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

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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.

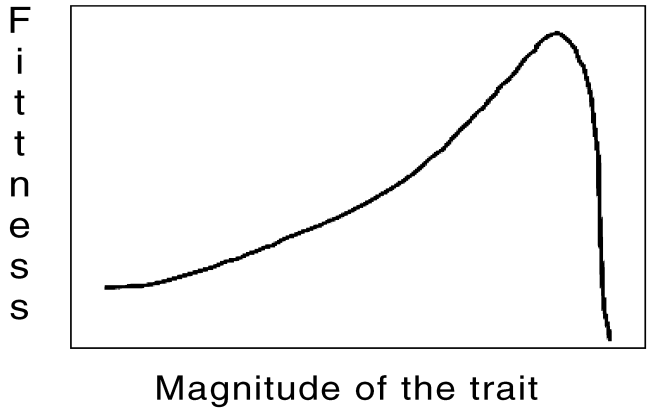

Figure 1 (Nesse). A cliff-edged fitness function: As the trait increases, fitness increases increasingly rapidly, then crashes.

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

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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