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Resolving the paradox of common, harmful, heritable mental disorders: Which evolutionary genetic models work best?

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Abstract: Given that natural selection is so powerful at optimizing complex adaptations, why does it seem unable to eliminate genes (susceptibility alleles) that predispose to common, harmful, heritable mental disorders, such as schizophrenia or bipolar disorder? We assess three leading explanations for this apparent paradox from evolutionary genetic theory: (1) ancestral neutrality (susceptibility alleles were not harmful among ancestors), (2) balancing selection (susceptibility alleles sometimes increased fitness), and (3) polygenic mutation-selection balance (mental disorders reflect the inevitable mutational load on the thousands of genes underlying human behavior). The first two explanations are commonly assumed in psychiatric genetics and Darwinian psychiatry, while mutation-selection has often been discounted. All three models can explain persistent genetic variance in some traits under some conditions, but the first two have serious problems in explaining human mental disorders. Ancestral neutrality fails to explain low mental disorder frequencies and requires implausibly small selection coefficients against mental disorders given the data on the reproductive costs and impairment of mental disorders. Balancing selection (including spatio-temporal variation in selection, heterozygote advantage, antagonistic pleiotropy, and frequency-dependent selection) tends to favor environmentally contingent adaptations (which would show no heritability) or high-frequency alleles (which psychiatric genetics would have already found). Only polygenic mutation-selection balance seems consistent with the data on mental disorder prevalence rates, fitness costs, the likely rarity of susceptibility alleles, and the increased risks of mental disorders with brain trauma, inbreeding, and paternal age. This evolutionary genetic framework for mental disorders has wide-ranging implications for psychology, psychiatry, behavior genetics, molecular genetics, and evolutionary approaches to studying human behavior.

Keywords: adaptation; behavior genetics; Darwinian psychiatry; evolution; evolutionary genetics; evolutionary psychology; mental disorders; mutation-selection balance; psychiatric genetics; quantitative trait loci (QTL)

1. Introduction

Mental disorders such as schizophrenia, depression, phobias, obsessive-compulsive disorder, and mental retardation are surprisingly prevalent and disabling. In industrialized countries such as the United States, an estimated 4% of people have a severe mental disorder (National Institute of Mental Health 1998), and almost half of people will meet the criteria for some type of less severe mental disorder at some point in their lives (Kessler et al. 2005). The annual economic costs in treatment and lost productivity are in the hundreds of billions of dollars (Rice et al. 1992). The less quantifiable personal costs of mental disorders to sufferers, families, and friends are even more distressing. For example, schizophrenia affects about 1% of people worldwide (Jablensky et al. 1992), typically beginning in early adulthood and often following a chronic lifelong course. People with schizophrenia often imagine hostile, confusing voices; they have trouble thinking clearly, feeling normal emotions, or communicating effectively; and they tend to lose jobs, friendships, and sexual partners. In response, many people with schizophrenia kill themselves, and a much larger proportion dies childless.

This is an evolutionary puzzle, because differences in the risk of developing schizophrenia and other common, debilitating mental disorders are due, in large part, to differences in people's genes. Given that natural selection has built the most exquisitely complex machinery known to humankind – millions of species of organic life-forms – why do so many people suffer from such debilitating and heritable mental disorders? If these mental disorders are as disabling as they appear, natural selection should have eliminated the genetic variants (*susceptibility alleles*) that predispose to them long ago. Does the prevalence of heritable mental disorders therefore imply that mental

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disorder susceptibility alleles were selectively neutral or perhaps even advantageous in the ancestral past, or has natural selection been unable to remove susceptibility alleles for some hidden reason?

1.1. The goal of this article and who should read it

This article tries to develop an understanding of the evolutionary persistence of susceptibility alleles underlying common, heritable, harmful mental disorders. We compare and contrast the three broadest classes of evolutionary genetic models that explain persistent genetic variation: ancestral neutrality, balancing selection, and polygenic mutation-selection balance. Such models have been tested mostly by evolutionary geneticists on traits such as bristle numbers in fruit flies, survival in nematode worms, and growth rates in baker's yeast. Yet these models make strong, discriminating predictions about the genetics, phenotypic patterns, and fitness payoffs of any trait in any species, and so should be equally relevant to explaining mental disorder susceptibility alleles. However, these three main models of persistent genetic variation have never before been directly compared with regard to their theoretical and empirical adequacy for explaining human mental disorders. That is our first main goal.

Our second main goal is to promote more consilience among evolutionary genetics, human behavioral/psychiatric genetics, and Darwinian psychiatry/evolutionary psychology. Trying to integrate these disparate fields is hard, not just because each field has different goals, terms, assumptions, methods, and journals, but also because each field has various outdated misunderstandings of one another. For example, we will argue that Darwinian psychiatry often relies too heavily on balancing selection, whereas psychiatric genetics often assumes fitness neutrality or ignores evolutionary forces altogether. Although balancing selection and neutral evolution were historically seen as primary causes of genetic variation, they have proven less important than expected in explaining persistent genetic variation in traits related to fitness. Conversely, the third model – polygenic mutation-selection balance – has enjoyed a theoretical and empirical renaissance in evolutionary genetics, but remains obscure and misunderstood in psychiatric genetics and Darwinian psychiatry.

Cross-fertilization between these fields promises not only to shed light on deep quandaries regarding the origins of mental disorders; it also may help resolve some ongoing frustrations within each field by guiding research and theory more effectively. Evolutionarily oriented mental health researchers, such as Darwinian psychiatrists and evolutionary psychologists, often go to torturous lengths to find hidden adaptive benefits that could explain the evolutionary persistence of profoundly harmful mental disorders such as schizophrenia or anorexia, but these accounts are often frustratingly implausible or hard to test. New ideas from evolutionary genetics and data from psychiatric genetics can help this audience better understand which evolutionary genetic models are theoretically credible and empirically relevant to mental disorders.

Many psychiatric and behavioral geneticists try to find the specific susceptibility alleles that underlie common, harmful, heritable mental disorders. They are often frustrated that even the most promising loci explain little overall population risk and rarely replicate across studies or populations. Traditional methods for gene hunting implicitly assume that mental disorder susceptibility alleles will be at relatively high frequencies and common across populations. Such a convenient scenario, we will argue, could arise from ancestral neutrality or balancing selection, but is much less likely to arise from a mutation-selection balance. Evolutionary genetics could help guide more fruitful gene hunting based on more realistic assumptions.

Evolutionary geneticists try to understand the origins and implications of natural genetic variation across traits and species. The beautiful empirical and theoretical work in evolutionary genetics is under-funded and too often thought irrelevant to human welfare. Greater familiarity with evolutionary genetics might help funding agencies appreciate the potential relevance of this work to understanding some of the leading causes of human suffering, and may introduce evolutionary geneticists to rich genetic data sets on complex human traits such as mental disorders that can be used to test evolutionary models.

1.2. What this article owes to Darwinian psychiatry

In developing our ideas, we build upon Darwinian psychiatry as it has developed over the last 20 years (McGuire & Troisi 1998; Nesse & Williams 1994; Stevens & Price 2000a). Our starting point is the Darwinian psychiatric view that dysfunction is difficult to infer without an understanding of function (Troisi & McGuire 2002; Wakefield 1992). Mental disorders, by this viewpoint, reflect a failure of one or more psychological adaptations to perform their proper, naturally selected, prehistoric functions (Troisi & McGuire 2002; Wakefield 1992). The heart is an adaptation designed to pump blood, for example, and its failure causes blood-circulation

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problems that are functionally distinguishable from a pancreas's failure to regulate blood sugar or a lung's failure to oxygenate blood. Likewise, there is a clear mental health problem when a brain is unable to feel social emotions or make sense of reality. This perspective has some important corollaries.

First, a better understanding of normal psychological adaptations should help delineate harmful dysfunctions in those adaptations. Research on adaptive function (e.g., evolutionary psychology; Barkow et al. 1992; Buss 1995) and research on maladaptive dysfunction (e.g., Darwinian psychiatry) are mutually illuminating. This is equally true when mental disorder symptoms have only indirect relationships to psychological adaptations. For example, reading disorders cannot result from a dysfunction in a "reading adaptation," because the visual and linguistic adaptations that enable reading evolved long before the invention of writing a few thousand years ago (Wakefield 1999a). Likewise, auditory hallucinations in schizophrenia probably do not result directly from dysfunction in a "hallucination-suppression adaptation," but indirectly, as side-effects of dysfunctions in more plausible mechanisms that, for example, coordinate and store short-term information, or that filter irrelevant stimuli (Cannon & Keller 2005).

Second, many mental disorders are probably extreme points along a continuum of symptom severity that ranges from patently *unaffected* to extreme forms of the disorder. This makes distinctions between "normal" and "abnormal" somewhat arbitrary (Farmer et al. 2002), because psychological adaptations often show continuous degradation of performance. In this dimensional view of mental disorders, schizophrenia is an extreme form of schizotypal and schizoaffective personality disorders, mental retardation is an extreme form of low intelligence, chronic depression is an extreme form of normal depressive reactions, and so forth. Even mental disorders that look like discrete categories at the phenotypic macro-level (mainly eating, dissociative, post-traumatic stress, melancholic depressive, and antisocial disorders; Haslam 2003) may be influenced by the cumulative effect of many minor dysfunctions at the micro-level of genes and brain development (Gottesman & Shields 1967).

Third, some apparently pathological behaviors may not really be disorders at all from an evolutionary perspective because they do not reflect genuine maladaptive dysfunctions. In particular, some clinically defined mental disorders such as certain phobias or depressions may be *reactive defenses* analogous to fever, nausea, and bodily pain, which protect against infections, toxins, and tissue damage, respectively (Gilbert 1998; McGuire & Troisi 1998; Nesse & Williams 1994). Aversive defenses are cues that something in the environment is wrong, not pathologies themselves.

Consider, for example, depression in light of the reactive defense model. In response to major failures or losses, normally expressed depressive symptoms (e.g., pessimism and fatigue) may adaptively withdraw effort from unpropitious situations when the marginal fitness returns are likely to be low, and emotional pain may motivate avoidance of such situations in the future (Keller & Nesse 2005; 2006; Nesse 2000). These normal reactions are illustrated by the regression line in Figure 1; more severe situations provoke more protracted and severe

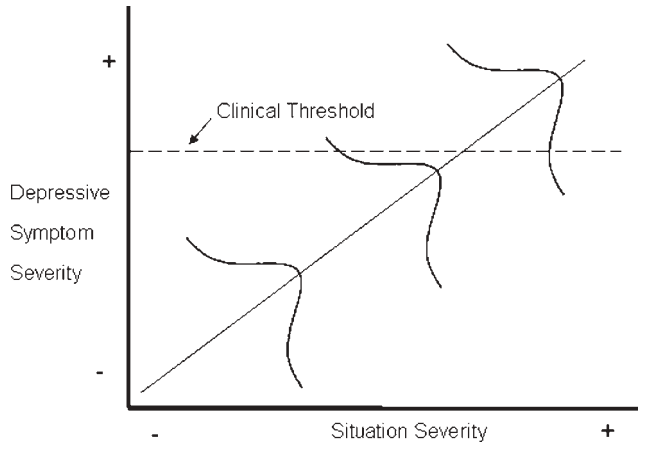

Figure 1. The reactive defense model as applied to depressive reactions (see T.A. text).

reactions. The Gaussian distributions in Figure 1 illustrate interpersonal differences, including genetic differences, which influence symptom severity, given a certain level of situation severity. Since severe situations (e.g., major failures, death of kin) can cause nearly anyone to experience depressive symptoms (Monroe & Simons 1991), some cases of severe and prolonged depressive symptoms (i.e., clinical depression; see above the dashed line in Fig. 1) may simply be normal and adaptive responses to very adverse situations. At the same time, depressive symptoms that are abnormally severe, given the situation (the positive extremes of the Gaussian distributions), may signify malfunctions in the mechanisms responsible for depressive symptoms. Thus, clinical cut-offs based solely on symptom severity and duration, and which do not consider the fitness-relevant precipitating situation, may fail to distinguish truly pathological from non-pathological depressive symptoms (Wakefield 1999a).

These insights are generally appreciated in Darwinian psychiatry and eventually should help build a comprehensive theoretical framework for psychiatry. However, there remains a gaping hole in Darwinian psychiatry's account of mental disorders: there are no good explanations of why human brains seem to malfunction so often, and why these malfunctions are both heritable and disastrous to survival and reproduction. That is, there is still no good answer for why such susceptibility alleles have persisted despite thousands of generations of natural selection for adaptive human behavior.

1.3. What phenomena this article tries to explain

This article tries to develop an understanding of the evolutionary persistence of susceptibility alleles: regions of DNA – broadly defined to include both coding as well as non-coding, regulatory regions (see sect. 6.3) – that differ between individuals in the population and that increase the risk of common mental disorders. In other words, this article is concerned with explaining the genetic rather than the environmental variation associated with mental disorders (with complications such as gene-environment interactions considered later [sect. 4.4]). The reactive defense model offers insight into the environmental triggers for certain disorders – the normal

reactions to environmental stressors and the suites of species-typical, fixed alleles that code for these reactions. However, the reactive defense model is not helpful in explaining genetic variation, because adaptive defenses should be activated by environmental triggers, not heritable risk alleles that differ between individuals.

Although we have continually referred to mental disorders such as schizophrenia, depression, or mental retardation as "common," these disorders are *uncommon* in an absolute sense, generally having lifetime prevalence rates of less than 2%. Rather, they *are* common relative to the thousands of other heritable states that are known to be harmful to fitness, such as achondroplastic dwarfism or Apert's syndrome.

Most rare, harmful, single-gene disorders (*Mendelian disorders*) have frequencies consistent with *mutation-selection balance* – a balance between genetic copying errors that turn normal alleles into harmful mutations, and selection eliminating these mutations (Falconer & Mackay 1996). Mutations arise in parental germ-line cells and are passed on to offspring (and all their cells, including their own germ-line cells) at some low rate (m) per gene, per individual, per generation. Those that affect the phenotype are almost always harmful for the same reason that random changes to a computer's circuitry are almost always harmful: entropy erodes functional complexity (Ridley 2000). Selection removes these mutations at a rate proportional to the fitness cost of the mutation, represented by the selection coefficient (s) against the mutation. If s is reproductively lethal ($s = 1$), the newly arisen mutation exists in only one body before being eliminated from the population, but if s is fairly small, the mutation may pass through and affect many bodies through many generations before being removed by selection. The result of this balance between mutation rate m and selection coefficient s is usually a low equilibrium frequency (p) of mutant alleles that have not yet been removed from the population by selection. Specifically, mutations are expected to have population frequencies of $p = m/s$ if dominant, $p = \sqrt{m/s}$ if recessive, and somewhere in between otherwise (*additive* alleles are exactly midway between). As mutation rate m decreases or selection coefficient s increases, the mutation's frequency p should drop. This process accurately describes, in most cases, why Mendelian disorders are so rare.

The *cumulative* frequency of all Mendelian disorders – around 2% of all births (Sankaranarayanan 2001) – is high only because so many genes are subject to mutation (around 25,000). Heritable harmful disorders that are individually this rare ($<1/5{,}000$) pose no evolutionary paradox; no one wrings their hands about trying to find hidden adaptive benefits for such disorders because their frequencies are consistent with a simple balance between mutation and selection. Thus, a more accurate way to classify mental disorders as "common" or "rare" is to assess whether they are much more common than would be expected from a single-gene mutation-selection balance.

Table 1 compares the frequencies of several mental disorders with the frequencies of several Mendelian disorders, all of which are consistent with mutation-selection expectations (except for sickle-cell anemia, discussed in sect. 5.4). Stunningly, common mental disorders tend to be hundreds and even thousands of times more prevalent than expected from a single-gene mutation-selection model. This discrepancy has led many researchers (e.g., D. R. Wilson 1998) to dismiss mutation-selection

Table 1. *Comparisons of frequencies between a small subset of Mendelian disorders and common mental disorders*

Disorder	Genetic basis	Lifetime prevalence per 100,000 in U.S.A.
Mendelian disorders		
Dyskeratosis congenita	Recessive mutations at 3q25	<1
Granulomatous disease, type I	Recessive mutations at 7q11.23	<1
Apert's syndrome	Dominant mutations at 10q26	<1
Juvenile onset Parkinson's	Recessive mutations at 1p & 6q26	<1
Achondroplastic dwarfism	Dominant mutations at 4q	2–3
Sickle-cell anemia	Recessive mutation at 11p15.5	1,000[a]
Common mental disorders		
Autism	Unknown; $h^2 \cong .90$	20–50
Tourette's syndrome	Unknown; $h^2 \cong .90$	50
Anorexia nervosa	Unknown; $h^2 \cong .65$	100
Bipolar disorder	Unknown; $h^2 \cong .60$	800
Schizophrenia	Unknown; $h^2 \cong .80$	1,000
Mild mental retardation[b]	Unknown; $h^2 > .65$	2,000
Obsessive-compulsive disorder	Unknown; $h^2 \cong .45$	2,000
Panic disorders	Unknown; $h^2 \cong .30$	1,700–3,500
Depression	Unknown; $h^2 \cong .45$	5,000–17,000

Note: Data obtained from *Online Mendelian Inheritance of Man* (n.d.) for Mendelian disorders and from the National Institute of Mental Health (1998) for common mental disorders unless otherwise noted. When single or best estimates of heritability or prevalence were unavailable, we used the average of the reported estimates.
[a]Among African Americans.
[b]Heritability and prevalence data derived from Vogel and Motulsky (1997).

balance as a viable explanation for certain mental disorders, and to doubt that mental disorder susceptibility alleles were ancestrally maladaptive. However, such a conclusion is unwarranted. While single-gene mutation-selection models can clearly be eliminated as explanations for the mental disorders listed in Table 1, multiple-gene (polygenic) models (e.g., Shaner et al. 2004) cannot.

This article focuses on the susceptibility alleles of mental disorders that are much more common than would be expected from a single-gene mutation-selection balance; roughly, this corresponds to mental disorders with lifetime prevalence rates above 50 per 100,000 in reproductively aged adults. The best-studied of such disorders are listed in Table 1, but we do not attempt to provide an exhaustive list of precisely what mental disorders this entails, in part because we suspect that the sundry categories of modern mental disorders are not very meaningful biologically (see sects. 6 and 8), but also because our focus is on understanding the persistence of susceptibility alleles in general rather than on understanding mental disorders individually. Nevertheless, the types of common mental disorders that pose the largest paradox are those that are the most harmful (anorexia, bipolar disorder, schizophrenia, mental retardation, and obsessive-compulsive disorder). When we refer to *mental disorders*, these are the types of disorders we have in mind. If we can explain the susceptibility alleles for disorders that are this debilitating, then the same explanations should provide insight into susceptibility alleles for somewhat less debilitating disorders (panic disorders and depression). The following section examines the central paradox of susceptibility alleles in more detail.

2. The paradox of common, harmful, heritable mental disorders

The complexity, optimality, and diversity of life on Earth reveal the awesome power of natural selection. Common, harmful, and heritable mental disorders (as well as other disorders that are not the focus of the current article) seem to be glaring exceptions. They pose an evolutionary paradox because natural selection is expected to make harmful, heritable traits very uncommon very quickly. Over evolutionary time, selection favors higher-fitness alleles; alleles at most genetic loci have gone to *fixation* (virtually 100% prevalence) because they promoted survival and reproduction under ancestral conditions better than other alleles did on average. Such alleles comprise the species-typical human genome; its normal neurodevelopmental product is human nature. Lower-fitness alleles, on the other hand, even those with very minor negative effects, tend to go extinct fairly quickly. Alleles that reach fixation or extinction cause no genetic variation, and so cannot contribute to heritable variation in traits, such as mental disorders. This expectation that selection should minimize genetic variation in fitness-related traits was canonized in evolutionary theory as a major implication of Fisher's *fundamental theorem of natural selection* (Fisher 1930/1999). For decades, biologists expected that the stronger the selection on a trait, the less heritable variation the trait should show, and early empirical data seemed supportive.

Based on such reasoning, evolutionary psychologists have usually argued that genetic variation in human psychological traits is likely to be either adaptively neutral (e.g., Tooby & Cosmides 1990) or adaptively maintained by balancing selection (e.g., Mealey 1995). Both explanations require that the alternative alleles underlying a trait's heritable variation have net fitness effects that are exactly equal to each other, when averaged across evolutionary time and ancestral environments. These explanations seem less relevant to mental disorders, which appear to be the very embodiment of maladaptive traits. Nevertheless, the expectation that selection knows best, and that genetic variation in any common trait cannot be maladaptive, led to something of a cottage industry among Darwinian psychiatrists trying to explain the evolutionary persistence of alleles that increase the risk of such mental disorders as schizophrenia (Horrobin 2002; Huxley et al. 1964; Jarvik & Deckard 1977; Polimeni & Reiss 2002; Stevens & Price 2000a), bipolar disorder (Sherman 2001; D. R. Wilson 1998), depression (D. R. Wilson 2001), and anorexia (Guisinger 2003). In response, clinicians more familiar with psychiatric hospitals, prisons, and detox centers were understandably skeptical that such apparently Panglossian evolutionary ideas could explain real mental illness (e.g., Brüne 2004; McCrone 2003).

Can an evolutionary account of mental disorder susceptibility alleles be reconciled with the clinical view of mental disorders as genuine dysfunctions? Because they reveal interesting misunderstandings of the problem, we begin by considering the most commonly invoked *nonviable* possible evolutionary explanations of mental disorder susceptibility alleles. We next consider the (chiefly theoretical) merits of three explanations – ancestral neutrality, balancing selection, and polygenic mutation-selection balance – that are better grounded in modern evolutionary genetics. We then discuss six pieces of empirical evidence, concerning the relationships between mental disorders and fertility, brain trauma, paternal age, inbreeding, comorbidity, and frequencies and effect sizes of mental disorder susceptibility alleles that help distinguish between these explanations. We conclude with implications for future research.

3. Non-resolutions to the paradox of common, harmful, heritable mental disorders

3.1. Mental disorders are not really heritable

After decades of consistent behavioral genetic research, the hypothesis that genes play no role in mental disorders (e.g., Ross & Pam 1995) is simply no longer tenable. Using different methodologies, behavioral geneticists have consistently found that mental disorder heritability estimates range from about .2 to about .8, meaning that 20% to 80% of the differences between individuals in mental disorder liability are accounted for by differences in alleles between people. Without acknowledging genetic influences on mental disorders, only the most convoluted, post hoc arguments could explain why (a) adopted children are consistently more similar to their biological than to their adoptive parents, (b) siblings and twins reared apart are about as similar as siblings and twins reared together, (c) similarity in extended families

decreases monotonically as a function of genetic similarity, and (d) identical twins are consistently more similar than fraternal twins (Bouchard et al. 1990; Plomin et al. 2001).

Three issues regarding mental disorder heritability estimates do merit clarification, however. First, heritability describes how much genetic or environmental factors play a role in causing *differences* in a trait; it tells us nothing about the causes of *similarities* in a trait. Both environmental and genetic factors are 100% necessary for the species-typical expression of every trait, including every mental disorder. While true, this fact does not provide an answer to why alleles that create differences in mental disorder risk persist. Second, finding positive heritability for a mental disorder does not vindicate the mental disorder as a diagnostic category. To a first approximation, every reliably measured behavioral trait shows positive heritability – even constructs such as television viewing (Plomin et al. 1990) and political attitudes (Eaves et al. 1999). Any arbitrary "disorder" composed of unrelated but heritable symptoms will show credible heritability.

Last, heritability is a statistical construct that averages over a lot of complexity. The causal pathways between genes and the heritable behaviors they influence must be mediated by many factors, both genetic and environmental in nature. If these factors differ across populations, cohorts, or environmental conditions, then heritability estimates – and even the specific genes responsible for the heritability – might also differ across populations, cohorts, or environmental conditions. For example, if body size is associated with successful aggression in one particular society, then genes that normally influence size will also influence aggression in that society (this concept is sometimes called *reactive heritability*; Tooby & Cosmides 1990). Thus, in some cases, contemporary heritability may not accurately reflect ancestral heritability in magnitude or in composition – a point we consider in more depth later (sects. 4.2 and 4.4) when discussing gene-by-environment interactions.

3.2. Mental disorders are not common enough to hurt the species

One might argue that the cumulative frequency of severe mental disorders, around 4%, is not high enough to imperil the survival of the human species. Alternately, one might argue that the genetic variation underlying mental disorders persists because it is the essential raw material for future evolutionary progress (Embry 2002). These points ignore the central lesson of evolutionary genetics: selection acts on competing alleles within a species, without regard to long-term species viability or evolvability (Williams 1966). Natural selection is a purely mechanistic and iterative process whereby alleles from one generation have a non-random probability of being represented in subsequent generations. Natural selection does not – indeed cannot – hedge bets by stockpiling genetic variation in the hope that currently maladaptive alleles might become adaptive in the future.

3.3. Mental disorders are not really harmful to individual fitness

It is sometimes argued that mental disorders were not fitness reducing in ancestral environments because humans reproduced earlier than they do today (e.g., Hardcastle 2004; Weisfeld 2004). However, every mental disorder in Table 1 strikes well before ancestral humans would have finished reproducing. A harmful mental disorder that struck even as late as the forties would have led to a small but evolutionarily significant decrement in number of future offspring (e.g., see the fertility function of hunter-gatherers in Daly & Wilson [1983]), even apart from its negative effect on inclusive fitness through reduced ability to aid relatives (Kaplan et al. 2000). Thus, if mental disorders were debilitating in ancestral conditions, their developmental timing would have harmed fitness given any reasonable model of ancestral life-history profiles.

Another version of the not-really-harmful argument concerns the fitness effects of susceptibility alleles rather than mental disorders per se: mental disorders may be harmful to fitness, but their genetic architecture may be so complex that natural selection has been unable to eliminate the alleles that predispose to them. Used in this sense, "genetic complexity" basically means *nonadditive genetic variation*: variation in fitness effects that depend on particular combinations of alleles, and that selection therefore affects at a much slower rate (Merilä & Sheldon 1999). Such nonadditive effects include *dominance* (interactions between two alleles at the same locus) and *epistasis* (interactions between alleles at different loci). However, for the same reasons that main effects almost always exist in addition to interaction effects in statistical analyses, dominant and epistatic alleles almost always have some average, or additive, phenotypic effects (contributing to *additive genetic variation*) that are more visible to selection (Falconer & Mackay 1996; Mather 1974). Available empirical evidence on mental disorders is consistent with this expectation. Although the vast majority of behavioral genetic studies have used a design (the classical twin design) that cannot simultaneously estimate additive, nonadditive, and shared-environment effects (Eaves et al. 1978; Keller & Coventry 2005), behavioral genetic studies using designs better able to distinguish these (such as the extended twin design; reviewed in Coventry & Keller 2005) have found at least some additive genetic variation for those mental disorders investigated to date: depressive symptoms, panic disorders, and neuroticism (a correlate of many mental disorders). Thus, the harm that mental disorders do is almost certainly visible to natural selection to some degree.

It could also be argued that mental disorders simply have not affected survival and reproduction, and so are not under selection. At least in *modern* environments, however, many mental disorders are associated with markedly lower fertility (summarized in Table 2). These mental disorders seem to undermine fertility not so much through reducing survival, but through reducing attractiveness or ability in the mating arena. Of the studies that examined this issue, reductions in fertility were principally the result of lower marriage rates rather than fewer offspring once married. At this level of socio-sexual competition to attract and retain mates, there may not be so much difference between the fitness effects of mental disorders in prehistoric and contemporary societies (Miller 2000a).

