would also argue that these new findings conflict with Crow's cerebral asymmetry hypothesis. Like Crow, I would argue that schizophrenia is indeed "the price we have paid for being fully human" (Crow 1997a), but for different reasons.

8.1. Evolution of brain size

Semendeferi has analysed data from in vivo MRI scans of the primate brain (collected by James K. Rilling and Thomas R. Insel at Yerkes Regional Primate Centre) and has demonstrated that, with increasing brain size, the frontal lobe does not increase relative to total hemispheric size in hominoids (Semendeferi 2001; Semendeferi et al. 1997; 2002) (see Fig. 3 below). Likewise, the parieto-occipital lobes enlarge consistently relative to total hemispheric size. However, the relative temporal lobe size (relative to whole brain size) is greater in humans than in apes (Rilling & Seligman 2002). Interestingly, the size of the cerebellum is progressively reduced (with significance) as one moves from the phylogenetically older apes to humans (Rilling & Insel 1998; Semendeferi & Damasio 2000).

The observation that the frontal lobes are not relatively larger in humans is not new. Von Bonin first described this in 1948 (Von Bonin 1948; 1950), and it was later pointed out by Holloway in a number of papers (Holloway 1966; 1968; 1975). Holloway has challenged the popular supposition that size alone correlates with cognitive ability. He cites as evidence the case of microcephalics who do obtain some

Table 2. *Table illustrating the stages in the evolution of brain and cognition. IBNS = increasing brain and neocortex size; ToM = theory of mind; FT = frontotemporal; FP = frontoparietal*

Years ago	Species	Anatomical changes	Cognitive changes	Evidence
100,000	*H. sapiens*	IBNS + complex FT and FP connectivity	Full ToM	- Complex social cognition - Culture, religion, etc.
2 million	*H. erectus/ ergaster*	IBNS + evolving connectivity	"Metamind"	- Acheulian tool culture - Symbolic art
5 million	*H. habilis* *Australopithecus*	IBNS + evolving connectivity		- Oldowan tool culture
15 million	*Great apes*	IBNS + evolving connectivity	"Representational Intelligence" and early ToM	- Complex tool use - Attribute causality - ToM tasks
30 million	*Old and New World monkeys*	IBNS	Increasing memory and social skills	- Group relations - Finding fruit
40 million				

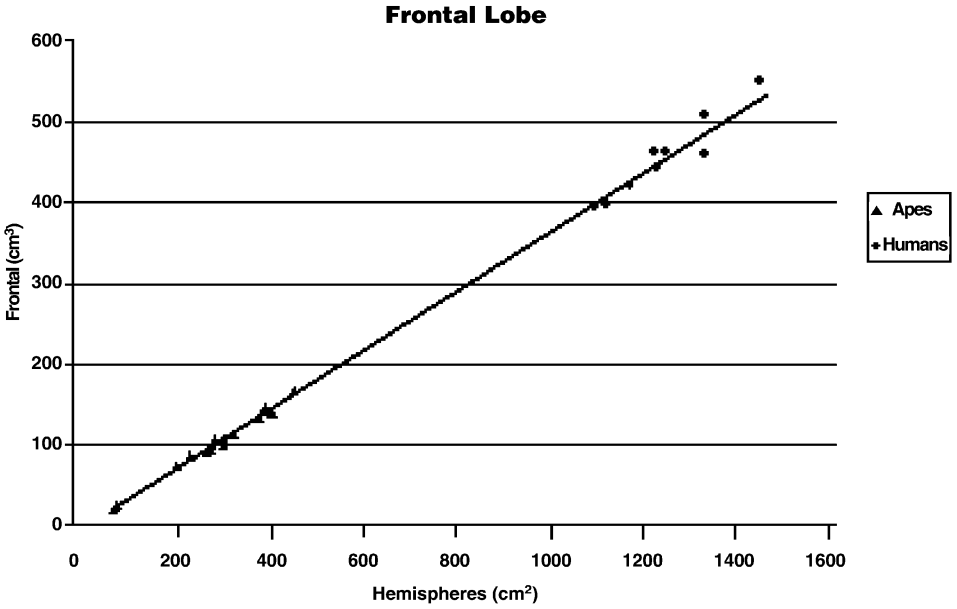


Figure 3 (Burns). Allometric relationship between the frontal lobe and the cerebral hemispheres (reproduced from Semendeferi [2001] with kind permission).

language ability, as well as the extensive variation in brain volume (without variation in cognition) noted in both fossil hominids and modern humans. More recently, Aboitiz has proposed that increasing brain size produces increases in processing capacity only if accompanied by significant connectional rearrangements (Aboitiz 1996). Clearly, size is important, as a number of authors have argued (Falk 1985; Gibson et al. 2001; Jerison 1973), but in the tradition of Holloway, I would maintain that size increase alone is insufficient to account for the cognitive advances during human descent.

8.2. Cortical reorganization and connectivity in evolution

Holloway first raised the argument that evolutionary changes in cognition reflect reorganization of systems internal to the brain (Holloway 1966; 1967; 1975; 1995), rather than increased brain size as championed by Jerison (1973). Drawing on both endocast analyses and archaeological evidence of complex cognitive skills in *Australopithecines,* Holloway suggested that reorganization dates to at least 2.5–3 mya and, in his 1973 James Arthur Lecture, tied the role of social behaviour into a theory of human brain evolution (Holloway 1975). Hofman has shown that in hominoids, it is white matter that increases substantially (relative to brain size) rather than grey matter (Hofman 1989), and this has been confirmed using MRI (Rilling & Insel 1999b; Semendeferi et al. 1994). Furthermore, it is specifically *intrahemisheric connectivity* that increases disproportionate to increasing brain size and neocortical surface area. Conversely, *interhemispheric connectivity,* as expressed by the cross-sectional area of the corpus callosum, decreases with increasing brain size (Rilling & Insel 1999a), suggesting that Crow's reliance on the corpus callosum in his cerebral asymmetry hypothesis (Crow 1995c) is flawed.

This leads me to consider comparative primate data, as well as fossil evidence, regarding the specific FT and FP interconnected regions I have identified as constituting both the social brain and the primary sites of pathology in schizophrenia. From the last study cited above (Rilling & Insel 1999a) one might anticipate that these major *intrahemispheric* circuits have been subject to significant evolutionary change in the hominid line. I am encouraged in this task by the findings of Rilling and Seligman regarding temporal lobe evolution in primates (Rilling & Seligman 2002). They scanned 11 species of anthropoid primates using MRI and found that the human temporal lobes were larger than expected for brain size, and that the departure from allometry was most pronounced for the white matter of the temporal lobes. This is particularly noteworthy, as it implies selection for deviation from typical rules of brain growth in anthropoids. The authors note that each of the four main functional subdivisions of the primate temporal lobe projects heavily to the PFC, and they suggest that a possible interpretation of their finding of "the disproportionate size of the human temporal lobe white matter" is that this "reflects an augmented number of connections linking temporal and prefrontal cortex". They further speculate that this augmentation may relate to the evolution of language. With the advent of new imaging techniques such as DT-MRI, it is feasible that these connections might be examined in greater detail in hominoids, giving us a clearer understanding of the evolution of structures such as the UF, the AF, and the AC.

8.2.1. ACC circuits. The first region of the social brain I wish to consider, then, is the ACC and its connections. There is recent evidence from a comparative primate study that the ACC evolved a unique type of projection neuron in the hominoid clade (Hof et al. 2001; Nimchinsky et al. 1999). This large spindle-shaped cell which is characterised by immunoreactivity to the calcium-binding protein, calretinin, is unique to hominoids and increases in density as one compares the ACC of the orangutan with that of the gorilla and with that of the chimpanzee, and finally is greatest in humans. Nimchinsky and colleagues argue that this indi-

cates that the ACC experienced strong adaptive pressure related to communication during the past 16 million years of primate evolution. They conclude that the ACC plays a significant role in recently evolved cognitive processes including self-awareness, attention, emotional control, and communication.

8.2.2. OFC circuits. Second, a comparison of the macroscopic and microscopic morphology of the OFC in great apes supports both the notion that this region is implicated in social cognition and my argument that it has been subject to reorganisation in hominoids. Semendeferi compared Brodmann's areas 10 and 13 across hominoids and demonstrated that area 13 is significantly smaller in orangutans than in gorillas and chimpanzees (and humans) (Semendeferi 1994; Semendeferi et al. 2001). Area 13 lies posteriorly and medially in the OFC and is considered to be part of a circuit connecting to the limbic temporal lobe that is relevant to emotion, particularly related to social stimuli. As mentioned previously, ablation of this area in wild monkeys results in significant reductions and losses of behaviours that are considered important for the maintenance of social bonds (Kling & Steklis 1976). Furthermore, in terms of the cytoarchitecture of area 13, Semendeferi has demonstrated a marked decrease in cortical cell density in the orangutan relative to the African hominoids, especially in infragranular layers V and VI (which have connections with subcortical limbic structures). It therefore appears that there is decreased representation of the "limbic" OFC in the orangutan, a phylogenetically more distant species. She suggests that this region is important for the survival of members of complex social groups and speculates that the relative immaturity of the frontal limbic cortex in orangutans may relate to the more solitary lifestyle and less complex social organization of this primate compared with its African cousins (Semendeferi 1999; van Schaik & Van Hoof 1996). Further speculation might suggest that the OFC, like the ACC, has experienced strong adaptive pressures related to social living during the course of hominoid evolution.

8.2.3. Amygdala circuits. As discussed earlier, the primate amygdala contains neurones that respond selectively to facial expression and eye gaze, and when surgical lesions are placed in this structure, the animal fails to evaluate new stimuli and puts itself at risk. This is a clear example of a brain structure that has evolved in relation to social demands on the individual. Obviously the fear response is a very primitive adaptation, and comparative studies have confirmed that the amygdala is present in most vertebrate species. However, when the amygdala is divided into its component nuclei, there is evidence of extensive variation in mammals including primates. Barton and Aggleton have compared amygdaloid nuclei across 43 species of primates and shown that the relative size of the corticobasolateral (CBL) nucleus is significantly greater in primates than in insectivores, and among primates is significantly greater in apes and monkeys than in prosimians (Barton & Aggleton 2000). This is complemented by histological evidence for increasing organisation of this nucleus during phylogeny (Pitkanen et al. 2002). Barton and Aggleton also found that CBL size correlates with neocortex size as well as social group size in monkeys and apes, suggesting that this nucleus and its connections with higher cortical regions were subject to social selective pressures. The CBL has been shown to have far more widespread cortical connections in monkeys than in cats (Young et al. 1994) and has extensive reciprocal connections with the OFC (via the uncinate fasciculus) and the STG. Barton and Aggleton conclude that this amygdaloid nucleus has experienced disproportionate enlargement and connectedness in higher primates as part of a recently evolved network regulating social cognition.

8.2.4. IPC circuits. Preuss has pointed out that the frontal, temporal, and parietal association cortices account for most of the increased brain area in humans compared with apes (Preuss 2000; 2001). In humans the primary visual cortex (V_1, BA 17) is displaced posteriorly, being approximately 121% *less* than its allometrically expected size, thus allowing for the greater expansion of the parietal association cortex (PAC) (Holloway 1995). According to Holloway, endocasts from two *Australopithecine* fossils (the Taung specimen and Hadar AL 162–28) reveal an intermediate position of the lunate sulcus, between that of the human and that of the chimpanzee, suggesting that the PAC was significantly enlarged and reorganized as early as 3 mya (Holloway 1972; 1975; 1983a; 1984; 1985; 1996). The lunate sulcus separates the primary visual cortex from the PAC and is notoriously difficult to identify on endocasts; therefore, its position in these specimens is a point of controversy in physical anthropology (see Falk 1980; 1985; for opposing viewpoint). Controversy aside, it is clear that the PAC has enlarged and reorganized significantly during hominid descent. Comparative primate studies support this as well. For example, functional imaging suggests that the human intraparietal cortex contains visuospatial processing areas that are not present in monkeys (Vanduffel et al. 2002). Regarding the IPC specifically, Gilissen has scanned chimps using MRI and shown that this structure is more symmetrical in chimps than in humans (Gilissen 2001). While there is some right-greater-than-left asymmetry of the IPC in chimps, it does not compare with the marked asymmetry in humans, suggesting that the human right IPC – a notable component of the social brain – has enlarged disproportionately in the human line.

In summary therefore: There is good evidence that the social brain has evolved markedly in hominids through a process of brain reorganization and increasing intrahemispheric white matter connections linking the PFC to the temporal and parietal association cortices. Since these are the same regions and connections that are abnormal in schizophrenia, I believe this supports my argument that schizophrenia represents a trade-off in the evolution of the social brain. Conversely, interhemispheric connectivity has diminished during hominoid phylogeny, posing a serious problem for Crow's asymmetry hypothesis.

8.3. Cerebral asymmetry and language

The study of cerebral asymmetry and the evolution of language has old origins, and the literature and controversies are manifold and certainly beyond the scope of this paper. Of relevance to my thesis, however, are two issues: First, Crow has founded his evolutionary hypothesis of schizophrenia on the premise that both asymmetry and language have recent origins and are associated with a speciation event in modern *Homo sapiens* (Crow 2002); and second, in the study of schizophrenia, abnormalities of both cere-

bral asymmetry and language are well recognised (Crow 1990; De Lisi 2001; Luchins et al. 1979). In terms of my thesis, I would argue that human cerebral asymmetry has ancient origins within the hominoid lineage and that it represents an aspect of brain reorganisation, as suggested by Holloway (Holloway 1983b; Holloway & de la Coste-Lareymondie 1982). Several authors have argued that leftward brain asymmetries may have evolved as a consequence of reduced interhemispheric connectivity and the increase in more efficient localised networks in each hemisphere (Hopkins & Rilling 2000; Rilling & Insel 1999a). Laterality was thus an emergent property of increasing brain size and reorganisation in primates.

LeMay's work on cortical petalias (*petalia* describes the extension of one cerebral hemisphere beyond the other) (LeMay 1976; LeMay et al. 1982) boosted the study of cerebral asymmetry in primates and linked it to handedness. This author (LeMay et al. 1982) and others (Geshwind & Galaburda 1984) have found petalia asymmetries similar to the human pattern in pongids, while Holloway and de la Coste-Lareymondie argue, on the basis of their examination of 190 hominoid endocasts, that the human petalia pattern is specific to both modern and fossil hominids (*Homo habilis* and *Homo erectus*) (Holloway & de la Coste-Lareymondie 1982).

However, when it comes to specific structures within the language networks, the evidence for very early origins of lateralisation/asymmetry is quite convincing. While the fossil record has yielded up only one specimen that shows evidence of a modern, humanlike Broca's speech area (the KNM-ER 1470 habiline) (Holloway 1976), comparative data in extant primates offers more clarity. For example, Gannon and colleagues reported in *Science* their discovery of marked asymmetry in the chimpanzee planum temporale (PT) – a key site in Wernicke's posterior language area (Gannon et al. 1998) (Fig. 4). They found that the left PT was significantly larger in 94% (17 of 18) of chimpanzee brains examined post-mortem, and they state:

> The evolutionary origin of human language may have been founded on this basal anatomic substrate, which was already lateralized to the left hemisphere in the common ancestor of chimpanzees and humans 8 million years ago.

Three further studies, one post-mortem (Gannon et al. 1998) and two using MRI to image the brains of a variety of sedated primates (Hopkins & Marino 2000; Hopkins et al. 1998), demonstrate asymmetry of both the PT and Heschl's gyrus as well as the insular region of the sylvian fissure in the great apes, but not in monkeys. Another recent study by Cantalupo and colleagues, reported in *Nature,* demonstrates left-greater-than-right asymmetry of Broca's area (Brodmann's area 44) in three great ape species, *Pan troglodytes, Pan paniscus,* and *Gorilla gorilla* (Cantalupo & Hopkins 2001). It should be noted that at least one histological study (Buxhoeveden et al. 2001) has confirmed that there are some human specific features of PT asymmetry architecture.

Gannon argues that these findings set the date for the origins of a lateralised "proto-linguistic" area in great apes and humans, at approximately 18 to 16 mya, just after the gibbon ancestor diverged from that of the other hominoids (Gannon et al. 2001). Furthermore, he argues for a polymodal role for the PT in a connectionist model of "language" perception. In other words, a diffuse network of lateralised neuronal connections corresponding to the left PT and related association areas constitute a region underlying communicative skills in great apes and humans. Gannon cites the following findings in support of his argument:

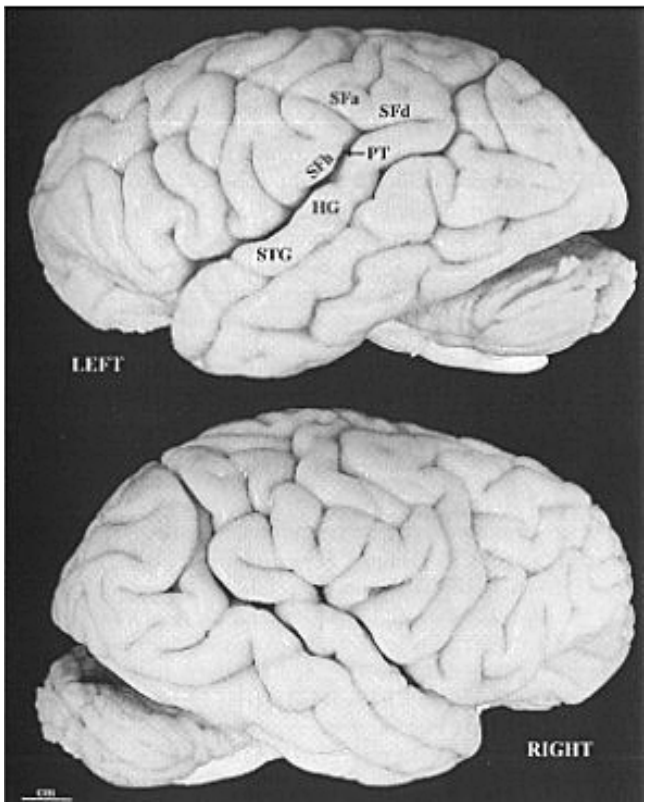


Figure 4 (Burns). Left and right hemispheres of an adult, female chimpanzee (*Pan troglodytes).* Abbreviations: STG = superior temporal gyrus; SFh, Sfa, and SFd = horizontal, ascending, and descending limbs of the Sylvian fissure; PT = planum temporale; HG = Heschl's gyrus (reproduced from Gannon et al. [2001] with kind permission).

1. The complex communicative skills of great apes, including both referential and intentional gesturing and vocalisation (Corballis 1992) and their use of sign language (Savage-Rumbaugh 1990; Savage-Rumbaugh et al. 1978; Shapiro 1982; Shapiro & Galdikas 1999).

2. Evidence from functional imaging of deaf-from-birth humans that signing activates classic left hemisphere language areas (Neville et al. 1998).

3. Auditory hallucinations in psychotic individuals activate language areas without discernible motor or audible components (Suzuki et al. 1993).

There are strong arguments from "neural network theory" against Chomsky's idea of a domain-specific, innate "human language organ" (Chomsky 1972) and in favour of "broadly distributed, domain-general neural systems" that subserve complex communication in humans and great apes (Bates & Elman 2000).

So my conclusions regarding language are: that cerebral asymmetry and language areas began to evolve 18 to16 mya as a part of emerging cortical reorganisation and are found in all extant great ape species; that these areas are diffuse and involve connectivity rather than localised domains; that they represent regions involved in complex communication rather than pure language; and finally, that these findings do not support Crow's hypothesis that asymmetry and lan-

guage evolved recently and provide the substrate for psychosis.

9. Evolutionary ontogeny of the brain

Any discussion of the evolution of cerebral connectivity must include an analysis of how neurodevelopmental processes have changed during evolution. This will illustrate the mechanism by which the hominoid brain might have become larger and more connected. It will also allow us to speculate about abnormal ontogenic processes in the genesis of the schizophrenic brain.

9.1. Heterochrony in brain evolution

The term *heterochrony* was coined by Ernst Haeckel in his "biogenic law" at the end of the nineteenth century to describe the evolution of differences in the timing of development – in other words, the acceleration or deceleration of maturation of an organ relative to its developmental timing in an ancestor (McKinney & McNamara 1991). Several authors argue that this change in timing is the key evolutionary mechanism driving the enlargement of the brain. Louis Bolk popularised the notion of *neoteny,* whereby a delay in the plateau of brain growth resulted in a prolongation into adult life of some features of infant ancestors (Bolk 1926). Gould has argued that "human beings are 'essentially' neotenous" (Gould 1977). However, more recent authors have raised doubts about these claims (McKinney & McNamara 1991; Shea 1989), arguing that "there is no single heterochronic process that accounts for all of human evolutionary change" (McKinney & McNamara 1991). However, these authors go on to suggest that "there is one process that accounts for much of it . . . it is hypermorphosis." *Hypermorphosis* is the "phyletic extension of ontogeny beyond its ancestral termination, such that adult ancestral stages become preadult stages of descendants" (Lock & Peters 1999). McKinney and McNamara argue that it is a misconception that human development is generally retarded or slow across the life span. As Lock and Peters put it, "humans do not grow more slowly than other primates but grow for a longer time in each phase of growth."

