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

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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

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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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