However, modern fertility has an unknown relationship to ancestral fertility (Symons 1989), which is more relevant

Table 2. *Available fertility estimates (1960–2005) of common mental disorders*

Disorder	Fertility[a]	Birth cohorts, location	Sample	Reference
Psychotic disorders				
Schizophrenia	58% ♀	1890–1919, U.S.	4,041 inpatients & outpatients	Erlenmeyer-Kimling et al. 1969
Schizophrenia	36%	1890s–1950s, Germany	306 inpatients	Vogel 1979
Schizophrenia	45% ♀	1890s–1940s, U.K.	1,086 inpatients & outpatients	Slater et al. 1971
Schizophrenia	70% ♀	1911–1940, U.S.A.	4,023 inpatients & outpatients	Erlenmeyer-Kimling et al. 1969
Schizophrenia	40% ♂; 57% ♀	1914–1968, Spain	142 inpatients & outpatients	Fananás & Bertranpetit 1995
Psychosis[b]	29% ♂; 83% ♀	1920s–1970s, Australia	282 primary-care patients	McGrath et al. 1999
Schizophrenia	23% ♂; 51% ♀	1921–1976, Canada	36 primary-care patients	Bassett et al. 1996
Schizophrenia	101% ♀	1932–1951, U.S.A.	223 outpatients	Burr et al. 1979
Schizophrenia	29% ♂; 62% ♀	1930s–1970s, Japan	553 outpatients	Nanko & Moridaira 1993
Schizophrenia	25%	1930s–1970s, Ireland	285 from population register	Kendler et al. 1993
Schizophrenia	27% ♂; 45% ♀	1950s, Finland	11,231 from population register	Haukka et al. 2003
Psychosis[b]	46% ♀	1953–1982, U.K.	4,556 primary-care patients	Howard et al. 2002
Schizophrenia	23% ♂; 12% ♀	20th century, Denmark	27 from adoption database	Rimmer & Jacobsen 1976
Schizophrenia	37%	20th century, Palau	70 unknown	Sullivan & Allen 2004
Mood disorders				
Affective disorder[c]	70%	1890s–1950s, Germany	165 inpatients	Vogel 1979
Bipolar disorder	50% ♂; 62% ♀	1890s–1950s, U.S.A.	134 inpatients	Baron et al. 1982
Bipolar disorder	69% ♀	1890s–1940s, U.K.	2,692 inpatients & outpatients	Slater et al. 1971
Affective disorder[d]	47% ♂; 89% ♀	1920s–1970s, Australia	60 primary-care patients	McGrath et al. 1999
Affective disorder[c]	66% ♀	1953–1982, U.K.	1,705 primary-care patients	Howard et al. 2002
Developmental disorders				
Mental retardation[e]	40% ♂; 72% ♀	1870s–1930s, Minnesota	1,450 descendants of inpatients	Reed 1971
Low intelligence[f]	88%	1870s, Michigan	78 from school register	Bajema 1963
Mental detardation[e]	95%	1870s–1930s, Minnesota	1,300 descendants of inpatients	Waller 1971
Organic disorders[g]	53%	1890s–1950s, Germany	275 inpatients	Vogel 1979
Other disorders				
OCD[h]	47% ♀	1890s–1940s, U.K.	235 inpatients & outpatients	Slater et al. 1971
"Neurosis"[i]	64% ♀	1890s–1940s, U.K.	5,596 inpatients & outpatients	Slater et al. 1971
Mixed[j]	53%	1890s–1950s, Germany	316 inpatients	Vogel 1979

Note: Data include all available studies in 1960–2005 in which overall fertility rates were reported or derivable and in which a suitable comparison group was reported.
[a]Number of offspring as a proportion of number of offspring among general population matched on age, gender, and other pertinent demographic variables.
[b]Schizophrenia, schizoaffective disorder, schizophreniform, delusional disorder, and paranoid psychosis.
[c]Major depression and bipolar disorder.
[d]Bipolar disorder, bipolar disorder with psychosis, mania, mania with psychosis, and depression with psychosis.
[e]IQ < 70.
[f]IQ < 85.
[g]Mental retardation and psychoses caused by trauma.
[h]Obsessive-compulsive disorder.
[i]Usage not described.
[j]Panic disorder, obsessive-compulsive disorder, drug and alcohol dependence, sexual deviance, and personality disorders.

to understanding the evolutionary persistence of susceptibility alleles. Additional and perhaps more persuasive evidence that mental disorders were associated with decreased ancestral fitness is simply based upon the ubiquitous evidence of their deviance and disability in modern societies, irrespective of their effects on fertility (Troisi & McGuire 2002; Wakefield 1992). Any psychiatric book or journal reveals many such examples, which do not need to be enumerated here. If mental disorders existed in ancestral environments in much the same form as they do now, it is reasonable to assume that, *at some level of severity*, they would have resulted in lower ancestral fitness.

Nevertheless, mental disorders may *not* have existed in ancestral environments as they do now. This final version of the not-really-harmful view merits more careful consideration – the idea that, although mental disorders or their susceptibility alleles are harmful under modern conditions, they may not have been harmful under ancestral conditions, when humans lived in small-scale, hunter-gatherer societies. We assess this hypothesis next.

4. Can ancestral neutrality explain common, harmful, heritable mental disorders?

It seems unlikely that mental disorder susceptibility alleles had no effect on ancestral fitness, given that mental disorders are associated with lower fitness (Table 2) and severe impairment in modern environments. Nevertheless, it is possible that mental disorders were associated with more benign symptoms or less ostracism ancestrally so that they were effectively neutral traits. For example, a common speculation is that perhaps prehistoric individuals with schizophrenia were valued shamans, with a special social role as religious visionaries, so perhaps they were not socially and sexually ostracized as in contemporary societies (Polimeni & Reiss 2002; Preti & Miotto 1997). Alternatively, perhaps alleles that increase the risk of mental disorders today had no such effect in ancestral environments. From an extended-phenotype perspective, both cases are examples of gene-by-environment (G–E) interactions, which occur when the effects of alleles differ depending upon the physical or social environment. Is it possible that the fitness effects of mental disorder susceptibility alleles were equal to the fitness effects of non-susceptibility alleles in ancestral environments, enabling them to persist?

4.1. Neutral evolution maintains genetic variation only when combined with recurrent neutral mutation

To assess whether ancestral neutrality is a viable explanation for the persistence of mental disorder susceptibility alleles, we must first understand the conditions under which neutrality maintains genetic variation. The frequencies of neutral alleles are governed by *genetic drift* – random sampling error over evolutionary time. Over the long term, drift leads to genetic uniformity because neutral alleles either fixate or are lost through sampling error. Drift almost never maintains neutral alleles at intermediate frequencies where they could explain heritable variation in mental disorder susceptibility. Drift is stronger in smaller populations, such as ancestral hominid populations, which are more susceptible to sampling error. Without some additional force that either replenishes lost alleles (see the next paragraph) or that counteracts the process of random drift (see the next section), one neutral allele eventually fixates and the alternative alleles go extinct.

Depending on the way that new mutations affect mental disorder risk, recurrent neutral mutations might counteract the loss of genetic variation caused by drift. Mutations can occur anywhere along a locus, the coding region of which is typically about 2,000 base pairs long; like lightning, mutations are very unlikely to hit precisely the same location twice, and thus alleles introduced into the population via recurrent mutation are very unlikely to be the same. If neutral mental disorder susceptibility alleles are specific, in the sense that only one or a few of all the possible mutations at that locus would affect mental disorder risk, while all others would not, then recurrent mutation is too rare an event to replenish lost susceptibility alleles. In this case, random genetic drift would lead to loss or fixation of the mental disorder susceptibility allele. Therefore, models that hypothesize that mental disorders are complex phenotypes, coded by specific alleles that are alternatives to the normal alleles, are not consistent with what is known about the properties of neutral evolution. However, it is probably more biologically plausible that *any* mutation along the locus could increase or decrease mental disorder risk; in this case, random genetic drift plus recurrent mutation could in principle account for substantial genetic variation.

The degree of genetic variation contributed by such a neutral locus, where any mutation affects mental disorder risk, can be quantified. As already noted, only loci that are polymorphic (where more than one allele exists in the population) contribute to genetic variation. Genetic polymorphism can be measured by H, the proportion of heterozygotes at a locus in a population. Kimura (1983) showed that for neutral loci, $H \cong 4N_e\mu/(1 + 4N_e\mu)$, where μ is the probability of a new mutation at the locus per individual per generation, and N_e is the *effective population size* (roughly the harmonic mean of the breeding population size across generations, which tends to be close to the minimum actual population size during genetic bottlenecks). N_e is often estimated to be around 10,000 for humans (Cargill et al. 1999). Assuming μ is around 10^{-6} to 10^{-5} for most loci (Nachman & Crowell 2000), the expected heterozygosity H across neutrally evolving human loci should be around 4% to 29%. Because neutral loci have relatively high average values of H, they can contribute substantially to heritability in human traits and perhaps mental disorders.

To say that neutral evolution *could* maintain the genetic variation underlying mental disorders is very different than saying that such a process is likely. In sections 4.2 and 4.3, we review two reasons that neutral evolution is probably not a general resolution to the paradox of common, heritable, harmful mental disorders, and then we review the types of phenotypes that might be best explained by a weaker version of this process (sect. 4.4).

4.2. Ancestral neutrality must be implausibly precise

For an allele to be truly neutral over the evolutionary long term, the allele must have fitness effects *extremely* close to neutrality within each generation. This statement can be

quantified simply. For an allele to be neutral (to be governed by genetic drift more than by selection), the selection coefficient s against an allele must be less than $\sim 1/4N_e$. Thus, only if the average fitness of people with an allele is between 99.997% and 100.003% of the fitness of people without this allele (i.e., if $s < 1/40{,}000$) has the frequency of that allele been governed mostly by neutral drift across human evolution. This is an extraordinarily small selection coefficient, equivalent to a difference of just one offspring more or less than average, not in the next generation, but 15 generations into the future, given a roughly constant population size.

Not only must neutral mental disorder susceptibility alleles have been almost exactly neutral in ancestral environments, they must have been *consistently* so. If the alleles were neutral in most but not all environments, or in most but not all cultures, or in most but not all bodies, then averaged across evolutionary time, these alleles would not be neutral. As we have argued, there are strong reasons to believe that the mental disorders listed in Table 2 are fitness-reducing in modern societies. If susceptibility alleles were neutral in ancestral environments but highly dysfunctional today, this implies very large G–E interactions. Yet, very large G–E interactions are implausible, given this consistency requirement that mental disorder susceptibility alleles had to be unfailingly neutral across many different ancestral environments.

Although many evolutionary biologists believe that neutral mutations are the main source of genetic polymorphisms across DNA in general (since most DNA has no phenotypic effect), few now believe that neutral mutations are the main source of phenotypically expressed variation (Ridley 1996). The very fact that neutral alleles have no fitness effects makes them unlikely to affect phenotypic development. By contrast, mental disorder susceptibility alleles do affect the phenotype in modern environments, and it is likely that they would have done so in ancestral environments as well. It is hard to believe that phenotypically expressed alleles associated with conditions that have such harmful effects in modern environments would have been precisely neutral ($s < 1/40{,}000$) across all ancestral environments.

4.3. Ancestral neutrality is hard to reconcile with modern mental disorder prevalence rates

A strictly neutral hypothesis about mental disorder genetic risk factors would dictate that all levels of genetic risk have equal fitness effects. Under such a scenario, any prevalence rate of mental disorders, from 0% to 100%, should be about equally likely. Contrary to this, Table 1 shows that the most harmful mental disorders are consistently rare in an absolute sense, none being more common than about 2%. If neutral evolution were a general answer to the paradox, one would have to explain why the most harmful mental disorders are so consistently rare. The exceptions that prove the general rule are late-onset disorders such dementia (which affects about 30% of people over age 75; Thomas et al. 2001), which are more likely to have been close to selectively neutral under ancestral conditions.

Perhaps the low frequencies of modern mental disorders suggest that they became fitness-reducing only recently and are currently being selected out of human populations (e.g., Burns 2004; T. J. Crow 2000). How plausible is this? As illustrated in Figure 2, alleles with even small fitness effects are quickly driven to extinction. For example, if schizophrenia in Finland has been as disadvantageous over the last 20 generations, as it appears now ($s \sim .50$), and is caused by a single recessive allele with $p = .10$ (explaining the current disease prevalence of 1%), it would follow from standard evolutionary genetics that 42% of Finns were schizophrenic in 1600 – clearly a nonsensical result. Selection on dominant or additive alleles is even faster. Thus, it is not evolutionarily credible to claim that mental disorders are caused by one or even a few genes and have a low but significant prevalence because they became harmful only several thousand years ago.

4.4. Disorders that ancestral (near) neutrality might help explain

We have argued that it is highly unlikely that alleles with substantial fitness-reducing effects today were precisely and consistently neutral across ancestral environments. However, alleles affecting certain disorders might have been much *closer* to being neutral in ancestral environments, and therefore the modern prevalence rates and heritabilities of these disorders may be higher than predicted from modern fitness estimates. This is a plausible hypothesis for heritable disorders that show the hallmarks of G–E interactions: large cross-cultural variation in prevalence rates, increased (or decreased) rates in recent historical time as environments change, and a credible mismatch between ancestral and modern conditions that affects the mental disorder.

Data showing that depression rates vary enormously between cultures, and seem to be rising to very high levels in industrialized nations (Weissman et al. 1996), are consistent with – but by no means prove that – G–E interactions are important in depression. It is also easy to imagine a credible mismatch scenario for depression. For example, social support from kin and friends was probably more available in small-scale ancestral societies

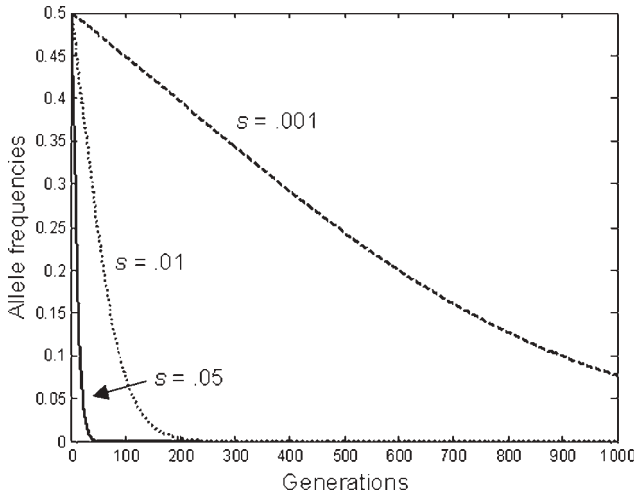

Figure 2. Expected changes (ignoring genetic drift) in allele frequencies across generations, given different levels of selection (s) acting on additive deleterious alleles of minor effect.

than in modern cities, and such social support may help rescue people from normal periods of transient depression (Kessler 1997). Although heritable shyness may have had little effect on social support in ancestral conditions, "shy alleles" could decrease the social support available when times get tough in modern cities, becoming susceptibility alleles for depression that show strong G–E (or more specifically, in this case, G-culture) interactions.

Other disorders that could plausibly be affected by alleles that were more benign in ancestral environments include: (a) obesity and diabetes, due to unnaturally consistent and appealing food surpluses; (b) asthma, due to unnatural levels and types of antigens and pollutants; and (c) addictions to highly purified, evolutionarily novel drugs, such as heroin or cocaine (Nesse & Berridge 1997). These disorders are heritable within cultures, but their frequencies differ enormously between cultures and environments. They have also probably increased in frequency in cultures most affected within the last 50 to 100 years (Wright & Hastie 2001), as likely environmental risk factors were increasing. It is also reasonable to assume that their environmental risk factors were usually absent in ancestral environments. Finally, in societies with the environmental risk factors, the frequencies of these disorders are not consistently low (e.g., obesity rates are approaching 50% among younger U.S. cohorts).

Nevertheless, it is unlikely that alleles that increase mental disorder risk today were precisely and consistently neutral ancestrally – even those alleles that have become more harmful only recently. Given that natural selection purges even slightly harmful alleles (Fig. 2), the persistence of alleles that were only close to, but not precisely, neutral still requires an explanation. The polygenic mutation-selection paradigm, reviewed in section 6, provides this explanation.

5. Can balancing selection explain common, harmful, heritable mental disorders?

The genetic variation underlying mental disorders, far from being invisible to selection, might have been actually maintained by selection. For example, mental disorders which look harmful and dysfunctional, and which show below-average fitness under some conditions, might show above-average fitness under other conditions. This type of selection, known as *balancing selection*, has been one of the most popular ideas among evolutionary thinkers for resolving the paradox of common, harmful, heritable mental disorders (Allen & Sarich 1988; Barrantes-Vidal 2004; Karlsson 1974; Longley 2001; Mealey 1995; Stevens & Price 2000a), with some researchers even implying that balancing selection is the only possible resolution to the paradox (D. R. Wilson 1998). One purpose of this article is to rebut such claims by showing that there are at least two other potential resolutions to the paradox: neutral evolution and mutation-selection balance.

Balancing selection may be popular among Darwinian psychiatrists in part because it keeps natural selection front and center as the causal force explaining a trait – a comfortable position for adaptationists. Balancing selection might also be appealing for social and moral reasons, because it attributes hidden adaptive benefits to mental disorders in ways that might reduce their social stigma. Morality aside, how feasible is it that balancing selection resolves the paradox?

5.1. Natural selection usually depletes genetic variation

As noted in section 2, selection usually leads to genetic uniformity and therefore depletes heritability. Certain evolutionary models, such as those for phobias and depression (e.g., Keller & Nesse 2005; Watson & Andrews 2002), posit adaptive functions for capacities that are *universal* features of human nature, affected by *universal* suites of genes (i.e., little or no genetic variation), and triggered by adverse situations. These explanations are potentially useful for understanding environmental variation, but do not explain, nor were they intended to explain, the *genetic* variation in phobias and depression.

Other evolutionary models hypothesize that heritable disorders themselves are adaptive without explaining why the disorders have not fixated in the population. Consider three recent hidden-benefit models: Guisinger (2003) viewed symptoms of anorexia as an adaptive response to fleeing famine under ancestral conditions of starvation; Sherman (2001) viewed bipolar disorder as an adaptation to long, severe winters and short summers; and T. J. Crow (2000) viewed schizophrenia as an inevitable risk arising as a side effect of language evolution (see also Burns 2004). None of these offer a compelling explanation for the persistence of heritability in these disorders. If anorexia was simply adaptive under starvation conditions, then the adaptive anorexia alleles would be virtually fixed within those human groups whose ancestors gained such advantages, and the condition should not be heritable within these groups. In truth, however, very few people show these symptoms, and the phenotypic differences between those who do versus those who do not are largely due to genetic differences (Guisinger 2003). Similar arguments can be made for bipolar disorder or schizophrenia. These hidden-benefit models may or may not help explain why humans in general are susceptible to anorexia, bipolar disorder, or schizophrenia, but they do not explain the central paradox addressed in this article: why mental disorder susceptibility alleles have not either fixated, if adaptive, or gone extinct, if maladaptive. This is one of our key points: *Explaining heritable polymorphisms requires special and stringent types of evolutionary explanations that are different from those used to explain species-typical traits*. Most types of selection offer no explanation for mental disorder heritability. Balancing selection can.

5.2. Balancing selection is the only type of selection that actively maintains genetic variation

Balancing selection actively maintains two or more alternative alleles because their net fitness effects balance each other out, being positive in certain genetic or environmental contexts and negative in others. For balancing selection to maintain a stable genetic polymorphism across evolutionary time, (a) the fitness effects of the alternative alleles must be equal across ancestrally relevant genetic and environmental contexts, and (b) some mechanism must assure that these equally fit

alleles are not lost by chance (genetic drift). For the most robust types of balancing selection, if an allele drifts by chance to a lower level, its fitness increases, which then buoys its frequency back up. So long as the equilibrium frequency of one of the alleles is not too low, such a homeostatic mechanism greatly reduces the risk of equally fit alleles being lost by genetic drift.

Before assessing the general utility of balancing selection in explaining mental disorders, we review the explanatory power of four specific forms of it: spatial and temporal variation in selection, heterozygote advantage (also known as heterosis or overdominance), antagonistic pleiotropy, and frequency-dependent selection. Although these are often considered separate evolutionary processes, they have important common features at the evolutionary genetic level that give them similar strengths and weaknesses in explaining mental disorders.

5.3. Temporal or spatial variability in fitness landscapes

Balancing selection can occur when an allele's fitness oscillates over evolutionary time or location. We are aware of no models that try to explain mental disorder heritability by using this mechanism. For this to explain the paradox, a convincing case would need to be made that mental disorders or their susceptibility alleles were advantageous across about half of ancestral populations in different locations or about half of the time, but this seems a priori unlikely, though not disproved, in light of the consistent harmfulness of mental disorders in current environments. A deeper, theoretical problem for this explanation is that no homeostatic mechanism protects alleles against loss through drift; rather, the evolutionary oscillations in an allele's fitness must occur at just the right rate across time or space to keep the allele from fixating or going extinct (Bürger 2000). Such loss of alleles would be especially likely in small prehistoric human populations.

Although this mechanism seems theoretically unlikely to maintain mental disorder susceptibility alleles at *equilibrium*, it is important to remember that we are catching but a snapshot of evolution. It is certainly possible that some susceptibility alleles are at intermediate frequencies because they are sweeping toward fixation or extinction. Such a process may be occurring with a susceptibility allele for heart disease and Alzheimer's disease: APOE*4. APOE*4 is the ancestral allele, being rarest among human groups that have had the longest exposure to agriculture, and is probably headed over the next several thousands of years toward extinction (for two views on why this might be, see Corbo & Scacchi [1999] and Finch & Sapolsky [1999]). Nevertheless, it is unlikely that enough alleles are rising or lowering in frequencies for this to be a general answer to the paradox, given the short time that alleles with fitness effects are at intermediate frequencies (Fig. 2).

5.4. Heterozygote advantage

A genetic polymorphism may be maintained when the heterozygote at some locus has higher fitness than either homozygote (e.g., genotype *Aa* has higher fitness than both *AA* and *aa*). The classic example is sickle-cell anemia. Individuals who are homozygous for the more common allele (*AA*) at the β-hemoglobin locus are susceptible to malaria, whereas those homozygous for the less common allele (*aa*) are more likely to die from sickle-cell anemia. However, heterozygotes (*Aa*) have the best of both worlds: they do not develop anemia, and they are much more likely to survive a malarial infection. In equatorial areas of Africa and Asia where malaria is endemic, heterozygotes have higher fitness than either homozygote. If genotypes rather than genes could be passed to offspring, *Aa* genotypes would have fixated long ago, but this cannot happen. For example, matings between two most-fit heterozygotes nevertheless produce $\frac{1}{4}$ *aa* and $\frac{1}{4}$ *AA* offspring on average. The population frequencies of the two alleles become stable when the average fitness effects of alleles *a* and allele *A* are equal. Here, a homeostatic mechanism keeps alleles from being lost through genetic drift: if the frequency of one allele in the population drifts to a lower level, that allele has an increased chance of finding itself in a heterozygote body, and its average fitness, and hence frequency, increase.

In the case of sickle-cell anemia, Allison (1954) showed that, given the fitness estimates for each genotype at the β-hemoglobin locus, evolutionary genetic theory predicted very well the observed phenotypic frequencies. The sickle-cell story had a large impact on evolutionary biologists in the 1950s, and many suggested that heterozygote advantage might be a general explanation for observed levels of genetic variation in nature (e.g., Lerner 1954). More recently, several evolutionists have theorized that mental disorders such as schizophrenia (Huxley et al. 1964), bipolar disorder (D. R. Wilson 1998), and depression (D. R. Wilson 2001) are maintained by heterozygote advantage.

However, for several reasons, evolutionary biologists have become less enthusiastic about heterozygote advantage as an explanation for persistent heritability in most traits. First, heterozygote advantage appears to be rare in nature: Thirty years of intensive research following the sickle-cell story yielded only six additional examples of polymorphisms maintained in this way (Endler 1986). Second, there are theoretical reasons to doubt that species could sustain widespread maladaptive polymorphisms in this way without going extinct (Crow & Kimura 1970). Third, selection would strongly favor genetic events that overcome the costs of producing homozygotes, such as unequal crossover events that positions both *A* and *a* on the same chromosomal arm, so they can be passed on together without disruption (Ridley 1996), or mutations that reduce the fitness costs of either homozygote. Such genetic events become quite likely across a whole population over evolutionary time, so heterozygote advantage is likely to be an evolutionarily transient stopgap. This is consistent with the fact that the *a* allele at the β-hemoglobin locus evolved fairly recently (Hamblin et al. 2002).

5.5. Antagonistic pleiotropy

Pleiotropy occurs whenever one allele affects more than one trait. Given that traits do not rely on mutually exclusive sets of genes, pleiotropy is ubiquitous. *Antagonistic pleiotropy*, which is also probably ubiquitous, occurs whenever an allele increases the fitness payoffs of one

trait but reduces the fitness payoffs of another trait. For example, an allele might increase fertility but decrease longevity, or increase intelligence but decrease emotional stability.

Generally, this process leads to the fixation of whichever allele has the highest fitness, averaged across the various effects it has on different traits. Even if the net fitness effects of two alternative alleles are precisely equal, which is a priori unlikely, there is no homeostatic mechanism that counteracts the homogenizing effect of genetic drift (Curtisinger et al. 1994; Hedrick 1999; Prout 1999). In fact, this theoretical work suggests that antagonistic pleiotropy is likely to maintain genetic polymorphisms only under a highly restrictive scenario: when individuals with both alleles receive the fitness benefits but not the costs from each allele – a situation called *reversal of dominance*. In this situation, heterozygotes would have the highest fitness, a scenario conceptually equivalent to heterozygote advantage, and which shares the same explanatory weaknesses. The conclusion from theoreticians is that antagonistic pleiotropy cannot maintain genetic variation on its own; it requires a very special type of allelic effect, reversal of dominance, which evolutionary biologists consider unlikely.

Despite these theoretical concerns, antagonistic pleiotropy is probably the most common evolutionary explanation for the persistence of susceptibility alleles. Several researchers have hypothesized that susceptibility alleles underlying bipolar disorder and schizophrenia have two effects: one, to increase creativity, but the second, to increase the risk for the mental disorder (Barrantes-Vidal 2004; Karlsson 1974). These susceptibility alleles are thought to persist because their negative fitness effects from mental disorder risk are precisely offset by their benefits from creativity. The idea that mental disorders are associated with higher creativity is widespread, and supported by some biographical evidence (Jamison 1993) and evidence that relatives of those with mental disorders have higher creativity (reviewed by O'Reilly et al. 2001). However, a literature review of 29 studies found little support for the idea that highly creative people showed an increased rate of mental disorders (Waddell 1998).

5.6. Frequency-dependent selection

Frequency-dependent selection (or more technically, negative frequency-dependent selection) occurs when alleles' fitness effects increase as they become rarer. This process can maintain a stable mix of alleles resulting in persistent trait heritability. Heterozygote advantage can be seen as a special case of this process. Frequency-dependent selection more generally occurs when individuals compete for different resources, such that individuals who are rare relative to their preferred resource are favored (Barton & Keightley 2002).

The classic example of frequency dependence is the evolutionary maintenance of the 50:50 sex ratio (Fisher 1930/1999). If males outnumber females, females necessarily have higher average reproductive success than do males. A mutation increasing the probability of having daughters would be positively selected, and would spread in the population until females began to outnumber males, in which case selection would begin to favor having sons. The evolutionary equilibrium is that both strategies (being male or being female) reach equal frequency, although, in other cases, alternative strategies may have non-equal equilibrium frequencies. Frequency-dependent selection can maintain high levels of heritable genetic variation for as long as the selection pressures remain.

For a few mental disorders such as psychopathy, frequency dependence may be a plausible model. Mealey (1995) argued, forcefully in our opinion, that psychopathy persists at a low base rate as a socially parasitic strategy: it brings high fitness benefits when rare, but becomes less rewarding at higher frequencies because of increased anti-cheater vigilance in the population. Indeed, at the current low base rate (around 1%), male psychopaths seem to have higher-than-average fitness, at least in modern environments – unlike almost all other mental disorders listed in Table 1. In general, frequency-dependent selection can explain polymorphic alleles only when there is a credible explanation of why each allele's fitness increases as its frequency decreases. This is a fairly high standard of evidence. Moreover, there are several problems with balancing selection in general as an explanation for mental disorders, which we explore next.