These arguments have resuscitated the largely discredited notion of *recapitulation* originally suggested by Haeckel. The phrase "ontogeny recapitulates phylogeny" was popular during the late nineteenth and early twentieth centuries and refers to the idea that the stages of phylogenetic evolution are repeated during the stages of individual development. While most authors would reject the idea that recapitulation occurs as an all-encompassing process in human evolution, the increasing recognition of *mosaic evolution* – that is the evolution of different components of a phenotype at highly unequal rates (Lock & Peters 1999) – has helped to rehabilitate the scientific community's perception of recapitulation as a possible phenomenon. Mosaic evolution implies that some aspects of the phenotype may have evolved through developmental retardation while others have been accelerated. There is thus room for accepting both neotenic and hypermorphotic processes in human evolution (Chaline 1998).

Regarding the evolution of the social brain in particular, I would tentatively suggest that it resulted from a process of sequential hypermorphotic development (sequential to a neotenous delay of maturation) (Fig. 5). Brüne has previously suggested that hypermorphosis may have played a role in the evolution of the social brain (Brüne 2000). McKinney (2000) states:

> Many of our mental abilities are largely attributable to extension of brain development to produce a proportionately scaled-up version of the ancestral ape brain. Sequential hypermorphosis of behavioural and cognitive development is accompanied by prolonged stages of neurogenesis, dendritogenesis (and dendritic pruning), synaptogenesis and myelination.

Ontogeny may, therefore, recapitulate phylogeny as far as the social brain is concerned. From the discussion of brain evolution so far, it appears that the trend towards increasingly complex connectivity in subsequently more sophisticated regions of the cortex during development reflects the trend during our evolutionary history towards increasingly complex cortical connectivity, social cognition, and metarepresentation (Brüne 2000; Deacon 1990; Finlay & Darlington 1995; Gibson 1991). McKinney stresses that it is "terminal extension" (of connectivity and cognitive function) that occurs, rather than "terminal addition" (McKinney 2000). Furthermore, he traces the prolonged stages of neurodevelopment back to "our originally larger endowment of embryonic neurons." Finlay and Darlington have

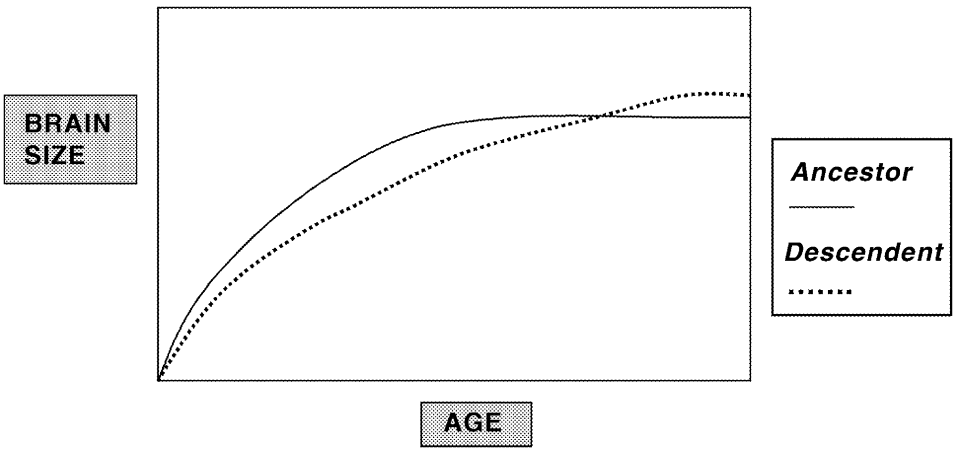


Figure 5 (Burns). Sequential hypermorphosis in evolution of the social brain.

argued that it is developmentally easier to generate a larger brain by extending prenatal brain growth than by altering the rate of growth. McKinney suggests that this delay in foetal brain growth in humans (25 days longer than in extant monkeys) "seems to have cascading effects on neuronal complexity by prolonging the development of individual neurons, allowing more complex dendritic and synaptic outgrowths and connections."

If delaying foetal brain growth is the basis of increasing brain complexity, then what mechanism causes this prolongation? According to Deacon and others, it is the timing and duration of neuronal generation that determines adult brain size and complexity (Deacon 2000; Finlay & Darlington 1995). The later the onset of neurogenesis and the longer its duration, therefore, the larger and more complex the resulting structure. This is because the longer period of time before neuron production commences allows more mitotic cycles for the production of stem cells to occur. Moreover, the later a neuron's birth date, the further it migrates, the higher the laminar position it finally occupies, and the more complex its connectivity (McKinney 2000). Changes in the expression of regulatory genes such as homeobox genes may therefore alter the proportion of late-maturing embryonic stem neurones (Chaline 1998). In this case, "the ultimate heterochronic event underlying human brain evolution would be traceable to mutations in (or altered expression of) homeotic genes" (McKinney 2000).

In addition, it is well recognised that within primates the period of postnatal brain growth relative to prenatal is progressively lengthened, with humans having the most prolonged postnatal period of continued maturation (Finlay & Darlington 1995; Deacon 2000). Bogin has even argued that childhood and adolescence are developmental stages unique to humans (Bogin 1999). Importantly, this delay in brain maturation results in both a larger brain (Finlay & Darlington 1995), and in the extension of dendritic and synaptic growth, so that the human brain has more interconnections among neurons than the brains of other primates (Gibson 1991). Langer points out that, relative to other primates, humans, as well as having prolonged and accelerated cognitive and intellectual development (hypermorphosis), have retarded physical and physiological development (except of course, of the brain) (neoteny), allowing for a longer period of dependency and cognitive and social learning and maturation (Langer 2000). Deacon argues that both of these changes could result from a heterochronic shift in the time course of the expression of segmental genes.

Is this model compatible with epigenetic theories of evolution? These theories emphasise the continuous interaction of the environment with the biology of the individual. Epigenetic theories view a developing organism's response to environmental changes as a mechanism for phylogenetic change (Bjorklund & Pellegrini 2002). This is important both in terms of the social brain hypothesis and the argument for evolving cortical connectivity upon which it is based. Synaptic plasticity is an inherent feature of the modern human brain, and increasingly, research is suggesting that behavioural novelty may influence brain evolution (Bateson 1988; Gottlieb 1987; 2000; see Bjorklund & Pellegrini 2002 for a review). Advocates of epigenetic theory are at pains to point out that the mechanisms they propose are not Lamarckian, but are in keeping with the "modern synthesis," in that evolution is still conceived of as changes in gene frequencies in populations of individuals. If, as these authors argue, the benefits accrued by the individual in terms of synaptic reorganisation can lead to adaptive genetic changes in descendants, then one could hypothesise that heterochronic prolongation of brain maturation has served to escalate the potential for epigenetic change in brain evolution. In other words: A longer period of synaptogenesis and remodelling allows for increasing plasticity of networks; and this in turn increases the degree to which epigenetic effects can play a role. This might explain how the social environment became the driving force in the evolution of cortical connectivity and the social brain. One might speculate that such a process might have latterly been responsible for the explosion in neural, cognitive, and cultural complexity during the last 60,000–100,000 years.

Finally, a note of caution. It may be that heterochronic mechanisms are too blunt an instrument to explain the evolution of cortical connectivity and the social brain. It may be that sequential hypermorphosis can account for the increase in primate brain size and cortical surface area as demonstrated by Finlay and Darlington (1995), but that the evolution of connectivity involved more complex mechanisms. Grove and others have shown that there is a morphogenic gradient of growth factors across the cortex that is translated into distinct fields of gene expression (Fukuchi-Shimogori & Grove 2001). These "patterning" genes may include *Emx* and *Pax6* (Mallamaci et al. 2000). One of the referees on this paper, Jack Price of the Institute of Psychiatry (London, UK), has suggested that evolutionary changes in the extent of cortico-cortical connectivity may have resulted from changes in the sequential nature of cortical wiring. He points out that in mammalian nonprimates, cortical areas develop and connect more or less synchronously (e.g., in the rodent embryo, the hippocampus and the neocortex and their connections develop almost synchronously), while in primates – and in humans in particular – developmental events become asynchronous (e.g., in the 19 week human embryo, the hippocampus is highly differentiated in contrast to the neocortex, which is still undifferentiated [Hevner & Kinney 1996]). Thus, he argues, within the primate lineage the development of some cortico-cortical connections could become contingent upon others. Finally, Price stresses the point that the emergence of asynchrony and contingent events in neurodevelopment pre-dated the first humans, appearing first in earlier primate ancestors. Asynchrony and contingent events were therefore not unique to hominid ancestors and cannot alone account for the massive advances that characterised human cognitive descent.

In terms of the evolution of cortical connectivity, one might speculate whether heterochronic mechanisms may have played a role (at a molecular level) in the timing of expression of individual developmental genes, thereby altering the sequencing of cortical wiring. Is it possible, for example, that a relative delay in the expression of genes determining neocortical development might account for the differences in differentiation between the neocortex and hippocampus in the 19 week embryo? If so, then the emergence of asynchrony and contingent events within the primate ancestry may have depended upon heterochronic mechanisms. And that these features pre-dated the first hominids is consistent with the hypothesis that the social brain began to evolve earlier during primate descent.

Finally, one might speculate that the emergence of asyn-

chrony and contingent events during primate cortical evolution was associated with increasing degrees of vulnerability and increasing potential for insult. Since these mechanisms of change were most radically manifest in the human line, it was in the hominid brain that insults were most likely to occur.

9.2. Evolutionary ontogeny of schizophrenia

How does this discussion of the evolutionary ontogeny of the brain inform our understanding of schizophrenia? Can concepts such as heterochrony and sequential hypermorphosis enhance our understanding of this disorder? And are they useful concepts in terms of an evolutionary theory of schizophrenia? These are important questions given that schizophrenia is widely accepted as a disorder of neurodevelopment.

First, to recap the pathological findings that are well supported in schizophrenia. In section 6.2, I cited Harrison's review (Harrison 1999) arguing that the main findings of smaller cortical neurons, reduced axospinous processes and arborisation, reduced neuropil, denser packing of neurons, and decreased synaptic marker proteins, all pointed towards later ontogenic processes such as arborisation, synaptogenesis, and apoptosis. I also argued that the high occurrence of morphological defects such as abnormal dermatoglyphics and craniofacial dysplasias suggest that neurogenesis may be disturbed. I proposed a scenario where abnormal neurogenesis led to a cascade of disturbances in subsequent ontogenic phases. Speculations about the molecular basis of abnormal neurogenesis are premature as we have little idea of potential candidates. For example, we cannot exclude the *Emx-1* and *Emx-2* homeobox genes on the grounds that mutations result in gross structural defects such as agenesis of the corpus callosum and schizencephaly. This is because schizophrenia may be a consequence of gene sequence variants that result in changes in gene expression (rather than mutations). There are others such as *BF-1, Caspases-3* and *-9,* and *POU 111* gene family (including *Brn-1* and *-2, SCIP,* and *Oct-6* genes) that could also be implicated. Indeed, *Oct-6* gene, usually expressed in embryonic stem cells, has shown increased expression in the temporal lobes and hippocampi in patients with schizophrenia (Ilia et al. 2002). Weickert and Weinberger have identified *POU 111* class genes as candidate molecules (Weickert & Weinberger 1998). I would also consider *Caspase-1* and *-3,* both involved in founder cell apoptosis and thus influential in neurogenesis (Haydar 1999; Kuida 1998). Interestingly, certain caspases map to chromosome 11q22, which is adjacent to a known schizophrenia gene locus, 11q23. In the event that neurogenesis is the "site" of initial insult, it would seem intuitive that pathologies of the synapse and neuropil represent secondary effects of the primary disturbance. However, it is just as likely that a number of genes regulating different phases of development might be implicated in different individuals, given the extraordinary heterogeneity of pathological, morphological, and clinical findings in this disorder. New methods, such as microarray technology, are providing powerful research strategies for identifying genes involved in synaptic processing in schizophrenia (Bunney et al. 2003; Mirnics et al. 2001). It is likely we shall arrive at a better understanding of the molecular basis of this disorder in the not too distant future.

If genes regulating neurogenesis were implicated in schizophrenia, one would anticipate that the disorder might be characterised by an altered trajectory of neurodevelopment. Is there evidence for this? A number of authors have suggested that there is delayed brain maturation in schizophrenia (James et al. 1999; Saugstad 1994; 1998). Delayed motor and language development (Cannon et al. 2002a; Isohanni et al. 2001), earlier male onset, and preponderance of pathomorphological changes (in accordance with the male slower rate of maturation) (Flaum et al. 1995; Saugstad 1999) and high levels of fluctuating asymmetry (Gruzelier 1999; Mellor 1992) all suggest a relative delay in neurodevelopment. Later milestones increase risk for schizophrenia (Isohanni et al. 2001), while late maturing male adolescents have been shown to score higher than early maturers on measures of schizotypy (Gruzelier & Kaiser 1996). Several authors have shown that the average age of puberty has been declining over the last few centuries (Bogin 1999; Kaplan et al. 2000) and Saugstad relates this to the reduction in "the most malignant non-paranoid forms (of schizophrenia)" (Saugstad 1998). He argues that this relationship is to be expected if schizophrenia is conceptualised as a disorder of delayed brain development.

Several authors have responded to these observations (about delayed brain development in schizophrenia) by attempting to invoke heterochrony in the genesis of the disorder (Bemporad 1991; Crow 1995b; Feierman 1994). In particular, they have suggested that schizophrenia may be related to a failure of neoteny. There are models for the role of heterochrony in other neurodevelopmental disorders (Wilson 1988). Brüne has examined the evidence for and against heterochronic mechanisms in schizophrenia and concludes that neither neoteny nor sequential hypermorphosis alone sufficiently explains the aetiology of schizophrenic disorders (Brüne 2000). However, I think there is some worth in considering certain morphological observations in schizophrenia which may, I would argue, suggest a disturbance of heterochronic mechanisms during cortical evolution. Specifically, data on head and brain size across the developmental life cycle are intriguing.

A meta-analysis of brain and cranial size in adults with schizophrenia found that there is a small but significant reduction in brain size compared with controls, while extracranial size is nonsignificantly *increased* (Ward et al. 1996). In another study, Bassett and colleagues found significantly increased head circumference (HC) in male patients and, as one possible explanation, they state "head size increases may be due to overgrowth, secondary to pleiotropic expression of a developmental gene" (Bassett et al. 1996). While reduced brain size is likely to reflect the effects of excessive pruning of abnormal synapses, increased HC reflects the limit of brain growth during development (and prior to onset of pruning). In terms of earlier development, the only data on cranial and brain size in schizophrenia are those from measures of HC at birth (Cantor-Graae et al. 1998; Kunugi et al. 1996; McNeil et al. 1993). These studies show significantly reduced HC at birth in those who subsequently develop schizophrenia. In the study by Cantor-Graae and colleagues, the patient group showed smaller HC at birth, but increased HC in adulthood compared with controls. Most authors conclude that these findings point towards delayed cerebral development in utero. Taken in conjunction with findings of craniofacial dysmorphogenesis and abnormal dermatoglyphics, Wad-

dington and colleagues identify foetal weeks 9 to 15 as the likely timing of insult (Waddington et al. 1999). Importantly, if HC is smaller at birth but bigger in adulthood compared with controls, and if maximal brain size determines HC, we can surmise that *sometime prior to the onset of pruning, the schizophrenic brain was larger than normal.* Of course, larger size does not imply normal architecture. In this light, the finding in the Edinburgh High Risk Study of relatively increased brain size premorbidly in male high-risk subjects who later developed psychosis is not surprising (Johnstone et al. 2002).

Figure 6 attempts to graphically illustrate the hypothesised neurodevelopmental trajectory, based on these data, in schizophrenia compared with normal. I would argue that this trajectory is reminiscent of the pattern that characterises *sequential hypermorphosis.* Is this merely coincidence, or is it feasible that the disorder represents a disturbance of heterochronic processes implicated in the evolution of the social brain? If the answer is yes, then, in the light of comments made at the end of section 9.1, it would seem logical that these disturbances served to alter the pattern of expression of individual developmental genes across the cortical plate. This may be possible to test if future methods of research allow us to map the sequence of gene expression in the developing cortex of individuals destined to have schizophrenia compared with normal individuals.

I would therefore speculate that, some time prior to the migration of *Homo sapiens* out of Africa 150,000–100,000 years ago, one or more genetic events gave rise to a phenotype characterised by disturbances in the sequencing of expression of cortical developmental genes. These "schizophrenic genes" were perhaps not regulatory genes themselves, but rather were closely associated with regulatory genes directly involved in heterochronic processes and responsible for the evolution of the social brain. Thus, the maladaptive "schizophrenic genes" may have survived in the genome because of their association with adaptive social brain genes.

In summary, then, I would argue that the hominid social brain evolved in part through heterochronic processes including sequential hypermorphosis. I would also speculate that the neurodevelopmental pattern that characterises schizophrenia represents a disturbance of normal heterochronic processes; and that therefore it seems likely that the genetic basis of the disorder involves a disturbance of regulatory genes governing the timing of neurodevelopment. Clearly, this disturbance results in a cascade of abnormal developmental events that interact with epigenetic factors, leading to abnormal synapses and gross pruning during adolescence. The circuits most severely affected are those that evolved most recently, and they comprise the connected regions of the social brain. Finally, I think it is sobering to consider that the mechanism "employed" by evolution to allow for the expansion and reorganisation of the social brain, which itself was demanded by an increasingly complex social environment, also rendered the organism extremely vulnerable to both genetic and environmental insult and subsequent disorder.

10. Concluding comments and outlook

I have argued that schizophrenia reflects the severe end of a spectrum of abnormal cortical connectivity that appeared in our hominid ancestors approximately 150,000–100,000 years ago. The disorder can be seen as a costly trade-off at two separate stages in our descent:

First, the significant advantages conferred by the evolution of complex circuitry as a substrate for metarepresentation and social cognition rendered the early hominid brain vulnerable to genetic and environmental insults (which have yet to be fully understood). Evidence of an early "metamind," as well as a trend towards increasing specialisation of FT and FP circuits in our nearest relatives, the apes, suggests that these changes evolved during the period 18–5 mya. The ontogenetic mechanism that facilitated this advance in intrahemispheric connectivity was sequential hypermorphosis. Thus, under selective pressure to evolve a brain well adapted to the complex social environment in which they lived, our ancestors experienced progressive prolongation of brain maturation. For some reason, these changes were accompanied by a particular sensitivity or vulnerability in the developmental processes of these cortical

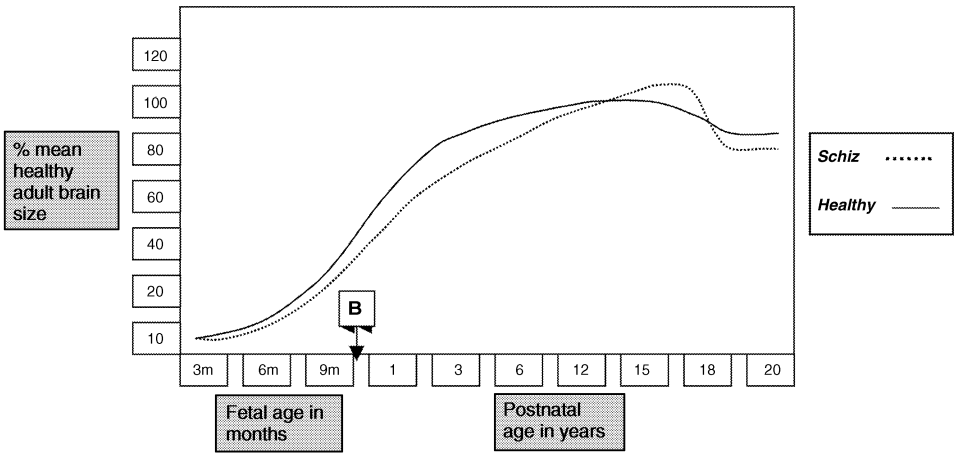


Figure 6 (Burns). Graphic illustration of hypothesised trajectory of brain development (size) from fetus to adult in schizophrenia compared with healthy individuals. (Adapted from Lemire et al. 1975). (B = birth).

circuits. This process occurred in the apes as well, but to a much lesser degree, leaving their ancestors' brains less vulnerable to insult. This could account for the apparent absence of psychosis in other primates.

