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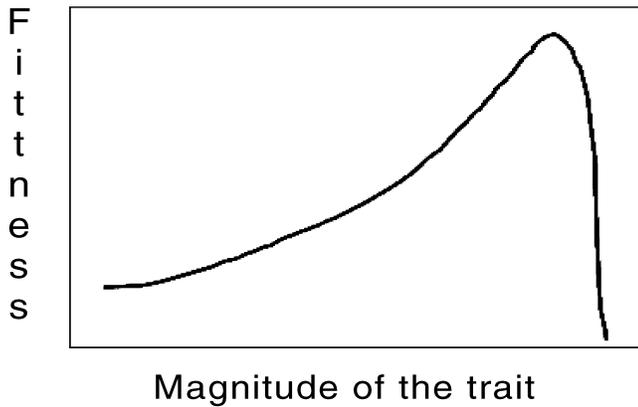
Figure 1 (Nesse). A cliff-edged fitness function: As the trait increases, fitness increases increasingly rapidly, then crashes.

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 exist abundantly for specific symptoms (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

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 fascinat-

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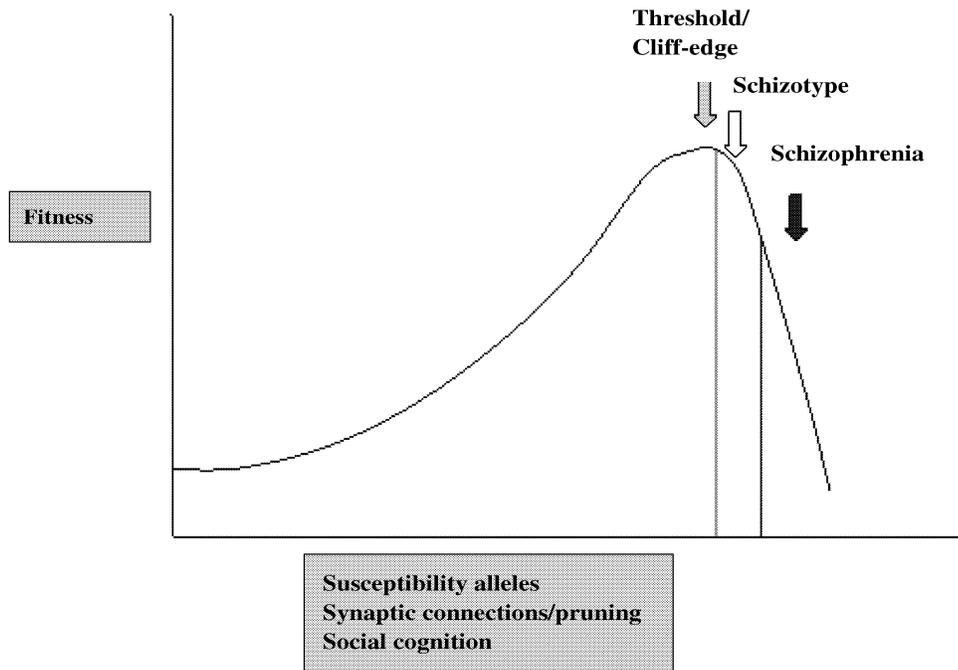
Figure R1 (Burns).   Evolutionary genetic model for the "survival" of schizophrenia susceptibility alleles.

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-