5.7. General problems with balancing selection explanations for mental disorder susceptibility alleles

Mental disorders are not a random sample of human traits; they are considered "disorders" precisely because they have salient maladaptive outcomes. Rare phenotypes with such severe costs, as opposed to common phenotypes that are not debilitating, are probably the least likely candidates for traits maintained by balancing selection. This is because the devastating negative effects of susceptibility alleles must be balanced by commensurately large, and therefore probably noticeable, positive effects (e.g., sickle-cell anemia being balanced out by malarial resistance). Balancing selection may explain some heritable personality traits such as extroversion and some personality disorders such as psychopathy. Yet it seems a poor candidate as a general explanation of the susceptibility alleles of mental disorders, since their susceptibility alleles would have to show some hidden adaptive benefits that counteract the strongly maladaptive symptoms of these mental disorders.

Another problem for models of both spatio-temporal variation and frequency-dependent selection is that behavioral flexibility, as opposed to fixed, heritable strategies, would probably be favored in the face of differing fitness landscapes (Tooby & Cosmides 1990; although see D. S. Wilson 1994). Fixed, heritable strategies make sense for basic morphological specializations such as growing a male or female body, when it is hard to switch from one to the other after growth. However, the whole point of growing a central nervous system is that different behavioral strategies, which have context-dependent fitness payoffs, can be pursued by the same individual across different situations. Such flexibility circumvents the costs of pursuing fixed strategies when their frequencies are at the wrong level to maximize fitness. Given the extraordinary behavioral flexibility of the human brain, it would be puzzling if such genetically fixed strategies explained mental disorder heritability. Despite these two broad

problems, and the problems specific to the various types of balancing selection, balancing selection cannot be ruled out as a resolution to the paradox on purely theoretical grounds. In section 7, we review several pieces of empirical evidence that support our expectations that balancing selection is not a general explanation for mental disorder susceptibility alleles.

5.8. What balancing selection might explain

Balancing selection might, in theory, maintain mental disorder susceptibility alleles for reasons completely unrelated to mental disorder symptoms. For example, pathogens and parasites are usually poorly adapted to attacking the rarest host genotypes, so rare alleles may help protect the host (Garrigan & Hedrick 2003; Haldane 1949). This anti-pathogen variation could give rise to mental trait variation as a side effect (Tooby & Cosmides 1990), and some researchers have suggested this might explain the high prevalence of schizophrenia susceptibility alleles (J. S. Brown 2003). For this to work, the fitness benefits of improved host defense must outweigh the fitness costs of increased mental disorder risk (Turelli & Barton 2004). Because most loci probably do not affect immunological systems, the vast majority of loci are probably unaffected by parasite-host coevolution. Moreover, selection should have favored minimal overlap between the genes that control anti-pathogen defenses and those that affect other systems, such as the nervous system, although there may be a limit in how far natural selection can go in removing such pleiotropic effects of genes. Although it is certainly possible that some psychological variation is a by-product of frequency-dependent selection for other traits, empirical evidence discussed in section 7 makes it unlikely to be a *general* resolution to the paradox.

We have argued on both theoretical and empirical grounds that antagonistic pleiotropy is unlikely to explain the persistence of mental disorder susceptibility alleles, but a weaker version of it may work better. This version suggests that alleles with conflicting fitness effects on different traits should tend to be *closer* to neutral than alleles without such antagonistic effects, so perhaps they will persist longer at intermediate frequencies and contribute more to heritable variation. If such a near-neutral allele has opposite fitness effects on two traits, those traits should show a negative genetic correlation (Lande 1982). More generally, if antagonistic pleiotropy accounts for substantial genetic variation, most genetic correlations between fitness-related traits should be negative. This logic is compelling, but the evidence among animal traits is not very supportive. A meta-analysis of genetic correlations between fitness-related traits in nonhumans found that 61% were positive (i.e., the higher fitness end of one trait tended to go with higher fitness end of other traits; Roff 1997) – a result less congruent with antagonistic pleiotropy than with polygenic mutation-selection balance models (Charlesworth 1990). Nevertheless, it is plausible that some portion of the genetic variation underlying mental disorders is due to near-neutral alleles that increase mental disorder risk under certain genetic or environmental conditions, but that have some positive benefits in other conditions. Much like the scenario discussed in section 4 for non-pleiotropic near-neutral alleles, this mechanism still begs for an explanation of why near-neutral alleles have not fixated or gone extinct – a topic we turn to next.

6. Can polygenic mutation-selection balance explain common, harmful, heritable mental disorders?

The simplest polygenic mutation-selection model elegantly parallels the single-gene models described earlier: the equilibrium genetic variation (V_G) maintained in a trait affected by many loci is $V_G = V_M/s$, where V_M is the increase in a trait's genetic variation due to new, harmful mutations per generation, and s is the average selection coefficient against these mutations (Barton 1990). It generally takes a while for these harmful mutations to work their way out of the gene pool. For example, a mutation causing a 1% reduction in fitness will persist in the population until it has passed through an average of 100 individuals (García-Dorado et al. 2003). Mutations with the most harmful effects are removed the fastest, so if one is observed, it is probably rare and of recent origin. Mutations with milder effects are removed more slowly, so they tend to be more common (although still very uncommon in an absolute sense) and older, inherited from parents, grandparents, and so forth. Therefore, genetic variation caused by mutation-selection balance is predominantly the result of old mutations that have yet to go extinct, rather than new mutations, a point that is commonly misunderstood. Most mutations are a family legacy, not an individual foible.

Several recent theoretical papers have emphasized the role of mutation in maladaptive human traits (Gangestad & Yeo 1997; Hughes & Burleson 2000) and late-onset diseases (Wright et al. 2003). Such polygenic mutation-selection models suggest that much of the persistent heritability in traits may be due to a large number of harmful alleles that are individually very rare at any given locus in the population, but that are collectively very common across loci. These models recognize that we do not live in the best of all possible worlds. Genetic information is constantly and inevitably eroded by genetic copying mistakes: mutations. Applied to human mental disorders, mutation-selection models suggest that, if a mental disorder appears maladaptive, maybe it really is maladaptive – and always has been.

6.1. Is polygenic mutation-selection a viable explanation for the genetic variation in traits?

For several reasons that now appear misguided, researchers have often doubted that mutation-selection could explain mental disorder susceptibility alleles. First, the results of many animal studies seemed to suggest that just a few loci (around 2–20) account for much of the genetic variation in traits that had been studied (Falconer & Mackay 1996) – too few for mutation-selection balance to play much of a role in mental disorders. However, there are good reasons to think these studies underestimated the number of loci and overestimated their effect sizes (Barton & Keightley 2002). Moreover, the traits analyzed in these studies generally have little relevance to fitness (e.g., number of abdominal bristles in fruit flies), and mutation

plus drift at few loci can maintain substantial genetic variation in nearly neutral traits. Second, it is estimated that approximately 7 million single-nucleotide polymorphisms (SNPs) have minor allele frequencies greater than 5% (Kruglyak & Nickerson 2001). However, more than 98% of these 7 million SNPs are outside of protein coding regions and are unlikely to affect mental disorder risk (Wright et al. 2003). SNPs that do affect protein production tend to have minor allele frequencies below 5% (Fay et al. 2001), which is consistent with mutation-selection balance.

Third, as discussed earlier (sects. 2, 4.2, and 5.1), there were strong theoretical expectations that maladaptive states should be rare in nature. Fisher's Fundamental Theorem seemed to suggest that additive genetic variation should be lowest in traits under the strongest selection. This prediction seems supported by observations that traits under more intense selection have lower heritability estimates (Roff & Mousseau 1987). However, heritability is but one way to measure additive genetic variation, and alternative measures of additive genetic variation has turned the canonical story about genetic variation in fitness related traits on its head.

Heritability ($h^2 = V_A/V_P$) is the proportion of total phenotypic variation (V_P) due to additive genetic effects (V_A). V_P is influenced by all sources of variation – not just V_A, but also by environmental variation, random noise, and non-additive genetic effects. Low heritability may well be a result of low V_A, but it might also be caused by high V_P (Charlesworth 1987; Price & Schluter 1991). Charlesworth (1984), Houle (1992), and others have argued that the coefficient of additive genetic variation ($CV_A = \sqrt{V_A}/\bar{x}$) is a better way to measure V_A (i.e., to remove *scale dependence* of V_A), because it is standardized by the trait's mean ($\bar{x}$) rather than by V_P and is therefore not confounded by environmental factors, random noise, or nonadditive genetic effects. (Unfortunately, the use of CV_A requires that the trait can be measured on ratio scales, such as number or time, and is therefore unsuitable for measuring genetic variation in most psychological traits.)

In a seminal study, Houle (1992) found that *traits under stronger selection show substantially higher mean-standardized additive genetic variation than do traits under weaker selection*, despite showing lower heritability. For example, fruit-fly wing length (a trait under relatively weak selection) has a heritability of .36, whereas number of offspring (a trait under intense selection) has a heritability of only .06. However, wing length has a CV_A of only 1.6, whereas number of offspring has a CV_A of 11.9. Across many such comparisons, the mean-standardized V_A of traits under the strongest selection is three to ten times *higher* than that for traits under weaker selection, the opposite of what Fisher's Fundamental Theorem would seem to predict. Similar results have been replicated now in many species, including humans (Hughes & Burleson 2000). These results were astonishing at first and created quite a stir among evolutionary geneticists, leading to a paradox that both parallels and informs the paradox of common, harmful, heritable mental disorders.

6.2. The watershed model explains why traits under the strongest selection have the highest genetic variation

Traits under the most intense selection (*fitness-related traits*, such as successful growth or mating) tend to require the adaptive functioning of many subsidiary biological and behavioral processes, and so depend on very many genes (Charlesworth 1987; Houle 1992; Price & Schluter 1991). The most massively polygenic "trait" is, of course, fitness itself – successful survival and reproduction – which requires the functional coordination of every adaptive mechanism in the body. The mutational "target size" of fitness is quite obviously the entire genome with any effect on fitness, which is probably the vast majority of genes with any phenotypic effect.

The biological network of mechanisms that must function together to create adaptive behaviors can be conceptualized by using a watershed analogy. Much like the numerous tributaries of the Amazonian watershed that coalesce and eventually empty into the Atlantic Ocean, there are many "upstream" micro-biological processes (e.g., rates of neuron proliferation, dendritic pruning, glucose metabolism) that flow into (affect) further "downstream" macro-biological processes (e.g., finding food, making friends, securing mates). A mutation at a locus that affects an upstream process disrupts not only that upstream process, but also every trait downstream of that process. A slightly harmful mutation that affects dendritic pruning may not affect glucose metabolism, but will probably undermine downstream processes such as learning ability, attracting mates, and eventually fitness itself. Figure 3 illustrates this watershed analogy.

The watershed analogy suggests that fitness-related traits have high additive genetic variation because they integrate many processes, and so are massively polygenic. Thus, they are vulnerable to harmful mutations at many loci, and have higher additive genetic variation due to new and old mutations. Fitness-related traits have high V_A, *despite* being under intense selection, not because of it. Their high V_A reflects that they tend to be massively

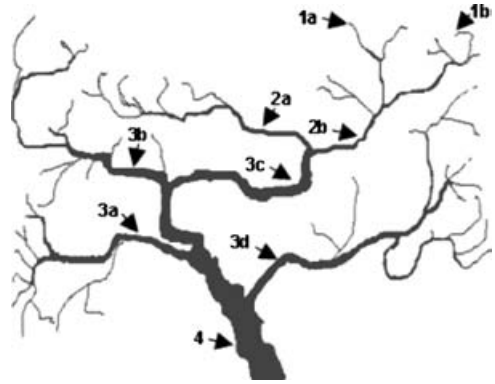

Figure 3. The watershed model of the pathways connecting upstream genes to downstream phenotypes. Mutations at specific loci (1a, 1b) disrupt narrowly defined mechanisms such as transmission of dopamine in the prefrontal cortex (2b). This and other narrowly defined mechanisms contribute noise to more broadly defined mechanisms, such as working memory (3c). Working memory in conjunction with several other mechanisms (3a, 3b, 3d) affects observable phenotypes, such as cognitive ability (4). If enough noise is present in particular upstream processes, specific behavioral syndromes may arise, such as mental disorder symptoms. All tributaries eventually flow into fitness. (Reprinted, with permission, from the *Annual Review of Clinical Psychology, volume 2*. © 2006 by Annual Reviews www.annualreviews.org. [Cannon & Keller 2005])

polygenic. This is not symmetrical: neutral traits are not necessarily influenced by few genes, but fitness-related traits are almost always influenced by many genes. There is now a good deal of support for this model, at least in fruit flies – the animal model of choice for evolutionary geneticists. Among the most compelling pieces of evidence are the high, positive intercorrelations between (a) the estimated number of loci influencing different traits, (b) the estimated trait-level mutation rates, and (c) traits' CV_A (Houle 1998). Charlesworth and Hughes (1999) further estimated that rare, harmful mutations account for 33% to 66% of the additive genetic variation in fitness-related traits in fruit flies.

The watershed model also clarifies why fitness-related traits typically have very high phenotypic variation and therefore moderate to low heritabilities. Downstream traits accumulate any type of noise from upstream traits – not only mutational noise, but also environmental noise (e.g., bad luck with injuries, predators, pathogens, and mates), random noise (e.g., the inherent stochasticity of development), and non-additive genetic effects. Because selection has much less power to reduce the variation in these latter factors compared to additive genetic variation, these factors tend to be proportionately more influential for fitness-related traits, leading to their lower heritabilities (Houle 1992; Merilä & Sheldon 1999).

6.3. The mutational target size of the human brain

The watershed model suggests that fitness-related traits have high genetic variation because they are massively polygenic. How might the watershed model help explain mental disorders? The answer depends upon how many loci influence the mechanisms that, when dysfunctional, cause the behavioral syndromes defined as mental disorders.

Consider the complexity of human brain function in watershed terms. The human brain is the most complex system known to science, with about 100 billion neurons and about a thousand times that many synapses. At least 55% of coding DNA is probably expressed in the human brain (Sandberg et al. 2000). Thus, the brain has an enormous mutational target size – out of the 25,000 protein-coding genes estimated in the human genome, mutations in at least half of them are likely to disrupt brain function, and hence behavior, to some extent (Prokosch et al. 2005).

Yet, there is more to the human genome than protein-coding regions. About as much non-coding DNA as coding DNA is evolutionarily constrained between species, implying that non-coding, regulatory regions are about as important to fitness as protein-coding regions (Keightley & Gaffney 2003). Importantly, non-coding regulatory regions of DNA rarely contribute to Mendelian disorders (McKusick 1998). Thus, harmful mutations in non-coding, regulatory regions seem to have mainly subtle quantitative effects rather than producing dramatic Mendelian catastrophes, and may be especially relevant in explaining the continuously distributed liabilities thought to underlie mental disorders.

How high is the typical human mutation load in brain-expressed loci? Based on conservative estimates, each human carries about 500 to 2,000 slightly harmful older point mutations inherited from ancestors in protein-coding regions (Fay et al. 2001; Sunyaev et al. 2001), plus an average of one or two new fitness-reducing mutations (Eyre-Walker & Keightley 1999). These mutation-load estimates should be at least doubled to account for mutations in non-coding, regulatory DNA, and should be increased slightly to account for mutations involving insertions, deletions, and other changes to chromosomal structure. Given that perhaps half of these mutations affect the brain, we estimate that the average human brain is disrupted by an average of at least 500 genetic mutations.

Apart from a high average mutation load, humans are likely to show high variation in mutational effects. If the numbers of mutations across individuals follows a Poisson distribution, as it would under random mating (S. Gangestad, personal communication, March 3, 2005), the mean and variance in numbers of mutations would be equal, implying a standard deviation of at least 22 mutations ($\sqrt{500}$). However, because humans probably assortatively mate for genetic quality through mutual mate choice (Miller 2000a), the variation in mutation number would be further amplified, so some people should inherit many fewer, and others many more, brain-expressed mutations than average. Moreover, the genetic variation caused by these varying numbers of mutations would be higher still, given that different mutations vary enormously in their effect sizes. The end result will be continuous distributions with respect to almost all psychological dimensions. Individuals with a high load of mutations that affect a particular configuration of upstream cognitive processes would be at higher risk of having mental disorders associated with deficits in downstream behaviors, and would tend to pass this risk on to their offspring. The importance of brain-expressed mutations is consistent with evidence for good genes sexual selection for human mental traits (e.g., Haselton & Miller 2006; Keller, in press; Miller 2000a; 2000b; 2000c; Miller & Todd 1998; Prokosch et al. 2005; Shaner et al. 2004).

6.4. How many loci affect mental disorders?

Before considering this question, it is important to note that the *number of loci affecting a trait* means something different to psychiatric geneticists versus evolutionary geneticists. To psychiatric geneticists, this phrase usually refers only to the loci that currently contribute to the bulk of a trait's genetic variation, which we refer to as the number of *polymorphic loci*. To evolutionary geneticists, however, the "number of loci affecting a trait" usually refers to the much larger number of loci that *could* affect the trait if those loci were polymorphic. It is this latter meaning, which we refer to as the number of *potential loci*, that is relevant to mutation-selection models. Pritchard (2001) estimated that only about 10% of a trait's potential loci will actually be polymorphic at any given time (assuming weak selection), a figure corroborated using a different method by Rudan et al. (2003b).

Recent reviews have invariably concluded that polygenic models (including at least two polymorphic loci) best describe the inheritance of mental disorders such as unipolar depression (Johansson et al. 2001), bipolar disorder (Blackwood et al. 2001), schizophrenia (Sobell et al. 2002), mental retardation (Plomin 1999), and autism (Folstein & Rosen-Sheidley 2001). Beyond this,

however, little is known regarding how many polymorphic loci affect mental disorders, because there has been so little success in actually finding them or modeling their numbers. For example, the data on schizophrenia inheritance are fit equally well by models that predict just a few polymorphic loci (e.g., Risch 1990) and by models that predict an "infinite" number of loci (e.g., Sullivan et al. 2003). The differences in conclusions are largely due to differences in assumptions (additive or epistatic allelic effects; a distinctive syndrome or an extreme of a normally distributed liability) about which no definitive information is available. Nonetheless, it is becoming clear from gene-mapping studies that many loci, at least 5–10 and perhaps many more, must influence the best-studied mental disorders: schizophrenia and bipolar disorder (Kendler & Greenspan, in press).

Rather than further considering assumption-laden models or preliminary empirical results, perhaps it is worthwhile to take a step back and consider carefully what mental disorders, as categories, truly are. Mental disorders are much less objective qualities than age, gender, height, or white blood cell count. Mental disorders are constellations of aberrant behaviors that were lexicalized as unitary disorders by psychiatrists in the nineteenth and early twentieth centuries. There are several possible reasons why mental disorder categories were chosen as they were. First, maybe each mental disorder really has a unitary etiology – a single consistent genetic, neurological, or environmental cause – but few psychiatrists subscribe to such a notion today. Most mental disorders show too much heterogeneity within categories, comorbidity across categories, and continuity with normality, to qualify as discrete, unitary diseases.

Second, as Bleuler (1911) and Jaspers (1923) argued regarding "the schizophrenias," an apparently unitary mental disorder may be a heterogeneous group of dysfunctions in different mechanisms whose final common behavioral pathways lead to similar symptoms. Upstream biological processes that ultimately affect abstract psychological traits are largely hidden from human perception (see 3a and 3b in Fig. 3). They are microscopic neuroanatomical problems hidden within the brain. When these upstream processes dysfunction, humans can usually observe only the downstream behavioral outcomes, and not the specific dysfunctions themselves. Such etiological heterogeneity becomes apparent only in rare cases when dysfunctions in specific upstream mechanisms leave a unique phenotypic signature, in addition to normal symptoms of mental disorders. For example, at least 20 genetic conditions, such as the XXX and XYY karyotypes, congenital adrenal hyperplasia, Wilson's disease, and velocardiofacial syndrome, increase schizophrenic symptoms (Propping 1983). As Vogel and Motulsky (1997) put it,

> Survival of this diagnostic concept was achieved – at least in part – by an interesting strategy: whenever symptoms characteristic of schizophrenia were observed in association with findings that suggested organic disease, the diagnosis of schizophrenia was withheld. . . . [W]hen all [such] patients . . . were excluded, a disease group remained for which specific causative factors could not be found." (p. 700)

Third, and most radically, a mental disorder may be perceived as a coherent category not because it is a "natural kind" with a common etiology at any level, but because it was evolutionarily or culturally adaptive for people to categorize others in particular ways in order to make certain social decisions about them. Thus, insanity may be like ugliness, dishonesty, or aggressiveness – things to avoid and stigmatize in social and sexual interactions – not because they have a unitary etiology, but because they have a common set of fitness costs for observers.

The latter two explanations are not mutually exclusive, of course. We find it likely that apparently unitary mental disorders are partly in the dysfunctions of the sufferer, and partly in the person-perception adaptations of the beholder. Mental disorder categories may reflect a mix of historical convention, diagnostic convenience, innate categorization biases in person perception, and common final pathways of partially overlapping yet distinct dysfunctions. This suggests that *the number of loci affecting a mental disorder depends in large part on the way human minds categorize behavioral symptoms*. The search for endophenotypes (Cannon & Keller 2005; Gottesman & Gould 2003) is critically important because it enables researchers to discern more directly the varied upstream processes whose dysfunctions increase mental disorder risk, while relying less on perceived symptom similarity. The most useful endophenotypes should be those that are further upstream and etiologically less complex. If the past is any guide, the heterogeneity documented in mental disorders so far may be only the tip of the iceberg. Underneath a few simplistic mental disorder categories may lie a vast diversity of potential behavior-impairing mutations across the thousands of genes involved in brain development.

7. Empirical evidence on the three models for common, harmful, heritable mental disorders

We have reviewed several theoretical reasons why polygenic mutation-selection balance may explain the genetic variation underlying mental disorders, much as it explains rare Mendelian disorders. We have also presented some theoretical and empirical reasons to doubt that neutral evolution or balancing selection are good general resolutions to the paradox, although they may play a role under certain specific conditions that we delineated. Fortunately, empirical evidence can help distinguish which of these models goes the farthest in explaining mental disorder susceptibility alleles. We now review six lines of evidence that, taken together, strongly suggest that harmful mutations underlie a substantial portion of the genetic risk in mental disorders.

7.1. Fitness and mental disorders

As noted above (sect. 3.3), mental disorders are associated with lower fertility (due in large part to reduced mating opportunities; see Table 2) and a high level of disability in modern industrialized environments. This is consistent with mutation-selection models, but is less easily reconciled with models of ancestral neutrality and balancing selection. There is one classic example of balancing selection maintaining a highly deleterious condition in humans – sickle-cell anemia – where the strong selection against anemia is balanced by strong selection favoring malarial resistance. To our knowledge, such benefits that balance the harm done by mental disorders have not

been reliably documented for any mental disorder. Indeed, recent evidence on schizophrenia casts doubt that susceptibility alleles for schizophrenia have any hidden benefits, at least in modern environments. If schizophrenia susceptibility alleles are being maintained by either heterozygote advantage or antagonistic pleiotropy, non-affected siblings of schizophrenics should have higher fitness than the general population. However, the best-controlled and largest study of its kind found that 24,000 siblings of 11,000 schizophrenics (sample sizes from all previous studies were fewer than 200 schizophrenics) had the same reproductive success (99.8%) compared to the general population (Haukka et al. 2003). The 2003 study by Haukka and colleagues had plenty of power to detect even minor differences in fitness among relatives of schizophrenics, such as those (around 5%) that might be required if heterozygote advantage maintains the susceptibility allele (Allen & Sarich 1988). Because modern reproductive success may not correlate with ancestral fitness, as we discussed earlier (sects. 3.3 and 4), such evidence does not disprove heterozygote advantage or antagonistic pleiotropy as mechanisms responsible for schizophrenia, but it does weigh against them.

7.2. The effect of trauma on mental disorders

Major genetic abnormalities and environmental insults tend to increase rather than decrease mental disorder risk. For example, chromosomal abnormalities such as trisomy, translocations, and mutations of major effect cause syndromes consistent with autism, mental retardation, schizophrenia, bipolar disorder, and major depression (reviewed in MacIntyre et al. 2003). Traumatic brain injuries increase the risk of mental retardation, schizophrenia, anxiety disorders, and depression (Max et al. 1998; Rao & Lyketsos 2000; Schoenhuber & Gentilini 1988). This type of evidence poses a serious challenge to balancing selection models, particularly those that posit that mental disorders themselves are alternative, complex adaptations maintained by selection. Given that adaptations require the complex coordination of many mechanisms, traumas should disrupt adaptive complexity, not lead to it. Receiving a blow to the head, for example, should not lead to higher intelligence or attractiveness. The direction in which traits move after traumas provide information about the direction of fitness. The mutation-selection model seems most consistent with this evidence: the fact that major phenotypic disruptions (traumas and genetic abnormalities) increase the risk for mental disorders is consistent with the hypothesis that minor phenotypic disruptions (mutations of generally minor effect) do likewise.

7.3. The effect of paternal age on mental disorders

Female humans are born with their full supply of 400+ eggs, and these eggs have gone through only 23 replications, a number that does not change as females age. By contrast, males must continue to produce new sperm throughout life. At age 15, sperm cells have gone through about 35 chromosomal replications, increasing to 380 by age 30, and 840 by age 50 (J. F. Crow 2000). Because each chromosomal replication carries a small chance of a copying error (mutation), the probability of germ-line mutations increases, at a greater than linear rate, with paternal age. Consistent with a mutation-selection model, higher paternal age, but not maternal age, is associated not only with many Mendelian disorders, but also – tellingly – with lower intelligence (Auroux et al. 1989), and an increased risk of mental retardation (Zhang 1992), schizophrenia (Brown et al. 2002; Malaspina et al. 2001; Sipos et al. 2004; although see Pulver et al. 2004), and mental disorders in general (Hare & Moran 1979). Perhaps 15% to 25% of all cases of schizophrenia are a result of this paternal age effect (Malaspina et al. 2001; Sipos et al. 2004), which would be consistent with most other cases being a result of milder, older, more numerous mutations. These paternal age effects are a direct challenge to neutral and balancing selection explanations of mental disorders, but are exactly what would be expected under a mutation-selection model (J. F. Crow 2000).

7.4. The effect of inbreeding on mental disorders

Older harmful mutations tend to be more recessive than new mutations because selection quickly removes mutations with the largest and most dominant harmful effects. *Inbreeding*, or mating between close genetic relatives, reveals the full harmful effects of these old, mostly recessive mutations because offspring of close relatives are homozygous at more loci. Consistent with a mutational role in mental disorder risk, inbreeding in humans has been associated with mental retardation and low intelligence (Vogel & Motulsky 1997), unipolar and bipolar depression (Rudan et al. 2003a), and schizophrenia (Abaskuliev & Skoblo 1975; Bulayeva et al. 2005; Gindilis et al. 1989; Rudan et al. 2003a; although see Chaleby & Tuma 1986; Saugstad & Ödegard 1986). If true, this phenomenon of *inbreeding depression* not only implicates partially recessive harmful mutations in mental disorder risk among *non*-inbred populations; it also shows that selection acted to minimize mental disorder risk in the ancestral past. It is well known in evolutionary genetics that inbreeding depression occurs among traits that have been under directional selection. Ancestral neutrality and balancing selection cannot explain why inbreeding increases mental disorder rates. For example, if schizophrenia risk alleles were maintained by frequency dependence, then inbreeding would be as likely to reduce as to increase schizophrenia risk. Selection only enriches the gene pool with recessive alleles when higher trait values (in this case, higher mental disorder risk) lead to lower fitness.