The second trade-off that gave rise to the schizophrenic genotype and is responsible for its persistence in the human genome, occurred during the period 150,000–100,000 years ago, prior to the migration of *Homo sapiens* out of Africa. Importantly, this change or series of changes occurred gradually (and against a background of similar evolutionary change in hominids) and therefore did not represent a speciation event. In some individuals, changes in the morphology or expression of regulatory genes involved in the timing of neurodevelopment may have altered the developmental trajectory of vulnerable FT and FP cortical circuits, resulting in aberrant connectivity in the social brain. This was or is expressed phenotypically as schizophrenia and related disorders. It is likely that those individuals with the greatest expression of the genotype perished quickly in the ancestral environment. The presence of a continuum of variation in the expression of the genotype meant that some individuals (with perhaps a milder degree of dysconnectivity and subsequent pruning that actually enhanced cognition) manifested special cognitive abilities, while others manifested schizophrenia. The genotype itself is unlikely to confer a reproductive advantage on the schizotype, but because of its association with genes that code for the development of the social brain in the species, the disorder has persisted in the human genome.

Psychosis is therefore one, and maybe the greatest, of the prices paid by humans for evolving complex cognitive and social abilities. It is precisely because we have the capacity to have a ToM and to function in a socially appropriate manner, that we also have the capacity for aberrant cortical connectivity and an illness such as schizophrenia. One benefit of harbouring this potentially disastrous genotype in our human gene pool is that in some cases individuals, occupying a tamer position in the spectrum, may exhibit unusual creativity, brilliance, and iconoclasm. It is quite likely that these individuals are among those responsible for pioneering and creating the great artistic, technological, and cultural advances of human history.

Henry Maudsley, one of the fathers of British psychiatry, toyed briefly with eugenic principles (Crow 1995c), but later admitted:

> To forbid the marriage of a person sprung from an insanely disposed family might be to deprive the world of a singular genius or talent, and so be an irreparable injury to the race of men. . . . If, then, one man of genius were produced at the cost of one thousand or fifty thousand insane persons, the result might be a compensation for the terrible cost." (Maudsley 1908)

Finally, I wish to propose a number of ways in which this evolutionary hypothesis might inform future schizophrenia research and clinical practice:

1. In terms of molecular research, regulatory genes that control the timing of neurodevelopment, and in particular the timing of neurogenesis and stem cell differentiation, should be considered as candidates in schizophrenia. So too should genes known to interact with and modulate these regulatory genes. Furthermore, it may transpire that the disorder is caused by altered expression rather than mutation of genes. Therefore, the search for the genes for schizophrenia is sure to be a Herculean task. It is also likely that if such a genotype is identified, it will be implicated in only some people with schizophrenia – the phenotypic heterogeneity suggests that multiple factors, both genetic and environmental, may disturb neurodevelopmental processes, thus giving rise to psychosis.

2. More speculatively, since I have argued that the social brain and schizophrenia emerged gradually from an evolutionary process already present in hominoid ancestors, I would anticipate that both human-specific cognition (e.g., language) and schizophrenia have a molecular basis in genes we already share with extant apes. I would predict that what separates us cognitively is differences in gene expression rather than differences in gene composition. For this reason, the search for both the genes that make us human and for those that cause schizophrenia is likely to be far more complicated than a mere contrasting of human and chimpanzee genomes in the not too distant future (see Gagneux & Varki [2001] for a review).

3. In terms of future imaging in schizophrenia, more studies are needed of the social brain and the exact nature of its impairment in the disorder. Techniques such as DT-MRI and fMRI may help us to identify both structural and functional deficits within the FT and FP circuitry. fMRI studies using paradigms that activate different components of social cognition should be a priority. For example, further studies examining the neural basis of self-recognition may help increase our understanding of the neurology of social cognition. Also, specific cortical connections (such as the UF and AF) merit further attention, and new methods of scanning and data processing may help unravel the core pathologies that characterise the brain in schizophrenia.

4. New imaging techniques could also be used effectively in comparative primate studies to further our understanding of brain evolution, and specifically the changes I have hypothesised in the social brain. In this endeavour, I would suggest that DTI studies of extant apes might be particularly informative, providing critical data on white matter connectivity, hitherto inaccessible with standard MRI methods. In terms of the "social brain hypothesis," I would predict such data would show a progressive phylogenetic increase in the density of FT and FP tracts in primates.

5. And lest we forget that all meaningful research should have direct clinical implications for those whom we find intellectually interesting, I would suggest that this model can inform our management of patients in two important ways. First, if the pathologies we see in the brain have their origins as early as midgestation, and if subsequent ontogenic events constitute a cascade of aberrant developmental processes all sensitive to epigenetic factors, then surely, as many authors have suggested, *prevention* is the main avenue for intervention. We cannot hope to prevent early genetic effects (unless genes can be identified in utero), but later, damaging developmental events could be retarded and the trajectory of aberrant neurodevelopment corrected by means of early detection and intervention. These interventions might include dietary, pharmacological, and psychosocial measures, and may serve to reduce or even abolish vulnerability to subsequent disorder. And second, this model highlights the importance of social deficits in schizophrenia, and consequently a large part of our clinical and research effort should be dedicated to understanding and confronting the social, cultural, economic, and political obstacles that face our patients. If these vulnerable individuals, who have particular difficulties with comprehending and responding to the social world, are isolated, stigma-

tised, and subjected to societal prejudices, then they have no hope of averting a lifelong struggle with incapacitating mental illness.

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Open Peer Commentary

Genes can disconnect the social brain in more than one way

André Aleman and René S. Kahn

Rudolf Magnus Institute for Neurosciences, Department of Psychiatry, A01.126 University Medical Center, 3584 CX Utrecht, The Netherlands.
a.aleman@azu.nl r.kahn@azu.nl

Abstract: Burns proposes an intriguing hypothesis by suggesting that the "schizophrenia genes" might not be regulatory genes themselves, but rather closely associated with regulatory genes directly involved in the proper growth of the social brain. We point out that this account would benefit from incorporating the effects of localized lesions and aberrant hemispheric asymmetry on cortical connectivity underlying the social brain. In addition, we argue that the evolutionary framework is superfluous.

Although several authors have maintained that schizophrenia is primarily a cognitive disorder (Elvevag & Gold 2000), there is an increasing awareness that abnormalities in the processing of social (including emotional) information are at the core of the syndrome (Pinkham et al. 2003). Indeed, evidence that brain systems underlying social cognition are compromised in schizophrenia is accumulating at a high rate. For example, structural and functional abnormalities of the amygdala have been reported (Gur et al. 2002; Hulshoff Pol et al. 2001) and deficits in emotion processing have been shown to relate to social dysfunction (Hooker & Park 2002). In addition, we recently observed abnormal trustworthiness evaluation in patients with schizophrenia (Baas et al. 2004), showing the same pattern as has been described in patients with bilateral amygdala lesions and in patients with autism (Adolphs et al. 2001). Trustworthiness evaluation on the basis of facial appearance of others plays a significant role in social interaction. Furthermore, ventromedial prefrontal volume reductions have been shown to relate to social dysfunction in schizophrenia (Chemerinski et al. 2002).

Taking this into account, we welcome Burns' hypothesis on the role of dysfunctional genes that are closely associated with regulatory genes directly involved in development of the social brain in the pathogenesis of schizophrenia. Indeed, this hypothesis will be a potentially useful heuristic in planning studies regarding the genetic basis of neuronal processing deficiencies in schizophrenia. However, research should take a broader approach than that outlined in the target paper. The target article devotes much attention to theory of mind (ToM) problems in schizophrenia and to the role of cortical connectivity in social information processing. However, with regard to ToM dysfunction, it is important to note that several studies have failed to find a relation between ToM dysfunction and symptoms of schizophrenia, such as delusions (Drury et al. 1998; Langdon et al. 1997). Moreover, we question the need of invoking ill-defined concepts such as "existential ToM" and "cognitive fluidity." In addition, the conceptualization of the human mind as "a fluid and connected entity that allows for integration of specialised information in the formation of abstract and symbolic thought" (target article, sect. 4, para. 3) might not be a novel proposal as suggested by the author, but can be found already in the writings of Karl Lashley and Donald Hebb.

Intact cortical connectivity is central to the adequate functioning of the social brain. Indeed, cortical activation is intimately tied with the neuronal connectivity, and more than 99% of the axons in the white matter serve corticocortical and transcallosal communication. However, the latter aspect of cortical connectivity, that is, transcallosal communication, remains largely neglected in the target article, but might yield important clues to the pathophysiology of schizophrenia. A recent study observed focal white matter density changes in 159 patients with schizophrenia who were compared with 158 matched control subjects, reflecting reduced interhemispherc connectivity (Hulshoff Pol et al. 2004). Abnormalities in lateralization have consistently been documented in schizophrenia (Sommer et al. 2001) and have been hypothesized to arise from a reduced inhibitory influence of one hemisphere over the other. Reduced hemispheric asymmetry has not only been reported for typical "left-hemisphere" tasks, such as language production, but also for typical "right hemisphere" tasks, such as perception of emotional chimeric faces (David & Cutting 1990). Deficits in functions typically mediated by the right hemisphere, such as processing of emotional prosody, have also been reported in schizophrenia (Ross et al. 2001). Research should therefore also be aimed at investigating the genetic basis of hemispheric connectivity and its role in dysfunctional social cognition in schizophrenia. In addition, localized structural lesions can also affect functional connectivity, as is the case with the amygdala. For example, Grossberg (2000) proposed a model in which emotional centers of the brain, in particular the amygdala, interact with sensory and prefrontal cortices to generate affective states and elicit motivated behaviors. In this model, a defective amygdala can even lead to hypofrontality.

Finally, the evolutionary framework in which Burns' hypothesis is embedded might be superfluous. Indeed, the same five implications of his hypothesis for schizophrenia research, which are formulated at the end of the target article, can be deduced from his social neuroscience approach when it is stripped away from the highly speculative evolutionary scenario. Lewontin (1998) has questioned the possibility of a scientific theory regarding the evolution of higher human cognitive abilities. One of the major serious problems Lewontin notes in the reconstruction of human cognitive evolution is that we do not have any close relatives, nor do we know who our ancestors are. He points out that the chimpanzee is estimated by evolutionary theorists to be separated by 20 million years of evolution from humans, and that we are not even sure that Neanderthal man, classified together with us in the species *Homo sapiens,* is a direct ancestor rather than a parallel line that died out without issue. With regard to the target article, the evolutionary theorist must convince us that there was a heritable variation for social cognition in our remote ancestors, when the human species was still evolving into its present form, and that those who possessed this ability in the remote past left more offspring by virtue of that ability. Furthermore, any imaginative reconstruction of that advantage must show that individuals or family groups, rather than the species as a whole, had such an advantage. The putative mechanism of natural selection operates within populations to increase the frequency of some types and decrease others through differences in reproductive rates of individuals.

The fact that psychosis seems to be a de novo state, with no homologies in other known organisms, questions the relevance of an evolutionary approach. We should not confuse plausible stories with scientific theories or evidence. Or, as Lewontin (1998) puts it: "There is no end to plausible storytelling."

Schizophrenia is a disease of general connectivity more than a specifically "social brain" network

Conrado Bosman, Enzo Brunetti, and Francisco Aboitiz

Departamento de Psiquiatría and Centro de Investigaciones Médicas, Facultad de Medicina, Pontificia Universidad Católica de Chile, Marcoleta N 387, 2 Piso, Santiago 1, Chile. **cbosman@med.puc.cl**
ebrunett@med.puc.cl **faboitiz@puc.cl** **www.neuro.cl**

Abstract: Dysfunctions of the neural circuits that implement social behavior are necessary but not a sufficient condition to develop schizophrenia. We propose that schizophrenia represents a disease of general connectivity that impairs not only the "social brain" networks, but also different neural circuits related with higher cognitive and perceptual functions. We discuss possible mechanisms and evolutionary considerations.

In his target article, Burns provides an excellent opportunity to evaluate the evolutionary aspects of schizophrenia. The idea of schizophrenia as a costly trade-off for the acquisition of a high degree of connectivity and social abilities gives a probable explanation for the origins and maintenance of this disease, despite the fact that it is associated with lower fecundity. In addition, Burns places the development of a specialized network regulating social behavior as one of the most important evolutionary steps in the acquisition of schizophrenia by hominids. However, besides the impairment of the "social brain," alterations in other cognitive and perceptual functions are well demonstrated and not explained merely by the dysfunction of the neural circuits implicated in social abilities. Moreover, many of the cognitive functions that are impaired in schizophrenia are implemented by large-scale networks in the brain. For that reason, we consider that schizophrenia may represent, more than the dysfunction of a specific network, a disease of general connectivity that involves different networks supporting several cognitive and perceptual processes.

There is a growing corpus of evidence in concordance with the concept of schizophrenia as a network disease. For example, two recent microarray studies demonstrated a decreased expression of genes related to regulation and maintenance of the presynaptic secretory machinery (Mirnics et al. 2000) and myelination (Hakak et al. 2001) in the prefrontal cortex, suggesting that large-scale cortical and subcortical networks may be impaired in two ways: On the one hand, there may be a deficient synaptic connectivity between neurons, and on the other hand, there may be deficits in axonal transmission in these large-scale networks. Moreover, abnormalities in different types of inhibitory GABAergic interneurons in different areas of the brain (e.g., corticolimbic circuitry) have been described (Benes & Berretta 2001). These neurons may be critical for the maintenance of reverberatory circuits in large-scale networks (Freund 2003), which would support the concept of a general disconnection syndrome in schizophrenia. As a consequence, a failure in the implementation of large-scale networks involving corticocortical and corticosubcortical circuits might provide a general mechanism that impairs not only circuits related to social behavior but also circuits involved in other higher cognitive functions.

In this context, the question arises of how the connectivity of these large-scale networks works in the generation of higher cognitive functions. Phillips and Silverstein (2003) raise an interesting possibility. They define this process as "cognitive coordination" and point to the idea of a regulation of perceptual mechanisms by cognitive functions such as working memory and attention, which permits the integration and contextualization of perceptual information. These processes may be integrated by the action of neurons belonging to anteroposterior large-scale corticocortical networks. The exact nature of this regulatory mechanism is under discussion, but there is growing evidence supporting the hypothesis of integration by means of neuronal synchrony (Engel et al. 2001). Synchronic, oscillatory neural activity is observed at multiple spatial scales (from neuron-to-neuron communication to large-scale networks) and is associated with a variety of perceptual and cognitive processes, including attentional tasks and working memory (Fries et al. 2001; Tallon-Baudry et al. 1998; Varela et al. 2001). Moreover, the impairment of large-scale, high-frequency rhythmic neuronal synchrony has been related to perceptual and cognitive deficits observed in schizophrenic patients (Kissler et al. 2000; Spencer et al. 2003). Although the anatomical localization of this large-scale neuronal synchronic activity has to be precisely determined, fMRI studies based on the measure of effective connectivity between different areas of the brain in normal subjects (Büchel & Friston 1997) and in schizophrenic patients (Schlosser et al. 2003) point to the activation of fronto-temporoparietal cortical networks during cognitive and perceptual tasks.

Could the development of these networks be an important evolutionary step to the appearance of schizophrenia? Probably yes, because these networks provide a high degree of behavioral plasticity and the possibility of generating different strategies to resolve conflicts (Miller & Cohen 2001). Therefore, a selective pressure for the optimization of these primitive networks is conceivable. This optimization could be partly achieved by means of the establishment of highly connected and myelinated networks between the anterior and posterior brain (Aboitiz et al. 2003). In hominid evolution, the elaboration of these networks, associated with an increasing brain size, led to the development of sophisticated social behavior and language (Aboitiz & García 1997a; 1997b). The implementation of most top-down processes by these networks, plus the protracted neural development necessary to make up these networks, may have placed hominids in a vulnerable position to suffer destabilizing insults leading to a disorganized connectivity. The diverse symptoms of schizophrenia, including perceptual, cognitive, and social impairments, may have arisen as a consequence of the developmental fragility of these complex networks. Perhaps this explanation describes best the high heterogeneity of symptoms observed in this disease.

Summarizing, we agree with Burns in that schizophrenia is probably a costly trade-off of increasing brain size and complexity. We also propose that the development of anterior-posterior networks regulating top-down and bottom-up processes was very important in the development of high behavioral plasticity. This is not to exclude the importance of corticosubcortical, especially corticolimbic networks. High-frequency neuronal synchrony may operate as a binding mechanism for establishing and maintaining the large-scale coordinated activity that is essential for several aspects of perception, cognition, and social behavior. A disruption of mechanisms related to the establishment of these networks might be at the basis of schizophrenia, promoting instability of these dynamic ensembles. In our view, more than a disease of the social brain, schizophrenia is a disease of general connectivity, which is reflected in an impairment of integrative processes in perception, cognition, and social behavior.

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Understanding the symptoms of "schizophrenia" in evolutionary terms

Martin Brüne

Centre for Psychiatry and Psychotherapy, University of Bochum, 44791 Bochum, Germany. **martin.bruene@ruhr-uni-bochum.de**

Abstract: An evolutionary theory of schizophrenia needs to address all symptoms associated with the condition. Burns' framework could be extended in a way embracing behavioural signs such as catatonia. Burns' theory is, however, not specific to schizophrenia. Since no one single symptom exists that is pathognomonic for "schizophrenia," an evolutionary proposal of psychiatric disorders raises the question whether our anachronistic psychiatric nosology warrants revision.

Burns' "social brain" hypothesis of schizophrenia sets up new standards of evolutionary thinking in psychiatry by integrating evolutionary ontogeny, cerebral connectivity, psychopathology, and molecular genetics. A couple of additional issues relating to a possible evolutionary background of schizophrenia are worth mentioning.

Firstly, referring to Burns' pleiotropy model of schizophrenia, it is by no means clear that the alleged adaptive advantage of heterozygous carriers of genes predisposing to schizophrenia would lie within the realm of the nervous system (i.e., cognition, emotion, behaviour). Huxley et al.'s (1964) proposal, for example, originally suggested that such an advantage could also be unrelated to the CNS. This possibility has been discussed in relation to other genetically transmitted diseases that primarily affect the nervous system, such as Tay-Sachs disease and Huntington's disease (Polimeni & Reiss 2003). With respect to schizophrenia, Yovel et al. (2000) have shown a greater activity of natural killer cells in patients with schizophrenia, a finding that could buttress earlier hypotheses of a greater resistance in schizophrenic patients and their relatives against infectious diseases, and therefore deserves further consideration.

Secondly, an evolutionary theory of schizophrenia ought to account for all possible symptoms associated with the condition. Whereas most evolutionary hypotheses, including Burns' theory, focus on Schneiderian first-rank symptoms such as thought insertion, thought withdrawal, or delusions of mind-reading, they relatively neglect psychomotor symptoms – for example, catatonia. Burns rightly highlights the putative role of so-called spindle cells located in the anterior cingulate cortex (ACC) that only recently emerged in the great apes and humans but have been found absent in lesser monkeys (Nimchinsky et al. 1999). Although the exact function of spindle cells is not known, they are probably involved in complex tasks of motor control and control of cognitive impulsivity. Bilateral lesions of the ACC, on the other hand, lead to akinetic mutism and insufficient suppression of automatic subroutines (Paus 2001). These pathologies strikingly resemble catatonic symptoms such as stupor, mutism, and stereotypies (Brüne 2004a). In extension to Burns' theory, a second cell type found in the prefrontal and temporal cortex in primates' brain areas that constitute parts of the social brain may shed further light on the origin of catatonic symptoms. Rizzolatti and coworkers (Rizzolatti & Arbib 1998; Rizzolatti et al. 2002) have described what they have called "mirror neurons" located in the ventral premotor cortex of monkeys. These cells have also been found in Broca's area and the superior temporal sulcus in humans. Their functional significance clearly lies within the social domain: they are selectively active when observing hand and mouth movements in conspecifics and when imitating the observed behaviour (Rizzolatti & Arbib 1998). The existence of mirror neurons in Broca's area of the human brain has fuelled the hypothesis that human language evolved in the first place from gestural communication, and that the human Brodmann area 44 is also involved in action understanding and imitation (Rizzolatti et al. 2002). I have speculated elsewhere that a disinhibition of mirror neuron activity could be involved in a subset of catatonic echo phenomena, namely echopraxia, echolalia, and automatic obedience, as well as *mitgehen* and *mitmachen* (Brüne 2004a). To my knowledge this hypothesis has not yet been empirically tested.

