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

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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-

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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.

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