7.5. Comorbidity between mental disorders

Studies have typically found strong associations between mental disorders; for example, a recent study found that mental disorder comorbidity ranged from 44% to 94%, depending on the mental disorder (Jacobi et al. 2004). This comorbidity appears to be driven in part by pleiotropic genes that simultaneously affect different disorders: there are positive genetic correlations between unipolar depression and generalized anxiety disorder (Kendler et al. 1992), unipolar depression and bipolar disorder (McGuffin et al. 2003), bipolar disorder and schizophrenia (Craddock et al. 2005), autism and unipolar depression (Piven & Palmer 1999), and schizophrenia and several

types of mental retardation (Vogel & Motulsky 1997). Mental disorders are also highly comorbid with many heritable somatic conditions, such as asthma and hypertension (Buist-Bouwman et al. 2005). Comorbidity and positive genetic correlations among mental disorders are nicely explained by mutation-selection models, but would not be expected under ancestral neutrality or balancing selection models. For example, if susceptibility alleles for schizophrenia and bipolar disorder were both ancestrally neutral in their fitness effects, or if their alleles were maintained by balancing selection, there would no particular reason for them to become genetically correlated with each other. On the other hand, if mental disorders are influenced by mutations at hundreds of (potential) loci, which is in the neighborhood of what would be needed for mutation-selection models to explain their prevalence, it would be vanishingly unlikely for each disorder to arise through a mutually exclusive set of genes, given that the human genome includes only about 25,000 protein-coding loci. The genetic risk alleles for mental disorders must overlap quite a lot. This is where the watershed metaphor falls apart: a small mutation (a tributary) can contribute to many different symptoms (rivers); the mapping from genes to mental disorders is many-to-many rather than many-to-one.

7.6. The likely frequencies of mental disorder susceptibility alleles

To guide the search for mental disorder susceptibility alleles, it is crucial to know whether susceptibility alleles are common (one or a few susceptibility alleles per disease locus at high frequencies in the population), or individually rare (one exceedingly predominant non-susceptibility wild-type allele and many different rare susceptibility alleles at each disease locus). Gene mappers differentiate these two possibilities; the first is called the common disease, common variant (CDCV) hypothesis, whereas the latter has been dubbed the common disease, rare variant (CDRV) hypothesis (Wright et al. 2003). To the degree that the CDCV hypothesis reflects the state of the world, current methods of gene mapping should suffice for finding mental disorder susceptibility alleles. On the other hand, the CDRV model suggests that future progress in locating susceptibility alleles will continue to be slow, because the statistical association, between common "marker" alleles and rare susceptibility alleles that gene mapping requires, will be low or nonexistent (Terwilliger & Weiss 1998; Weiss & Clark 2002; Wright & Hastie 2001). Moreover, if susceptibility alleles are rare, they must exist at a large number of loci to explain mental disorder rates and heritabilities, which would further decrease the power of gene-mapping studies. Understandably, the CDRV model has not been well received among psychiatric geneticists. A speaker at a major gene-mapping conference conceded that this CDRV scenario was too depressing to contemplate, and so it was better to proceed as if it were not true (Wright & Hastie 2001).

The three models of selection each leave different signatures in the genome that correspond roughly to the CDCV model or the CDRV model (Bamshad & Wooding 2003; Kreitman 2000). One of the strongest predictions from practically every model of balancing selection is that it will lead to relatively few polymorphic loci, each harboring just a few (usually two) different alleles at fairly high frequencies (minor allele frequencies greater than about 5%, which we call *common alleles*), that account for most of the genetic variation in the trait (Barton & Keightley 2002; Roff 1997). This appears to hold whether the balancing selection is for discrete or continuous trait variation (Mani et al. 1990).

Whereas the prediction that balancing selection leads to common alleles appears robust, the prediction that balancing selection leads to just one or a few loci being polymorphic is more nuanced. The latter prediction applies only to the number of loci that influence traits directly under balancing selection. If a trait is not under balancing selection (i.e., is under directional or stabilizing selection), some of the alleles that influence the trait may nevertheless be pleiotropic and under balancing selection for reasons unrelated to the trait in question (e.g., Turelli & Barton 2004). In this case, there is no limit on the number of loci under balancing selection that might influence the trait. For example, it is possible that schizophrenia risk has always been maladaptive (under directional selection), but that many of the (pleiotropic) loci affecting schizophrenia risk also affect immune functioning and have been under frequency-dependent selection for immunity (see sect. 5.8). Therefore, if mental disorder risk is a pleiotropic side effect of genes that are under balancing selection on other traits, then common alleles – but at an unknown number of loci – should be responsible for most of the mental disorder genetic risk. If mental disorder risk is directly under balancing selection, as many Darwinian psychiatrists have postulated, common alleles at just a few loci should be responsible for most of the genetic risk of mental disorders. Regardless, if balancing selection maintains susceptibility alleles for whatever reason, there should be only a few common susceptibility alleles at each risk locus, and the CDCV model should be true.

Neutral evolution predicts that alleles will be somewhat less common than they would if governed by balancing selection. If neutral susceptibility alleles happened to be common in ancestral human populations, they should still be common today (Reich & Landers 2001). However, as noted earlier (sect. 4.1), genetic drift in small ancestral human populations tends to drive neutral loci to fixation, through random sampling error. Indeed, most neutral loci seem to have one predominant allele and, due to the recent increase in human population size, many individually rare alleles, although some neutral loci also have common alleles (Cargill et al. 1999; Halushka et al. 1999). Thus, neutral evolution should lead to a situation somewhere between the CDCV model and the CDRV model.

Widespread mutation-selection, on the other hand, should lead to a world where the CDRV hypothesis is true. A trait's genetic variation should be a result of mutations at many different loci. The more deleterious and common the trait was ancestrally, the more loci would have to be involved; very serious and common mental disorders may be affected by hundreds or even thousands of potential loci, but only a portion of these should contribute to the bulk of standing genetic variation in any given population at any given time (Pritchard 2001). At each locus, numerous different mutations should exist,

none of which should be at high frequencies (e.g., minor allele frequencies of less than 5%). However, in cases where selection against susceptibility alleles has been minute (e.g., $s < 1/5{,}000$), such as might occur in the case of gene-by-environment interactions (sect. 4.4), some susceptibility alleles could be at high frequencies, despite selection, due to random genetic drift (Pritchard 2001).

The historical success or failure of psychiatric gene hunting helps clarify which of the three evolutionary models – ancestral neutrality, balancing selection, mutation-selection balance – best explains the existence of the bulk of susceptibility alleles. The CDRV model, most consistent with mutation-selection, predicts the least progress in psychiatric gene hunting; whereas the CDCV model, most consistent with balancing selection, predicts the most. Where does the evidence stand? Once again, mutation-selection seems to best fit the evidence. Only a handful of replicable susceptibility alleles for mental disorders have been found despite two decades of intensive research involving thousands of scientists and hundreds of millions of dollars. Acclaimed discoveries of mental disorder susceptibility alleles have typically been followed by repeated failures to replicate (Terwilliger & Weiss 1998; Weiss & Clark 2002). At the same time, the molecular bases for over 1,700 Mendelian phenotypes have been definitively found to date (*Online Mendelian Inheritance of Man*, April 10, 2006), showing that current methods are wildly successful at finding alleles responsible for single-gene, Mendelian disorders.

Even for these susceptibility alleles that have been located, the effect sizes have been very small. One of the more comprehensive recent meta-analyses (Lohmueller et al. 2003) showed that only two of the eight most-studied mental disorder susceptibility alleles (at the DRD3 and HTR2A loci) were reliably associated with a mental disorder (schizophrenia). The meta-analysis estimated the true odds ratio for the larger of the two associations was just 1.12, meaning that given 1,000 people with the DRD3 susceptibility allele and 1,000 people without it, 11 people in the first group and 10 in the second group will probably develop schizophrenia (given its 1% base rate). Several other meta-analyses have also recently concluded that discovered mental disorder susceptibility alleles tend to have small effects (odds ratios less than 1.5; Kendler 2005). The susceptibility alleles underlying most of the genetic risk for mental disorders have not yet been found. If those that have been found represent the "low-hanging fruit" (explaining the most variation in the population), then the remaining susceptibility alleles may be even rarer and harder to detect.

We are not casting doubt on the entire enterprise of gene hunting. Susceptibility alleles explaining the most risk variation in the population, many of which may have been found already, could be common because of balancing selection on separate traits, recent bottlenecks among certain groups, or genetic drift (caused by fitness effects that were closer to neutral ancestrally). If such susceptibility alleles happened to reach frequencies above 5% in ancestral times, their current allelic complexity should still be low, and gene-hunting techniques should be sufficient for finding them (Reich & Lander 2001). Some protective alleles may be sweeping toward fixation caused by recent selection. Some lineage-specific susceptibility alleles may be missed within an analysis or not replicated across analyses because of hidden population substructures that arose across evolutionary history. Technological advancements may eventually enable discovery of even the rarest susceptibility alleles, the base-pair sequences of which would provide important information about the relative importance of ancestral neutrality, balancing selection, and mutation-selection balance (Bamshad & Wooding 2003; Otto 2000). Nevertheless, the slow progress in finding mental disorder susceptibility alleles so far, and the small amount of explained population risk of those that have been found, are generally consistent with the mutation-selection model and the CDRV model. If balancing selection, and to a lesser degree ancestral neutrality, were general explanations for mental disorders, then psychiatric genetics probably would have already found the susceptibility alleles responsible for most of the genetic variation underlying them.

8. Conclusions: Toward a resolution of the paradox of common, harmful, heritable mental disorders

Evolutionary anthropologist Donald Symons observed that "you cannot understand what a person is saying unless you understand who they are arguing with" (Cosmides & Tooby, n.d.). In this article, we are arguing mostly against those evolutionary thinkers who assume that adaptive forces are the only possible explanations for common, heritable polymorphisms such as mental disorders, even when those traits look profoundly harmful to survival and reproduction. We are also arguing against those psychiatric geneticists who disregard evolutionary theory when trying to understand mental disorders or their susceptibility alleles. This article has tried to show how evolutionary genetic theories are important to both fields.

Evolutionary psychologists have struggled to explain genetic variation in the context of species-typical adaptive design – sometimes ignoring it, sometimes citing mismatches between ancestral and current environments, and sometimes trying to find hidden adaptive benefits maintained by balancing selection. These approaches all draw upon the familiar adaptive toolbox, in which the optimizing power of natural selection is assumed. This is a great toolbox to use when trying to reverse engineer universal aspects of human nature such as vision, mate choice, or normal reactions to depression-inducing situations. Indeed, the search for possible adaptive functions of mental disorder symptoms, especially when the capacity to express these symptoms is universal and they are environmentally triggered, is an important counterbalance to the prevailing assumption that subjective distress equals biological disorder. However, a very different set of tools is required to explain persistent genetic variation, especially in traits related to fitness. These tools must be drawn from contemporary evolutionary genetics.

Psychiatric genetics has, with some pride, traditionally been an empirically driven field. This approach is commendable to a degree. However, as Einstein once observed, "It is the theory that decides what we can observe," and evolutionary genetics provides a rigorous

mathematical framework that could better guide psychiatric gene hunting (e.g., Pritchard 2001; Reich & Lander 2001; Rudan et al. 2003a; Wright et al. 2003). For example, mutation-selection models suggest that susceptibility alleles with the largest effect sizes may also be the rarest, the most recent, and the most population specific – an insight with important implications for the methods most likely to locate mental disorder susceptibility alleles (see Wright et al. 2003). Moreover, mutation-selection explanations further justify the search for less polygenic, and more genetically mappable, endophenotypes (Cannon & Keller 2005).

The existence of common, heritable, harmful mental disorders creates an apparent evolutionary paradox, but we think it can be resolved by recognizing the enormous mutational target size of human behaviors. According to this model, behavioral traits are especially susceptible to harmful mutations because they depend on the most complex organ in the human body. The brain is affected by over half of the hundreds of mutations that all humans carry. Some of these mutations have large, distinctive effects, and so are reliably recognized as Mendelian disorders. Tellingly, some of *these* mutations cause syndromes inherited in Mendelian fashion but that are otherwise phenotypically identical to mental disorders (MacIntyre et al. 2003). Mendelian disorders are rare because selection keeps very harmful mutations very rare.

Most other mutations, especially in regulatory regions of the genome, have much milder effects and cause mostly quantitative differences in traits. Individuals with an especially high load in mutations that disrupt a particular configuration of brain systems will tend to act in aberrant, harmful ways that provoke social comment and psychiatric categorization. Lacking a map of the neurogenetic watershed, psychiatrists have struggled to identify criteria that could enable these behavioral syndromes to be meaningfully categorized. Current criteria reflect perceived similarity of symptoms and prognoses, which is potentially influenced not only by actual etiological similarity, but also by the cultural and inherent person-perception biases of those perceiving the sufferer, and the categorization demands of legal, medical, and research systems. Common mental disorders are common because they are defined that way.

It was natural that these mental disorder categories became reified, and that scientists looked for single genes underlying them, which was so successfully accomplished with Mendelian disorders. But common mental disorders are probably fundamentally different than Mendelian disorders – not, as has often been presumed, in that the former were not selected against while the latter were – but rather, in that common mental disorders are influenced by a much larger number of environmental and genetic factors, most of which have only minor influences on overall population risk.

Everyone alive, according to this model, has minor brain abnormalities that cause them to be a little bit mentally retarded, a little bit emotionally unstable, and a little bit schizophrenic. If so, this framework may help explain much more than just mental disorders; it may help explain genetic differences between people in personality, health, athleticism, intelligence, attractiveness, and virtually any other trait related to Darwinian fitness. If scientists so chose, they could define the low-fitness extremes of any of these dimensions as "disorders." The susceptibility alleles contributing to such "disorders" would be the same ones responsible for genetic variation across the whole dimension in the general population. All other things being equal, someone of below-average athleticism harbors an above-average number of athleticism-degrading mutations. Adaptive organic complexity is exquisite as an abstraction, but riddled with errors within any living, breathing individual. We are all very imperfect versions of that Platonic ideal, the species-typical genome. This perspective may help explain evidence of ubiquitous maladaptation; for example, why nearly everyone suffers from some type of heritable physical ailment, or why about half of people will meet DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, *4th edition*) criteria for a mental disorder at some point in their lives (Kessler et al. 2005).

The theoretical and empirical evidence reviewed in this article is most consistent with a polygenic mutation-selection balance model for explaining common, harmful, heritable mental disorders. Ancestral neutrality and balancing selection almost certainly play roles in maintaining some susceptibility alleles, but, as general explanations, they are difficult to reconcile with empirical evidence that mental disorders are associated with (1) reduced fitness, (2) brain trauma, (3) higher paternal age, (4) inbreeding, (5) genetic comorbidity, and (6) many susceptibility alleles that explain little population risk. So far, the evidence suggests that mutation-selection plays an important role in maintaining susceptibility alleles of mental disorders, whereas the other forces play less certain roles. At the very least, we hope to have demonstrated that there is no necessary paradox in the existence of common, heritable, harmful traits, such as mental disorders, and we hope to have shown the types of empirical evidence that can test different evolutionary theories of susceptibility alleles. It is possible, of course, that new empirical evidence, or new understandings of how genes affect phenotypes, will show that our conclusions were substantively wrong. It is also possible that we have made mistakes in interpretations of data or theory. This is, after all, a persistent danger in multidisciplinary work, but we feel strongly that the difficulties of integrating such disparate fields are far outweighed by the potential advantages. We look forward to a future in which Darwinian psychiatry, psychiatric genetics, and evolutionary genetics become more mutually informative and supportive.

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Open Peer Commentary

Praise for a critical perspective

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Abstract: The target article skillfully evaluates data on mental disorders in relation to predictions from evolutionary genetic theories of neutral evolution, balancing selection, and polygenic mutation-selection balance, resulting in a negative outlook for the likelihood of success finding genes for mental disorders. Nevertheless, new conceptualizations, methods, and continued interactions across disciplines provide hope.

The insightful and balanced treatment in the target article takes a pessimistic view of the likelihood of finding genes for mental disorders. In the view of the authors, if polygenic mutation-selection balance truthfully characterizes the complex genetics of mental disorders, our task may be more difficult than we had hoped, barring new approaches. Nevertheless, several points in the article resonated with us, including (1) an appreciation for evolutionary genetics, (2) the watershed analogy, (3) the concepts of endophenotype and of genetic correlation, (4) the implied necessity of animal models, and (5) the need for cross-fertilization among disciplines. We touch on each of these aspects in our commentary.

The authors' analogy of the neurogenetic watershed is simplistic but useful. One of us (Shelton) has created and used a genetic reference population of cultured human fibroblasts to investigate intracellular signal transduction cascade differences in patients with mood disorders. Using this system, it was discovered that patients with the melancholic subtype of major depression have reductions in the activity of protein kinases A and C (critical to the synthesis of, for example, brain-derived neurotrophic factor and the glucocorticoid receptor), and altered serotonin receptor 2A–mediated phosphoinositide signaling (Akin et al. 2004; 2005). These findings have been demonstrated in human postmortem brain tissue, as well. This research illustrates the ex vivo study of endophenotypes very proximal to genes implicated in depression (kinases, HTR2A), that is, very upstream in the watershed model. Another approach, still in humans, uses "imaging genetics" to study endophenotypes more downstream at the level of neural systems. For example, genetic variation in important serotonin genes (TPH2, the gene for tryptophan hydroxylase, and SLC6A4, the serotonin transporter) has been associated with activation of the amygdala by fearful stimuli (Brown et al. 2005; Pezawas et al. 2005). Notably, in both approaches, relatively smaller samples were required to detect differences, implying genetic simplification followed the phenotypic simplification.

While the authors point out that heritability refers only to the role of genetic variation in differences between individuals, and not the similarities, they also highlight the usefulness of the genetic correlation. A genetic correlation between two measured traits implies shared allelic variants or genes in linkage disequilibrium. From an evolutionary standpoint, it is usually the former that is more interesting (Airey et al. 2000) as common developmental programs are implicated. The genetic correlation is a heavily used concept and tool in mouse genetics (Crabbe 1999). We look forward to the further development of this concept in psychiatric genetics coupled with measured endophenotypes.

The explicit emphasis on endophenotypes as measured (continuous) traits, and the arguments against expectations of distributional bimodality in affected (diagnosed) and unaffected (undiagnosed) individuals, were welcome. Although perhaps not the usual medical model, continuous variation opens the door to a more complete understanding of mechanisms underlying individual differences, broadly defined. To be fair, psychiatric genetics has made significant inroads, showing that genetic variation in psychiatric candidate genes like DAT, COMT, TPH2, and SLC6A4 is associated with cognitive and emotional dimensions in the normal human range (Bertolino et al. 2006; Brown et al. 2005; Mattay et al. 2003; Pezawas et al. 2005).

We would like to point out that researchers focusing on other complex genetic illnesses have successfully used population-based sampling schemes to support the common disease rare variant hypothesis. Cohen et al. (2005) found enrichment of rare nonsynonymous variants of large effect size in candidate genes for plasma levels of high-density-lipoprotein (HDL) cholesterol from the lower 5% tail of a large population-based sample. More recently, and in line with the target article's predictions, Cohen et al. (2006) have found enrichment of rare variants of a gene involved in cholesterol absorption, but where the effect sizes of the variants were more moderate. Certainly, this leaves open the possibility of effect sizes that are smaller still, as the target article predicts. These works represent reasonable models for the study of the genetics of mental disorders. A downside to this approach is that it is candidate gene based. Because the approach relies on sequencing and polymorphism discovery, rather than on typing known markers, the approach is not feasible for genome scans. In other words, the onus is on the investigator to understand enough about the biology of their disease to nominate candidate genes for rare variant discovery.

The study of endophenotypes is presented as integral to progress despite the implications of polygenic mutation-selection balance. However, it cannot be avoided that the study of endophenotypes in humans is limiting. Most neural endophenotypes remain inaccessible. Therefore, genetic model organisms can be used to widen the scope of understanding universal (translatable) brain mechanisms and to nominate candidate genes for the aforementioned nonsynonymous rare variant methods.

The target article skillfully evaluates data on mental disorders in relation to predictions from evolutionary genetic theories of neutral evolution, balancing selection, and polygenic mutation-selection balance. Although the arguments for the latter theory are persuasive, we think it best, as Keller & Miller (K&M) have done, to continually and critically evaluate theories that are borrowed into secondary fields.

Genes for susceptibility to mental disorder are not mental disorder: Clarifying the target of evolutionary analysis and the role of the environment

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Abstract: In this commentary, we critique the appropriate behavioural features for evolutionary genetic analysis, the role of the environment, and the viability of a general evolutionary genetic model for all common mental disorders. In light of these issues, we suggest that the authors may have prematurely discounted the role of some of the mechanisms they review, particularly balancing selection.

Keller & Miller's (K&M's) integration of quantitative evolutionary genetics with evolutionary approaches to psychiatric disorder is timely and important. Their article convincingly argues that the role of polygenetic mutation-selection balance has not been

adequately recognised within evolutionary psychiatry. Although we are generally in agreement with their argument, we would like to offer critical commentary on three issues.

The first concerns determining appropriate behavioural features for evolutionary analysis. Much of K&M's argument is framed in terms of the concept of mental disorder, although they also provide an incisive critique of the concept. However, their treatment is often inconsistent in terms of the phenomena it considers. The evidence they review is usually relevant to case-level mental disorder, but, in places, they focus on variations in underlying susceptibility traits, and, in others, on genes that confer susceptibility for mental disorder. Our own view is that evolutionary genetic analysis should not focus upon mental disorders per se, but on genetic factors that underlie susceptibility to disorders – on genes that result in extreme variation in polygenetic traits, and on how such variation causes individual differences in the functioning (e.g., threshold of activation, propensity for regulation/dysregulation) of evolved psychobiological mechanisms. Heritable variation in such traits can be maintained by a range of factors that potentially include each of those discussed by K&M, depending on the trait.

This point of view results in the following agenda for genetic evolutionary psychiatry. First step is an analysis of the adaptive basis of a species-typical psychobiological mechanism, including the recurring ancestral adaptive problem(s) that it solved, and how the design of the feature provided an efficient, domain-specific solution to the problem(s) (Buss 1995). Such analyses are typical in evolutionary psychology, an example being our own work on depressed mood (see Allen & Badcock 2003). Second, there should be an analysis of the likely sources of genetically maintained variation in the functioning of the trait. Finally, the theorist should consider the circumstances under which the operation of the mechanism is dysfunctional (i.e., no longer performing its naturally selected function; Wakefield 1999a).[1]

Such an agenda has implications for the issues considered by K&M. For example, a central concern is why genes that confer susceptibility to mental disorder are maintained by natural selection when such disorders are patently maladaptive. As evidence for this claim, K&M refer to findings that fertility rates amongst those suffering from case-level disorders are persistently lower than for non-psychiatric populations. The approach just outlined, however, would suggest that their analysis should instead concentrate on the socio-reproductive consequences of trait variation in the functioning of evolved mechanisms. For example, personality is a salient descriptor of individual differences in susceptibility to mental disorder (Clark 2005; Kruger & Tackett 2003), and can be thought of as representing phenotypic differences in the functioning of evolved mechanisms for dealing with, for example, social and environmental threat (neuroticism; Nettle 2004) or seeking out propitious environments (extraversion; Depue & Collins 1999). A study of personality and reproductive fitness in humans found that optimal levels of fertility were observed at two loci: those displaying high neuroticism and low extraversion (a group who are likely to have susceptibility genes for mental disorder), and those displaying high extraversion and low neuroticism (Eaves et al. 1990). Such data indicate that although mental disorders themselves may be associated with low fertility, the genes that confer susceptibility to these disorders may not. K&M's dismissal of the ancestral neutrality and balancing-selection models may therefore have been premature for some disorder susceptibilities.

Our second contention is that K&M appear to underestimate the role of environmental influences. As noted by others (e.g., Hall 1999; Lickliter & Honeycutt 2003; Oyama et al. 2001), the developmental outcome of the self-regulating, multileveled system that characterises an organism (and the more specific psychobiological design features it exhibits) is not prescribed by the genes alone, but by the regulatory dynamics of a complex, gene-in-a-cell-in-an-organism-in-an-environment system. For example, recent research has demonstrated that selection for a personality trait with high heritability fluctuates across years within a natural bird population, suggesting that fluctuations in gene-environment interactions can maintain genetically specified personality variation (Dingemanse et al. 2004). These data imply that even relatively minor variations within environments may result in the maintenance of an allele in the population despite its deleterious effects in particular contexts. Indeed, for most of the common mental disorders analysed by K&M, strong gene-environment interactions in their aetiology are the rule rather than the exception (e.g., Caspi et al. 2003; Kendler & Eaves 1986). Thus, when phylogenetic explanations focus on susceptibility alleles that underlie endophenotypic trait deviation in the functioning of adaptive mechanisms – rather than disorders per se – ancestral neutrality and balancing-selection models become more plausible.

Third, and finally, we believe that searching for a general set of evolutionary genetic models that explain all common mental disorders, irrespective of their specific features, may be a fraught goal. Disorders differ in prevalence, heritability, whether they are continuous or discontinuous with normal functioning, and the importance of environmental precipitants – both in terms of their variation in modern ecologies, and the influence of historical changes in environments (such as those between ancestral and recent times). These factors, amongst others, will help adjudicate the likely role of ancestral neutrality, balancing selection, and polygenetic mutation-selection balance in the maintenance of susceptibility alleles. As such, it may be more fruitful to examine these issues within each disorder (or, more specifically, in terms of maladaptive deviations from well-defined adaptive psychobiological mechanisms), than for a general class of disorders. Indeed, committing to the power of any one explanatory model to account for the full diversity of psychopathologies (and the complex interplay of phylogenetic and ontogenetic processes responsible for each) invariably runs the risk of neglecting alternate, equally viable, and possibly complimentary hypotheses. Nevertheless, we welcome K&M's contribution to the literature and trust that it will enkindle a more rigorous and scientifically principled development of models within evolutionary and genetic psychiatry.

NOTE

1. By "no longer performing its naturally selected function," we mean that the action of the mechanism either exacerbates the problem(s) it was designed to solve or creates a new problem that is more severe or debilitating.

The social environment compresses the diversity of genetic aberrations into the uniformity of schizophrenia manifestations

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Abstract: Genetically and neurodevelopmentally, there may be a thousand schizophrenias, yet there would be no schizophrenia at all without active contribution from all of us; none – outside the primitive processes that regulate our relationship with one another. In order to understand the nature of schizophrenia as it unfolds relatively uniformly in the social context, we need to depart from an evolutionarily more feasible understanding of society.

As long as we are sane and he is insane, it will remain so. But comprehension as an effort to reach and grasp him, while remaining within our own world and judging him by our own categories whereby he inevitably falls short, is not what the schizophrenic either wants or requires. We have to recognize all the time his distinctiveness and differentness,

> *his separateness and loneliness and despair. . . . Schizophrenia cannot be understood without understanding despair.*
>
> —R.D. Laing (1960, p. 39)

In Keller & Miller's (K&M's) thorough exposition, one conjecture remains unconvincing. The question as to how the multitude of susceptibility alleles – maintained by *mutation selection* and expressed in a multitude of neurodevelopmental "imperfections" – channels into discrete disorders such as schizophrenia cannot simply be sidestepped by claiming that "mental disorder categories became reified" (sect. 8, para. 6) and the "similarity of symptoms" is merely "perceived" (sect. 8, para. 5). Let us try to reconcile their elegant model with the fact that schizophrenia does, after all, represent a fairly separate entity, a unitary disease, that is not primarily the product of "historical convention," "diagnostic convenience" (sect. 6.4, para. 6), or requirements "to make certain social decisions" (sect. 6.4, para. 5). Let us ask how nonspecific deficits in adaptability can translate into the rather specific phenomenology of psychotic breakdown experienced episodically by schizophrenic patients (who do not, by the way, "imagine hostile, confusing voices" [sect. 1, para. 1] but actually *hear* them). I argue that K&M's model, which emphasises the etiological and neurodevelopmental heterogeneity of schizophrenia, does not necessarily imply that schizophrenia cannot be a "natural kind" (sect. 6.4, para. 5). Although underneath schizophrenia there may "lie a vast diversity of potential behavior-impairing mutations across the thousands of genes involved in brain development" (sect. 6.4, para. 6), the manifest homogeneity of schizophrenia may still be real. The argument is that "individuals with an especially high load in mutations" who "act in aberrant, harmful ways" do indeed "provoke social comment" (sect. 8, para. 5). But it is precisely the type of response from the social environment to such aberration that shapes an individual's mental illness into what then tertiarily provokes "psychiatric categorization" (sect. 8, para. 5) as schizophrenia.