Third, there is a more serious problem with evolutionary hypotheses of schizophrenia in general. It follows from what I have outlined above – in line with Burns' proposal – that a symptom or syndrome-based approach to psychosis in evolutionary perspective is crucial to the understanding of schizophrenia. According to Bentall et al. (1988), however, not a single one sign or symptom exists that is specific or pathognomonic to schizophrenia. Although it has been suggested that the prevalence rate of "core schizophrenia" is cross-culturally similar (Jablensky 2000) and thus relatively independent of environmental influences (which would support a common origin of the disorder), we simply do not know whether schizophrenia or its subtypes represent true "disease entities," or, as Burton-Bradley (1990) once put it, whether our diagnostic system is too narrow for a valid cross-cultural comparison. The assertion of cross-culturally similar prevalence rates of schizophrenia is, however, vital for every evolutionary hypothesis that argues for compensatory advantages in heterozygous gene carriers, regardless whether favouring a pleiotropy model, as Burns does, or a single mutation model like Crow's (1995b). Burns' social brain theory of schizophrenia implicitly assumes that schizophrenia is a useful concept in cross-cultural perspective. On the other hand, I am wondering whether it is specific enough to schizophrenia. Functional impairments of social brain connectivity have similarly been described in bipolar affective disorder and in obsessive compulsive disorder (OCD). Brain imaging studies in OCD, for example, have revealed an increased metabolism or regional blood flow in the orbitofrontal cortex, the anterior cingulate, the basal ganglia, and the thalamus (Saxena & Rauch 2000). Furthermore, in a functional brain imaging study using a symptom provocation paradigm in patients with OCD, Breiter et al. (1996) found a significant bilateral activation of the anterior and posterior orbital gyri, the superior, middle, and inferior frontal gyri, the anterior cingulate cortices, the temporal cortices, the right caudate and left lenticulate, as well as in the left insula and bilateral amygdala – precisely those brain structures which Burns identifies as being involved in the pathogenesis of schizophrenia.

I am tempted to say that virtually all psychiatric disorders fall into the category of "social brain disorders." If we as clinicians would dare abandon the anachronistic psychiatric nosology (this is what we already do in clinical practice, e.g., regarding psychopharmacological treatment), Burns' framework of social brain evolution could be a significant contribution to an empirically testable evolutionary conceptualisation of the dimensions of psychiatric disorders.

Language and asymmetry versus the social brain – where are the testable predictions?

T. J. Crow

SANE POWIC, Warneford Hospital, Oxford OX3 7JX, England.
tim.crow@psychiatry.oxford.ac.uk
www.psychiatry.ox.ac.uk/powic/index.htm

Abstract: I agree with Burns that an evolutionary theory is required, but I question his multifactorial premise. The arguments for an evolutionary theory are stronger, and one that is more precise than that presented by Burns has already been formulated. This theory, that schizophrenia is "the price that Homo sapiens pays for language," (Crow 1997a; 2000b, 2004c), generates testable predictions absent from Burns' presentation.

I concluded that an evolutionary explanation was necessary when I convinced myself (Crow 1984) that the theory that schizophrenia is due to the spread of a slow virus between genetically predisposed individuals (Crow 1983) was wrong (for data and argument see Crow & Done [1986]. Not only is there no evidence for

an exogenous virus as an aetiological agent, but there is no substantive evidence for any other environmental precipitant (e.g., Crow 1995a; 2000a). Only when this is apparent is one forced to consider an evolutionary explanation. But Burns does not exclude an environmental influence. In his abstract he refers to schizophrenia as "multifactorial but highly genetic" and writes "sequential hypermorphosis . . . rendered the hominid brain vulnerable to genetic and environmental insults." He nowhere tells us what these "multifactors," other than genetic, or "environmental insults," are, and he thereby fails to constrain his thinking about the nature of the brain changes and their genetic basis.

I missed reference to Huxley et al. (1964), who drew attention to the paradox that schizophrenia is apparently genetic but associated with a fecundity disadvantage. The first two authors, Huxley and Mayr, are distinguished "architects of the modern evolutionary synthesis." But the answer they gave – that the disadvantage of schizophrenia is balanced by an advantage to the affected individual of resistance to wound shock or stress – is obviously in error, as Kuttner et al. (1967) were quick to point out. It makes more sense to suppose that the advantage of the gene, whether to close relatives or to the population as a whole, relates to a human psychological characteristic. Kuttner et al. listed three – intelligence, the capacity for complex social interactions, and language – and opted for the second, as does Burns in his use of the theory of mind concept.

I have discussed the concepts of "Machiavellian intelligence" and the "social brain" as precursors in primate evolution relevant to psychosis (Crow 1991; 1993b) but particularly since 1995 I have believed that Kuttner et al.'s third option – that the balancing advantage is language – generates a more precise and heuristic evolutionary theory (Crow 1993a; 1995d; 1996a). From this perspective I see Burns' theory as deficient in three areas:

1. It provides no explanation of the cortical changes. According to the language/asymmetry concept these are anomalies of development of the sapiens-specific "torque" from right frontal to left occipital (Crow 1990a; 1997b; 2004d; Crow et al. 1989; Esiri & Crow 2002). Burns writes of "dysconnectivity"; but dysconnectivity of what, and why? His Table 1 lists 19 putative neuropathological features of schizophrenia. I suspect that many are not robust (for a review of post-mortem findings see Esiri & Crow 2002). Which does Burns regard as primary?

2. It provides no explanation of the nuclear symptoms. According to the language/asymmetry hypothesis, thoughts spoken aloud and running commentary voices are activated neural engrams misidentified as the phonemes of perceived speech (i.e., relating to Wernicke's area and its nondominant homologue), while thought insertion, withdrawal, and broadcast are anomalies of the transition from thought to speech production (relating to neural transmission from right to left frontal, including Broca's area [Crow 1997a; 1998b; 2004c]).

3. It generates no genetic predictions. In section 9.2, Burns lists ten genes that either "cannot be excluded" or "might be implicated" (para. 2), but nowhere discusses how abnormal structure or function of any one of these genes follows from his theory, or how any such prediction (were it to be made) is to be tested.

By contrast, the language/asymmetry theory is based on the premise that the torque is the characteristic that defines the human brain (the Broca-Annett axiom – for a critique of the evidence for directional asymmetry in other primates which Burns relies on, see Crow 1998c; 2003; 2004a; 2004b) and predicts that the genetic variation relating to psychosis accounts for the variations in cortical structure. From evidence relating to sex chromosome aneuploidies, I predicted (Crow 1994) a gene for asymmetry in a region of homology between the X and Y chromosomes, and an association within families between sex and handedness (Corballis et al. 1996). The Xq21.3/Yp region of homology created by a duplicative transposition at 3mya (a candidate for the Australopithecus-*Homo* transition) from the long arm of the X to the short arm of the Y generated genetic change relevant to human characteristics, and this region has been subject to subsequent change eg an undated paracentric inversion. Within the region a gene pair (Protocadherin X and Y – PCDHX and PCDHY) is expressed in both forms in the human brain, including (at least for PCDHX) the germinal cell layer of the cerebral cortex (Priddle et al. 2002). The gene pair codes for cell surface adhesion (transmembrane) molecules that may act as axonal guidance signals. In comparisons with the sequence of the X linked gene (Pcdhx) in the great apes, the ectodomain of PCDHX and the cytodomain of PCDHY have been shown to be under positive selection – that is, selection for change – in hominid evolution (Crow & Williams 2004). These genes are in a new situation with respect to protection from X inactivation, and thus, gene expression (Crow 2002a). The PCDHX/Y gene pair is a candidate mechanism for the evolution of cerebral dominance and the origins of language, itself a problem for the classical gradualist account of speciation (Crow 2002b; Maynard-Smith & Szathmary 1995). My argument, therefore, is that the language/asymmetry theory of the origins of psychosis raises questions for evolutionary theory and generates predictions testable in brain structure and function, and their relationship to chromosomal and genetic changes that are known to have taken place in the hominid lineage. Unless it is more precisely formulated, the theory that schizophrenia is a disorder of the social brain leads to no such predictions.

Threat, safeness, and schizophrenia: Hidden issues in an evolutionary story

Paul Gilbert

Mental Health Research Unit, Kingsway Hospital, Derby DE22 3LZ, United Kingdom. **p.gilbert@derby.ac.uk**

Abstract: There is evidence that people with schizophrenia have difficulties in some (recently evolved) competencies for processing social information. However, a case can be made that vulnerabilities can also lie in (previously evolved) threat and safeness processing systems. Evolutionary models may need to consider interactions between genetic sensitivities, early experiences of threat/safeness, and later cognitive vulnerabilities. Psychological treatments must address issues of experienced threat and safeness before working on more cognitive competencies.

Burns has provided a breathtaking overview of a vast literature. He attempts to identify the evolved origins and phenotypes for dispositions to schizophrenia, and their linkage to specific functional brain circuits and psychological symptoms. There are, of course, concerns with the concept itself, being highly heterogeneous in presentation, course, and treatment response (Bental 2003). Linking genes to phenotypic outcomes is also difficult and many researchers hold to some model of stress-vulnerability or protection interaction. For example, monkeys with the short version of the 5-HT transport gene are highly reactive to early stresses and vulnerable to anxiety, depression, and aggression. However, Suomi (1997; 1999) has shown that if "at risk" infants are cross-fostered to highly responsive mothers, their developmental outcomes can be significantly altered; these monkeys can do exceptionally well in their groups. Early developed phenotypes can influence a variety of processes, such as sensitivity to specific stressors, creating social stressors, (e.g., relational breakup due to poor bonding skills), symptom formation, coping responses, and treatment response. Burns navigates around these difficulties and focuses on evolved, genetically mediated processes (such as changes in neuronal interconnectivity, the emergence of the frontal cortex, and the organisation/interaction of cortical and limbic systems) that have given rise to our complex abilities for "self and other" cognitions.

While Burns does a good job in illuminating how these (top-down) social-cognitive competencies may be involved in schizophrenia, it may also be useful to consider bottom-up processes that can have multiple effects on the subsequent development of

cognitive-affective competencies. There is now good evidence that humans process information through at least two pathways; one is the route that Burns focuses on. It is relatively slow and cortically focused, and it involves symbolic processing. The other route is far older. It operates through thalamic and amygdala tracts (LeDoux 1998), is preconscious and is the basis for automatic processing (Bargh & Chartland 1999) and emotional reasoning (Haidt 2001). This limbic-based system is key to rapid judgments of threat versus safeness, and can then recruit cognitive processes "to fit" and explain an emotion (Gilbert 1989; 1992; Haidt 2001). One cannot rule out the possibility therefore that (gene-linked) problems in these systems (e.g., people are shifted to threat- rather than safeness-processing in early life and have difficulties in feeling safe when with others) have effects on subsequent maturation of frontal cortical processing systems. There is increasing evidence that early experience does influence cortical maturation and the regulating pathways between cortex and limbic system (Saplosky 2000; Schore 2001), with genes also influencing the specific, emergent choreographies of experience with neuronal networking. Early vulnerability may emerge from a lack of felt safeness, marked by low positive affect, poor sooth-ability, and social disengagement; and later, low social confidence and fear of others. Threat processing systems (rather than safeness creation and affiliation) seem to dominate signal interpretation and role formation (Gilbert 1993). This is supported in Burns' review on the link between amygdala processing and frontal cortex regulation. Phenotypic variations in threat sensitivity (related partly to sensitivities in the amydala), may exist within the general population, but such sensitivities may become more extreme because of the further impact of traum, threat, and lack of safeness. Our abilities to learn about others, mature a theory of mind, and be able to explore our own minds, may depend on at least some modicum of safeness, that allows (affiliative) interactions for learning.

There is increasing evidence that a sizable subgroup of people suffering from this disorder have been traumatised in various ways and suffer from posttraumatic stress disorder (Neria et al. 2002; Resnick et al. 2003). While major traumas, including various forms of abuse, may interact with genetic vulnerabilities, there are a host of other ways that children can grow up in a climate of high threat and low safeness. Birchwood and Chadwick (1997) have shown that voice-hearers usually experience their voices as omnipotent, powerful, and dominating. Moreover, the more subordinate a person feels to others in general in their every day lives, the more subordinate does the person feel to their voice(s) (Birchwood et al. 2000), and of course malevolent voices are also repetitive threat signals (Gilbert et al. 2001).

People may generate hostile voices using similar processing systems for simulating and predicting the social behaviour of others, and for simulating, thinking about, and understanding self-generated thoughts and intentions (Gilbert 2000). Thus, for example, when people feel ashamed, they are self-critical and engage in the same type of self-talk (e.g., I am useless, ugly, a pervert) as would another person who sought to shame them might (e.g., you are useless, ugly, a pervert). They may cue emotional memories of others who have shamed them and where they have internalised these judgements of the self (e.g., "they think I am useless therefore I am useless"; Gilbert 2003).

Many forms of cognitive therapy focus on threat-filled cognitions related to evaluations of other people's intentions, or the source, power, and origins of internal voices (Byrne et al. 2003; Morrison 2002). Helping people with feelings of shame or stigma for this disorder itself, fear of the disorder, and grief, can be major interventions. Any coherent model of psychosis and psychotic phenomena must therefore direct attention not only to various social cognitive processing difficulties but also to the origins and organisation of threat and safeness processing located in old brain systems. Trying to build relationships in which a person can feel safe may be one of the most salient of interventions for people with this distressing disorder.

Schizophrenia: A benign trait

Valerie Gray Hardcastle

Department of Science and Technology in Society, Virginia Tech, Blacksburg, VA 24061-0247. **valerie@vt.edu** **http://mind.phil.vt.edu**

Abstract: While schizophrenia may be genetically determined up to a point, neither it nor its nearest relatives offer any sort of reproductive advantage to its sufferers. Instead, from an evolutionary point of view, schizophrenia is benign – it neither promotes nor inhibits survival to reproduction. Because it is benign, its rate of occurrence should remain fairly constant over time.

Let us assume that everything Burns said about the evolution of the human brain being one of progressive demodularization is correct. Further, let us assume that demodularization coupled with increased neural complexity and connectivity produces an organ more vulnerable to insult, injury, and disease. Finally, let us assume that developmental diseases can have a cascading effect across the human brain, so that one rather minor glitch has the potential to wreak devastation across many regions. All of these are points that Burns skillfully and persuasively argues for in the text. The question I want to examine is whether these claims are enough to support the conclusion that schizophrenia is a heritable trait that has been maintained at a relatively constant level in our population for centuries because it is linked to other genes that offer a selective advantage. I believe that they are not.

I am willing to concede that schizophrenia has a genetic component, though environment certainly plays a large role in its etiology. How are we to explain the fact that approximately 1% of the human population, across cultures and time, is schizophrenic? If schizophrenia were just an overwhelming and ruinous mental disorder, than surely it would have been weeded out over evolutionary history, for many schizophrenics are incapable of caring for themselves, much less reproducing successfully. The conclusion that Burns draws is that there must be something about schizophrenia – or something about what schizophrenia is tied to – that confers an evolutionary advantage.

Burns argues that (1) our social brain is advantageous; (2) genes for schizophrenia predate our evolution into hominids (though they likely weren't expressed as such before our cortex developed such complexity); and (3) genes for schizophrenia are closely tied to the neuroregulatory genes that facilitate our brain development. Therefore, he concludes, genes for schizophrenia piggyback on the neuroregulatory genes such that if both are present, then both are inherited.

Let me suggest that there is a problem with this argument, even if we agree to all of Burns' premises. Consider two obvious facts. First, not everyone has genes for schizophrenia – or even some sort of schizotypal trait. Second, according to Burns, those with schizophrenia are less likely to reproduce than those without. If these premises are true, and Burns seems to believe that they are, then, over time, the carriers of the schizophrenia genes would reproduce less than those who don't carry the gene. Hence, over time, the incidence of schizophrenia should decrease and ultimately disappear altogether.

The only way that rates of schizophrenia could remain constant is if schizophrenia or one of its neighboring traits offered some sort of evolutionary advantage that offsets the reproductive disadvantage of full-blown schizophrenia. In this case, schizophrenia would be something like sickle-cell anemia: carriers of the partial disease would be fitter than normals, which could compensate for the decreased fitness of those with the disease proper.

But, as Burns points out, we have no way of making that argument, for there doesn't seem to be any reproductive advantage given to schizoptypal individuals.

So, then, how are we to explain schizophrenia's constancy across time and cultures? If it does not convey a reproductive advantage, then why didn't natural selection weed it out long ago? Let me suggest an alternative analogy in explanation. Schizophrenia is not

like sickle-cell anemia. Rather, it is like Huntington's Chorea, another genetic disease; but this one kills its victims after destroying their brains. Huntington's Chorea has managed to survive over evolutionary history because its symptoms don't present themselves until the victim is middle-aged, long after he or she has already reproduced.

I submit that schizophrenia is very similar. Although its symptoms are often visible earlier, the average age of the psychotic break associated with schizophrenia is early twenties. For most of our history, we would have already reproduced by then. Hence, like Huntington's Chorea, schizophrenia strikes after it could make any evolutionary difference at all. From the perspective of evolutionary history, schizophrenia would then be a benign trait, neither enhancing nor curtailing survival to reproduction. It is only from the perspective of recent modern times, in which we reproduce so much later than we ever have before, that schizophrenia decreases fitness. For most of our history, it hasn't. Hence, for most of our history, its rate of occurrence has remained constant.

Auditory hallucinations, network connectivity, and schizophrenia

Ralph E. Hoffman,[a] Michelle Hampson,[b] Maxine Varanko,[a] and Thomas H. McGlashan[a]

[a]*Department of Psychiatry, Yale University School of Medicine, Yale-New Haven Psychiatric Hospital, New Haven, CT 06519;* [b]*Department of Diagnostic Radiology, Yale University School of Medicine, New Haven CT 06520-8043.* **ralph.hoffman@yale.edu michelle.hampson@yale.edu maxine.varnako@yale.edu thomas.mcglashan@yale.edu**

Abstract: Multidisciplinary studies indicate that auditory hallucinations may arise from speech perception neurocircuitry without disrupted theory of mind capacities. Computer simulations of excessive pruning in speech perception neural networks provide a model for these hallucinations and demonstrate that connectivity reductions just below a "psychotogenic threshold" enhance information processing. These data suggest a process whereby vulnerability to schizophrenia is maintained in the human population despite reproductive disadvantages of this illness.

Burns proposes an evolutionary model of schizophrenia based on impaired theory of mind abilities that provides an interesting framework in which to consider this disorder. Below we consider one prominent manifestation of schizophrenia that does not readily fit Burns' explanatory model of schizophrenia: auditory hallucinations, or voices.

Auditory hallucinations reflect the misidentification of self-generated language as spoken speech arising from some nonself agency. Burns argues that if our brains hadn't evolved a capacity to infer intentions of others, there would be no vulnerability for hallucinated voices, because there could be no attribution of alien, nonself willfulness. He therefore posits that disruptions in theory of mind cause these hallucinations. Our research challenges this view.

We are conducting a phenomenological study to determine what factors prompt individual patients to differentiate their voices from their ordinary verbal thoughts. Most commonly, patients rely on three factors: (1) the voice actually sounds like another speaker with distinct, recognizable acoustic characteristics (e.g., low pitched, growling male voice); (2) the verbal content of the hallucination – which is often vulgar, aggressive, or self-critical – is not characteristic of their ordinary verbal thoughts; and (3) voices are experienced as occurring outside of their own willful control. These preliminary data suggest that the otherness attribution of voices arise from inferences about the mind that are actually reasonable. Unintended speech percepts sounding like another speaker saying things that one ordinarily does not say to one's self are common occurrences for all of us – they occur generally when we perceive ordinary utterances produced by actual other speakers. That persons with schizophrenia often attribute language events with these features to other speakers therefore suggests the intactness of at least some experience-based inferences that differentiate self versus nonself agency.

On the other hand, the neurobiological basis for schizophrenia proposed by Burns (namely, disrupted functional connectivity in the brain) is consistent with our research on auditory hallucinations. Computer simulations of parallel-processing neural networks have demonstrated that eliminating connections based on "Darwinian" principles (pruning connections that are functionally the weakest) produces attractor states that intrude into information processing (Hoffman & Dobscha 1989; Hoffman & McGlashan 1997). Complexity and flexibility of neural responses under these conditions are reduced, and spurious outputs are produced in the any absence of sensory inputs, thus simulating hallucinated voices (Hoffman & McGlashan 1997). Such outputs, if generated by actual human speech perception networks, could be cast in the speaking voices of other speakers and experienced as alien and unintended. A model of auditory hallucinations considered as autonomous outputs of speech perception neurocircuitry does not require postulation of specific breakdown of theory of mind capacities.

Consistent with a speech perception neurocircuitry activation model of voices is recent fMRI work by our group. These data demonstrate activation of subregions of the superior temporal gyrus (STG) and Broca's area during auditory hallucination periods that overlaps with activation elicited by listening to external speech in the same patients (Hoffman et al., in preparation; see also Dierks et al. 1999). We also have detected activation unique to hallucination periods in the anterior cingulate and prefrontal cortex that involve neurocircuitry implicated in theory of mind processes, per Burns' discussion. Therefore, our fMRI data do suggest involvement of higher-order neurocognitive processes. However, direction of causality is unclear. Cingulate activation could, for example, arise from attentional/arousal shifts due to intrusion of hallucinated speech percepts.

The aforementioned computer simulation studies demonstrated a second unexpected finding that led us to evolutionary speculations relevant to the model described by Burns. Darwinian pruning of networks to levels just below the "psychotogenic threshold" actually enhanced network performance in detecting linguistic meaning (Hoffman & McGlashan 1997). Burns asserts that the basic mechanisms causing schizophrenia are not in themselves adaptive. Instead, the persistence of this disorder, which is known to produce distinct reproductive disadvantages, is due to linkage between vulnerability loci (presumably generating connectivity loss) and other adaptive loci that enhance function of the social brain. In contrast, our neural network findings highlight information-processing enhancements due to connectivity reductions themselves and suggest that schizophrenia is an extension of this ubiquitous neurodevelopmental process. Consequently, we have hypothesized that there has been and may continue to be an adaptive advantage to robust network pruning which enhances cognitive functioning until it pushes up against a psychotogenic threshold (McGlashan & Hoffman 2000). In this model, higher levels of pruning are selected over generations, with only the small number of individuals at the highest end of the "pruning" curve suffering from frank breakdowns in cortical integration, induction of spurious attractors, and perceptual impairments.

Burns rejects such ideas, because they seem to force the view that schizotypal individuals (who carry genes for schizophrenia but do not suffer from overt illness) should demonstrate some reproductive advantage. We concur with Burns that there is little evidence that individuals with attenuated forms of the schizophrenic phenotype are more fertile. However, there is good statistical evidence to suggest that schizophrenia arises primarily from 2–3 gene epistasis, where multiple distinct susceptibility alleles interact to produce illness risk (Risch 1990). If so, schizotypal individuals in the population could be those who carry "at-risk" combinations of susceptibility alleles but who have not converted to

overt schizophrenia – such cases must occur, since monozygotic twin concordance of overt schizophrenia is often observed to be less than 50%. In these cases reproductive fitness may be normal or somewhat subnormal. In contrast, carriers of single susceptibility alleles – which could be relatively numerous and benign in the general population (to produce rates of gene-gene combinations high enough to sustain population rates of schizophrenia on the order of 1%) could still demonstrate modest levels of enhanced reproductive fitness sufficient to sustain vulnerability for schizophrenia in the general population). In short, the absence of a reproductive advantage for schizotypal individuals is not definitive evidence of the absence of some reproductive advantage for other non-ill carriers of susceptibility alleles for schizophrenia.

Evolutionary theories of schizophrenia must ultimately explain the genes that predispose to it

Matthew C. Keller

Center for Society and Genetics, University of California – Los Angeles, Los Angeles, CA, 90095-1405. **matthew.c.keller@gmail.com**
http://www.matthewckeller.com

Abstract: If alleles that predispose to schizophrenia have reduced Darwinian fitness, their persistence in modern times is puzzling. Burns identifies the evolutionary genetics of schizophrenia as a central issue, but his treatment of it is not clear. Recent advances in evolutionary genetics can help explain the persistence of alleles that predispose to debilitating disorders such as schizophrenia, and can buttress Burns' core argument.

Burns provides an evolutionary account for schizophrenia that integrates advances in cognitive neuroscience with theories of human psychological evolution. In support of his theory that selection for increased social reasoning ability has placed humans at risk for schizophrenia, Burns presents data suggesting that abnormal development in social brain networks plays a role in schizophrenia. While Burns' theory is commendable for its scope and innovation, its treatment of the evolution of the genetic basis of schizophrenia is unsatisfactory for many reasons. This commentary focuses on this central issue, critiquing Burns' views and forwarding alternatives that are better grounded in modern evolutionary genetics. These alternatives might actually strengthen Burns' core hypothesis.

Schizophrenia is highly heritable ($h^2 \sim .80$; National Institute of Mental Health 1999), meaning that genetic differences (differences in alleles[1]) between people are responsible for most of the risk of developing the disorder. The lack of progress in identifying alleles that predispose to schizophrenia (hereafter referred to as *susceptibility alleles*) make it clear that schizophrenia is underscored by many loci and numerous alleles of small effect, although their exact numbers remain unknown. An evolutionary account of schizophrenia must explain this genetic variation. Why do susceptibility alleles persist?

Burns' preferred explanation for the genetics of schizophrenia, the "pleiotropic model of selection," in which "maladaptive genes are associated with adaptive genes," can be interpreted in one of two ways. This ambiguity stems from the unclear usage of "genes" in the paper, which can be interpreted to mean either "loci" or "alleles." If "loci" was the intended meaning, the model suggests that loci shared by all humans (or equivalently, all the alleles at these loci) became malignant in the context of novel brain changes. This explanation fails to explain genetic variation in schizophrenia susceptibility, however. Given that all people share the same loci, all people should be at equal risk for developing schizophrenia, which tells us nothing about the origins of genetic differences in schizophrenia susceptibility between people. Similarly, if susceptibility alleles "hitchhiked" alongside adaptive alleles due to physical proximity on the chromosome, the susceptibility alleles would be at fixation in the population along with the adaptive alleles, which offers no explanation for genetic differences predisposing to schizophrenia.

The more likely (allelic) interpretation of Burns' pleiotropic model is that alleles that today predispose to schizophrenia were at high frequencies prior to modern Homo sapiens and became malignant only in the context of novel brain changes that occurred around 100,000 years ago. However, this explanation also fails to account for the persistence of susceptibility alleles into the present day. If the susceptibility alleles reduced fitness following these changes, as Burns suggests, they should have long since gone extinct. For example, assume that one particularly common susceptibility allele was at a frequency of 50% 100,000 years (~5,000 generations) ago, which caused a 1% reduction in fitness among carriers after the putative brain changes. A simple recursive equation[2] shows that selection will have reduced the frequencies of such a susceptibility allele to very low levels ($<<10^{-5}$) by the present day. Thus, Burns' pleiotropic model of selection does not seem to offer insight into the existence of susceptibility alleles.

There is another alternative, one that Burns considers briefly but then dismisses, that might help explain the existence of schizophrenia susceptibility alleles: mutation-selection balance. Although at times dismissed as a minor factor in maintaining genetic variation in traits important to fitness, mutation-selection has enjoyed a resurgence among evolutionary geneticists in the past 20 years (Charlesworth 1987; Houle 1992; Houle et al. 1996; Hughes & Burleson 2000). In mutation-selection models, maladaptive alleles are maintained at an equilibrium that results from their introduction via mutation and their eventual removal (usually many generations later) via selection. Given that mutation rates per locus are very low ($\sim 10^{-5}$), mutation-selection might seem to play a commensurately minor role in maintaining genetic variation, but recent empirical evidence suggests otherwise (e.g., Houle et al. 1996). The key insight, championed by Houle, is that "downstream traits," those that are affected by many biological processes, have very high trait-level mutation rates, because downstream traits subsume a large number of loci. To the degree that many loci are involved in schizophrenia, mutation-selection balance may provide an explanation for a substantial portion of susceptibility alleles. Burns' explanation for schizophrenia – that neural connectivity associated with the evolution of the social brain placed humans at risk for schizophrenia – can be seen as consistent with a mutation-selection model: Because social cognition requires the interrelationship of many different processes, it is vulnerable to genetic perturbations arising from recurrent mutations in a large number of loci.

A second common explanation for genetic variation is balancing selection, such as antagonistic pleiotropy, overdominance, or frequency-dependent selection. In balancing selection models, two or more alternative alleles are maintained at relatively high frequencies at equilibrium because their marginal fitness effects are equal to each other. Applied to schizophrenia, this would imply that susceptibility alleles have the same fitness, on average, as no-susceptibility alleles, which seems unlikely given that schizophrenia shows reduced fitness in modern populations (Markow & Gottesman 1994). Such evidence does not necessarily preclude balancing selection as an explanation of schizophrenia, however. First, modern fitness effects can differ from ancestral ones. And second, a small number of susceptibility alleles may be beneficial (perhaps improving creativity, as mentioned in Burns' article), while too many may be maladaptive. Models have shown that this latter possibility, which is a form of antagonistic pleiotropy, is unlikely to account for much genetic variation (Hedrick 1999; Prout 1999). Nevertheless, balancing selection cannot be ruled out in general as an explanation for the existence of some proportion of susceptibility alleles.

In summary, Burns' theory does not explain one of the central paradoxes of schizophrenia: its genetic variation. However, the core of his argument – that the evolution of social cognition has placed the human brain at risk for schizophrenia – is not incon-

sistent with modern accounts explaining genetic variation. I suggest that Burns' theory could be substantially strengthened by integrating his insights with recent advances from evolutionary genetics.

NOTES

1. "Allele" is used broadly here to include not only genetic variants in the protein-coding regions within loci, but also genetic variants in the regulatory regions that surround loci.

2. In a large, randomly breeding population, the expected frequency (q') for the susceptibility allele after one generation of selection is given by the recursive equation

$$q' = \frac{q^2 w_2 + pqw_1}{p^2 + 2pqw_1 + q^2 w_2}$$

where q is the frequency of the susceptibility allele before selection, p is the frequency of all other alleles at that locus before selection, and w_1 and w_2 are the fitnesses of those carrying one or two susceptibility alleles, respectively, relative to those carrying no susceptibility alleles. (MATLAB script iterating this equation available from the author on request.)

Cliff-edged fitness functions and the persistence of schizophrenia

Randolph M. Nesse

Departments of Psychiatry and Psychology, The University of Michigan, Ann Arbor, MI 48104. **nesse@umich.edu**
www-personal.umich.edu/~nesse/

Abstract: Strong recent selection for social cognition may well explain the persistence of genes that predispose to schizophrenia. The specific mechanism responsible may be a skewed fitness function in which selection pushes the mean for advantageous mental traits perilously close to a "fitness cliff" where the system fails catastrophically in some individuals.

The target article addresses the excellent question of why genes that predispose to schizophrenia persist, given the dramatic negative effect of psychosis on Darwinian fitness. Simply asking this question straightforwardly is a wonderful contribution, and the review of most previous suggestions is unparalleled. As we approach an age of genomic engineering, such questions will become profoundly practical for many diseases, but especially for schizophrenia where, as Burns notes, the answer may also help us to understand more about what it means to be human.

The broad thesis of the target article is that schizophrenia results from the effects of strong recent selection for sophisticated social cognition. This seems plausible in general and is similar to a notion I have entertained (Ridley 2003, pp. 122–23), but the exact mechanism thought to account for persistence of the responsible genes remains somewhat unclear. Early in the article, deleterious genes are posited to persist because they are "associated with" beneficial genes. If this means genetic linkage, that can sometimes explain the presence of deleterious traits. However, as Burns notes, the uniformity of schizophrenia prevalence rates in different populations means that the responsible genes have been with us for at least 100,000 years. Even if linkage were at its maximum of D = 0.25 at time zero, after only 320 generations with a recombination rate (R) of only 1%, linkage would decrease to 0.01 and by 540 generations it would be at the inconsequential level of D = 0.001 [$D_n = D_0 (1 - R)^n$]. Linkage persisting for 5,000 generations is not a viable explanation by itself. The argument is also said to be based on a kind of pleiotropy. While this does not seem to refer exactly to multiple effects of single genes, antagonistic pleiotropic effects of many genes may well be involved. The term *trade-offs,* used later in the article, may be more accurate, but exactly what the trade-offs are among is not clear.

Consideration of the effects of asymmetrical fitness functions for complex polygenic traits may clarify these ambiguities and provide a crucial piece of the puzzle. For most traits with some variation, such as height or kidney size, fitness falls off in something like a normal distribution on either side of the optimum level for the trait, which is usually near the actual mean. For other traits, however, fitness increases as the trait increases up to a "cliff-edge" beyond which fitness falls off precipitously (see Fig. 1). This was first described as a possible explanation for the tendency of some birds to lay fewer than the apparently optimal number of eggs, perhaps to avoid the risk of all the offspring dying if food supplies proved insufficient (Mountford 1968). Race horses are another example: Breeding has resulted in longer and thinner leg bones that increase running speed but are vulnerable to catastrophic failure, as is tragically obvious to race fans who see a champion put down after breaking a leg. We humans have uric acid levels much higher than those of other primates, probably because it protects against oxidative tissue damage. This is a great boon for most members of a long-lived species, but the levels are so high that crystals of uric acid precipitate in the joints and cause gout in a few unfortunate individuals (Nesse & Williams 1994). Both of these examples are specific trade-offs that result in vulnerability to disease; speed versus fragile bones for horses and slower aging versus the risk of gout for humans. Such trade-offs seem very close to those Burns suggests.

A fitness cliff model could potentially explain the core dilemma of psychiatric genetics. The high heritability of the serious mental disorders and their severe effects on fitness initially spurred hopes that we would find the causes in a few defective genes, or perhaps specific genes with pleiotropic benefits. However, there is little evidence for reproductive benefits associated with having genes for major mental disorders (with the possible exception of mania) and growing evidence suggests that these disorders result from the effects of many genes, none of which explains even 5% of the variance. These findings, although somewhat unwelcome, are exactly what a fitness cliff model predicts.

What kind of mental trait would give a major benefit with increasing levels and would, at the extreme, increase the risk of catastrophic cognitive breakdown? The target article emphasizes the benefits and complexity of social cognition. That seems like a likely candidate. But fitness might well increase with increased tendencies to make meaningful theories out of experience in general. Moving towards the social, a capacity for theory of mind (ToM) provides an intentional context that can make sense out of ambiguous words in a way unavailable to any computerized voice recognition system. Sexual selection could also account for elaborate human mental traits that leave us vulnerable to schizophrenia (Shaner et al. 2004). Finally, strong tendencies to use metarepresentation and ToM increase the ability to predict other people's behaviors, how they might be influenced, and how they might be trying to manipulate you. It is only one step further, over the cliff's edge of psychotic cognition, as it were, to finding secret meanings and evidence for conspiracies in other people's most casual gestures, to believing idiosyncratic grand theories and religions, and to thinking that others are controlling your thoughts. Those who have worked with schizophrenics know the eerie feeling of being with someone whose intuitions are acutely tuned to the subtlest unintentional cues, even while the person is incapable of accurate empathic understanding.

This formulation may itself, however, attribute excess meaning to the situation. There may be no single characteristic whose extreme leads to schizophrenia; and, as many have suggested, there may be many schizophrenias. Also, it may be an error to portray the extreme as a recognizable phenotype. What is pushed to an extreme may well be, as Burns suggests, a mechanism that prunes neurons to a finely tuned but delicate network, or, more broadly, an excess of interconnectivity. Defining exactly what traits and mechanisms are involved is a very good goal, one that may well be accomplished best by our growing knowledge about the functions of nerve pathways that are influenced by genes whose variations predispose to schizophrenia.

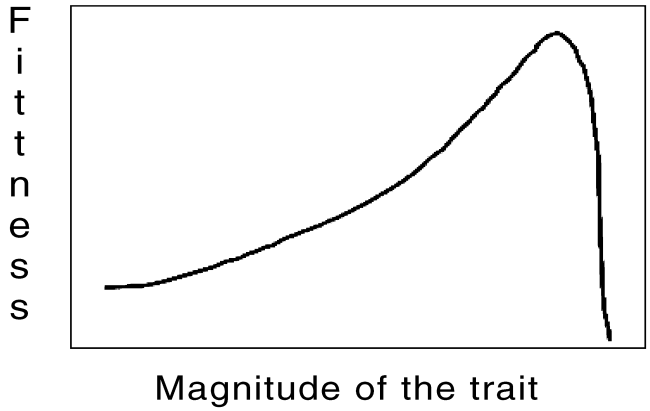

Figure 1 (Nesse). A cliff-edged fitness function: As the trait increases, fitness increases increasingly rapidly, then crashes.

This perspective makes it unnecessary to seek specific adaptive benefits for schizophrenia or schizotypy, even while it suggests that both conditions may nonetheless offer clues about beneficial characteristics that may select for mental characteristics related to the disorders. It suggests looking for traits and mechanisms that give such a substantial advantage that selection would have quickly pushed the mean to an extreme where the system fails in some individuals. Such cliff-edge fitness functions are especially likely when selection has recently been strong for a particular trait, as it has for horses' legs or uric acid levels in humans, and as it presumably has been for social cognition. After another few thousand generations, modifier genes may well reduce the risk. Since we don't want to wait, intense pursuit of the questions addressed by this target article will be most worthwhile.

Schizophrenia: The elusive disease

Jaak Panksepp and Joseph Moskal

Falk Center for Molecular Therapeutics, Department of Biomedical Engineering, Northwestern University, Evanston, IL 60201.

jpankse@bgnet.bgsu.edu **j-moskal@northwestern.edu**

http://caspar.bgsu.edu/%7eneuro/Faculty/Faculty_jpanksepp.shtml

Abstract: All mammals have social brains, and there is presently no evidence that humans have relatively more genetically dictated social brain circuitry than other species. The postulation that schizophrenia arises from disruption of brains systems uniquely devoted to social traits is obviated not only by the large number of anatomical and biochemical brain differences, but also by nonsocial symptoms of schizophrenic disorders.

Ever since Kraepelin and coworkers started to examine demented brains anatomically a century ago (Panksepp 2004), the neuroscientific study of schizophrenia, as the quip goes, has been the graveyard of neuroanatomists. With so many brain changes, but few of *general* etiological significance, no discrete neural theory of schizophrenia has survived the test of time. Enter Burns, with his vision of the unique cortical interconnectivities of the human "social brain." Anyone interested in schizophrenia should read this article. It is erudite, novel, and weaves abundant information into a fascinating hypothesis. However, the central idea – that schizophrenia reflects genetically promoted derangement of the higher humanoid "social brain" connectivities – remains dubious.

Cognitive/evolutionary psychological views commonly ignore too many of the foundational social circuits of the cross-mammalian limbic brain, including systems for sexuality, maternal care, separation distress, social bonding, and play (Panksepp 1998). The genetic analysis of the limbic "lower social brain" shared by all mammals (Panksepp et al. 2002) will be considerably easier than clarification of neocortical aspects unique to humans. But Burns believes schizophrenic genotypes and phenotypes are restricted to our own species. Early comparative literature was replete with descriptions of psychotic animals (Lindsay 1879), and productive modern models for specific symptoms exist abundantly (e.g., Gainetdinov et al. 2001; Kilts 2001). Also, let us not forget that among domestic animals there surely has been enforced culling of those that seemed to exhibit troublesome symptoms of insanity.

With similar core deficits, simpler brains may not be as functionally impaired as humans'. For example, rearrangement of cortical layering in animals with heterozygous *reelin* deficits – a genetic model of schizophrenia (Costa et al. 2002) – may impair mice less than men. Because of our ultracomplex corticocognitive apparatus, many schizophrenic symptoms may reflect the costs of complexity rather than genetically dictated *social* features.

Burns' proposal hinges on dubious genetic and neuronal assumptions, as do most "modular" views of evolutionary psychology. Much of heteromodal cortex in humans is capable of nonspecialized information processing which becomes specialized only epigenetically. How would Burns defuse the following major concern? That the higher social brain of humans, which readily elaborates theories of mind and complex sociocognitive strategies, reflects epigenetic programming within general-purpose computational spaces, guided by limbic socioemotional functions rather than by genetic sociocortical connections unique to humans (Panksepp & Panksepp 2000)?

We also wish guidance on linkages with established neurochemical vectors of schizophrenia – dopamine hyperactivity and glutamate/GABA hypoactivity perspectives. These chemistries are not uniquely devoted to elaboration of social processes. Dopamine-generated appetitive seeking urges (Panksepp & Moskal 2004) and glutamatergic general information processing (Riedel et al. 2003) provide abundant opportunities to modulate social thoughts and emotions independently of any genetic prescriptions. Dopamine facilitation of core symptoms of schizophrenia (e.g., paranoid delusions, also modeled in animals; Lipska & Weinberger 2000) makes sense from the ability of hyperdopaminergic states to promote causal inferences from correlative relationships (Panksepp 1998, Ch. 8). Social wiring problems are *not* a prerequisite for such symptoms. Likewise, glutamatergic mediation of all memory and cognitive processes in all mammals, makes "higher social brain" assumptions unparsimonious. Although modern brain imaging is well positioned to evaluate the abundant *correlative* changes in schizophrenic brains (Kubicki et al. 2003; Winterer et al. 2003), animal models allow causal analysis. Can Burns' many inferential possibilities be winnowed for specific sociocausal influences?