Intraspecific aggression provides the motivational impetus to social structures and group dynamics in many higher vertebrates, including humans, although our desire to regard our species as standing above the animal kingdom prevents us from fully appreciating this (Lorenz 1963/2002). Through *ritualisation* in phylogenesis and cultural evolution, aggressive impulses arising spontaneously in social situations became partly inhibited and adopted indirect expressions, thus contributing to the wide range of social behaviours (Lorenz 1963/2002; see also Behrendt 2006). We *need to relate* to others to keep at bay existential anxieties (that is, anxieties originally experienced by the infant who comes to realise his existential dependence on his caregiver), yet in groups we are constantly faced with others' concealed readiness to attack. Unless we prefer the insecurity and existential anxiety that loneliness makes inescapable (or escapable only in one's unconscious "omnipotent" phantasy), we have to develop complicated, adaptive behaviour patterns aimed at appeasement, submission, and assertion that in fluctuating group constellations respond to a multitude of cues indicative of others' social ranking, aggressive potential, and intentions. It is important to understand social *conformity* essentially as a mechanism that deflects aggressive impulses naturally arising from the social environment with which we engage. If we fail to negotiate our social rank successfully under changing circumstances, and if we fail to maintain the most complex etiquette and attitudes which we have learnt are demanded by the situation, we will face rejection and resurging existential anxieties (against which we have to develop elaborate defensive systems that themselves may test to the limit higher cognitive abilities).

Indeed, many mechanisms can "disrupt adaptive complexity" (sect. 7.2) and thus undermine our *ability to conform*. Schizophrenia is not just a "heritable" disease, as K&M recognise, but more generally a neurodevelopmental disorder that apart from mutation loading is associated with prenatal exposure to viral infections (Brown & Susser 2002), obstetric complications (Verdoux et al. 1997), and childhood brain disease, manifesting not only in abnormal brain development with morphological and cytoarchitectonic alterations, but also in postural and movement deficits in childhood (Walker et al. 1994), minor physical abnormalities, cognitive impairment, and developmental delays (Jones et al. 1994). Although it is often argued that aberrant early development is part of the schizophrenic process, it is clear that if children or adolescents thus affected lack compensatory strengths and alternative sources of support, they may be placed on a trajectory of social rejection, fears of rejection, social maladjustment, and unappeasable existential anxieties that may lead to and – at times of additional social stresses and insecurities – clinically present as schizoid or schizotypal, perhaps paranoid, personality disorder or, indeed, schizophrenia – if the individual has a hallucinatory predisposition in addition (Behrendt & Young 2004).

Compliance with social rules and others' expectations is designed to keep in check others' aggression, yet conformity is precisely what is difficult to achieve – for various reasons – by those who are at risk of developing schizophrenia, allowing existential anxieties to prevail. Laing (1960) described the schizoid individual as having a "heightened sense of being always seen," as being "frightened that he will look a fool, or that other people will think he wants to show off" (pp. 113–14):

> In a world full of danger, to be a potentially seeable object is to be constantly exposed to danger. . . . Indeed, considered biologically, the very fact of being visible exposes an animal to the risk of attack from its enemies, and no animal is without enemies. Being visible is therefore a basic biological risk; being invisible is a basic biological defence. We all employ some form of camouflage. (Laing 1960, p. 117)

What better camouflage, what better way to avert attack, than our "false self" or *persona* representing our strivings for conformity? Defences employed against the "many anxieties about being obvious, being out of the ordinary, being distinctive, drawing attention to oneself" – in essence representing fears of rejection – "often consist in attempts to merge with the human landscape, to make it as difficult as possible for anyone to see in what way one differs from anyone else" (p. 118). For the schizoid individual to enter into essential exchange with others means to lay himself open to attack, insofar as he cannot conform. He maintains "his outward semblance of normality by progressively more desperate means" until his "defences against the world fail even in their primary functions: to prevent persecutory impingements" so that anxiety "creeps back more intensely than ever" (p. 150). Alternatively, "in order to be safe from the persistent threat and danger from the world," he has to cut himself off "from direct relatedness with others" (pp. 149–50). Withdrawal into "omnipotent" phantasy affords transient lowering of existential anxieties; however, this comes at a price of increasing estrangement from the shared reality, eventually driving the individual into psychosis.

Children who later develop schizophrenia are more anxious at school and more likely to play alone (Jones et al. 1994). Poor social adjustment and lack of confidence are common characteristics in children and adolescents who later develop schizophrenia (Jones et al. 1995) but may be nothing more than consequences of sustained subtle or overt aggression from peers. Vulnerable children are at risk of attracting others' aggression quite naturally through their being slow, weak, unattractive, or simply different, and this would be even more so if they were anything but content with the lowest rank in their peer group. Failure by individuals to conform disinhibits our instinctive aggression, which is why those who are about to develop schizophrenia start to observe their social environment fearfully, especially at times when parents' and society's expectations as to the individual's ability to conform and fulfil acceptable roles is greatest – that is, in puberty and early adulthood. The association of schizophrenic relapse with exposure to criticism and hostility in a patient's family (Brown et al. 1972) and the

association with urban upbringing (Pedersen & Mortensen 2001) – which implies instability of links with social groups – attest to the importance of intraspecific aggression and our fear thereof in schizophrenia; as do hallucinations of *other people's* voices during psychosis, which in their content are often critical and derogative (Birchwood et al. 2000; Linn 1977), reflecting patients' fears of rejection and marginalisation.

Evolutionary psychiatry is dead – Long liveth evolutionary psychopathology

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Abstract: Keller & Miller (K&M) propose that many psychiatric disorders are best explained in terms of a genetic watershed model. This view challenges traditional evolutionary accounts of psychiatric disorders, many of which have tried to argue in support of a presumed balanced polymorphism, implying some hidden adaptive advantage of the alleles predisposing people to psychiatric disorders. Does this mean that evolutionary ideas are no longer viable to explain psychiatric disorders? The answer is *no*. However, K&M's critical evaluation supports the view that psychiatric disorders are not categorically distinct from normalcy, and that evolutionary psychopathology should be grounded in rigorous empirical testing.

Keller & Miller's (K&M's) proposal of how to best conceptualize the genetic underpinnings of psychiatric disorders will certainly induce an uproar among those evolutionary psychiatrists who believe that psychiatric disorders reflect adaptations to selectively relevant problems in the human evolutionary history. Adaptive properties have been assigned to a great diversity of psychiatric problems, such as anxiety disorders, depression, and even vaguely defined disorders such as schizophrenia, either on account of their mere prevalence in the population or due to a presumed function of susceptibility alleles in heterogeneous carriers (for a critique, cf. Dubrovsky 2002). In contrast, K&M's suggestion that many psychiatric disorders emerge if the number of "unfavourable" alleles is sufficiently great in an individual, thereby rendering this individual vulnerable to environmental stress, challenges the adaptationist perspective on psychiatric disorders, because it would seem that the search for genes predisposing people to psychiatric disorders and for a hidden adaptive advantage of such genes could be a fruitless endeavour.

Does K&M's account discredit an evolutionary approach to psychopathology altogether? My answer is no. However, K&M's thoughtful review of possible genetic models of psychiatric disorders unveils several weaknesses of the adaptationist perspective in psychiatry.

First, the adaptationist perspective holds that some psychiatric disorders, while perhaps being maladaptive themselves, convey adaptive advantages in first-degree relatives of the affected individuals outweighing the reproductive disadvantage of the symptom carriers, similar to the oft-cited example of sickle-cell anaemia. Such a hypothesis could, however, be empirically tested only if such disorders were well defined at the phenomenological, neurophysiological, and genetic levels (sickle-cell anaemia is monogenetically transmitted). This is not the case for almost all psychiatric disorders, as there is a broad overlap between psychiatric disorders at all levels. For example, abundant research now points to the fact that schizophrenia and bipolar affective disorder share several clinical features (e.g., thought disorders) and neurophysiological characteristics (e.g., elevated dopamine levels), and run in the same families (i.e., genetic susceptibility).

Second, some evolutionary psychiatrists assert that psychiatric disorders themselves were adaptive responses to adverse environmental conditions. For instance, depression could reduce social stress by causing a person to assume a subordinate behavioural strategy instead of fighting for resources, if the chance of succeeding in contest is perceived to be low. This view is much more delicate, because it is plausible for minor forms of reactive depression, for example, after loss of social status or after divorce. It becomes, however, much more difficult to explain severe, melancholic, or "endogenous" depression, which, rather than being adaptive, appears to be similar to what ethologists call *vacuum behaviour* (behaviour occurring without appropriate stimulus). This example may illustrate the difficulty in drawing a line between an adaptive "second-best" strategy and maladaptive behaviour, based on severity of the symptomatology or the presence or absence of stimuli (Nettle 2004). In any event, it needs to be emphasised that sadness is not depression, and that suspiciousness does not equal delusional thinking, although in both examples the former may develop into the latter. The problem of continuity between normalcy and pathology has not yet been acknowledged by many evolutionary psychiatrists, perhaps because the majority of them still think in categorical dimensions.

Ironically, K&M's review of the possible genetic underpinnings of psychiatric disorders from an evolutionary perspective strengthens the view that environmental factors are perhaps at least equally important for explaining psychopathology in evolutionary terms (this is not to say that genetic variation does not play a role in psychopathology). If it is true that every one of us carries several hundreds of "unfavourable" alleles rendering all of us more or less susceptible to developing psychiatric disorders, it would be much more advisable to carefully investigate potentially unfavourable environmental conditions eliciting psychopathology. For example, Belsky et al. (1990) have proposed an intriguing model of how behaviour rendered "deviant" in modern environments may emerge if infants grow up under adverse conditions, including harsh parental rearing styles, lack of sufficient resources, and so on. The model basically suggests that, under favourable circumstances, parents could afford to invest heavily in their offspring, hence promoting in children the development of an *inner working model* of trustworthiness; whereas it might also have been adaptive for offspring in adverse ancestral conditions to assume a view that the world is an insecure and unpredictable place, where (in terms of reproductive fitness) it was advisable to focus on immediate resource extraction, including the exploitation of others. From a psychopathological perspective, the extremes of the latter "strategy" (no conscious reflection implied) may fall into the categories of antisocial personality disorder (ASPD) or borderline personality disorder (BPD), both of which can be seen as pathological (and therefore maladaptive) exaggerations of an adaptive mechanism.

Another strength of evolutionary psychopathology is certainly to help clarify sex differences in behaviour. With respect to the foregoing example, ASPD is much more common in males, whereas BPD is more often diagnosed in females, although the precipitating condition may be analogous or even identical. This might reflect sex-dependent competitiveness in different social arenas. Similarly, traditional psychiatry has been unable to explain sex differences in the content of delusional disorders, where evolutionary psychopathology can offer testable hypotheses about why erotomania reflects the pathological exaggeration of a female mating strategy, whereas delusional jealousy reflects the pathology of a male mating strategy (Brüne 2003). There is no psychiatric framework other than evolutionary psychopathology to explain such differences between the sexes (Brüne 2002).

In summary, evolutionary psychopathology (as a field) would do better if it chose a more symptom-based or syndromal approach rather than clinging to nosological categories that have proven more and more outdated – except for the purpose of bringing evolutionary issues of psychopathology to a broader audience of psychiatrists and clinical psychologists. This is one important message from K&M's thought-provoking thesis.

The evolutionary genetics of personality: Does mutation load signal relationship load?

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Abstract: The mutation-selection hypothesis may extend to understanding normal personality variation. Traits such as emotional stability, agreeableness, and conscientiousness figure strongly in mate selection and show evidence of non-additive genetic variance. They are linked with reproductively relevant outcomes, including longevity, resource acquisition, and mating success. Evolved difference-detection adaptations may function to spurn individuals whose high *mutation load* signals a burdensome *relationship load*.

Keller & Miller (K&M) must be applauded for a brilliant article that provides the most compelling theory we now have for the evolutionary genetics of many mental disorders. This commentary extends the logic of their arguments to the evolutionary genetics of normal personality dimensions.

Mental disorders originating from a high mutation load, according to K&M, undermine reproductive success primarily by reducing the mating attractiveness of those afflicted. A similar argument can be made for normal personality variation.

The ends of some personality dimensions are known to be highly desirable in long-term mates (Buss & Barnes 1986; Buss et al. 1990). A study of 37 cultures found that, after "mutual attraction and love," "dependable character" (conscientious) and "emotional stability and maturity" were the most highly valued among 18 characteristics rated for their desirability in a long-term mate. Using a ranking procedure, "kind and understanding" (synonyms for agreeableness) and "intelligent" topped a list of 13 characteristics as the most desirable in a mate. The high ends of many major dimensions of personality, in short, figure importantly in an individual's "mate value" (Buss 2003).

Recent evidence reveals that major personality traits are polygenic and show substantial non-additive genetic variation (Eaves et al. 1998; Keller et al. 2005). These findings are consistent with the polygenic mutation-selection hypothesis.

Whereas mental disorders impair reproductive success, the positive ends of attractive personality traits facilitate fitness-relevant outcomes (Buss & Greiling 1999). Those high in conscientiousness, for example, tend to excel in resource acquisition and ascend status hierarchies (Kyl-Heku & Buss 1996; Lund et al., in press). They also live longer (Friedman et al. 1995). Those low in emotional stability (high on neuroticism) have greater difficulty holding jobs and sustaining marriages. Whether these difficulties historically undermined, or currently undermine, reproductive success remains unknown.

If a person's overall mate value is comprised of many different personality traits (along with non-personality variables such as physical attractiveness), then a given level of mate value can be attained through different combinations of personality traits (Buss & Barnes 1986). If people mate assortatively based on overall mate value, rather than on individual personality traits, one would expect low but positive assortment coefficients for the individual personality traits. That is precisely what assortative mating studies reveal (Buss 1984). Another prediction that follows is that higher assortative mating coefficients should be obtained by creating composite measures, summing the scores of each of the different desirable personality traits. High scorers – individuals with a highly attractive composite mating personality – should attract other high scorers. Those of lower mate value settle for commensurately lower-value partners. This prediction remains to be tested.

All of these findings – the importance of personality in mate selection, the importance of non-additive genetic variance for personality traits, the links between personality and reproductively relevant outcomes, and the low positive assortment coefficients for personality – are consistent with, but do not definitively verify, the hypothesis that mutations degrade personality performance. The arguments of K&M in the context of mental disorders, however, logically extend to the realm of normal personality functioning, at least for personality dispositions central to solving critical adaptive problems.

Evolved personality-assessment mechanisms (Buss 1996) – the categories we use to appraise and evaluate others in our social world – may function, in part, to assess the mutation load carried by potential mates. They might also function to assess the quality of allies, coalition partners, or even children who might be especially attractive targets of parental investment.

These evolved difference-detecting adaptations provide answers to some of the most important social problems that people have faced while traversing the adaptive landscape (Buss 1996): Will X be a good cooperator (agreeableness)? Will X be a hard-working resource provider and reliable in provisioning my children (conscientiousness)? Does X have the fortitude and resilience to hold steady during times of trouble (emotional stability)? Conversely, will X cause psychological damage (aggressiveness), betray my trust (impulsiveness), or neglect my children (undependability).

Individuals with certain personality characteristics inflict fitness costs on those with whom they become enmeshed. People low on emotional stability and low on agreeableness, for example, create tremendous conflict in mating relationships, absorbing valuable fitness-relevant resources that could be better allocated elsewhere (Buss 1991). In these ways, *mutation load* may signal *relationship load*.

Finland's Galapagos: Founder effect, drift, and isolation in the inheritance of susceptibility alleles

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Abstract: The target article excludes ancestral neutrality as a cause for the inheritance of schizophrenia, with an argument relating to selection against a single allele in the Finnish population. However, drift would predominate over selection within subisolates of the Finnish population. Comparisons of subisolates with heterogeneous populations may provide clues to the endophenotypic structure of complex polygenetic heritable mental disorders.

It is paradoxical that, though individuals who have mental disorders are more likely to die childless, the predisposition to these disorders seem to be inherited and the incidence rates seem not to decline across generations. Natural selection still has not uniformly eliminated the sets of gene codings in human DNA, the *susceptibility alleles*, which predispose some humans to mental disorder. The target article contrasts three extant models of the evolution of mental disorder. These models offer solutions to this apparent paradox, and this commentary discusses these models in the context of schizophrenia and autism.

The first of these models, ancestral neutrality, assumes that, within the environment of our evolutionary ancestors, the selection disadvantage of predisposition to mental disorder present in modern environments was absent. Accordingly, it is just a matter of time before the susceptibility alleles become eliminated.

The second balancing-selection model assumes that, although mental disorder has a selection disadvantage, that disorder also

offers selection advantages. An instance of this model is that schizophrenia is the price that humans pay for the single allele that determines the lateralization of function that permits language (T. J. Crow 2000).

The third, favoured, polygenetic mutation-selection balance model offers a view that predisposition to mental disorder has no selection advantage. Rather, inheritance of mental disorder reflects harmful germ-line mutations. Large numbers of these mutations are a necessary by-product of the development of a complex organism, and the deleterious effects of these mutations derive from multiple mutant alleles at different genetic loci. This ties in well with the assumption that neural systems supporting mental processes and behaviour are thus under polygenetic control. Accordingly, the human brain can be affected by more than half of the hundreds of mutations that we all carry.

Although a single allele can result in a Mendelian disorder with near disastrous consequences such that selection pressures nearly eliminate their incidence (see Table 1), the mutation of just a single gene tends to be relatively benign. These mutations, when they bring modestly deleterious effects, do not severely impair reproductive success and therefore are not strongly selected against. The consequence is that such mutant alleles can produce a sub-threshold abnormality that can be inherited.

The target article excludes the alternative ancestral neutrality model in the context of schizophrenia (sect. 4.3). Keller & Miller's (K&M's) argument here considers a hypothetical schizophrenia in Finland, determined by one or even a few susceptibility alleles, to demonstrate that if selection pressure against this gene were the same as it is now, 42% of Finns would have been schizophrenic in 1600. Whilst this argument remains compelling, it would be interesting to see how well it holds by contrast to a population other than the Finnish one.

The Finnish population would seem a curious choice to use in this argument, because in some regards the population is unique. Factors such as the small number of initial founders, famines and war, and rapid expansion during the last 80–100 generations have left Finland with an anomalous genetic background (Auranen 2000). Only the coastline of Finland and the southeast and southwest areas were inhabited up until the 16th century. The immigration of farmers to the inland established the late settlement region in central Finland, creating small regional subisolates which have remained rather secluded from any further immigration. Investigation of the genetics of these subisolates has proved effective in identifying novel susceptibility alleles for a number of conditions, including autism. This finding supports the hypothesis of enrichment of different autism-predisposing alleles in the Finnish population, due to founder effect, genetic drift, and isolation.

The heritability of autism is amongst the highest of the common mental disorders (Table 1), whereas its prevalence is amongst the lowest – which may lead one to think that autism somewhat resembles the Mendelian disorders. Indeed, fewer significant risk loci have been enriched in the Finnish population than in the larger and genetically more heterogeneous population of the United States. However, indications in both populations are that of a polygenetic disorder (Ylisaukko-Oja et al. 2006).

The first settlers to Kuusamo in north-eastern Finland arrived from the late settlement region in 1676. Isolation from subsequent outbreaks of disease across more densely populated areas permitted the faster expansion of this Kuusamo subisolate relative to the rest of Finland: From just 40 founding families, descended 18,000 people with triple the risk of a schizophrenia of the national population, yet with comparable clinical phenotype (Arajärvi et al. 2004; Hovatta et al. 1999). Even this Kuusamo subisolate exhibits multiple susceptibility alleles for schizophrenia, corroborating the target article's argument for a polygenetic disorder (Hovatta et al. 1999).

However, the argument against an ancestral neutrality account of schizophrenia excludes the effects of genetic drift (sect. 4.3; see also the caption of Fig. 2). Within subisolate populations, drift predominates over selection, particularly when the effects of an allele are relatively benign. This argument against ancestral neutrality would be more compelling were the authors to contrast the assumed effects of drift and selection on this hypothetical allele in heterogeneous populations and those containing subisolates.

Ultimately, the third, favoured, polygenetic mutation-selection balance account may offer a more convincing explanation of data concerning heritable mental disorders. An individual allele may manifest as a sub-threshold abnormality, an *endophenotype*, such as impaired immediate memory or decreased efficiency of dorsolateral prefrontal cortex (Bertolino et al. 2004; Campbell 2005; Egan et al. 2001; Tuulio-Henriksson et al. 2003), which, though harmful, is neither necessary nor sufficient for disorder.

Expressed together, clusters of such endophenotypes, however, may cause complex conditions like schizophrenia. Particular endophenotypes might also be clinically useful in determining the choice of drug (Bertolino et al. 2004). This assumption of endophenotypes within the polygenetic mutation-selection balance model thus offers something additional that Crow's balancing-selection account of schizophrenia would seem not to. Indeed, the correspondence of endophenotypes of a disorder to susceptibility alleles in subisolate populations could also offer clues to the endophenotypic structure of the disorder in more heterogeneous populations.

The natural selection of psychosis

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Abstract: Diverse evidence from genomics, epidemiology, neurophysiology, psychology, and evolutionary biology converges on simple general mechanisms, based on negative secondary effects of strong selection, for how mental disorders such as psychosis have evolved and how they are sustained.

The core of my argument is that selection can explain the observed genetic and phenotypic data on common mental disorders. I focus on psychosis in general and schizophrenia in particular. My thesis is predicated on a history along the human lineage of selection for social cognition, creativity, and language. I also contend that schizophrenia is a maladaptive by-product of this strong selection. This general argument has been made by Horrobin (1998) in the context of brain phospholipid metabolism, and by Crow (1997), Burns (2004), and Nesse (2004) in the context of language and social intelligence. It translates into some combination of two selective processes, each with conjoined positive and negative effects on phenotypes: (1) a history of strong selection coupled with antagonistic pleiotropy or linkage, and (2) the maintenance of variation via overdominance (balancing selection) across multiple loci. Three primary lines of evidence support this argument.

First, many genes associated with psychosis have been subject to positive selection – that is, selection for specific, favored amino acid changes. Genes associated with schizophrenia or bipolar disorder that show evidence for positive selection in the human lineage include APOL1, APOE, DRD4, FOXP2, GRM3, HOPA, IMPA2, MAOA, MAOB, NRG1, SLC6A4, and SYNJ1 (Abdolmaleky et al. 2005; Andres et al. 2004; Balciuniene et al. 2001; Costas et al. 2005; Diller et al. 2002; Ding et al. 2002; Enard et al. 2002; Gardner et al. 2006; Harrison & Weinberger 2005; Jansson et al. 2005; Kitano et al. 2004; Muglia et al. 2002; Saito et al. 2001; Sanjuan et al. 2006; Spinks et al. 2004; Stopkova et al. 2004; Voight et al. 2006; Yoshikawa et al. 2001; Zhang et al. 2002). Overwhelming evidence from domesticated

species and laboratory experiments indicates that strong selection leads to maladaptive, more or less transient by-products, on account of linkage and antagonistic pleiotropy in populations out of equilibrium (e.g., see Andolfatto 2001; Lu et al. 2006). These data suggest that selection for the traits that have "made us human" (cf. Horrobin 1998), especially the neural systems underlying language and social cognition, have led to psychosis as a secondary result. Data are now available to test this hypothesis more directly, using the human haplotype map to test for selective sweeps in regions associated in genome scans with psychosis, such as 1q21 (Voight et al. 2006). Many of the selective sweeps inferred from such data (Voight et al. 2006) are remarkably recent (less than 20,000 years old). As a result, allele frequencies may be out of equilibrium, and equilibrium-based population-genetic models for explaining standing levels of variation, based on antagonistic pleiotropy or related mechanisms, do not apply.

Second, evidence for multilocus overdominance comes from multiple studies showing increased fitness, compared to the general population, in first-order relatives of schizophrenics. The study by Haukka et al. (2003) found such an effect for females, but not for males, and they cite four previous studies supporting such a difference. A stronger pattern in females fits with the less-debilitating nature of psychosis in this sex (Moriarty et al. 2001), and such a sex bias was also found by Fananas and Bertranpetit (1995) and Bassett et al. (1996). Nettle and Clegg (2006) also report an association between increased mating success and measures of schizotypy. The sample in Haukka et al. (2003) is indeed very large, but no single such study can be definitive or serve to estimate selective parameters quantitatively, given population-specific effects and the evolutionary time scale involved. The upshot is that six independent studies support a general pattern of balancing selection, apparently related to positive aspects of schizotypy.

Third, there is substantial evidence for mechanisms that can generate multilocus balancing selection on relevant aspects of cognition. The causal links between measures of schizotypy and measures of creativity and divergent thinking are much stronger than Keller & Miller (K&M) imply, and they comprise diverse evidence from functional imaging, neurophysiology, neural network modelling, genomics, and psychological experiments, as well as the biographical and survey studies discussed by Waddell (1998) (Abraham et al. 2005; Brugger 2001; Fisher et al. 2004; Folley et al. 2003; Folley & Park 2005; Hoffman et al. 2004; Lauronen et al. 2004; Nettle 2001; in press; Smalley et al. 2005). Many of these studies converge on a key role for increased right-hemisphere activation in language function (Mohr et al. 2005). They also emphasize that understanding psychosis requires analyses of its healthy analogue in components of schizotypy, given the clear pathologies and fitness reductions caused by psychosis itself, and the proposed "cliff-edged" form of the balancing fitness function (Nesse 2005).

Finally, strong recent selection on language and cognition coupled with antagonistic pleiotropy or linkage, and multilocus overdominance, are not the only possible mechanisms for the evolution and maintenance of psychosis in which selection plays a central role. A non-exclusive model involves effects of intragenomic conflict, mediated by sexual conflict or by genomic imprinting in brain development (Badcock & Crespi 2006; Burt & Trivers 2006). The clearest evidence for genomic-imprinting effects come from the oppositely imprinted disorders Prader-Willi syndrome, which engenders high rates of psychosis (Vogels et al. 2004), and Angelman syndrome, which shows a high incidence of autism (Cohen et al. 2005; Peters et al. 2004). Genome scans also demonstrate strong imprinted-gene effects in schizophrenia (Francks et al. 2003), bipolar disorder (Kennedy et al. 2003), and autism (Badcock & Crespi 2006). Genomic conflict may help maintain genetic variation via continual strong selection for divergent optima, as in host-parasite conflicts mediated by major histocompatibility complex (MHC) loci, the most polymorphic loci in the human genome. Genomic imprinting effects also provide a persuasive hypothesis for the paternal age effect on schizophrenia risk (Malaspina 2001; Sipos et al. 2004), given that mutations during spermatogenesis appear insufficient to explain such patterns (Farrer et al. 1992; Reik et al. 1993; Tiemann-Boege et al. 2002). To the extent that intragenomic conflict is involved in cognitive traits, discussions of adaptation must focus at the level of genes, as organism-level adaptive value can no longer be assumed (Burt & Trivers 2006).

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Why the adaptationist perspective must be considered: The example of morbid jealousy

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Abstract: We describe delusional disorder–jealous type ("morbid jealousy") with the adaptationist perspective used by Darwinian psychiatrists and evolutionary psychologists to explain the relatively common existence and continued prevalence of mental disorders. We then apply the "harmful dysfunction" analysis to morbid jealousy, including a discussion of this disorder as (1) an end on a continuum of normal jealousy or (2) a discrete entity.

An evolutionary psychological approach to explaining the relatively common existence and continued prevalence of mental disorder historically has required explaining a disorder's potential adaptive benefits. As Keller & Miller (K&M) note, Darwinian psychiatrists and evolutionary psychologists assume an adaptationist position, thus keeping natural selection at the etiologic forefront. If it is theoretically possible and empirically verifiable that mental disorder susceptibility alleles increased fitness in some ancestral conditions, then a balancing-selection explanation of the existence and prevalence of mental disorders may be justified.