Burns' analysis ignores much data from molecular genetics. In which of the 15 already demonstrated susceptibility loci (see Pesold et al. 2004) would he search for "social genes"? Would Burns share new molecular biology predictions concerning hominid-specific "evolved complex cortical interconnectivities"? Don't general deficits, such as those related to myelin, cytoarchitectural, and synaptic activity regulation (Pesold et al. 2004) cast doubt on his disrupted socioanatomical pathway hypothesis and potentially also explain lower fecundity and increased early mortality associated with schizophrenia?

It seems more likely that schizophrenia is *not* actively maintained in the genome, but that certain genes predispose or make one vulnerable to epigenetic and environmental factors that promote schizophrenic phenotypes (Kato et al. 2002). DNA methylation can alter gene expression during development and alter cellular function, with major impact on behavior and cognition. Genetic anticipation, chromatin rearrangements, viral integration into the genome, and epigenetic modulation of neurochemical systems may all play a role in schizophrenia (Jones & Cannon 1998; Petronis et al. 1999).

Considering what we already know about schizophrenia, we think Burns' alternative has much to explain before it can be

deemed a major title contender. Although psychiatric genetics is in a state of crisis (DeLisi 2000), with little reproducible data (except for childhood disorders; Peterson & Panksepp 2004), molecular biology in conjunction with functional neuroscience will nevertheless eventually tell us what actually is contained in the neural ground-plan of the genome. Evolutionary theorists need to be quite clear on how they might facilitate the molecular and neuropsychological search.

Since evolutionary speculation is such fun, let us also consider how real-life social processes may affect the genetic survivability of schizophrenia with no costly genetic trade-off with the evolution of complex social cognition. Schizophrenic genotypes may subsist in human populations if high background incidence, coupled with comparatively low penetrance, offer some benefits – for example, the capacity to enthrall others around the endless social "campfires" of our ancestral past and entertainment-obsessed modernity. Humans enjoy stimulating story-telling, ranging from slapstick to mystical. Our fascination with human quirks may have created cultural spandrels for the survival and propagation of individuals who survived less well without such cultural supports. Consider the classic "stress-diathesis" model: Schizophrenic phenotypes may diminish as supportive cultural practices allow afflicted individuals to keep their symptoms in check or socially useful. Also, with the insistent sexuality of mature males, genetic dispositions for schizophrenia could be sustained if borderline women, partly through helplessness, are more likely recipients of male lust than non-schizophrenic ones.

We hope Burns' fascinating proposal will have a better shelf life than past neuroantomical hypotheses, but at present, the distance between fact and theory remains vast. We need concrete hypotheses to enable this intriguing theory to be tested robustly, and potentially falsified.

The ontogeny and asymmetry of the highest brain skills and the pathogenesis of schizophrenia

Vadim S. Rotenberg

Abarbanel Mental Health Center, Bat-Yam 59100, Israel.
vadir@post.tau.ac.il **http://rjews.net/v_rotenberg/book4.html**

Abstract: The most developed and the latest-to-mature mental skills represented in the creation of mono- versus polysemantic contexts are related respectively to the left and right frontal lobe. A polysemantic way of thinking is responsible for the subject's successful integration in the polydimensional world. The functional insufficiency of this right-hemispheric way of thinking displays a predisposition toward the development of mental disorders, including schizophrenia.

I agree with the main messages of the target article, that schizophrenia is a disorder of the social brain, that the development of this disease is related to the disturbed frontoparietal and frontotemporal connectivity, and that some peculiar features of human ontogenesis predispose subjects to these disturbances of connectivity. However, one important point is missed, related to the ontogeny and function of the orbitofrontal asymmetry.

The disturbance of this area does not cause definite and well-traceable single signs, like apraxia, spatial hemineglect, and so on. In contrast to these relatively local disorders, right anterior insult has interfered with the ability to explore an image in an organized fashion and with the more global functions like empathy, theory of mind, sense of self (Craik et al. 1999; Devinsky 2000; Keenan et al. 2001; Schore 2003; Shamay-Tsoory et al. 2003).

I suggest that in the most general form, the difference between two strategies of thinking related to the frontal functions of the left- and right hemispheres is reduced to opposite modes of organizing the contextual connection between elements of information (Rotenberg 1979; 1982; 1985; 1993; 2004; Rotenberg & Arshavsky 1979). Left-hemisphere frontal pole so organizes any sign material (whether symbolic or iconic) as to create a strictly ordered and unambiguously understood monosemantic context. The formation of this context requires an active choice from the many real and potential connections between the multiform objects and phenomena of a few definite connections that would facilitate an ordered analysis, building a pragmatically convenient but simplified and restricted model of reality based on probability forecasting and cause-and-effect relations.

In contrast, the function of the symmetrical structure of the right hemisphere is a simultaneous capture of an infinite number of connections and the formation of an integral, but ambiguous, polysemantic context. In such a context, the whole is determined by the interconnections between its elements that interact with each other on many semantic planes simultaneously, like images in dreams. Understanding of metaphors and sense of humor are dependent on the right hemisphere (Wapner et al. 1981; Winner & Gardner 1977).

These two types of context complete each other and have sense only in comparison with one another. For the right hemisphere disconnected from the left one, the world is holistic but not polysemantic. However, these types of context are not equal, because the polysemantic view on the world, although being opposite to the monosemantic one, actually includes the latter as a component, while the converse is not true. Polysemantic thinking is the highest human mental function, responsible for creativity and integration of past, present, and future experience (Wheeler et al. 1997). Great apes lack even the initial precursors of polysemantic thinking.

The advantage of the right frontal brain corresponds to the more prominent arborization of the neural net (Saugstad 1998) and to the activation of a much broader net of associations in comparison to the left hemisphere (Beeman et al. 1994; Chiarello 1998; Coney & Evans 1999).

Brain maturation starts with faster overall growth of the right hemisphere in the first years after birth, interrupted by the left hemisphere maturation gradient, followed by another shift to a leading role of the right hemisphere in early adolescence. The frontal lobes and particularly the right frontal lobe structures and connections are the last regions to mature (Thatcher et al. 1987; Saugstad 1998).

In the frame of the theory of contexts, this schedule of maturation has a following explanation: The main functions of the right hemisphere that precede the development of the polysemantic way of thinking (the ability to grasp the reality as a whole; the emotional attachment to the mother [Schore 2003]; the regulation of the withdrawal behavior in the inappropriate conditions [Davidson 1992]; the integration of affect, behavior and autonomic activity [Schore 2003]) are the basic functions of survival (Saugstad 1998), and for this reason they are the first to appear. In the next crucial stage of the development, a process of differentiation of the elements of reality appears: a distinguishing of self from the environment, the ability to analyze cause-and-effect relationships, the orientation in the time vector, and finally the creation of the conscious model of the reality and of self-concept. This process of differentiation requires the expertise of the left hemisphere and its ability to form a monosemantic context.

However, to be comfortably integrated in the polydimensional world and to cope with all contradictions, a subject has to overcome, on a new level, the restrictions of the monosemantic model that is included in the more broad polysemantic picture.

Females are characterized by earlier brain maturation (i.e., achieving the final point of maturation sooner) than males. In general, the longer the process of maturation, the higher the level of brain structure development achieved. This may be a reason why males more often display outstanding creativity (Saugstad 1998). However, the increased duration of maturation in males makes the right hemisphere more sensitive and vulnerable to any alterative influences and may cause its functional insufficiency that displays

a predisposition to different forms of pathology, including schizophrenia (Rotenberg 1979; 1982; 1995; Schore 2003).

Cutting (1992) proposed that schizophrenic patients with a preponderance of negative symptoms display right-hemisphere dysfunction. In schizophrenic patients, the right hemisphere is no more dominant in the functions it usually controls in normal subjects: perception of facial emotions (Borod et al. 1993), visuospatial task performance (Gabrovska-Johnson et al. 2003), attention (Kucharska-Pietura et al. 2002), and ability to grasp global forms (Ferman et al. 1999).

The basic initial symptoms of schizophrenia not responsible to the modern neuroleptics (peculiarity of nonverbal behavior; deficiency of self-image; difficulty in grasping information to form a polydimensional picture of the complex situation and picture of the world; affective blunting; lack of empathy) can be explained by the inability to create and process the polysemantic context (Rotenberg 1994).

On the other hand, patients with dominating positive symptoms are characterized by the increased physiological and metabolic activity of the dysfunctional left hemisphere (Flor-Henry 1976; 1983; Friedman et al. 2001; Galderisi et al. 1999; Gur 1978; Gur & Chin 1999; Romney et al. 2000).

I have made an attempt to explain the relationship between the right and left hemisphere dysfunctions in schizophrenia (Rotenberg 1994). Integration with the world by means of the polysemantic way of thinking is the most important feature of a subject's mental health. Without such integration, the subject finds himself in front of a very complicated reality full of inner contradictions, and can use as an option an attempt to resolve difficult task by creating a simplified "left-hemispheric" model of reality. It does not fit. And then, in subjects predisposed to schizophrenic disorders, the left hemisphere creates an artificial explanatory system, in the form of delusions, paranoid ideas, and verbal hallucinations.

According to this proposition, functional right hemisphere deficiency is not unique to schizophrenia. Depression is characterized by disrupted functional connections between anterior cingulate cortex and right orbitofrontal and prefrontal cortex regions (Pizzagalli et al. 2003) – very similar to what Burns suggest for the mechanism of schizophrenia. This means that the next problem we have to solve is what brain (and genetic) mechanisms predispose a subject who suffers from right hemisphere insufficiency to the development of the concrete forms of mental disorders. In the case of schizophrenia, what is it, for example, about the dopaminergic system that leads to a greater release of dopamine? (Zipursky & Kapur 1998).

Natural selection and schizophrenia

Roger J. Sullivan[a] and John S. Allen[b]

[a]*Department of Anthropology, California State University, Sacramento, Sacramento, CA 95819-6106;* [b]*Department of Neurology, The University of Iowa Hospitals and Clinics, Iowa City, IA 52242.* **sullivar@csus.edu jsallen38@aol.com www.csus.edu/indiv/s/sullivanr**

Abstract: Evolutionary theories of schizophrenia must account for the maintenance of putative alleles in past and present populations despite reduced fitness among the affected. Such models must also account for extant intersex and population-level variability in the expression of schizophrenia. We argue that genetic balanced-polymorphism hypotheses remain the most robust in terms of modeling and testing these processes in populations.

Although we applaud Burns' comprehensive review of several literatures exploring the biology and natural history of schizophrenia, we have several problems with his developmental "costly trade-off" scenario of the evolution of schizophrenia. Our main criticism is that the model does not adequately address why alleles expressing as social dysfunction in schizophrenia have not been removed by natural selection. Burns' very brief rationale is that such genes "may have survived in the genome because of their association with adaptive social genes" (target article, sect. 9.2, para. 6) and that they represent part of a "costly trade-off" related to "evolving complex cognitive and social abilities" in humans (sect. 10, para. 4). Burns' "costly trade-off" argument follows similar perspectives set forth by Book (1953), Gottesman and Shields (1982) and Crow (1990b) that we will gloss for the sake of brevity as "genetic load" arguments. Costly trade-off and genetic load models do not appear to be very amenable to testing or falsification, and it is thus unclear how they advance our understanding of schizophrenia. While not assuming that evolution operates without constraints, or results in optimality, we find it particularly problematic to argue that social functioning has been highly conserved in social primates, but that genes with a profoundly asocial expression have escaped the action of natural selection.

Taking natural selection seriously requires specifying how schizophrenic alleles are maintained in populations at frequencies higher than mutation rates would allow, given that individuals who are overtly schizophrenic suffer substantially reduced fitness (Allen & Sarich 1988). We believe that the most robust model accounting for the action of natural selection on such alleles remains some manifestation of balanced polymorphism, as originally proposed by Huxley et al. (1964). However, there is little evidence supporting the notion advanced by Huxley and others that the polymorphism is maintained by a "physiological advantage" (Carter & Watts 1971; Erlenmeyer-Kimling & Paradowski 1966; Huxley et al. 1964), nor do the genetic data support a simple heterozygous advantage model to maintain that polymorphism. We support the notion that schizophrenic alleles are maintained via selection of behaviors in the relatives of individuals with schizophrenia that confer higher than average reproductive success (Allen & Sarich 1988). As Burns points out, research results supporting the balanced polymorphism hypothesis are mixed. Such ambiguity is predictable given that an absolute selective advantage in the relatives of individuals with overt schizophrenia of ~5% would be adequate for the maintenance of the polymorphism and yet be difficult to demonstrate (Allen & Sarich 1988; Kidd 1975). The main issue is not to confuse ambiguity in results supporting the balanced polymorphism hypothesis with its viability as a testable genetic model.

A related problem is how Burns' description of a universal schizophrenic genotype can account for population and intersex variability in the expression of schizophrenia. The often reported generalization of a 1% global prevalence of schizophrenia should be thought of as a global average, not the uniform distribution implied in Burns' "constant prevalence of schizophrenia" (sect. 2.1, last para.). Micronesia, where we have been conducting cross-cultural research of the expression of schizophrenia for several years (Sullivan et al. 2000), is a good example, with point prevalence ranging from a low in eastern Micronesia of ~0.04% to a high of ~2.0% in the islands of western Micronesia (Allen & Laycock 1997; Hezel & Wylie 1992). In regard to sex differences in the expression of schizophrenia, the lifetime morbid risk of "strictly defined" schizophrenia in the Micronesian nation of Palau is 2.8% for males and 1.2% for females – a greater than 2:1 male to female risk ratio (Myles-Worsley et al. 1999). Not only is the expression of schizophrenia widely recognized to vary profoundly between males and females, but much of this variation occurs in the crucial domain of social functioning, with females tending to retain significantly more social functioning than males (Childers & Harding 1990, Sullivan & Allen 1999). The need to account for intersex variability in evolutionary models of schizophrenia has been acknowledged by Crow (1993b; 1996b), who has proposed that sex-differences in the expression of schizophrenia may reflect differences in male and female reproductive strategies during the course of human evolution.

The Palauan context is also a good example of reduced reproductive fitness among people with schizophrenia, particularly males. Fertility in a cohort of 49 males (mean age 38.5 years, SD

7.0) and 21 females (mean age 40.8 years, SD 10.1) with chronic schizophrenia was 0.5 (1.1) and 2.3 (1.7) offspring on average for the males and females respectively (unpublished data), compared to a total Palauan fertility of 2.8 at the time of the 1993 census (Levin et al. 1993).

We believe that an evolutionary account of schizophrenia must necessarily uncouple the selection events that led to the conservation of traits for social functioning in the environments of the past, and the environments of the present which may interact with behavioral phenotypes in ways that are entirely novel in evolutionary terms. For example, based on the assumption that the selective environment of schizophrenic alleles comprised small, face-to-face social groups, we have hypothesized (1) that negative selection against schizophrenic genes in small-scale societies with unavoidable social-competence demands was more profound than in the comparative anonymity of modern urban environments (Allen 1997); and (2) that social dysfunction among people with schizophrenia today will be maximized in face-to-face contexts (Sullivan & Allen 1999).

In summary, an evolutionary model of pathology must specify plausible selection pressures affecting the putative alleles in both the past and present contexts and must be able to account for population variability in the expression of the pathology in the present (Sullivan & Hagen 2002). Burns' developmental model is weak in addressing either of these criteria. Genetic balanced-polymorphism models of schizophrenia remain robust in that they can accommodate population-level variation in the expression of schizophrenia and the maintenance of alleles in extant populations despite reduced fertility in overt schizophrenics. In contrast, Burns' "costly trade-off" model does not adequately address these processes and will be difficult to test or falsify.

Are the DTI results positive evidence for George Bernard Shaw's view?

Rolf Verleger[a] and Rebekka Lencer[b]

[a]*Department of Neurology, University of Lübeck, D 23538 Lübeck, Germany;* [b]*Department of Psychiatry and Psychotherapy, University of Lübeck, D 23538 Lübeck, Germany.* **rolf.verleger@neuro.uni-luebeck.de lencer.r@psychiatry.uni-luebeck.de www.neuro.uni-Luebeck.de www.psychiatry.uni-Luebeck.de**

Abstract: We discuss how Burns' conception may be further extended to integrate research on eye movement abnormalities, but then point to a contradiction between Burns' conception of schizophrenia as the genetic price for human social life and the diffusion tensor imaging (DTI) data, which constitute his central piece of evidence.

Burns' target article fascinates by its integrative approach, conceiving schizophrenia as biologically determined pathology of those abilities that underlie social relations and behavior. This latter aspect, though certainly important from a clinical point of view, has often been neglected in studies that were conducted under the information-processing paradigm and that measured physiological variables (e.g., our own; Verleger & Cohen 1978), not sufficiently reflecting on the difference between schizophrenia and neurological diseases.

The target article thus offers a framework for integrating various fields of research. One aspect, unmentioned by Burns, is the ongoing research on eye-movement abnormalities in schizophrenic patients. Indeed, "disconnections" within frontoparietotemporal networks, as postulated by Burns, may also underlie the disturbances of eye movements leading to failures in initiating and maintaining smooth pursuit, higher error rates in antisaccade tasks, and disrupted exploratory eye movements. All of these can be observed in schizophrenic patients as well as their relatives (e.g., Crawford et al. 1998; Lencer et al. 2000; Kojima et al. 2001). For smooth pursuit eye movements (SPEM) a genetic linkage to a polymorphism on the short arm of chromosome 6 has recently been shown and replicated (Arolt et al. 1996; Holzman 2001). There is evidence that the SPEM-deficit is associated with negative symptoms in schizophrenic patients (Ross et al. 1996), as well as with traits for "sensitivity" and "suspiciousness" in relatives (Lencer et al. 2003) and in individuals with schizotypal personality (O'Driscoll et al. 1998). Note that this latter syndrome is mainly characterized by formal thought disorders, a syndrome that also could be explained by the disconnectivity hypothesis. The important point in relating this research to Burns' conception is that these disturbances of schizophrenic patients in moving their eyes may underlie their false perception of the environment, resulting in their misinterpreting social situations. In view of the notorious variability of schizophrenic patients in any study, it might prove useful to use these SPEM disturbances as a phenotypic marker which, being easily quantifiable and probably genetically determined, may be used to define more specific subgroups of patients to investigate more closely the hypothesis that specific psychopathological symptoms or neuropsychological signs are caused by disconnections within specified neuronal networks (see also Lee et al. 2001), using the DTI technique.

However, with regard to those neuroanatomical DTI results that form the central piece of evidence in the well-assembled mosaic presented by the target article, there appears to be a major problem: These results do not seem to fit well Burns' general framework, conceiving schizophrenia as the genetic price to be paid for human social life, as highlighted by his introductory citation of George Bernard Shaw saying that progress is thanks to unreasonable people who attempt to adapt the world to themselves. Elaborating on this notion, Burns argues as follows: Cognitive abilities in primates consist of modules only loosely interconnected. Human development is largely related to how those modules formed a network, mutually transforming each other and leading to a hypermorphosis of especially the frontal brain due to increasing fiber tracts connecting frontal cortex with parietal and with temporal cortex. The principal psychological correlate of this networking process is to attribute causality and sense to external events and to refine cognitive skills, but this process may also give rise to creative genius. Therefore, according to Burns, the hallmark of schizophrenia, precisely as suggested by Shaw's bon mot, is the overuse of this attribution, leading to delusional ideas and other main symptoms.

How can this conception be tested by neuroanatomical data? According to Burns, there is evidence from his recently published DTI data that these interconnecting fibers were less clearly marked in schizophrenic patients, forming evidence for weaker cortical connections (Burns et al. 2003). But is this DTI result a proof for Burns' argument? Would the target article have been less convincing if DTI had rendered the opposite finding – that is, if fibers had been more developed in schizophrenic patients? Clearly not! On the contrary, such a finding would have been of advantage for the general thesis: If schizophrenia is conceived of as over-networking, as a disease of the creative, synthetic, imaginative mind, then fiber tracts should indeed be more marked in these patients, not less. Reduced DTI signals were also found in studying the interhemispheric connections of schizophrenic patients' visual cortex (Agartz et al. 2001) which finding underlines the question about how specific the DTI results reported by Burns et al. (2003) in fact are. But as these results now stand, they might lead to the conclusion that George Bernard Shaw was wrong.

Some ethological perspectives on the fitness consequences and social emotional symptoms of schizophrenia

Glenn E. Weisfeld

Department of Psychology, Wayne State University, Detroit, MI 48202.
weisfeld@sun.science.wayne.edu

Abstract: Schizophrenia may not have reduced reproductive success in ancestral times as much as it does today, so explaining how genes for it evolved is more understandable given this prehistoric perspective. Ethological analysis of schizophrenia – understanding how basic emotional behaviors, such as dominance striving, are affected by the condition – might prove useful for comprehending and treating its social emotional symptoms.

I believe the target article is an excellent, even magisterial, interdisciplinary analysis of a puzzling illness. Most of my comments merely address ancillary issues.

First, I do not see the reduced fitness of schizophrenics to be a formidable theoretical problem. The lifetime incidence of about 1% is high for a clearly pathological trait, but the condition typically begins several years after reproduction would have commenced in prehistoric times. We usually think of ancestral populations as having reached reproductive maturity rather late. Menarche occurs in !Kung women at about age 16 and the first birth at about 19. However, most contemporary hunter gatherers, such as the !Kung, live in harsh environments, having been relegated there by more economically efficient populations. In ancestral times, these foragers may well have lived under better conditions and begun to reproduce in their mid-teens. The acceleration of both sexes' reproductive maturity in recent times attests to our species' potential to mature early under propitious conditions. Furthermore, forager men may have married when comparatively young, since men's eligibility to marry depends heavily on economic prowess. Hunting can be successfully pursued by an older adolescent. Moreover, a schizophrenic parent in prehistory would have been assisted in child rearing by the extended family, lending the children fair if reduced prospects for survival. It is also possible that ancestral humans with genes for schizophrenia underwent less stress than modern people, resulting in less frequent or severe symptomatology. Then too, if schizophrenia comprises a set of similar disease entities, the incidence of each may be well below 1%, placing it within the limits of plausible pathology. (See evidence reviewed by McGuire and Troisi [1998]). One study, showing 92% concordance for schizophrenia between pairs of right-handed monozygotic twins, suggests that at least one form is highly heritable and distinct from others (Boklage 1977).

Burns seems to be correct in characterizing schizophrenia as resulting from incomplete differentiation of late-developing, late-evolving cortical structures and their connections. Schizophrenia entails general deficits in higher-order reasoning, involving as it does the dorsolateral prefrontal cortex, association areas, and intrahemispheric tracts. Involvement of the hippocampus is consistent with Burns' emphasis on social cognition, since this structure mediates episodic memory consolidation and retrieval, and receives input from higher sensory processing areas. Deficits in various social behaviors and even evidence of abnormalities in other limbic structures would be expected, given the importance of cognition to the fulfillment of these social emotional needs and the interdependence of different brain areas during brain development. Yet one common symptom, hallucinations, is relatively asocial and seems to derive from anterior temporal lobe abnormalities.

One challenge to those who study schizophrenia will be to integrate understanding of these cognitive abnormalities with ethological interpretations of mental illness. Ethologists assert that behavioral abnormalities are best understood as perturbations of normal behavior (McGuire & Troisi 1998). They emphasize overt, observable behavior – motives or emotions – because natural selection acts most directly on behavioral outputs that serve fitness needs. These theorists view learning and cognition as merely promoting efficient fulfillment of these basic needs of nutrition, defense, reproduction, and so on. Emotion is said to be primary because even relatively simple organisms with limited cognitive capacities possess the panoply of specific motivational tendencies necessary for survival and reproduction. Ethologists and others are seeking to identify and understand our basic emotions, the human ethogram (Panksepp 1998), to serve as a model for interpreting pathologies.

Often there is a failure to recognize the specificity of these evolved emotions, especially the social emotions. For example, humans possess numerous distinct affiliative motives – parental, filial, amorous, friendship, and general kinship affinities. Although sharing some properties and mechanisms, these bonds exhibit distinctive hormonal and neural mediators, elicitors, functions, developmental patterns, and phylogenetic histories. Likewise, aggressive behavior is best broken down into its functional subtypes, including defensive aggression, play fighting, angry aggression, and dominance aggression (Moyer 1976). Each type is activated by a particular affect and possesses a distinctive behavioral form and neural mediation.

Analysis of dominance aggression may illustrate how appreciation of a basic social emotion might enhance understanding of behavioral pathologies. Dominance aggression functions to prompt the individual to compete for scarce resources. Children initially fight for dominance, but later they resort to various other means of establishing supremacy. This distinct emotional mechanism for seeking social success, which can be characterized affectively as pride and shame, is homologous to dominance striving in other primates (Weisfeld 2002). Participation in social hierarchies seems to involve the amygdala and orbitofrontal cortex. As Burns points out, lesions of these interconnected limbic structures can cause a monkey to fail to compete with peers or to comprehend its rank. Similarly, orbitofrontal patients such as Phineas Gage exhibit a specific decrement in concern with the opinions of others, in social competition – not a general failure of social cognition, increased impulsiveness, personality change, or lessened responsiveness to punishment. This primary deficit can lead to sequelae. A monkey with a lesion to the amygdala or orbitofrontal cortex often falls to the bottom of the hierarchy and withdraws socially. Intact animals and people who are low ranking likewise withdraw from these aversive social contacts. The reduction in affiliation that characterizes these individuals seems to be secondary to their low rank and not a separate pathological manifestation. Likewise, depression often arises from social failure and leads to social anxiety and adaptive withdrawal (Sloman & Gilbert 2000). A schizophrenic may withdraw socially because of rejection by others or preoccupation with his hallucinations, delusions, or other symptoms.

Ethologically oriented research on schizophrenia would seek to explain how particular social emotions are disrupted by the cognitive changes of the disease. These manifestations then might be palliated psychotherapeutically, with the more basic cognitive abnormalities being addressed pharmacologically.

Author's Response

Elaborating the social brain hypothesis of schizophrenia

Jonathan Kenneth Burns

Department of Psychiatry, Nelson Mandela School of Medicine, University of KwaZulu-Natal, Durban, 4000, South Africa. **jonny.eliza@3i.co.za**

Abstract: I defend the case for an evolutionary theory of schizophrenia and the social brain, arguing that such an exercise necessitates a broader methodology than that familiar to neuroscience. I propose a reworked evolutionary genetic model of schizophrenia, drawing on insights from commentators, buttressing my claim that psychosis is a costly consequence of sophisticated social cognition in humans. Expanded models of social brain anatomy and the spectrum of psychopathologies are presented in terms of upper and lower social brain and top-down and bottom-up processes. Finally, I argue that cerebral asymmetry evolved as an emergent property of primary intrahemispheric reorganisation in hominoids.

During the two years that have elapsed since I first submitted my target article "An evolutionary theory of schizophrenia: Cortical connectivity, metarepresentation, and the social brain" to *BBS,* I have examined and re-examined many aspects of the hypothesis. My ongoing research as well as the critiques of academic colleagues, not least the 14 commentaries submitted in this journal, has caused me to broaden my thinking and grapple with a number of troublesome questions. For example, the enigma that lies at the heart of schizophrenia research and which initially prompted me to write this paper: Why does a disorder such as schizophrenia, associated with reduced evolutionary fitness, survive in the human genome? This is the curiosity that has perplexed those engaged in study of the disorder for nearly a century. I am grateful to **Crow**, himself a pioneer in schizophrenia research, for reminding us of Huxley and Mayr's early attempts to solve this problem (cf. Huxley et al. 1964). The current debate has a long history, and many of the ideas raised in both the target article and the commentaries are by no means novel. However, I maintain my view that biomedicine is knee-deep in quicksand when it comes to unravelling the complexities of mental disorder, and that a comprehensive understanding of psychosis necessitates a broad sociobiological and evolutionary approach. Delbrück (1949) has said, "The animal or plant or micro-organism . . . [a mature physicist] . . . is working with is but a link in an evolutionary chain of changing forms, none of which has any permanent validity." Mayr (1988) adds, "There is hardly any structure or function in an organism that can be fully understood unless it is studied against this historical background." This is why I reject **Aleman & Kahn**'s position that "the evolutionary framework in which Burns' hypothesis is embedded might be superfluous."

R1. A methodology borrowed from archaeology

Aleman & Kahn quote Lewontin, underlining their scepticism regarding the possibility of a scientific theory of human cognitive evolution. I would agree with these authors that it is probably impossible to achieve such a theory if one relies solely on a narrow empirical method derived from reductionist physics. The construction of a sound evidence base for evolutionary hypotheses is not always easy. How does one generate data about the behaviour and mental state of our ancestors? Relationship dynamics, emotional states, and cognitive processes do not readily fossilise like bones, to be examined and analysed and presented as data. This is a problem that several authors have addressed. Lewis-Williams, a South African cognitive archaeologist and expert on the rock art of the San, recently published an intriguing book entitled *The Mind in the Cave,* in which he interprets the Palaeolithic art of Western Europe in terms of emerging consciousness in early humans (Lewis-Williams 2002). His task is similar to mine in that he faces the same constraints when assembling evidence for his hypothesis. He explains that there are too many gaps in the archaeological record to establish a clear line of argument and this prevents the scientifically reified formal, sequential testing of hypotheses. His solution to this problem is to draw on the work of Alison Wylie, a philosopher of science. Wylie describes a methodology that incorporates important scientific principles of hypothesis testing and that is well suited to the challenge of theorising about archaeological matters. This method she terms *cabling.* Unlike some arguments that form a logical "chain" of sequential links, the cabling method entails the intertwining of numerous strands of evidence. Wylie explains that very often, archaeologists construct an argument by drawing in a number of different strands of evidence from varied scientific sources. For example, the utility of an excavated structure might be elucidated by drawing upon ecological, ethnographic, and anthropological facts that have a bearing on the site. Lewis-Williams makes use of this method in his enquiry, drawing on evidence from extant hunter-gatherer traditions, from psychology and from neuroscience, in his construction of a hypothesis. He argues that the cabling method is sound in that it is both *sustaining* (a strand may compensate for a gap in another strand) and *constraining* (it "restricts wild hypotheses that may take a researcher far from the archaeological record").

In response to **Aleman & Kahn**'s scepticism regarding the possibilities of reconstructing human cognitive evolution, I would argue that such a cabling methodology is valid and indeed appropriate within evolutionary biology. These authors request evidence for "a heritable variation for social cognition in our remote ancestors, . . . and that those who possessed this ability in the remote past left more offspring by virtue of that ability." They are asking the impossible, because social behaviour does not fossilise. We need to approach this problem with a broader perspective than that derived from physical science. Byrne has listed the establishing of a reliable pattern of descent as one part of a methodology for inferring the history of primate cognition (Byrne 2000). Many authors have confirmed the close evolutionary relationship between simian and ape species and modern Homo sapiens, with strong data from comparative psychology, molecular biology, and physical anthropology. Thus, cladistic analysis provides us with living relative species with which we can test the hypothesis that there is a heritable variation for social cognition that increases fitness. Very recently Silk et al. published such a study in *Science* (Silk et al. 2003). They

analysed a huge database documenting social behaviours in 108 female baboons over 16 years. The results showed that a composite index of sociality was highly correlated with infant survival. This study provides the first direct evidence of the selective advantage of sociality in primates. I hope more studies of this nature will follow in other primate species, because this clearly is a research strategy that is feasible and that has the potential to verify the social brain hypothesis.

R2. The evolutionary genetics of schizophrenia

Several commentators have drawn attention to the vagueness of the model I proposed to explain the "survival" of this maladaptive disorder. **Hardcastle** and **Weisfeld** take the extreme view that schizophrenia is a benign trait not subject to natural selection, because reproduction occurred at an earlier age than onset of the disorder in ancestral times. I cannot agree with Weisfeld's somewhat romantic image of the Palaeolithic environment, with abundant food, nurturing families, and limited stress on predisposed individuals. This harkens to a past era where anthropologists idealised the "noble savage" and is in contradiction to most evidence that supports a harsher and more stressful ancestral lifestyle (Bogin 1999): A more severe world where drought, disease, and threat of predation was the norm would have pushed the reproductive age into or beyond the usual age of onset of schizophrenia, thus rendering the disorder subject to natural selection.

Panksepp & Moskal suggest that schizophrenia "is not actively maintained in the genome," and that certain genes make one vulnerable to "epigenetic and environmental factors that promote schizophrenic phenotypes." I certainly agree that the genetic basis of schizophrenia should best be conceptualised as conferring a vulnerability to disorder rather than a disorder itself. Twin studies have shown that genes contribute no more than 50% to aetiology, leaving a major role for developmental and environmental factors (although **Crow** would apparently disagree here). However, this is not sufficient reason to exclude an evolutionary scenario, since one would still expect genes that confer a 50% risk of vulnerability to an "unfit" phenotype to be subject to negative selection and therefore removed from the human genome. The enigma remains, and a putative mechanism for the survival of these genes is still required. In my view, to attribute both past and present survival of schizophrenic phenotypes to "cultural spandrels" is to avoid this central challenge.

Sullivan & Allen favour a balanced polymorphism model with some advantageous behavioural trait exhibited in relatives. Likewise, **Brüne** is prepared to consider a heterozygous advantage and cites new evidence that might support the advantage being located outside the CNS, thus resuscitating Huxley et al.'s original theory (Huxley et al. 1964). If, as Sullivan & Allen state, the 5% advantage required to maintain the polymorphism is difficult to demonstrate, then advocates of this model confront the same problem pointed out by **Crow** in respect of my model, namely, that it is difficult to test and validate.

Keller, **Nesse**, and **Hoffman**, **Hampson**, **Varanko**, **& McGlashan** (**Hoffman et al**.) have offered some fascinating ideas regarding the evolutionary genetics of schizophrenia that help to clarify and strengthen my hypothesis. While I agree with the criticism raised by some commentators – that my genetic argument is vague and ambiguous – I am not prepared to abandon my thesis that the genes for schizophrenia have survived natural selection owing to their association with genes responsible for the evolution of the social brain in our species. On the contrary, the insights of these authors now provide me with material with which I can formulate a more specific and robust model. Although their positions may differ, there appears to be some overlap and the model that follows attempts to integrate this common ground.

Keller rightly asks for clarity regarding my use of the word "genes" in the target article and in reply I confirm that my intended meaning was "allele" (rather than "locus"). I am grateful to this commentator for updating me on recent advances in evolutionary genetics, in particular his clear exposition on the concepts of *mutation-selection balance* and *balancing selection.* I agree that a simple pleiotropic model is inappropriate with regard to schizophrenia and that these two mechanisms may better explain the persistence of susceptibility alleles. While a mutation-selection model may well be suitable, especially in the light of Houle et al.'s (1996) work on "downstream traits," Keller's suggested *antagonistic pleiotropy* model seems to find common ground with **Nesse**'s concept of *cliff-edged fitness* and **Hoffman et al.**'s pruning model. Nesse also considers *antagonistic pleiotropy* a viable model. Consider the following attempt to integrate these ideas into a single model:

1. All humans have at least one susceptibility allele (SA) for schizophrenia because these alleles have been selected for their pleiotropic contribution to the evolution and development of the social brain.

2. There is variation between individuals in the number of SAs, and the presence of increasing numbers of SAs enhances reproductive fitness up to a threshold.

3. An increasing number of SAs corresponds with an increase in the magnitude of the phenotypic trait. In this model the trait is increasing cortical connectivity with associated neural pruning at the histological level and increasingly sophisticated social cognition at the behavioural/psychological level.

4. At a certain threshold (or cliff-edge), the presence of increasing numbers of SAs results in a sharp decrease in the fitness effects of the phenotype. This phenotype constitutes the schizotypal-schizophrenic spectrum. As suggested by **Hoffman et al**., both the schizotypal and schizophrenic phenotype exhibit reduced fitness. Since an increasing number of SAs corresponds with an increase in synaptic connections (both normal and abnormal) and increased peri-adolescent pruning, the schizotypal-schizophrenic brain is characterised by reduced final cortical connectivity. Thus, the diffusion tensor imaging (DTI) findings of reduced FT and FP connectivity are predicted by this model (and not a problem finding, as alleged by **Verleger & Lencer**).

5. As suggested by **Hoffman et al**., the at-risk carrier (the schizotype) exhibits normal or reduced fitness, thus negating the need for a balanced polymorphism model. Additional SAs, environmental factors, and epigenetic effects convert some of these at-risk individuals to full-blown disorder.

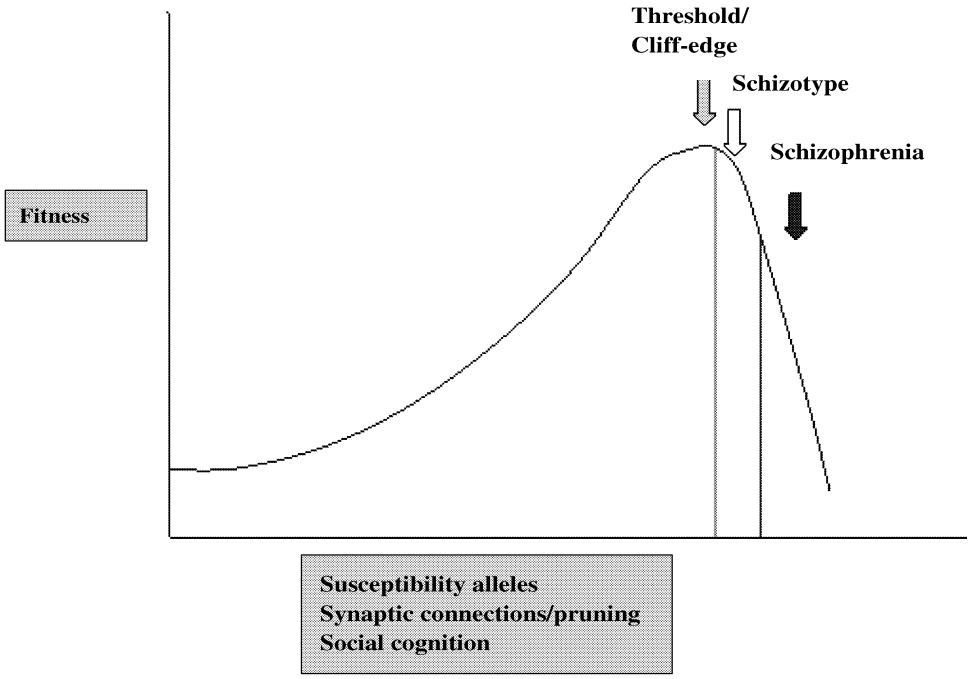

Figure R1 (Burns). Evolutionary genetic model for the "survival" of schizophrenia susceptibility alleles.

This model is depicted in Figure 1 and incorporates **Nesse**'s concept of "cliff-edged fitness" effects as well as **Hoffman et al**.'s proposal that both "at-risk" schizotypes and those with schizophrenia fall beyond the threshold and therefore exhibit reduced fitness effects. It also acknowledges the role of environmental and epigenetic effects in the conversion of the at-risk phenotype to the disorder phenotype, as stressed by **Panksepp & Moskal**. Finally, the model is consistent with **Keller**'s account of antagonistic pleiotropy.

R3. Linking genes to phenotypes

Crow and **Panksepp & Moskal** ask for predictions regarding which genes could be responsible for hominid-specific dysconnectivity in schizophrenia and how in fact these gene effects disturb the structure or function of the cortex. **Gilbert** highlights the difficulty encountered within schizophrenia research in linking specific genes to specific phenotypes. The clinical heterogeneity of the disorder, the variability in neuropathological findings, and the lack of progress in identifying specific gene mutations means that we are dealing with a complex multidimensional syndrome (rather than a specific disease entity) that probably breaks down into a number of disease processes with variable aetiologies. Crow has become an advocate for a single gene mutation model of schizophrenia – a bold and lonely stand in the face of overwhelming evidence to the contrary. This seems to contradict his earlier significant and well-supported concept of a spectrum of psychosis. It is true that protocadherin X and Y have been subject to positive selection in the hominid line, making this an attractive candidate for human-specific traits. However, there must be many other hominid-specific mutations as yet unidentified that could equally likely have played a role in the evolution of human cognition. Until the chimpanzee genome has been mapped entirely and compared against the human genome, we will not be in a position to predict the genes responsible for human cortical dysconnectivity. Furthermore, as I stated in my target article, a simple comparison of human and chimpanzee genomes will not necessarily yield these answers either, because the cognitive differences between us may well be a result of altered gene expression rather than gene mutation.

Furthermore, the chimp is derived from a common ancestor and therefore has undergone its own mutations, so differing loci identified in a side-by-side comparison of genomes may be hominid-specific or chimp-specific. In terms of predicting genes responsible for cortical dysconnectivity, then, I think it is premature to speculate beyond proposing that susceptibility alleles (SAs) for schizophrenia are likely to be among those that have a role in cortical generation. There are likely to be multiple SAs that regulate neurogenesis, differentiation, arborisation, synaptogenesis, myelination, and possibly apoptosis (see my discussion in the target article, sect. 6.2). Of interest is a recent study of caspases (apoptotic proteins) in schizophrenia, which showed that temporal cortical cells are vulnerable to apoptosis in the disorder (Jarskog et al. 2004). This might suggest that there is disordered circuitry prior to adolescent pruning, as suggested in the target article.