Delusional disorder–jealous type or "morbid jealousy" is a disorder that causes individuals to misinterpret everyday actions as cues to a partner's sexual infidelity. Constant accusations of infidelity, vigilant monitoring of a partner's behavior, and restricting a partner's actions are typical of individuals diagnosed with morbid jealousy (see the *Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Association [2000]; see also, Kingham & Gordon 2004; Shepherd 1961; Vauhkonen 1968). The benefits and costs of morbid jealousy are well documented (e.g., Buss 2000; Enoch & Trethowan 1979; Kingham & Gordon 2004; Mowat 1966; Shepherd 1961). If morbid jealousy is an extreme form of normal sexual jealousy, it is reasonable to hypothesize that morbid jealousy may thwart partner infidelity, perhaps more effectively than does normal sexual jealousy, thereby increasing the fitness of ancestral individuals with morbid jealousy. Whether the alleles associated with the costs of morbid jealousy – such as decreased daily functioning, increased risk of mate defection, and increased susceptibility to other debilitating mental disorders – would be exactly balanced through antagonistic pleiotropy by increases in the fitness payoffs of the associated benefits is unknown. Despite empirical challenges, an adaptationist perspective using balancing selection, specifically antagonistic pleiotropy, may explain the relatively common existence and continued prevalence of morbid jealousy and perhaps additional mental disorders.

Wakefield (1999a; 2005) has argued that mental disorders can only be classified as such when they are harmful dysfunctions. A *dysfunction* is a failure of a mechanism to perform as it was designed by natural selection. According to this definition, the disorder cannot be the function of a naturally selected mechanism. Therefore, a dysfunction of jealousy mechanisms would occur when they failed to motivate behaviors designed to prevent a partner's infidelity. Individuals diagnosed with morbid jealousy do deploy behaviors that function to prevent partner infidelity, even if the cues that activate the jealousy mechanisms are imagined by the individual. Perhaps morbid jealousy does not meet the dysfunction criterion and therefore should not be considered a mental disorder.

Wakefield's (1999a; 2005) harmful dysfunction analysis specifies a second criterion that must be met for a mental disorder to be considered as such. The disorder must generate harm, as defined by society. To conclude that morbid jealousy is not a disorder without assessing the associated harm would be a mistake, according to the harmful dysfunction analysis. Lives are disrupted, including the lives of the morbidly jealous individuals themselves as they constantly monitor their partner's behavior (e.g., Seeman 1979). Substantial stress is added to the relationship as morbidly jealous individuals constantly accuse their partner of infidelity (e.g., Vauhkonen 1968). Potential rivals may be derogated or attacked, partners of the morbidly jealous may be psychologically and physically abused, and sometimes this assault escalates to murder (e.g., Kingham & Gordon 2004; Mowat 1966; Shepherd 1961). Although morbid jealousy is harmful, is it more harmful than normal sexual jealousy? In fact, the greatest predictor of intimate partner homicide is sexual jealousy (Daly & Wilson 1988). It is possible that morbidly jealous individuals are more abusive toward their partners or are more likely to murder them than are individuals who experience normal sexual jealousy, but research has not investigated this possibility.

Morbid jealousy may be explained best not as a discrete categorical mental disorder, but as a continuation of normal sexual jealousy. Before this determination can be made, however, several factors must be examined (J. C. Wakefield, personal communication, March 20, 2006). First, we need to determine whether the morbid jealousy tail of a normal curve hides discrete points of jealousy disorders. For example, there are many causes of low intelligence. However, a smooth normal curve of intelligence would group these distinct causes together and would hide the individual causes of low intelligence. The same might be true of a normal sexual jealousy curve. Examining individual cases of morbid jealousy and comparing the symptoms and behaviors could help determine whether a normal sexual jealousy curve is grouping together distinct causes of morbid jealousy. If there are not multiple, distinct cases of morbid jealousy, then it could be argued that morbid jealousy is a continuation of normal sexual jealousy.

Second, we need to determine whether the morbid jealousy end of a sexual jealousy curve is fitness enhancing. Previous research has documented the adaptive benefits of normal sexual jealousy; notably, that it may prevent partner infidelity (e.g., Buss 2000). If morbid jealousy has similar adaptive benefits, this might provide further evidence that it should be viewed as part of a continuum of normal sexual jealousy.

Third, morbid jealousy may not be produced by a dysfunction of jealousy mechanisms, but instead by a dysfunction of related mechanisms. For example, individuals with morbid jealousy may have dysfunctions in mate-retention mechanisms. If this is the case, then morbid jealousy could not be considered continuous with normal sexual jealousy, as these related dysfunctions do not occur with sexual jealousy. This third issue could be investigated by examining individuals diagnosed with morbid jealousy to determine whether they have other, related dysfunctions.

Whether morbid jealousy is a discrete categorical mental illness or part of a continuum of normal sexual jealousy remains to be determined. We have discussed three research questions that could help address this question. Investigation of these questions through careful examination of individuals with morbid jealousy may lead to clarification of delusional disorder–jealous type, and may represent a model that could be used to clarify other mental disorders. Additionally, this clarification should lend support to continued use of the adaptationist approach and should provide a better understanding for the continued prevalence of disorders.

Mutations, developmental instability, and the Red Queen

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Abstract: We address two points. First, one must explain how different, rare mutations ultimately lead to common psychopathological conditions. The developmental instability model offers one solution. Second, Keller & Miller (K&M) perhaps miss the major processes other than variation fueled by rare deleterious mutations that account for interesting genetic variation in psychopathology, particularly when single alleles have non-negligible effects: Red Queen processes.

Keller & Miller (K&M) argue that much heritable variation in psychopathological conditions is fueled by deleterious mutation, rare at individual loci but ubiquitous in genomes. Ron Yeo, colleagues, and I offered a similar view a decade ago (Gangestad 1997; Gangestad & Yeo 1997; Thoma et al. 2002; Yeo & Gangestad 1993, 1998; Yeo et al. 1997, 1999), albeit less broadly applied to neurodevelopmental disorders (e.g., schizophrenia, dyslexia, attention deficit disorder). K&M do an excellent job of making this case.

Our quibbles pertain to details. We focus on two. First, mutations at many loci produce phenotypic variants much more common than individual mutations. Our model, curiously not mentioned by K&M, may explain how they do so. Second, K&M perhaps miss the most important alternative processes accounting for interesting genetic variation in psychopathology, particularly when single genes account for non-negligible ($>1\%$) variance.

The developmental instability model. Mutations at individual loci are rare. Neurodevelopmental disorders are much more common. A successful theory must explain how different mutations can produce similar outcomes. Though K&M discuss how different "upstream," specific defects can have common "downstream" effects (sect. 6.2), they do not present a particularly compelling, specific model for how this happens.

We have suggested one route: developmental imprecision. Microcircuitry of a computer chip must be manufactured in a dust-free environment, for only then can its design be actualized. Dust that inadvertently becomes part of the chip can affect the functioning of the circuitry in random ways, disrupting design. Similarly, mutations and other developmental stresses can act as "dust" in the environment in which epigenetic processes "manufacture" an organism's phenotype, introducing *developmental instability* and deviations from naturally selected design.

Neurodevelopmental errors may disrupt adaptive coordination of a broad array of processes within developmental systems, particularly as their frequency increases. As disrupted development may channel along particular paths, different perturbations (e.g., mutations) may ultimately have common outcomes. K&M argue that more than half of all human protein-coding genes are expressed in brain tissue and, hence, neural systems capture a large amount of mutational variation. As genes that affect

neural development need not be expressed in brain cells per se, however, mutations across an even larger proportion of the genome may affect neurodevelopmental disorders. As this theory expects, neurodevelopmental disorders covary with markers of developmental disruption or instability (e.g., minor physical anomalies and fluctuating asymmetry; see Yeo et al. 1999).

Disorder-specific features may arise because disruptions have different outcomes depending on their timing or differentially affect specific neural systems. Alternatively, disorders may be affected by specific factors in addition to developmental instability (see Yeo et al. 1999).

Antagonistic coevolutionary processes. K&M contrast three different kinds of evolutionary models of genetic variation: *mutation-selection balance*, *neutral variation*, and *balancing selection* – maintenance of variation because selection actually favors multiple alleles (e.g., through heterozygote superiority, spatiotemporal oscillations in selection, and frequency-dependent selection). But a fourth possibility they do not mention exists: rapid evolution at loci, particularly those involved in *antagonistic coevolutionary processes*.

Species may antagonistically coevolve with other species (e.g., in predator-prey or host-pathogen roles). New adaptations in one species evoke selection on the other to evolve counteradaptations. Antagonistic coevolution (or Red Queen processes; Van Valen 1973) may persist through evolutionary time, resulting in continual change in both species. Genetic conflicts of interest between males and females, mothers and fetuses, or pairs of cooperators may fuel persistent antagonistic coevolution of genes *within a species*, as well (Rice & Holland 1997).

Red Queen processes produce predictable evolutionary outcomes: (1) *Relatively rapid evolution*: Because new adaptations in a coevolving party change selection on the other party, alleles at coevolving loci should be subject to new positive selection relatively frequently (e.g., Swanson et al. 2001; Wyckoff et al. 2000). (2) *Interindividual variation*: More often than most loci, coevolving loci should be in states in which a new, favored allele has not yet become near-fixed in the population and coexist with alleles favored previously. (3) *A non-negligible level of maladaptation within populations*: Neither conflicting party is likely to adapt perfectly to the other party. The load of maladaptation will be carried disproportionately by individuals who lack newly favored alleles.

A Red Queen process that might explain some variation in psychopathological conditions is maternal-fetal coevolution (see also Gangestad & Yeo 1997). Fetal genes maximally benefit from a greater flow of nutrients from the mother than the level maximizing maternal fitness (Trivers 1974). Maladaptive outcomes of pregnancy (e.g., maternal hypertension, gestational diabetes) may be by-products of ensuing antagonistic coevolution (Haig 1993). Maladaptive by-products could include disruption of fetal epigenesis, resulting in neurodevelopmental disorder. In this model, some fetal genes associated with poor development (e.g., developmental instability) now once were not, for they once did not coexist with current maternal genes that promote counteradaptation. (The model is akin to spatially varying selection, but not as a form of balancing selection; cf. target article, sect. 5.3.)

Some fetal genes involved in this conflict are imprinted – expressed differently depending on parent-of-origin. Imprinting is selected because fetal genes from fathers are also in conflict with those obtained from mothers (Haig 2000). Among genes that account for more than a negligible amount of variance in psychopathology, imprinted genes (or other genes involved in the imprinting process; e.g., genes that control imprinting; Burt & Trivers 2000) may be over-represented, for example, on schizophrenia, autism, or bipolar disorder (see Bah et al. 2004 [GRIK2]; Corradi et al. 2005 [GNAL]; DeLisi et al. 2002 [chromosome 22]; Francks et al. 2003 [chromosome 2]; Xu et al. 2001 [CHRNA7]); on attention-deficit hyperactivity disorder (ADHD) (see Borglum et al. 2003 [dopa decarboxylase]; Hawi et al. 2005 [9 genes putatively associated with ADHD]; Kirley et al. 2002 [TH]; Mill et al. 2004 [SNAP-25]). Only a few percent of genes are imprinted (on the mouse genome, see Luedi et al. 2005).

Findings in linkage studies have historically been fragile. Cautious interpretation is advised. Nonetheless, even if most variation in psychopathology is a result of rare mutation, some single genes probably do have non-negligible effects. One evolutionary theory K&M do not mention points toward genes involved in Red Queen processes.

Autism: Common, heritable, but not harmful

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Abstract: We assert that one of the examples used by Keller & Miller (K&M), namely, autism, is indeed common, and heritable, but we question whether it is harmful. We provide a brief review of cognitive science literature in which autistics perform superiorly to non-autistics in perceptual, reasoning, and comprehension tasks; however, these superiorities are often occluded and are instead described as dysfunctions.

We appreciate Keller & Miller (K&M) grappling with the age-old evolutionary paradox of why certain human phenotypes are so common, so heritable, but so harmful. In their treatise, K&M provide several examples of what they refer to as mental disorders, clumping together numerous phenomena, including schizophrenia, bipolar disorder, depression, phobias, panic disorders, Tourette's syndrome, obsessive-compulsive disorder, low intelligence, anorexia, and autism. We – a cognitive scientist, a research psychiatrist, and an autistic (who conducts cognitive science research) – are most interested in K&M's inclusion of autism. Therefore, we restrict ourselves to that exemplar, agreeing that autism is common and heritable but questioning whether autism is harmful.

Autism is definitely a common phenotype – even more common than K&M report. Current prevalence estimates are 200 per 100,000 for DSM-IV (American Psychiatric Association 1994) defined "autistic disorder" and around 600 per 100,000 for the entire autism "spectrum" (Chakrabarti & Fombonne 2005). A rash of public attention has spotlighted what are considered dramatic recent increases in autism prevalence, but our most reasoned logic suggests that the increases are due to purposely broadened diagnostic criteria, yoked with dramatically raised public awareness and conscientiously improved case finding (Gernsbacher et al. 2005). And when some lay spokespersons mistakenly suggest that autism first appeared in society only in the 1940s (Kennedy 2005), they are confusing the codification of the phenotype with its onset (see Frith [1989] for a convincing, albeit speculative, history of autism in society).

Autism is also a highly heritable phenotype, based on estimates from twin studies and sibling-recurrence rates. However, the existing heritability estimates warrant caution in interpretation. The twin-based estimates are derived from only a handful of studies, which are based on only a few handfuls of twins, and estimating sibling recurrence requires a reliable population prevalence rate.

But is autism a "harmful" phenotype? Primarily, K&M employ an evolutionary connotation of *harmful*, namely,

lowered fitness (i.e., reduced fertility rates). Perhaps any extreme phenotype will be less reproductively fit, be it the low levels of intelligence that K&M include as an example or the extremely high levels of intelligence found in adults identified during adolescence by their academic precocity (Lubinski et al. 2006). Certain cognitive phenotypes might also lead to lowered fitness. The prolific inventor Nikola Tesla, who is reported to have been celibate and whose life history reveals numerous autistic traits, proclaimed:

> I do not think there is any thrill that can go through the human heart like that felt by the inventor as he sees some creation of the brain unfolding to success.... Such emotions make a man forget food, sleep, friends, love, everything.... I do not think you can name many great inventions that have been made by married men. (Pickover 1999, p. 35)

K&M also verge into the more vernacular meaning of "harmful." They refer to mental disorders as "harmful dysfunctions" (sect. 1.2, para. 2), which are "disabling" and "debilitating" (sect. 1, para. 2), which cause "human suffering" (sect. 1.1, para. 4), and which are "disastrous to survival" (sect. 1.2, para. 6). K&M view "mental disorders" such as autism as "glaring exceptions" to the "awesome power of natural selection" (sect. 2, para. 1.).

However, whereas K&M assert that Darwinian psychiatrists and evolutionary psychologists "often go to torturous lengths to find hidden adaptive benefits" (sect. 1.1, para. 3), we assert that cognitive scientists often go to torturous lengths to occlude obvious adaptive benefits. The empirical literature is replete with demonstrations of autistics' superiority in numerous perceptual, reasoning, and comprehension tasks: Across a wide range of age and measured intelligence, autistics perform significantly better than non-autistics on block design, a prominent subtest of Wechsler-type scales (Shah & Frith 1993); on embedded figures tests, which require rapid visual identification of a target figure amid a complex background (Shah & Frith 1983); on recognition memory (Toichi et al. 2002); and on sentence comprehension (Just et al. 2004); and autistics are more impervious than are non-autistics to memory distortions (Beversdorf et al. 2000) and misleading prior context (Ropar & Mitchell 2002). Such superiorities are not isolated phenomena; some theorists argue that such superiorities abound in autism (Mottron et al. 2006).

Quite compellingly, each of these statistically significant demonstrations of autistic superiority is labeled by its authors as a harmful dysfunction. Autistics' superior block-design performance is labeled "weak central coherence," symptomatic of dysfunctional "information processing in autism" (Shah & Frith 1993, p. 1351). Autistics' superior performance on embedded figures tests is considered "consistent with the cognitive-deficit theory proposed by Hermelin and O'Connor (1970) ... due to a central deficiency in information processing" (Shah & Frith 1983, p. 618). Autistics' superior recognition memory performance is attributed to deleteriously "enhanced attention to shallow aspects of perceived materials" (Toichi et al. 2002, p. 1424); their superior sentence comprehension is described as being "less proficient at semantically and syntactically integrating the words of a sentence" (Just et al. 2004, p. 1816); their superior imperviousness to memory distortions is explained by "representations in the semantic network [that] may be associated in an aberrant manner" (Beversdorf et al. 2000, p. 8736); and their superior resistance to misleading prior context is attributed to their perception being "less conceptual" (Ropar & Mitchell 2002, p. 652).

Disorders are defined by criteria that vary with cultural, societal, and medical values. As K&M write:

> Mental disorder categories may reflect a mix of historical convention, diagnostic convenience, innate categorization biases in person perception, and common final pathways of partially overlapping yet distinct dysfunctions. This suggests that *the number of loci affecting a mental disorder depends in large part on the way human minds categorize behavioral symptoms*. (target article, sect. 6.4, para. 6; emphasis in original)

We couldn't agree more. As autistic Suzanne Shaw opines:

> People say that in the world of the blind the one-eyed man is king, but I think they are mistaken. In the world of the blind the one-eyed man would be a freak, and his eye might even disable rather than enable him. Eyes are wonderful things to be sure, but they are only useful in a society that is built to require them. (http://www.as-if.org.uk/discrim.htm)

We would add that they are only useful in a society that is open to appreciating them.

Heritable mental disorders: You can't choose your relatives, but it is they who may really count

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Abstract: Keller & Miller (K&M) briefly mention and promptly dismiss the idea that genes for harmful mental disorders may confer certain advantages to affected individuals. However, the authors fail to consider that the same genes (in low doses or reduced penetrance) may be adaptive for relatives, and that this may in part explain why they are retained in the gene pool.

While Keller & Miller (K&M) here rightly address ancestral factors in developing their critique of the three evolutionary models under their consideration, they only briefly consider the idea that negative fitness effects from mental disorders (e.g., schizophrenia, bipolar disorder) may be offset by other potential benefits (e.g., creativity). They fail to consider that genes for mental disorders may be retained, even selected for, in the genome when they convey certain other advantages, perhaps in different environments or contexts, not necessarily in those directly affected by the disorder in question, but in close relatives, when present in low doses or exhibiting reduced penetrance. A model for this is the recent evidence that genes associated with a homosexual orientation in males (where retention and transmission in the genome are clearly less likely in the affected male) are also associated with increased fertility in close female relatives (Camperio-Ciani et al. 2004). It is also well established that close relatives of autistic individuals exhibit unexpectedly high frequencies of choosing certain types of career where they excel, especially those involving computation, information technology, programming, and accountancy, where social and communicatory skills are at a reduced premium (see Baron-Cohen & Belmonte 2005).

Similar factors may operate, additional to any possible compensatory effect in the affected individuals themselves (see Bradshaw [2001] for a review), with "song and dance" and ball skills associated with Tourette's syndrome, and excellence in tasks involving attention to detail or general or personal care or hygiene associated with obsessive-compulsive disorder. In uncertain times or in the case of war or threats, the capacity for suspicious and critical distrust (verging on the paranoic) associated with schizophrenia, and the diffuse attentional focus and impulsivity associated with attention deficit hyperactivity disorder (ADHD), may be beneficial. Despite the denial by K&M of a significant link between creativity and mood disorders, there is indeed considerable evidence to support such an effect – such as the study by Simeonova et al. (2005), who found that children of adults with bipolar disorder had higher scores than did controls on a measure of creativity (see also Andreasen 2005). Although K&M correctly draw our

attention to the reduced reproductive fitness in schizophrenia, they do not discuss the evidence that individuals with ADHD tend to have more children than do controls (Weiss et al. 1985).

K&M point out the arbitrariness between classification of what is "normal" and what is "abnormal" because most mental disorders are extreme points along a continuum of symptom severity. From this viewpoint, the "normal" spectrum of symptoms may have adaptive functions, such that normal depressed mood may motivate avoidance of similar situations in the future. Unlike somatic disorders, there is rarely an objective gold standard for diagnosis: Severities range widely and wax and wain over time in a given individual; boundaries with normality are fuzzy and shifting, depending often on society's own changing norms and expectations (Joan of Arc, a heroine in her day, would probably nowadays be committed to an institution); and boundaries between the disorders themselves are often fuzzy and arbitrary with much overlap, irrespective of questions of comorbidity, as if it all depends on which "joints" we happen to choose with which to "carve" nature. Cultural factors may influence the prevalence and severity of mental disorders, because cultural and societal tolerance for different behaviours vary (McArdle 2004). Using the same cut-off scores on a behaviour teacher rating scale for example, produces different rates of hyperactivity in children of different countries (e.g., in Scotland, 4.5% of children are classified hyperactive, whereas, in Spain, 16% of children are classified hyperactive using the same criteria; Gingerich et al. 1998).

Brown and Braithwaite (2004) found that, despite (and, initially in fact probably because of) variability in both groups, on average, fish introduced into high-predation environments in a very few generations tended to become more bold (showing a greater propensity to take risks and greater exploratory behaviour) than did fish (from the same original founder population) from low-predation sites. Presumably it is advantageous for fish in high-predation environments to explore a new environment thoroughly to become aware of escape routes and to ensure that no predators are present. Thus, "personality" or temperamental traits appear to be selected for, often in a very short time period, if they are advantageous in a particular environment. Generally, what is genetically transmitted is perhaps not so much a disorder per se, but rather a particular kind of general personality bias which may then predispose an individual to morbidity in a certain societal context – or perceived excellence in another. There certainly appears to be a connection between temperament, which is considered to be an early precursor to personality traits (Nigg et al. 2002), and psychiatric disorders, because difficult-temperament children are over-represented in psychiatric populations (Maziade et al. 1990a). However, difficult temperament predicts the presence of psychiatric conditions in preadolescence and adolescence only when family functioning is also taken into account (Maziade et al. 1990b). Thus, extreme temperament is not automatically equivalent to a psychiatric disorder, and reflects the importance of considering gene-environment interactions.

Inheritance of general personality factors may predispose an individual to the risk of developing one or more of a range or possible maladaptive (or even adaptive) behaviours, depending on the individual's environment (Legrand et al. 2005). Thus, the same genes for externalising tendencies may be expressed differently under different environmental conditions, and predispose, on the one hand, both to antisocial behaviour and drug and alcohol problems, and, on the other, to otherwise useful, if risky or dangerous, occupations (e.g., test pilots, fire fighters). Similarly, impulsive people may be well placed to take advantage of unexpected opportunities, whereas others' impulsive choice may lead to drug addiction in which addicts affect their health for the immediate rewards of the drug (Cardinal 2004; Evenden 1999).

Are common, harmful, heritable mental disorders common relative to other such non-mental disorders, and does their frequency require a special explanation?

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Abstract: Keller & Miller's (K&M's) conclusion appears to be correct; namely, that common, harmful, heritable mental disorders are largely maintained at present frequencies by mutation-selection balance at many different loci. However, their "paradox" is questionable.

The "paradox," which is largely set out in the first sentence of Keller & Miller's (K&M's) abstract, has two elements: the existence of common disorders agreed to be deleterious in present-day environments and shown by the authors to reduce reproductive performance (fitness) in many cases; and an effective mechanism for reduction of frequency of alleles predisposing persons to deleterious traits. The reality of the paradox requires consideration before assessment of K&M's explanation for the prevalence of disorders agreed to be common.

Mental disorders as a special category. We first address the case of mental disorders (MDs), since they are considered at length by K&M.

Table 1 lists a number of disorders well established as having high population prevalence and substantial heritability. Heritability (h^2) is used as an indicator of genetic importance in aetiology despite its well-known defects (mentioned by K&M), because for common diseases there is no problem of h^2 being misleading.

We see immediately that traits other than MDs which certainly reduce fitness, for example, type 1 diabetes and endometriosis, are also at high frequencies which require explanation on K&M's argument. We also tentatively conclude that, however special and important human mental abilities and disturbances thereto may be to humans living in society, there is no reason to separate them out for the purposes of assessing K&M's paradox. We shall therefore consider them separately only after dealing with the two general propositions which constitute K&M's paradox.

The existence of common deleterious traits. The majority of the traits shown in Table 1 are deleterious in present-day societies, in terms of reduction in reproductive fitness. The societies under discussion are for the most part characterized by large numbers of unrelated people living in close proximity, sustained by nutrition adequate to excessive for the low level of physical effort required normally to gain a living in employment and other activities which themselves differ greatly from those of the first 24,000 generations at least of the human species' putative 25,000 generations of existence.

Some of these traits have increased substantially in frequency in recent centuries. In some cases, environmental factors have been identified as causal, for example, diet and exercise patterns for ischaemic heart disease. Of type 1 diabetes, Hyttinen et al. (2003) have written:

> Type 1 diabetes among children ≤15 years has increased worldwide during [recent decades]. In light of population genetics, the rate of increase in the incidence ... is too rapid to be caused by changes in the population gene pool. Despite harmful effects of diabetes-associated alleles, they are common in many populations. Environmental risk factors may directly trigger the process leading to type 1 diabetes or may interact with diabetes susceptibility genes that modify the penetrance. Heritability [in our study] was found to be higher than that discovered before. If the increase in heritability is real, it should be at least partly interpreted as a changed penetrance of the diabetes susceptibility genes. (p. 1054)

Table 1 (*Mayo & Leach*). *Prevalence and heritability of some common disorders in various populations*

Disorder	Prevalence %	Heritability %	Source (Reference)
Autism	0.02–0.05	90	K&M
Anorexia nervosa	0.05	90	K&M
Bipolar disorder	0.1	65	K&M
Congenital heart disease	0.1	>60	Smith 1975
Type 1 diabetes	0.5	>80	Hyttinen et al. 2003
Schizophrenia	1	80	K&M
Mild mental retardation	2	>65	K&M
Asthma	2–5	50	Smith 1975
Ischaemic heart disease	3	>60	Smith 1975
Peptic ulcer	4	>35	Smith 1975
Depression	5–17	45	K&M
Endometriosis	8–10	50	Treloar et al. 2005
Allergy	15–20	50	Smith 1975

Hence, such a change must have been environmentally induced.

Other diseases, such as many infectious diseases, have declined in incidence and prevalence in recent centuries. In virtually all cases where explanations have been obtained, environmental factors have been shown to be causal, even where genetic susceptibility is implicated in causation of the disease. Environmental change has thus been important in changes in disease incidence and prevalence upwards and downwards; it would be of interest to know what diseases have remained unchanged in incidence or prevalence in recent centuries, but rare Mendelian recessive disorders could lie in this group. K&M present no evidence on constancy of frequency of their target category: "[M]ental disorders that are much more common than would be expected from a single-gene mutation-selection balance; roughly, this corresponds to mental disorders with lifetime prevalence rates above [0.05%] in reproductively aged adults" (sect. 1.3, para. 6). In the absence of evidence, one cannot reject the simple hypothesis that some changes in the human environment in the last thousand generations have contributed to an increase in the frequency of disorders that are particularly deleterious in large, organised societies not engaged in essential, risky, strenuous physical work. K&M address "ancestral neutrality" of causal alleles of relevant genes in sections 3.3 and 4 but reject it because of population-genetic considerations. Their argument concerning environmental change is brief and based on the implausibility of large G×E interactions and the rarity of strict neutrality (sect. 4.2). Leaving aside discussion of such strict neutrality, we simply note that very large G×E interactions are inherent in the increase in frequency of diabetes and various cancers; they are not inherently implausible. Indeed, K&M accept in section 4.4 that G×E interactions and nearly neutral variation could be important in the very high incidence of depression, where simple environmental causation of change in incidence has indeed been invoked from time to time (e.g., Hibbeln 1998).