R4. The anatomy of the social brain

A number of commentators critique the cognitive bias of my model of the social brain and its dysfunction in schizophrenia. **Panksepp & Moskal** make a case for greater focus on the role of the "foundational social circuits of the mammalian brain," whereas **Gilbert** feels I have stressed "top-down" processes to the exclusion of "bottom-up" effects on social cognition. **Weisfeld** argues for a greater in-

tegration of the ethological perspective in constructing a model of the social brain, and he joins Panksepp & Moskal in advocating an analysis of basic limbic-driven social emotions and motives in order to understand hominid-specific social cognition. While I fully acknowledge the bias in my target article toward cognitive aspects of social behaviour and cognition, I disagree with the assertion that, like other "cognitive/evolutionary psychological views," I have "ignored too many of the foundational social circuits of the cross-mammalian limbic brain" (Panksepp & Moskal). In section 3.3 of the target article, I included extensive discussion of the amygdala and OFC, structures generally accepted as limbic and of major evolutionary significance. Furthermore, I have acknowledged the role of basic social functions such as affiliative bonding, emotion regulation, and the representation of choice bias. It seems Panksepp & Moskal have misunderstood my conceptualisation of the social brain as an integrated, connected system and this may account for their comments. They group my approach together with "most modular views of evolutionary psychology," and this is unfair in my opinion, for I have explicitly attempted to move away from the modular/evolutionary psychology paradigm as espoused by Fodor (1983), Cosmides & Tooby (1992) and others. In section 4 of the target article I have formulated (vis à vis Mithen 1996) a model characterised by a "breakdown in this modularisation," "cognitive fluidity," and the "integration of specialised information" (target article). Perhaps a little clarification is required, because it was not my intention to ignore the derived limbic contributions to the social brain.

It may be useful to consider the social brain a system of integrated circuits, including both limbic and cortical structures and functionally operating in terms of both "top-down" and "bottom-up" processes. Within such a system one could, anatomically, identify both an *upper social brain* and a *lower social brain,* the former being the cortical aspects and the latter the subcortical aspects. In terms of my model this distinction is artificial; I do not support a modular view but rather an integrated, "fluid" view. However, this may be a useful model, because it acknowledges both primitive and newer aspects in the system. Furthermore, it may coincide with a dimensional approach to psychopathology (see discussion below). Top-down processes include the function of the heteromodal cortex "elaborat[ing] theories of mind and complex sociocognitive strategies" as suggested by **Panksepp & Moskal** and involve attentional, working memory, and executive functions. Bottom-up processes originate in the primitive subcortical regions and regulate basic emotions, motives, and drives (as discussed by **Gilbert** and **Weisfeld**). So, in schizophrenia, for example, Gilbert's "threat and safety systems," which are limbic-based, might interact in a bottom-up fashion with higher cognitive processes to give rise to malevolent voices and paranoid ideation.

This more generalised model of the social brain would also go some way to addressing the concerns of **Bosman**, **Brunetti**, **& Aboitiz** (**Bosman et al**.) who argue that schizophrenia is a disorder of generalised (rather than localised) connectivity. If the social brain is conceptualised in broader terms as an integrated system of both primitive (subcortical) and recently evolved (neocortical) components, then the deficits in attentional, perceptual, and higher functions that characterise the disorder are compatible with the hypothesis that schizophrenia is a disorder of the social brain. In the target article, I acknowledged the role of these generalised cortical functions in social cognition, theory of mind, and the psychopathology of schizophrenia. Furthermore, I believe that Bosman et al.'s discussion of neural synchrony and their work on "anterior-posterior networks regulating top-down and bottom-up processes" does not conflict with a broader view of the social brain. It may be that "high-frequency neuronal synchrony" operates as "a binding mechanism" in a bidirectional manner between the upper and lower social brain. Neural synchrony, according to these commentators, may be responsible for the integration process termed "cognitive coordination" by Phillips & Silverstein (2003). These concepts seem identical to concepts discussed in section 4 of the target article.

Likewise, the well-documented, generalised neurochemical abnormalities in schizophrenia are no longer a problem for the social brain hypothesis if one conceptualises the social brain in broader terms. **Bosman et al**. cite the role of inhibitory GABA interneurons in "the maintenance of reverberatory circuits in large scale networks," and both GABA hypofunction and dopamine hyperfunction in schizophrenia have been correlated with functional dysconnectivity in the disorder (Carlsson et al. 2001; Dolan et al. 1999; Heinz et al. 2003). Abnormal neuronal connectivity in both cortical and subcortical components of the social brain in schizophrenia is likely to correlate with neurotransmitter receptor abnormalities in these circuits, thereby accounting for the "established neurochemical vectors" of the disorder (**Panksepp & Moskal**).

I agree with **Panksepp & Moskal** that the upper social brain (USB) is in part epigenetically derived and is in part "guided by limbic socioemotional functions." But the converse is likely to be true also: The lower social brain (LSB) is unlikely to be wholly exempt from epigenetic modulation (given its long evolutionary history) and since we know that frontotemporal and frontoparietal cortical systems have ancient origins within the primate line, it seems likely that the LSB has been subject to "guidance" by these cortical systems during hominid descent. To limit the role of genes to the LSB and attribute USB components of the social brain solely to "epigenetic programming" is, in my view, reductionist and erroneous. Furthermore, Panksepp & Moskal are incorrect in stating that I have considered the "sociocortical connections unique to humans." In fact, in section 8 of the target article I extensively detailed a continuum of evolved connectivity in both ancestral and extant hominoids.

Likewise, in response to these commentators' comments on the evidence for psychosis in animals, I would draw their attention to section 2.3 of the target article, where I discuss **Crow**'s theory and his assumption that "other species do not have a capacity for psychosis"; this sentence continues: "to date, this is neither proven nor disproven" (cf. target article). In a sense **Panksepp & Moskal** are correct – I do believe "*schizophrenic* genotypes and phenotypes are restricted to our own species"; schizophrenia, as we know it and currently understand it, is a complex polygenic disorder with multiple aetiologies, including environmental and epigenetic processes uniquely evolved in Homo sapiens. Schizophrenia is the result of having highly evolved social brain circuitry. I certainly do not believe, however, that other species do not have the *capacity for psychosis.* The fact that I have elaborated the continuum of connectivity

that exists in primates implies that I would support Panksepp & Moskal's thesis that cortical derangement would "impair mice less than men" and would give rise to a vulnerability to psychosis-like behaviour. But I don't think one can call the syndrome of stereotypic disorganised behaviour induced by amphetamines and other psychotogenic substances an animal form of schizophrenia. In our psychiatric nomenclature, schizophrenia is a functional disorder, and we are hesitant to diagnose the disorder in the presence of acute drug intoxication. To my knowledge, there is very slim and mostly anecdotal evidence for "spontaneous" psychosis in other species. And even if there were, the absence of language and complex social cognition outside our species means such a syndrome would only approximate the disorder we recognise in humans.

R5. Psychopathology and the social brain

Brüne quite rightly points out that an evolutionary theory of schizophrenia must account for all possible symptoms, and his discussion of mirror neurons and catatonia is a useful addition. Brüne goes on to address the problems posed by the clinical heterogeneity of mental disorders for an evolutionary theory of schizophrenia. He stresses the need for cross-culturally similar prevalence rates of the disorder if an evolutionary perspective is to have relevance and then highlights the problems we have with identifying a core "disease entity." In their fascinating report of their work in Micronesia, **Sullivan & Allen** tell us of great variability in both prevalence rates and clinical presentation in their study population. Does this mean that an evolutionary perspective is rendered meaningless (as argued by **Aleman & Kahn**) and that **Hardcastle** is correct in suggesting that schizophrenia is "a benign trait"? I do not think so, but I do think Brüne gives us cause to reconsider what we mean by the term *schizophrenia.* In section 2.1 of the target article, I refer to the notion of "continua of variation" between schizophrenia and the affective psychoses and between "disorder" and "normality." Clearly, as Bentall (2003), Brüne (2004; and see Brüne's commentary in this issue) and others have maintained, all of the symptoms we attribute to schizophrenia manifest in other psychiatric disorders as well. And, of all of these symptoms, impaired social cognition is probably the most protean and widely found, as Brüne (2004; Brüne et al. 2003; and present commentary) has observed. What are the consequences of these troublesome facts for the social brain hypothesis of schizophrenia?

I believe that an expanded model of the social brain (as detailed above), with both upper and lower components and top-down and bottom-up processes, provides us with a framework within which to explain most mental disorders in terms of a spectrum of social brain dysfunction. **Brüne** tentatively suggests that "virtually all psychiatric disorders fall into the category of 'social brain disorders,'" and he advocates a nosological shift from syndrome- to symptom-based diagnosis: two potentially bold statements, both of which I support. There is good evidence for social brain dysfunction in autism (Baron-Cohen et al. 1985), bipolar disorder (Kinderman 2003), psychopathy (Mealey & Kinner 2003), and dementia (Snowden et al. 2003), and in time further research may well demonstrate similar problems in other psychiatric disorders. Clearly, the aetiological factors responsible for dysfunctional social cognition may vary according to specific expressions of psychopathology (see discussion in Brüne et al. 2003), but I would suggest that the anatomical and functional location of specific disorders within the structure of the social brain may also vary. Since the social brain is a broad system of interconnected cortical and subcortical structures, it is feasible that social brain disorders manifest differently from one another according to where in the system their focal point of pathology lies. For example, anxiety and depression are likely to be an expression of predominant lower social brain (LSB) dysfunction, based in a primary limbic and brain stem pathology with bottom-up processes leading to secondary cognitive disturbance. On the other hand, psychotic illness might be understood in terms of both lower and upper social brain (USB) pathology with bottom-up and top-down processes giving rise to a range of primitive (e.g., threat vs. safety judgements) and recently evolved (e.g., paranoid delusion) symptoms. This model would accommodate and possibly help explain the subgroup of schizophrenia sufferers referred to by **Gilbert** where post traumatic stress disorder is aetiological. Within the spectrum of schizophrenias, one might surmise that those individuals with prominent positive and affective symptoms (whose symptomatology may overlap with bipolar and unipolar mood disorders) have predominant LSB dysfunction, while those with negative schizophrenia have predominant USB dysfunction. See Figure 2.

R6. Auditory hallucinations and theory of mind

Hoffman et al. argue that the major psychotic symptom of auditory hallucinations is not accommodated by my social brain hypothesis of schizophrenia. These authors have modeled auditory hallucinations using intriguing computer pruning experiments that produce "attractor states that intrude into information processing." While I agree with their notion that pruning of developing circuits contributes to structural and functional dysconnectivity in social brain circuits in schizophrenia (see sect. 6.2 of the target article) and that this is the basis of psychotic symptoms, I must convey my scepticism regarding the use of computer technology as an accurate model of brain function. Conrad (1989) was a pioneer in investigating biological information processing and strongly supported what he termed the *brain-machine disanalogy;* that is, that computer modeling cannot be absolute in replicating complex brain function. Despite rapid sophistication in this field, most of his views have been confirmed in the decade since he published his major thesis (Ziegler 2002). Hoffman et al. maintain that since patients with schizophrenia attribute auditory hallucinations to an "other," it follows that they must have intact theory of mind (ToM), because they can distinguish "self" from "other." But in my model of schizophrenia, I explicitly stated that this disorder is characterised by the development of a ToM that later becomes disrupted as the psychosis ensues. So, yes, people with schizophrenia can differentiate self from other (because this ability developed during childhood), but with the emergence of neural dysconnectivity and *cognitive malintegration* (or *disjunction* [Cleghorn & Albert 1990]), the relationship between self and other is misinterpreted, giving rise to positive and negative symptoms.

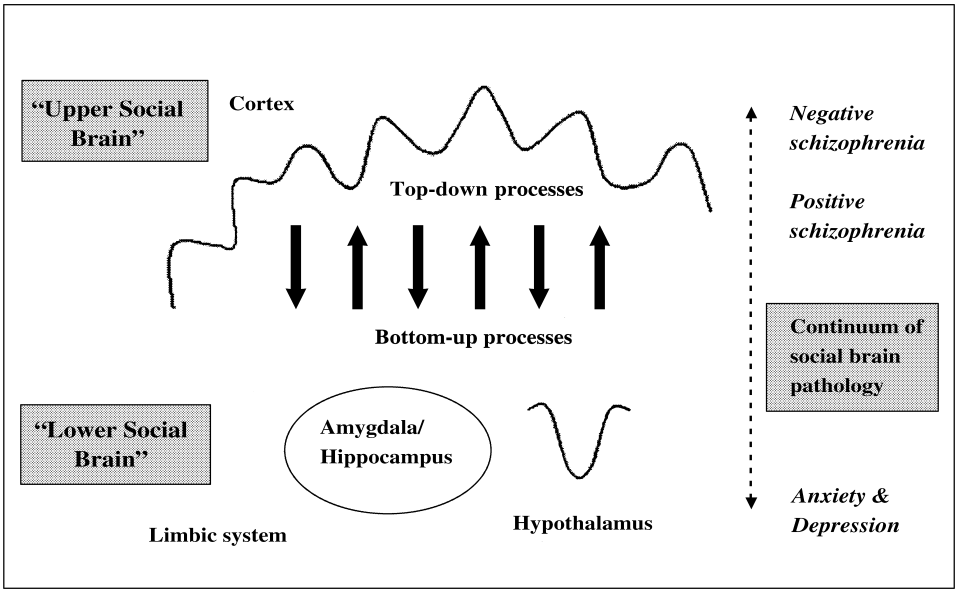

Figure R2 (Burns). Model of the social brain showing different components, processes, and the predominant location of pathology for a continuum of "social brain pathology."

R7. The question of cerebral laterality

Several issues arise from the commentaries regarding the question of cerebral laterality, interhemispheric connectivity, and the ontogeny of orbitofrontal asymmetry (**Crow**, **Aleman & Kahn**, and **Rotenberg**). Crow dismisses the social brain hypothesis of schizophrenia in favour of the language/asymmetry theory he developed; yet he offers no reasons other than that the latter is "a more precise and heuristic evolutionary theory." The three areas of deficiency he identifies in my theory are in my opinion redundant; all are addressed in the target article. He states: "It provides no explanation of the cortical changes," and "dysconnectivity of what, and why?" I protest! In section 9.2, I suggest that *sequential hypermorphosis* may "alter the pattern of expression of individual developmental genes across the cortical plate." This hypothesised mechanism might account for the abnormalities of cortical connectivity in frontotemporal and frontoparietal white matter systems associated with the schizophrenic brain. And surely the detailed discussion of *cognitive malintegration* in section 4 constitutes a thorough explanation of nuclear symptoms? Crow's third point is addressed, both in the target article and in section R3 above; perhaps he and I must agree to differ since the gap that separates us is based upon a fundamental theoretical divergence. He believes in a speciation event during the evolution of Homo sapiens, and this necessitates his adherence to a single gene mutation model. I believe in the gradual emergence of modern human cognition, and this necessitates my adherence to a multiple gene effect model. Therefore, I cannot predict how any one gene might give rise to structural dysconnectivity. Crow is asking me to defend something I don't believe in!

Aleman & Kahn complain that I have ignored the abnormalities of transcallosal white matter connectivity demonstrated in some studies of schizophrenia. Their complaint is justified and I agree that any theory of schizophrenia must acknowledge and account for the findings of both *interhemispheric* and *intrahemispheric* dysconnectivity. In my discussion of the evolution of cerebral asymmetry in section 8.3, I argue that asymmetry has ancient roots within the hominoid lineage and that it emerged as a result of decreasing interhemispheric connectivity and increasingly lateralised specialisation of functions. Therefore, there seems to have been a reciprocal relationship between inter- and intrahemispheric connectivity. If, as I have suggested, the elaboration of intrahemispheric tracts was associated with an increase in developmental vulnerability of these emerging networks, then it is no surprise that interhemispheric tracts would be similarly vulnerable to developmental insults. In schizophrenia where we find abnormal FT and FP connectivity, it follows logically, therefore, that there should also be some differences in transcallosal white matter. I would suggest that FT and FP abnormalities are primary and are genetically determined and that transcallosal abnormalities are a secondary developmental consequence of faulty wiring within the hemispheres. This relationship between inter- and intrahemispheric connectivity accounts too for the findings of reduced asymmetry in the disorder, since aberrant wiring within the hemispheres means that discrete functions are inadequately lateralised during development. In summary, therefore, I am suggesting that intrahemispheric dysconnectivity is primary in schizophrenia and that the findings of both interhemispheric dysconnectivity and reduced asymmetry are a secondary developmental consequence.

Crow does not respond in his commentary to the recent demonstration of directional asymmetries in extant ape species, but he has responded previously to this potential problem for the language/asymmetry hypothesis of schizophrenia (Crow 1998c; 2003; 2004a). Crow questions the validity of the methodology employed in studies showing directional asymmetry in apes. He argues that accurate measurement of, for example, the planum temporale, is dif-

ficult and that "the apparent asymmetries of function in the above studies (may be) secondary to differences in lesion topography that relate to asymmetries of the cerebral vasculature extrinsic to the brain rather than to asymmetries of the brain itself" (Crow 1998c). He may be right, and as he suggests, "systematic studies are clearly required." As is the case with all groundbreaking discoveries that force us to rethink accepted "truths," only replication of these findings will conclude the matter. Personally, I believe that directional asymmetry has early origins in hominoid descent and the discoveries of Gannon et al. (1998) and others will be vindicated.

Finally, we must address the issue, highlighted by **Sullivan & Allen**, of variability between the sexes in terms of prevalence and age of onset of schizophrenia. Why do males in general have earlier onset of the disorder and why, in Micronesia, does schizophrenia predominate in males and have greater social dysfunction than in females? **Crow** argues that the psychosis gene is subject to sexual selection and that this accounts for these gender differences. However, I think that the contribution from **Rotenberg** in this volume is instructive on this issue and may help to resolve this question without resorting to sexual selection. He refers to the specific ontology of the OFC, differentiating right and left hemispheres in terms of their respective functions and development. He maintains that right OFC maturation commences earlier, progresses faster, and continues longer than left OFC maturation, and he identifies the right frontal hemisphere as responsible for full integration in the "polysemantic context." Furthermore, he states that males have prolonged brain maturation relative to females, providing the potential for marginal increases in creativity but a corresponding increase in vulnerability to pathology.

In terms of the social brain hypothesis, I would suggest that the evolution of the hemispheres progressed as follows: We know from the work of Rilling and Insel (1999a) that intrahemispheric connectivity increases disproportionate to increasing brain size and that interhemispheric connectivity decreases, leading to these authors' conclusion that directional asymmetry was an emergent property of primary intrahemispheric reorganisation and localisation of functions (Hopkins & Rilling 2000; Rilling & Insel 1999a) – see discussion in target article, section 8.3. It follows that the ontological and functional features specific to the right hemisphere (as described by **Rotenberg**) are a consequence of the evolutionary processes described by Rilling and colleagues – that is, they are emergent properties of primary intrahemispheric reorganisation. The notion that the right hemisphere is responsible for the polysemantic context is thus compatible with my hypothesis that evolving FT and FP connectivity in hominid ancestors gave rise to a complex neural net responsible for social cognition in modern Homo sapiens. Likewise, Rotenberg's argument that the right hemisphere matures longer than the left, especially in males, is compatible with my thesis that increasing connectivity and capacity for sophisticated social cognition was associated with increasing vulnerability to developmental insult. It also explains why in certain contexts, males should be more vulnerable than females to neurodevelopmental disorders such as schizophrenia, and why these disorders generally manifest earlier in males than in females. If prolonged cortical development renders the phenotype more vulnerable to pathology, then it is no surprise that males show a disadvantage, since they have prolonged cortical maturation relative to females.

R8. Conclusion

I am grateful to the commentators for forcing me to address certain issues that were either vaguely or inexpertly handled in the target article. Likewise, I appreciate the insights and suggestions offered by those closer to the rock-face of brain research than I. These insights (for example, on current thinking in evolutionary genetics) have, I believe, enriched and strengthened my original thesis. Clearly, there are a host of unresolved and controversial viewpoints, and I make no claim to be nearer the truth than anyone else. However, it remains a fact that the concept of an evolved social brain in our species is gaining support from innovative research methods and the growing acceptance of social processes as a driving force in human descent. The social deficits that characterise most psychopathologies illustrate the unambiguous importance of mature social cognition for healthy individual and interpersonal functioning. Even if I am wrong in some of my speculations regarding the origins of schizophrenia, I hope that this dialogical process printed in the pages of this journal has helped to focus attention on the devastating social dysfunction suffered by individuals living with mental disorders such as schizophrenia.

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Letters "a" and "r" appearing before authors' initials refer to target article and response respectively.

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