In the absence of evidence of constancy of frequency of MDs over time, one cannot reject the hypothesis that environmental factors have increased their frequency, making highly deleterious alleles that were previously neutral, advantageous or slightly deleterious. Neutrality is a second-order question until the hypothesis stated has been tested.

Depletion of genetic variation by natural selection. Much of K&M's argument is based on the Fisherian concept that a population will, other things being equal, increase in fitness at a rate given by the additive genetic variance in fitness (see Ewens 2001). On K&M's argument, natural selection will therefore deplete variance in fitness rapidly, apart from that generated afresh by mutation. However, this conclusion ignores two matters: First, the environment is never constant and indeed may be viewed from the organism's perspective as constantly deteriorating (Fisher 1930/1999); and, second, variance in fitness and associated metrics (e.g., heritability) are not simply reduced rapidly to zero for "fitness traits" and left as they are for "non-fitness traits" (see Bürger et al. 1989; Keightley & Hill 1987; Mayo et al. 1990).

Traits which may be substantially influenced by the environment, such as all those listed in Table 1, should be considered in the light of the cautions just expressed; environmental change, potentially so much more rapid and far-reaching, should always be evaluated before considering genetic change. Indeed, Kirk et al. (2001) have drawn much the same conclusion from a very thorough direct study of the heritability of fitness in one human population.

Genetic contributions to causation of mental disorders. We argue that K&M have not made their case in regard to either the overall causation of MDs or the genetic evidence for mutation-selection balance as the prime source of genetic variance in MDs. However, as set out in the previous section, we consider such balance as the major source of genetic variance in many traits, among which could be MDs.

It is possible that those who hold the belief a priori that the genetic basis of multifactorial traits is oligogenic may still find this conclusion paradoxical in some way. However, we should note that evidence from experimental organisms shows that many traits are controlled by many – frequently hundreds – of genes, and that there are scores of interactions among these genes, even for simple quantitative traits in plants such as rice (for discussion, see Mayo 2004). For truly complex traits such as human mental development and function, influenced perhaps by thousands of genes, as noted by K&M, it should not be surprising that causation of variation is not oligogenic.

We note further that K&M have not made a convincing special case for MDs as against other common familial diseases, and conclude by quoting Bodmer (1999, p. 103), who has applied the same arguments to common cancers:

> [T]hese types of variants [rare variant alleles at many different loci] may thus represent a major new facet of the study of multifactorial disease inheritance, representing effects that lie between those of severe clearly inherited susceptibilities and relatively common multifactorial low-penetrance effects, such as are characterised by the many associations between polymorphic HLA variants and autoimmune diseases.

The romance of balancing selection versus the sober alternatives: Let the data rule

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Abstract: Schizophrenia has attracted more than its fair share of evolutionary-based theories. The theories involving balancing selection are based on the assumption that the incidence of schizophrenia is invariant across time and place. Modern epidemiology allows us to reject this dogmatic belief. Once variations in the genetic and epidemiological landscape of schizophrenia are acknowledged, more productive research models can be generated.

Keller & Miller (K&M) have provided a sobering analysis of the competing models explaining the persistence of various psychiatric disorders in the face of a reduction in fitness associated with these disorders. Their conclusions are both frustrating and liberating. Rather than the romantic and quasi-heroic notions associated with balancing selection, the evidence suggests that the genetic contributions to these disorders are probably due to the multi-generational accumulation of a wide variety of mutations in a wide range of genes.

My comments focus on schizophrenia, which has attracted more than its fair share of balancing-selection evolutionary theories. The major evolutionary theories of schizophrenia have been predicated on the belief that the incidence of schizophrenia is invariant across time and place. This has influenced researchers to link susceptibility genes for schizophrenia to distant speciation events (e.g., Burns 2004; T. J. Crow 2000). In these theories, symptoms or neurobiological correlates of schizophrenia are interpreted as trade-offs for adaptations related to key innovations of our species (e.g., language, theory of mind, social intelligence, creativity, etc.). These theories are ingenious and thought-provoking, but they also tend to be overly ambitious. They build theoretical mountains out of empirical molehills.

K&M's target article is timely because data from epidemiology are now overturning some of the dogma surrounding schizophrenia (van Os et al. 2005). It is now clear that the central notion underpinning balancing-selection theories of schizophrenia (i.e., that schizophrenia occurs with equal incidence around the world) is wrong (McGrath et al. 2004). Not only are there prominent variations in the incidence of schizophrenia between sites, the risk of schizophrenia varies substantially within populations. For example, subgroups that are at increased risk of developing schizophrenia include men, first-generation and second-generation migrants, those born and/or raised in cities, the offspring of older fathers, and those born in winter and spring.

When the detailed epidemiological landscape of schizophrenia is appreciated, schizophrenia becomes less exceptional and more like other disorders – its incidence varies across gradients in place and time (McGrath 2006). The data show that romantic and muddle-headed notions that schizophrenia respects human rights (i.e., is an "egalitarian" disorder) are wrong (McGrath 2005). As K&M note, theories based on balancing selection might be appealing for social and moral reasons. However, when data no longer support the dogma, data must rule. Theories based on polygenic mutation selection do not rely on a flat epidemiological profile of schizophrenia; hence, the recent advances in epidemiology should not undermine K&M's model.

The failure to appreciate variations in the incidence of schizophrenia may have also hindered recognition of the between-population variation in the prevalence of susceptibility genes. This issue is relevant to the scenario outlined by K&M in section 5.3 ("Temporal or spatial variability in fitness landscapes"). For example, while much research has focused on the association between polymorphisms in the *COMT* gene and risk for (and expression of) schizophrenia (Tunbridge et al. 2006), there has been less recognition that the prevalence of polymorphisms in this gene varies considerably between populations (Palmatier et al. 1999). Similarly, the dystrobrevin-binding protein dysbindin is a much-cited candidate gene for schizophrenia (Benson et al. 2004; Sullivan 2005) and perhaps also psychosis associated with bipolar disorder (Raybould et al. 2005). However, little if any attention has been given to the finding that this gene appears to be under strong positive selection in Europeans (perhaps related to its association with skin pigmentation) (Voight et al. 2006). With respect to modern theories of gene by environment interactions leading to depression, one of the leading candidate genes is the serotonin transporter gene (*SLC6A4*) (Levinson 2006). The region containing this gene also appears to be under positive selection in some, but not all, of the populations assessed to date (see http://hgwen.uchicago.edu/selection/haplotter.htm). Although the overall genetic calculus suggests that balancing selection is unlikely to account for the persistence of common heritable mental disorders, these examples may reflect more nuanced examples of fine-grained temporal fluctuations caught in the "snapshot" of evolution. It remains to be seen whether the factors influencing the positive selection of these candidate genes can be determined. Relying on the surface-level adult phenotype to understand how candidate genes influence the matrix of brain development can be a frustrating task.

Polygenic mutation-selection models also encourage us to shift focus with respect to the category of observation in psychiatric research. Rather than searching for an association between a few genes and one particular group of psychiatric disorders, it directs our scrutiny towards over-arching biological systems. The question is no longer which gene and associated protein causes the disease of interest, but which biological pathways in which cells are most vulnerable to the cumulative mutational burden.

It is important to recognize that the symptoms of psychiatric disorders are emergent properties of highly complex and robust systems. Evolutionary developmental biology (evo-devo) reminds us of how evolution builds robust systems (Carroll 2005; Kitano 2004). Important properties become highly buffered over phylogenetic development. When robust biological systems fail, occasionally we see catastrophic, cascading failures (e.g., akin to the loss of consciousness associated with grand mal epilepsy). However, in most circumstances, robust systems call up other mechanisms to maintain output. The systems can become fragile, though, in certain circumstances. In this respect, the broad sweep of mutations proposed in the K&M model may be sufficient to unmask fragilities, leading to the neurological equivalent of *graceful degradation* (a term from computer programming used to describe the ability of software to continue operating with reduced function rather than "crash") (Bentley 2004).

Can these notions provide directions for future schizophrenia research? Can we find the appropriate biological category of observation that will enable us to interpret the data that polygenic mutation-selection theories predict will be found? Evidence from genomics and proteomics based on post-mortem brain tissue is already providing candidate biological systems for closer scrutiny. For example, many genetic and environmental factors can subtly impact on the cross-talk between pathways involved in apoptosis and synaptic plasticity (Catts & Catts 2000; Glantz et al. 2006), or subtly reduce the efficiency of mitochondrial trafficking (which is increasingly being recognized as important for neuronal functioning) (Reynolds et al. 2004). When research finds the right category of observation, order may be found amongst disorder.

If common, heritable mental disorders are underpinned by multi-generational cumulative sweeps of ever-changing mutations, then the search for susceptibility genes will be a substantial challenge. In the context of schizophrenia, the complexity of

this model complements that growing awareness that the incidence of schizophrenia has prominent variations across time and place. However, I argue that variations in the incidence of schizophrenia should be seen as valuable opportunities to generate and test novel candidate exposures. These exposures operate against a diverse and ever-changing backdrop of susceptibility genes. Linking these genes into biological systems may provide us with clues about how the environment can help optimize brain development and reduce system fragility. Having a sober and data-based understanding of the complexity of genetic and environmental risk factors underpinning common mental disorder is a crucial step in helping neuroscience reverse-engineer the complex systems underpinning brain development.

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Reconciling the mutation-selection balance model with the schizotypy-creativity connection

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Abstract: Keller & Miller (K&M) make a persuasive case for the role of mutation-selection balance in the persistence of such disorders as schizophrenia. However, there is evidence relating illness liability to creativity, which seems to imply balancing selection. I argue for a hybrid position, where schizotypal personality traits can have fitness advantages or disadvantages, with mutational load and neurodevelopmental conditions determining which outcome is observed.

The authors of the target article make an elegant and extremely persuasive case for the role of polygenic mutation-selection balance in the persistence of traits that impair mental functioning in humans. Keller & Miller's (K&M's) article is very important for a number of reasons. First, within psychiatric genetics, there has been an implicit assumption that genes predisposing people to mental disorders will be easy to identify in the way that has been true of those involved in Mendelian disorders. The mutation-selection balance model shows persuasively why finding a few genes of major effect that have their effects in all populations is a naïve expectation. Second, within evolutionary psychology, there has been excessive attachment to the idea that traits of importance to fitness should show no heritable variation. This has led to some odd accounts which sought to imply that mental disorders usually or always represented the proper functioning of universal adaptations, and only seemed to be maladaptive because of the modern environment, or medical stigmatisation (see Nettle 2004). The target article rightly introduces evolutionary psychology to the fact, now well understood by evolutionary biologists, that even traits under strong selection can maintain abundant genetic variation, if the mutational target size is sufficient.

The authors rightly stress that strong empirical evidence for a mutational load account for serious disorders such as schizophrenia comes from such findings as paternal age effects and inbreeding depression. There are also non-heritable risk factors. The authors allude to brain trauma as one such risk, but neglect to point out that low birth weight, winter birth, maternal infection during pregnancy, urban residence, and exposure to house cats are all risk factors. Though these are non-genetic effects, they are generally supportive of K&M's position, because they imply, more generally, that *any* factor impairing neurodevelopment – be it deleterious mutations or early life stressors – is a potential risk factor for schizophrenia. This is consistent with the logic of the watershed model, where failures of attention and social cognition would be the result of many types of upstream instability, a point further reinforced by the finding that schizophrenia patients have increased levels of physical asymmetry compared to controls (Yeo et al. 1999).

For these reasons and more, the authors' dismissal of balancing-selection models in favour of mutation-selection models seems justified. The most commonly discussed balancing-selection model for serious mental disorders – that of a relationship to creativity – is given short shrift. However, the empirical evidence for such a linkage is really quite strong, and much stronger than the authors imply. The crucial finding is not that rates of mental illness are higher in creative groups (though they are; cf. Andreasen 1987; Ludwig 1995). Rather, the key finding is that there are measurable cognitive affinities between those successful in the creative professions and those diagnosed with serious mental illness (Nettle, in press; Nowakowska et al. 2004; Schuldberg 2000; Woody & Claridge 1977), whether or not the creative individuals show any symptoms of psychopathology. Thus, it seems likely that there is a shared endophenotype, including broad attentional sampling and an inclusive style of mental association, which is disproportionately found in both healthy creative individuals and psychotic patients.

Most commentators have taken this as evidence for balancing-selection effects (Nettle 2001). How then do we square such evidence with K&M's convincing case for the importance of mutational load? I suspect that the answer lies in how mutational load (and developmental instability in general) interacts with a schizotypal cognitive style. Clegg and I have suggested that where this cognitive style is coupled with stable neurodevelopment (low mutational load and benign environment), the result is healthy creativity, whereas where it is coupled with genetic and/or environmental instability, the result is serious mental illness, with all its concomitant neurodevelopmental delays, impairments, and fitness reductions (Nettle & Clegg 2006).

If this model is right, then the alleles leading to schizotypal cognitive style are probably nearly neutral, on average, and therefore a significant amount of variation is maintained. Thus, the model squares the evidence for a link between schizotypy and creativity with the evidence for mutational load and environmental effects on schizophrenia. The case for this model would be much strengthened if there were evidence for increased fitness associated with creativity. Note that the increased fitness need not be restricted to siblings of patients, as long as it was found in *some* individuals with a schizotypal cognitive style. Clegg and I showed (building on ideas in Miller's earlier work) that artists and poets, who show some schizotypal traits, have increased numbers of sexual partners relative to controls (Nettle & Clegg 2006). Therefore, I feel that a hybrid model, with balancing effects of schizotypal cognition, but mutational load and neurodevelopment determining whether it is the negative or positive sequelae that develop, is very plausible.

Mental disorders are not a homogeneous construct

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Abstract: The only commonality between the various psychiatric disorders is that they reflect contemporary problematic behaviors. Some psychiatric disorders have a substantial genetic component, whereas others are essentially shaped by prevailing environmental factors. Because psychiatric ailments are so heterogeneous, any universal explanation of mental illness is not likely to have any clinical or theoretical utility.

The target article by Keller & Miller (K&M) reviews potential evolutionary genetic explanations for psychiatric disorders. This is a welcome topic because the nascent field of adaptive genetic variation may be applicable to certain psychiatric conditions. However, some of the authors' ideas are founded on contentious suppositions.

K&M fail to distinguish between psychiatric conditions that are genetically based and those that are mostly precipitated by unique cultural factors. They mistakenly clump all psychiatric disorders as being both heritable and reflecting brain "malfunction" (see, e.g., sect. 1.2). For the majority of psychiatric ailments, the environment, and not heredity, is the primary determinant. Eating disorders, for example, were rare until food became plentiful in Western societies. Borderline personality disorder is uncommon in the absence of childhood neglect or abuse (Bandelow et al. 2005; Zanarini 1997). Depressive episodes are almost always precipitated by a loss of attachment or diminishment in status. It is acknowledged that genetic factors probably alter vulnerabilities to various psychiatric ailments, but no one knows how many genotypes could be relevant for any given emotional problem. It is possible that only three classic psychiatric disorders (bipolar disorder, schizophrenia, and obsessive-compulsive disorder) possess an appreciable genetic component.

K&M's greatest leap of faith is their non-categorical approach to mental disorders – a necessary perspective for their polygenic mutation-selection balance idea to work. Psychiatric disorders are simply not as homogeneous as K&M assert. Schizophrenia, bipolar disorder, obsessive-compulsive disorder, brain trauma, and Down's syndrome, for example, demonstrate remarkable similarities within each diagnostic group, yet are all distinctly different from one another. It is almost indisputable that schizophrenia and bipolar disorder tend to follow separate family genealogies (Cardno & Murray 2003; Lapierre 1994; Loranger 1981; Maier et al. 1993; Potash et al. 2003; Smoller & Finn 2003; Somnath et al. 2002; Taylor et al. 2002; Torrey et al. 1994). Improved diagnostic methodologies have shown that cerebral ventricular enlargement occurs in patients with schizophrenia and their unaffected kin, but not in bipolar disorder (McDonald 2006).

Schizophrenia and bipolar disorder may sometimes be difficult to distinguish clinically, but this in no way seriously invalidates each respective diagnosis (there are several possible mundane explanations for this apparent overlap).

K&M's polygenic mutation-selection balance hypothesis appears to be the genetic counterpart of Randall's "misconnections" model explaining schizophrenia (Randall 1983). First published in 1983, Randall proposed that novel neural pathways could be established randomly, resulting in "supernormal connections" or "misconnections," resulting in various mental disorders such as schizophrenia. A "biological trial and error of connection would produce a range of behavioral variants" (Randall 1998, p. 144). The inherent weakness of both Randall's proposal and the polygenic mutation-selection hypothesis is that neither idea can comprehensively explain the characteristic specificity of the various psychiatric disorders.

Contrary to popular belief, psychosis does not reflect random scrambled thoughts. Psychotic delusions and hallucinations have their own intrinsic patterns. For example, Polimeni and Reiss (2004) have clinically observed that the vast majority of psychotic delusions are either paranoid or spiritual in nature (consistent with our shamanism-group selection hypothesis for schizophrenia). Remarkably, paranoid delusions rarely reflect veritable dangers in proximity but usually involve suspicions outside immediate surroundings. Although difficult to prove, it appears that severe medical illness (without delirium) tends to mitigate schizophrenia, mania, melancholia, and obsessive-compulsive symptoms – as if these psychiatric ailments are fixed-action behaviors disrupted in medically compromised individuals. The presence of hallucinations and paranoid delusions (rarely spiritual delusions) in brain trauma, delirium, or dementia does not necessarily mean that these symptoms reflect disease states in every context. Vomiting, for example, is adaptive when expelling foreign toxins but reflects a disease state when caused by a brain tumor.

K&M imply that psychiatric conditions manifest themselves with the same severity in traditional societies; however, the anthropological literature does not support this view. Most contemporary psychiatric disorders, including post-traumatic stress disorder, agoraphobia, or classic obsessive-compulsive disorder, may be rare in traditional societies (Polimeni et al. 2005). Although schizophrenia-like symptoms are commonly described (typically in shamans), they are less incapacitating. Suicide is not infrequent, but often observed in the immediate aftermath of lost love.

K&M are correct that historical psychiatric epidemiology could well pose formidable problems for evolutionary theories and that this problem has generally been ignored. However, very little is known about the fecundity of various psychiatric conditions before the 1950s. Even less is known during the transition from traditional societies to modern life over the last few thousand years. Michel Foucault's suggestion that mental illness was socially unimportant before eighteenth-century industrialization is not farfetched (Foucault 1965/1988).

K&M suggest that evolutionary theorists are often too quick to invoke balancing selection because it is a convenient mechanism to explain the adaptive qualities of mental illness; however, this does not necessarily negate their position. In fact, when I first embarked on evolutionary research, I naively examined group selection with the mistaken belief that I was avoiding balanced-selection arguments. In the end, I came to realize that the necessary prerequisites for balanced selection are particularly prominent in bipolar disorder, schizophrenia, and obsessive-compulsive disorder. For example, there is varying evidence for heterozygote advantage and assortative mating in each of these conditions.

In an attempt to categorize the mechanisms of genetic variation, K&M may have oversimplified the dynamics of nature. For example, it is possible that multiple mechanisms may underlie any given type of variation, piggybacking or priming the other (i.e., neutral drift + heterozygote advantage + assortative mating). In other words, the machinations of genetic variation are still very much a black box (Mousseau et al. 2000).

Notwithstanding the glib and amorphous idea of spandrels, almost every physical attribute pertaining to a living organism has been adaptive for at least a few generations. Even the circuitous route of the laryngeal nerve is no exception. Although there may have been evolutionary design constraints, the entire "illogical" length of the laryngeal nerve is an adaptation! In humans, universal genetic-based behaviors such as anger, jealousy, humor, and attachment are no different. Although mental ailments may seem as imperfect as the circuitous laryngeal nerve, certain psychiatric conditions plausibly make adaptive sense in the primal world of traditional societies. Both disease and evolutionary models of psychiatric illness possess their own loose ends. K&M effectively demonstrate that neither camp can be dismissed outright.

Mental disorders, evolution, and inclusive fitness

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Abstract: Grouping severe mental disorders into a global category is likely to lead to a "theory of everything" which forcefully explains everything and nothing. Speculation even at the phenotypic level of the single disorder cannot be fruitful, unless specific and testable models are proposed. Inclusive fitness must be incorporated in such models.

Speculation about the evolutionary origin of mental disorders is a peaceful diversion from the challenge of attempting to treat people diagnosed as having severe mental disorders. Keller & Miller (K&M) efficiently dismantle this diversionary toy. What remains of Darwinian psychiatry after their compelling criticism is an approximate model of how the genes leading to severe mental disorders had not been phased out from the general population by natural selection. However, as K&M seem well aware, "severe mental disorders" are very much influenced "by the cultural and inherent person-perception biases . . . and the categorization demands of legal, medical, and research systems" (sect. 8, para. 5). So, what is the problem? Their designation of severe mental disorders as a global category predisposes to a "theory of everything" which explains everything and nothing, the most common fault of evolutionary psychopathology.

We introduce as examples several specific and testable models at the phenotypic level of the single disorder. First, let us consider sociopathy: People with sociopathy cheat in reciprocity games – they obtain resources and seldom return them. According to neo-Darwinian formulations, they challenge the cooperative subject (Axelrod & Hamilton 1981; Trivers 1971). Groups of altruists who cooperate and are unable to detect cheaters are easily exploited, leading to their extinction. However, groups of altruists who are able to detect cheaters and discriminate in their cooperative moves will protect their resources (Fehr & Fischbacher 2003). In this regard, sociopathic individuals may improve the altruists' fitness overall. Since the cognitive abilities leading to the cheater's detection are likely to be useful in all kinds of cooperative exchange (Stevens & Hauser 2004), groups of discriminative cooperators will outcompete over groups of non-discriminative cooperators. Sociopathy thus can select for individuals who are more able to detect cheating. Its permanence, thus, is of a parasitic kind: The hosts tolerate some sociopaths in their environment because the sociopaths continuously challenge the hosts' cognitive abilities, as parasites resident in our skin stimulate the immune system and act as a restraint against more virulent invaders.

Patients with schizophrenia often need permanent help: They deplete resources because they are unable to return anything. Let us assume that alleles for schizophrenia spring up in two clusters of families: the families that always help their kin, and the others who never help their kin. Some of the helped kin will arrive at reproducing their own susceptibility alleles, whereas those without help will become extinct. Since helping kin is a trait likely to favour inclusive fitness of the helper (Hamilton 1964), after some generations the alleles for schizophrenia will spread in the population, on account of their hitch-hiking on the helping trait, without adding any hidden benefit to humankind: They fixate in the universal gene pool because they are occasionally linked with some trait inherent to our more general adaptive outfit. Indeed, incidence of schizophrenia does not greatly vary across sites, confirming that the disorder is rooted in our common genetic heritage. Cultures more likely to display a helping attitude towards affected people (such as some Indian enclaves), however, are also more likely to have incidence rates that are higher than the mean (Jablensky et al. 1992), together with a more favourable outcome (Leff et al. 1992), leading in the long term to lower-than-average prevalence rates (Saha et al. 2005).

Female patients with severe anorexia nervosa, by maintaining their body weight below the threshold for ovulation, exclude themselves from reproduction; however, they often behave in a supportive way towards their kin, cooking for them what they themselves are unwilling to eat. This behaviour is assimilated to the "helping at the nest" behaviour described in the wild field and observed to improve kin's reproductive success (Arnold & Owens 1998). Indeed, what matters for the permanence of a gene set is persistence of that set in the pool, generation after generation: Humankind, for example, is thought to carry on the mitochondria of seven ancestral females (Sykes 2001). A "helping at the nest" hypothesis for anorexia nervosa is a testable one, different from the scenario of the "gene for facing famine" (cf. Guisinger 2003).

It is difficult to understand K&M's polygenic mutation-selection balance model: They consider balancing selection as a dynamics whereby two or more alternative alleles are maintained because their net fitness effects balance each other out, so the alleles are not lost by chance or genetic drift (Wilson 1998). A polygenic mutation-selection balance, therefore, is a model whereby a conditional balance is achieved: A mutation produces a decrease in fitness only given a concurrent genetic environment; in the absence of such an environment, the mutation is neutral. Past studies found that the genetic-controlled conditions increasing the risk of obstetric complications are also associated with a higher risk of schizophrenia, for example, in the case of Rh incompatibility (Hollister et al. 1996). Conversely, obstetric complications tend to recur within families, clustering in families that also show a higher representation of subjects diagnosed with schizophrenia (Walshe et al. 2005). Some time ago, we suggested that the genetics of schizophrenia might be explained in part by the genetics of the conditions increasing the risk of obstetric complications (Preti et al. 1998). Foetal brain anoxia likely to result from obstetric complications generally leads to death or to severe motor impairment: We therefore hypothesized that some brain-protecting gene would be necessary to balance the brain-damaging impact of obstetric complications (Preti & Miotto 2005). Whenever obstetric complications occur, schizophrenia develops only in the presence of the protecting gene. A subgroup of offspring of patients diagnosed with schizophrenia was found to bear a statistically reduced risk of developing schizophrenia in adulthood, indeed, as if they were carrying some protective gene (Gottesman & Erlenmeyer-Kimling 2001). Moreover, some studies reported a higher prevalence of successful creative abilities in the mathematical, visual, and spatial domains among the relatives of patients diagnosed with psychosis (Karlsson 1999). Anomalous lateralization (Dragovic & Hammond 2005) could be the link between schizophrenia and superior mathematical ability. In the absence of severe obstetric complications, protective, "left brain" genes would favour creative abilities in the visual and spatial domains; in the presence of such complications, schizophrenia would develop. Is this a possible example of the kind of polygenic balance K&M have in mind?

Behavioural ecology as a basic science for evolutionary psychiatry

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Abstract: To the evolutionarily oriented clinical psychiatrist, the discipline of behavioural ecology is a fertile basic science. Human psychology discusses variation in terms of means, standard deviations, heritabilities, and so on, but behavioural ecology deals with mutually incompatible alternative behavioural strategies, the heritable variation being maintained by negative frequency-dependent selection. I suggest that behavioural ecology should be included in the interdisciplinary dialogue recommended by Keller & Miller (K&M).

Keller & Miller (K&M) say that the heritability of mental disorders presents a problem for explanations in terms of function,

because alleles conferring function should increase in frequency to fixation. They claim the only satisfactory explanation for the high rate of mental disability is that mental disorders are caused by harmful mutations on hundreds of genes. This argument restricts evolutionary psychiatry to disorders which have zero heritability. However, the authors might have underestimated the prevalence and robustness of negative frequency-dependent selection.

I would like to draw the authors' attention to the discipline of behavioural ecology, which is the study of behaviour in relation to its function (Krebs & Davies 1993). Behavioural ecology could be said to be the basic discipline of evolutionary psychiatry. It is concerned with strategy sets, which are sets of alternative strategies for dealing with problems. For instance, the cold weather and reduced food supply of winter present a problem to many species. Sometimes all members of a species deal with the problem in the same way, but sometimes there are alternative strategies for dealing with the problem. Many bird species migrate; in some of these all the individuals migrate, in other species only a proportion migrate and the rest stay where they are. In very cold winters the rewards of migrating are greater than staying, but in mild winters the rewards of staying are greater. It is not of great concern to behavioural ecologists just how the decision, to stay or migrate, is made. It could be entirely genetic, so that a "staying" allele (or group of alleles) is competing with a "migrating" allele. Or it could be entirely environmental; for instance, it is thought that robins compete for territories in the autumn, and those birds who win territories stay and those who fail to win territories migrate. Probably for most partially migrating species the decision-making mechanism is not known. Similar considerations may apply to partially hibernating species of rodents; the territory owners stay awake, and those who do not have territories go to sleep.

Coming closer to evolutionary psychiatry, let us consider the case of pairwise contests. A rival for mates or other resources poses a problem for the individuals of most species, and various strategies have evolved to deal with it (Boone 1992; Crowley 2003). Most species have evolved the alternative strategies of escalation and de-escalation. In territorial species, you either fight or run away. In group living species, there is an alternative – appeasement – which enables one to continue living in the group, albeit at a lower social rank. Each strategy has costs and benefits. Behavioural ecologists such as Maynard Smith have studied the conditions under which alternative strategies could survive (Maynard Smith 1982; Parker 1984; Reichert 1998). Calling the escalating strategy the "hawk" strategy and the de-escalating strategy the "dove" strategy, they concluded that under certain conditions a mixture of hawk and dove is an *evolutionarily stable strategy* (ESS) in that it cannot be infiltrated and replaced by any other strategy, and in particular it cannot be replaced by a pure hawk or a pure dove strategy. Thus, variation in fighting behaviour is an ESS. The variation is maintained by negative frequency-dependent selection, because in a world of hawks it pays to be a dove, and in a world of doves it pays to be a hawk. It does not matter whether the choice between hawk and dove is genetically or environmentally determined. Nor does it matter whether the choice is a "once and for all" affair, such that type of parenting or some other variable made an individual hawk or dove, or whether each individual has the capacity to deploy both hawk and dove strategies, the choice depending perhaps on environmental cues or possibly on a random basis.

Both hawk and dove strategies have costs and benefits. We think on the whole that the costs of being a hawk tend to take the individual to the casualty department, whereas the costs of being a dove take him or her to the psychiatric clinic (Price et al. 2004). In other words, the costs of being a dove represent some of the "mental disorder susceptibility alleles" of K&M. And, since the choice between hawk and dove can be either environmental or genetic, the problem of the partial heritability of the mental disorders does not affect the argument.

Another issue is dispersal. Many species have both a maintenance phenotype, which is adapted to the natal territory, and a dispersal phenotype, which is adapted to occupying new habitats (Geist 1989). As each phenotype becomes rarer, its fitness increases, so both are maintained by negative frequency-dependent selection. During hominid evolution, rapid dispersal must have been advantageous, as receding ice sheets left new land available for occupation. However, human groups tend to be united by a common belief system which differs from the belief system of all the groups they are competing with. In order to facilitate dispersal, it may have been advantageous for an individual to undergo a change of belief system and to convert some of the group to the new belief system, and to take them off to a "promised land" (Price & Stevens 1999; Stevens & Price 2000b). Thus, two dispersal phenotypes may have evolved: One is the schizotype who has the capacity to undergo a change of belief system, and one is the suggestible or dissociative person who has the capacity to be converted from the belief system with which he or she was indoctrinated during childhood and to adopt the new belief system of a prophet or cult leader. The fitness costs of both these dispersal phenotypes would be grievous if dispersal was unsuccessful, but the benefits of successful dispersal might also be very great, leading to an adaptive radiation in a new habitat. In 45 years of psychiatric practice, I have seen many patients labelled schizophrenic who in different circumstances might have become effective cult leaders

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Bipolar disorder evolved as an adaptation to severe climate

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Abstract: Keller & Miller (K&M) assert that mental disorders could not have evolved as adaptations, but they fail to make their case against the theory of the evolutionary origin of bipolar disorder that I have proposed (Sherman 2001). Such an idea may be unorthodox, but it has considerable explanatory power and heuristic value.

In a previous publication (Sherman 2001), I proposed the theory that circular bipolar disorder (major depression with hypomania or mania) evolved as an adaptation to long severe winters and short summers, which implicates the circadian clock in its pathophysiology. This idea is inferred from theorizing and data about the seasonal effects of light and the small, but statistically significant, correlation between bipolar disorder and a pyknic, cold-adapted build. The hypothesis is consistent with recent research: Light therapy is as effective as antidepressant medications for seasonal depression, and three studies have demonstrated similar effectiveness for nonseasonal, major depression (Golden et al. 2005; Rosenthal 2006). Individuals with seasonal affective disorder, compared with healthy volunteers, generate a biological signal of change of season that is similar to the signal that mammals use to regulate seasonal changes in their behavior (Wehr et al. 2001). Other research genetically implicates the circadian clock in the pathophysiology of bipolar disorder (Yin et al. 2006).

I have suggested that circular bipolar disorder evolved among a small homogeneous population who lived in the northern temperate zone of the Old World during the ice ages. Bipolar

depressive behaviors include lethargy, social withdrawal, and loss of interest in food and sex. These behaviors conserved energy and reduced social conflict within small groups holed up together for the long, dark winter. Symptomatic cognitive impairment makes sense in this context: winter was a time to endure, not a time for thinking or action. During the short season of fair weather, the active, outgoing, goal-oriented behaviors of hypomania helped the group make up for lost time, accomplishing tasks necessary for survival. Hypomania is a positive mood and energy state associated with productive achievement, and bipolar disorder is correlated with intelligence and upper socioeconomic level (Goodwin & Jamison 1990), factors which Keller & Miller (K&M) failed to mention. In addition to the 1% of the population with severe symptoms, the authors' major focus, another 5% show milder forms of bipolar disorder with more positive associated behaviors (Jamison 2005).

Women in the ancestral bipolar disorder group may have had a reproductive advantage because a certain level of body fat is essential for ovulation, successful pregnancy, and breast-feeding. Reviews of the literature (Anastasi & Foley 1949; Eysenck 1947, 1953; Sherman 2001) agree with Kretschmer's (1970) early-twentieth-century observation of a relationship between circular bipolar disorder and a compact, pyknic build with cold-adapted fat accumulation (also see Eiben et al. 1980; Tóth et al. 2002). Women's activity level and eating behavior were adapted to their reproductive status, and eating heartily during fair weather to store fat for winter is mirrored in what is now called summer depression. Depression is at least twice as common among women, and recent data show that it may be more heritable among women (Kendler et al. 2006).

In contrast, mania, which is more frequent and intense among males, may have evolved as a response to emergencies. During mania, individuals have a superhuman ability to go without felt need for sleep or food. They think fast and move fast, which are characteristics that aid individual and group survival. Impulsive, frequent sexual activity is also common during mania, but the authors fail to consider the possible distortion of data because of children born out of wedlock. In any case, bipolar fitness is much higher than the level of fitness associated with schizophrenia.

Skepticism that circular bipolar disorder evolved as an adaptation is understandable when it is taken out of context and considered in its most extreme form. Psychosis is only sometimes associated with bipolar disorder, and the minority who experience a psychotic episode usually recover completely from the episode. In contrast, a schizophrenic diagnosis implies psychosis, and about one-third never recover. Another challenge to circular bipolar disorder as an adaptation is the current high rate of suicide associated with the diagnosis. However, the rate of suicide now may not be relevant to a time when individuals struggled merely to live and when social conditions were more favorable, in the sense that, because their behaviors were modal, individuals with bipolar disorder were not stigmatized, victimized, or forced to function at a high level during winter months.

The authors assert that bipolar disorder could not have evolved as an adaptation because it increases with negative factors, such as paternal age (no evidence cited), brain injury, and inbreeding. Adaptations, however, are necessarily positive only for the selective environmental pressures that produce their evolution. Although the authors discuss genes by environment interaction, they fail to explore adequately the concept in this case. Space constraints prevent further discussion of other problems with this argument.

K&M emphasize overlap among mental illnesses, but their argument that bipolar disorder is correlated with depression is moot. Many people with a diagnosis of major depression later have a hypomanic or manic episode and are then correctly reclassified. In regard to the genetic overlap of schizophrenia and psychosis associated with mania, the question is unresolved. The phenotypic behavior of the two states is similar, but correct differential diagnosis *is* crucial for the patient's effective treatment.

When asked why bipolar disorder genes survive in the gene pool, James Watson replied, "Survival might often depend on not if we think two and two is four, but on being slightly wild. . . . I think when we do science we see that a little madness does help, and you propose bizarre things which everyone says can't be true" (Jamison 2005, p. 275). Theory is meant to generate new ideas, and the theory I have proposed about the evolutionary origin of bipolar disorder generates many new ideas. For example: Could public health measures that promote timely exposure to more light lessen the incidence of depression in children and adults? Does exposure to bright light during nighttime destabilize the circadian clock and stimulate pathophysiology among those with bipolar disorder susceptibility alleles? Would daytime bright light and activity combined with nighttime dark and sleep help stabilize those with bipolar disorder?

Adaptationism and medicalization: The Scylla and Charybdis of Darwinian psychiatry

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Abstract: The target article shows that the application of the evolutionary theory to psychopathology should not necessarily consist in finding hidden adaptive benefits for each psychiatric syndrome. However, in rejecting lax adaptationism, Darwinian psychiatrists should not forget that the search for adaptive behavioral polymorphisms can be a powerful antidote against the normative attitude of mainstream psychiatry and its growing tendency to medicalize human diversity.

For evolutionary psychiatrists, the existence of psychopathology is perplexing. How can Darwin's theory of natural selection explain the persistence of psychopathology that places individuals at a reproductive disadvantage? In order to resolve the paradox of common and heritable mental disorders, most evolutionary psychiatrists have endorsed the adaptationist program. In evolutionary biology, the adaptationist program is a research strategy that seeks to identify adaptations and the specific selective forces that drove their evolution in past environments. Although everyone agrees that organisms have adaptations, adaptationism as a research strategy has not enjoyed consensual affection within evolutionary biology (Andrews et al. 2002). In the 1970s, it became the target of attacks by paleontologist Stephen Jay Gould and geneticist Richard Lewontin, who argued that adaptive explanations given for most human behavioral and cognitive traits were analogous to Rudyard Kipling's "just-so" stories. In effect, adaptive stories are easy to create and hard to falsify, and the risk of using inappropriate or insufficient standards of evidence for identifying adaptations and their functions is always present in the evolutionary study of human behavior. Such a risk is even higher in Darwinian psychiatry, where it is becoming more and more popular to pick a disorder out from current nosologies (which are of dubious validity) and to invent an adaptive explanation for its existence. Evolutionary psychiatrists have been certainly inventive in their search for a hidden genetic advantage to mental disorders. Genes for schizophrenia might have made certain individuals more charismatic and shamanistic. Distractible, risk-taking individuals who are currently diagnosed as having attention deficit/hyperactivity disorder (ADHD) might have had a competitive advantage in dangerous environments where survival would depend on being response ready. Anorexia nervosa might have evolved as a strategy for conserving reproductive resources in environments in which males are perceived as scarce and female competition for males is perceived to be intense. The unfortunate result of

such a proliferation of adaptationist hypotheses is that clinicians are skeptical of the validity and utility of Darwinian psychiatry and believe that the preferred activities of evolutionary psychiatrists are storytelling and the invention of outlandish explanations to elucidate the selection pressures that forged psychopathological traits (Dubrovsky 2002; McCrone 2003).

Keller & Miller (K&M) argue "against those evolutionary thinkers who assume that adaptive forces are the only possible explanations for common, heritable polymorphisms such as mental disorders" (sect. 8, para. 1) and suggest that the apparent evolutionary paradox of the existence of mental disorders can be resolved by recognizing the enormous mutational target size of human behaviors. K&M convincingly demonstrate that the application of the evolutionary theory to psychopathology should not necessarily consist in finding hidden adaptive benefits for each psychiatric syndrome. They should be commended because, in doing so, they avoid the risk of throwing out the baby with the bath water. K&M acknowledge that "the search for possible adaptive functions of mental disorder symptoms . . . is an important counterbalance to the prevailing assumption that subjective distress equals biological disorder" (sect. 8, para. 2). This is a crucial point because, if adaptationism is the Achilles' heel of Darwinian psychiatry, medicalization is the original sin of past and present psychiatry.

During the past two decades, psychiatric epidemiological studies have contributed a rapidly growing body of empirical knowledge on the prevalence data for mental disorders. Two large community surveys conducted in the United States – the National Institute of Mental Health Epidemiologic Catchment Area Program (ECA) and the National Comorbidity Survey (NCS) – showed overall 1-year mental and addictive disorder prevalence rates approaching 30% and lifetime rates approaching 50%. This means that, according to current diagnostic criteria, one out of every two persons will suffer from a mental disorder during his or her lifetime. These implausibly high prevalence rates have led to concerns about the validity of the current methods of psychiatric diagnosis and have reinvigorated the debate about the concept and definition of mental disorder (Troisi & McGuire 2002). According to many, the most basic problem with current criteria of psychiatric diagnosis is that they fail to distinguish mental disorders from "problems in living," that is, the vast array of problematic but nondisordered human conditions that reflect "the aches and pains of normal life" (Chodoff 2002, p. 627).

In psychiatry, the medicalization of the human condition is a long-standing problem. In the past, cultural prejudices and political aims were the major causes of the social construction of mental illness, as, for example, in the (in)famous case of drapetomania (the "mental disease" causing black slaves to run away) (Cohen 1981). In the last few years, the social construction of mental illness has partly been replaced by the corporate construction of psychiatric disorder. Pharmaceutical companies are actively involved in sponsoring the diagnostic definition of new diseases and promoting them to both prescribers and consumers (Moynihan et al. 2002). It seems that some new behavior is medicalized every day. The recent psychiatric literature has witnessed the conversion of sexual desire into an "addiction" complete with support groups, and excessive fear of social interaction into a mental disorder treatable with medication. One study (Laumann et al. 1999) has coined the term *female sexual dysfunction* to refer to sexual difficulties such as lack of desire for sex, anxiety about sexual performance, and problems with lubrication that are present in 43% of American women aged 18–59, even though leading sex researchers have argued that these difficulties may reflect healthy and functional responses in women faced with stress, fatigue, or threatening patterns of behavior from their partners (Bancroft 2002).

The necessity of avoiding medicalization of human behavior is not simply an intellectual exercise. The concept of disease acts not only to describe and explain, but also to enjoin to action. For this reason, labeling a psychological or behavioral condition as sick may have serious individual and social consequences. At the individual level, inappropriate medicalization carries the dangers of self-reproach, social stigma, inappropriate treatment decisions, and iatrogenic illness. At the social level, the resources invested in diagnosing and treating healthy people are likely to be diverted away from preventing and treating individuals with real diseases. Since a major contribution of evolutionary theory is the insight that individual differences are core biological features of any animal species, including *Homo sapiens*, the application of the concept of adaptive behavioral polymorphisms to psychopathology can be a powerful antidote against the normative attitude of mainstream psychiatry and its growing tendency to medicalize human diversity (Troisi 2005).

In Greek mythology, Scylla and Charybdis were two immortal and irresistible monsters who beset the narrow waters of the Strait of Messina, destroying ships as they attempted to navigate through. The two sides of the strait were within an arrow's range of each other, so close that sailors attempting to avoid Charybdis would pass too close to Scylla, and vice versa. The phrase *between Scylla and Charybdis* has come to mean being in a state where one is between two dangers and moving away from one will cause you to be in danger from the other. The Scylla and Charybdis of Darwinian psychiatry are adaptationism and medicalization. To be integrated into mainstream psychiatry without leaving behind its original contribution, Darwinian psychiatry will have to navigate through these equally misleading alternatives.

Population genetical musings on suicidal behavior as a common, harmful, heritable mental disorder[1]

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Abstract: Suicidal behavior is an interesting blank space in Keller & Miller's (K&M's) population genetical account on explaining the existence and persistence of common, harmful, heritable mental disorders. I argue that suicidal behavior is yet another of these disorders. It may well be consistent with all three evolutionary models considered by K&M.

First of all, I congratulate the authors, Keller & Miller (K&M), for their population genetical analysis, concerning the existence and persistence of common, harmful, heritable mental disorders; it is an outstanding contribution that without doubt will have a marked impact on the research fields addressed. One interesting omission (or avoidance) in the target article, however, is suicidal behavior. Only in their opening paragraph do the authors mention that "many people with schizophrenia kill themselves" (sect. 1, para. 1). Otherwise, the text is silent on this theme. This commentary addresses this blank space. In order to stimulate further inquiry along these lines, I briefly discuss whether suicidal behavior fits into the three population genetical scenarios evaluated by K&M for mental disorders in general. For simplicity, the focus is on completed suicide.

Is suicidal behavior a "common, harmful, heritable mental disorder," as defined by K&M? I think the answer is yes. Suicide is relatively common: Across many societies, it is the tenth-or-so leading cause of death (Mann 2003), with a lifetime mortality of around 0.5% in the general population (Bostwick & Pankratz 2000). Suicide is harmful: It ends the suicide victim's physical existence, as well as any chance for future reproductive success, and in most situations adversely impacts on the victim's

relatives. Risk factors for suicide are heritable: multiple lines of evidence – family, twin, and adoption studies (Baldessarini & Hennen 2004; Brent & Mann 2005); molecular genetical studies (Li & He 2006), supplemented by suggestive findings from geographical studies (Marušič 2005; Voracek & Formann 2004; Voracek et al. 2003) – converge to this conclusion (Bondy et al. 2006). And, finally, suicidal behavior may well be a distinct mental disorder: It is increasingly regarded as an independent, possibly dimensional, nosological entity (Leboyer et al. 2005). This emerging view is based mainly on genetic evidence that its transmission is noticeably independent of the transmission of the risk for mental disorders. Like these, suicides also run in families, but not necessarily in the same families; or, if so, they may take a different path through the pedigree (Brent & Mann 2005). Whereas alcohol-related, schizophrenia-spectrum, and mood disorders (particularly, depression) constitute major risk factors for suicide and frequently are ascertained among suicide cases, the vast majority (up to 80%–90%) of people affected by these disorders do not commit suicide (this is even valid for suicide attempt as a risk factor for subsequent suicide).

In what follows, I argue that the current suicidological knowledge appears consistent with all three evolutionary models considered by K&M, not just with the one they opine to be the most plausible (i.e., the mutational selection model). I commence with this one: polygenic mutation-selection balance. According to this model, among others, a multitude of susceptibility alleles for suicidal behavior should be expected, all of them having small effect sizes and many of them being population specific, thus resulting in slow gene-hunting progress, characterized by frequent replication failures. All of this is indeed true with respect to the search for genetic risk factors for suicide. No major "suicide genes" have been found, polymorphisms of suspected vulnerability genes account for small effects only and show population differences, and nonreplications are frequent in this area (Bondy et al. 2006). The serotonergic system has been strongly implicated in the neurobiology of both depression and suicide. Thus, past research has almost exclusively focused on this system's genetic bases (i.e., on the serotonin transporter gene, the genes for the various types of serotonin receptors, the monoamine oxidase A gene, and the two tryptophan hydroxylase genes). Because of this theoretically and clinically well-founded candidate-gene approach, genome scans have not been conducted in this area until quite recently, and the evidence from a first major genome scan (Cheng et al. 2006) was disenchanting: Several significant and suggestive linkage signals were found for suicidal behavior in a large pedigree sample of patients with bipolar disorder, but none of these linkage findings overlapped with any of the gene loci of the aforementioned serotonergic system constituents. This is expected under the polygenic mutation-selection balance scenario of mental disorders, and in this respect the evidence for genetic risk factors for suicide is consistent with this model.

What about the ancestral neutrality model of mental disorders? For several reasons, K&M do not give much credence, in general, to this model of neutral evolution of mental disorders. Their theoretical exception is that it could be a viable explanation for some mental disorders which show strong genotype-environment (G × E) interaction (as indicated through large cross-cultural variation in prevalence rates; recent historical changes in the rates, concurring with environmental changes; and mismatch of ancestral and modern environments). K&M mention depression as a possible candidate for this scenario. The aforementioned three characteristics also apply for patterns of suicide. More generally, it has been reasoned that G×E interaction might be common in psychopathology rather than rare (Moffitt et al. 2006). Suicide may be regarded as an analogue to late-onset disorders (i.e., the majority of suicides occur after the reproductive phase). Consequently, one sociobiological theory of suicide (de Catanzaro 1980, 1981) assumed that suicide frequently might not be highly maladaptive. Natural selection can act only on the residual reproductive potential. If this is low or nil, then there is little that natural selection can affect. Further, given the large increase in the average life span in modern environments, age-related expressions of vulnerability genes for suicidal behavior imply that they are now expressed under conditions different than those they were selected for in ancestral environments. The ancestral neutrality model might thus also have a role in explaining the persistence of suicidal behavior.

And what about the balancing-selection model? De Catanzaro (1980, 1981) noted the remarkable conformity of the social ecology of suicide to the pressures of natural selection (i.e., relations with sex, age, cohort, and fertility, and with group, health, and relationship status). He pointed out that many suicides tend to occur when the anticipated residual capacity to promote inclusive fitness is low and when staying alive could actually reduce an individual's inclusive fitness (particularly by being a burden to the kinship). This perspective of suicide appears consistent with the balancing-selection model; that is, the view that susceptibility alleles may sometimes increase (inclusive) fitness. Yet another variant of this model should also not be discounted, the logic of which unfolds as follows. Suicide is a biological anomaly: It is species general in humans, but absent in other species. It would therefore be surprising if certain higher cognitive traits, unique to humans, had no role in this unique behavior. It is difficult for natural selection to eliminate deleterious X-linked alleles (for which males are hemizygous) or antagonistically coevolved genes (Rice & Holland 1997). Early attempts to demonstrate X-linkage of intelligence (Lehrke 1997) have been met with skepticism, but it is now clear that the X chromosome harbors an excess of genes relevant for cognitive abilities (Zechner et al. 2001). Interestingly, two constituents of the serotonergic system (monoamine oxidase A receptor gene, Xp11.23; and serotonin receptor type 2C gene, Xq24) and the androgen receptor gene (Xq11–12) also reside on the X chromosome. Is this mere coincidence? Or could this imply that susceptibility alleles for suicide perhaps happened to coevolve with positively selected variants for higher cognitive abilities and with male-typed traits sensitive to testosterone? If true, this would throw new light on the robust sex difference seen in suicide prevalence (many more males than females commit suicide). I have not yet encountered this type of conjecture in the literature, but it is testable. Nineteenth-century suicide researchers were well aware of the link of higher education (a proxy for intelligence) and increased suicide risk (Morselli 1881). Using intelligence data or proxies thereof, this pattern has been replicated in recent geographical studies, both cross-nationally (Voracek 2004; 2005a) and intranationally (Voracek 2005b; 2006b; 2006d), as well as in cohort studies (Voracek 2006a; 2006c).

NOTE

1. This commentary was prepared in partial fulfillment of the author's D.M.Sc. degree requirements at the Medical University of Vienna.

High mental disorder rates are based on invalid measures: Questions about the claimed ubiquity of mutation-induced dysfunction

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Abstract: Three reservations about Keller & Miller's (K&M's) argument are explored: Serious validity problems afflict epidemiological criteria discriminating disorders from non-disorders, so high rates may be misleading. Normal variation need not be mild disorder, contrary to a

possible interpretation of K&M's article. And, rather than mutation-selection balance, true disorders may result from unselected combinations of normal variants over many loci.

Keller & Miller's (K&M's) impressive article will set a framework for future discussion of the genetics of mental disorders. Their discussion underscores the fruitfulness of understanding mental disorders as failures of evolved functions (Wakefield 1992; 2005). I consider three reservations about their argument.

Do current rates really reflect ancestral rates of true disorder? The first reservation concerns disorder rates. K&M's analysis is premised on relatively high rates of mental disorders; the higher the rates, the more puzzling it is that susceptibility alleles exist. However, rates may be much less than they seem.

The rates generally come from recent psychiatric epidemiological community studies (e.g., Kessler et al. 1994). Based on respondents' reports of experienced symptoms, these studies use symptom-based diagnostic criteria scored by computer to identify disorders. While such criteria are constructed to reflect clinically severe cases, the same symptoms may appear in individuals experiencing intense normal reactions to stress (Horwitz & Wakefield 2006; Narrow et al. 2002; Regier et al. 1998; Wakefield 1999b). This is potentially true even in severe categories; for example, hallucinated visits from a recently deceased spouse, common in many cultures and individuals, may be misclassified as schizophrenia; and reports of elation and irritability taken as indicative of mania may in community samples represent periods of normal elation or of irritability from marital squabbling.

The fact that rates of each disorder are small compared with non-disorder imposes brutal demands on specificity of measures to avoid false positives. Even a small error rate in recognizing non-disorders can yield enormous increases in apparent rates of disorder. For example, a true rate of 0.5% and perfect sensitivity in detecting disorders combined with an unusually high 95% specificity in recognizing non-disorders still yields an apparent rate of about 5.5%, a 1,000% increase over true prevalence. The same symptom-based methods are generally used internationally, so international comparisons suffer from related problems. Moreover, the threshold for a condition being harmful may move along the symptom continuum substantially as social circumstances change; for example, a schizotypic individual tending to isolation may have difficulty functioning in our society but in an Eskimo village could do well in the role of hunter, requiring weeks at a time alone away from the village (Wakefield 1994).

Symptom-based criteria also tend to confuse various kinds of mismatches between normal genetic makeup and current environments with true disorder, inflating rate estimates. For example, as the authors note, depressive responses were likely selected under conditions of high social support, and under such conditions episodes may have tended to terminate rapidly; but normal episode duration may be longer in current social environments lacking such support and thus be mistaken for disorders. Such mismatches could constitute a substantial percentage of depressive episodes (Horwitz & Wakefield 2005). Similarly, what today is classified as social phobia likely encompasses naturally selected fears now seen as inconvenient, given the mass-communicational demands of many occupations, so that formerly adaptive aversions to, say, speaking before large audiences, are now misclassified as disorders (Wakefield et al. 2005a, 2005b). To take a physical analogy, there may be genetic variation bearing on the efficiency of utilization of certain B vitamins, none of which were disadvantageous in a natural environment in which diets were rich in vitamins, but some of which yield vitamin-deficiency disease in vitamin-depleted modern diets; the deficiency is a disorder, and it has a heavy genetic-susceptibility component under current conditions, but if one puzzled about high rates of vitamin-deficiency susceptibility genes and speculated about mutation-selection balance, one would be barking up the wrong theoretical tree. Problems with inflated disorder rates pose challenges to behavioral geneticists in general, and to K&M in particular.

Normal variation or ubiquitous disorder? A second reservation concerns the understanding of normal variation. There is a possible direction of thinking about normal variation as also due to mutation-selection balance, toward which K&M might be interpreted as moving in comments near the end of their article. Even if they disavow this extension of their thinking, others may interpret their argument in this way. According to this view, we all suffer from multiple mutations that reduce our match to a species-typical Platonic ideal to which fixation has tended but which is not fully manifested because of many pesky mutations. This scenario seems to potentially reduce much normal variation to mild biological dysfunction (Wakefield 2005) and thus to disorder, a view that may be consistent with recent "positive psychiatry" claims that health is an ideal that is more than mere lack of overt disorder (Vaillant 2003).

There is hopefully a more pluralist alternative. Leaving aside the obvious possibility that trait levels confer equal fitness, consider that excellence within normal variation may reflect the fit between multiple components that have normal variants, none of which are exceptional in themselves. For example, Eclipse, a chestnut colt foaled during a total solar eclipse in 1764, is generally considered the greatest racehorse of all time. Autopsy results showed a large heart and lungs, but what leg structure enabled Eclipse to run so exceptionally fast? The answer, according to a recent computer-simulation analysis by members of the Structure and Motion Laboratory at the Royal Veterinary College based on Eclipse's preserved skeleton, is that Eclipse's various leg bones were all remarkably average and thus fit together in an optimally cohesive package (R. Weller, personal communication). Horses that are slower are not suffering from mutations but from a less striking confluence of normal variants over a large number of loci. Normal variation of mental traits may work like that: normal variants at multiple loci on which the trait is based (here we must accept the K&M "watershed" model) yield phenotype variation because of routine assortment.

Disorder as nonselected combinations of selected traits. Approaching normal variation from the above perspective suggests an analogous alternative to Keller and Miller's mutation-selection balance explanation for presumed high mental-disorder rates. For example, rather than the antisocial personality being frequency selected to fill an adaptive "cheater" niche or caused by accumulating mutational disadvantages at many loci, levels of conscientiousness, thrill seeking, and other personality dimensions may happen to converge in some individuals in a toxic combination of components, each of which is a normal variant. Together, these variants may add up to a phenotype that was not part of the range that yielded selection of the involved normal variants (Wakefield 1999a). Much pathology could be such normal-variant combinations falling outside the selected zone of multiple-loci combinations. Such a model is consistent with findings such as those of Eaves et al. (1990) that neither neuroticism nor extraversion alone had fitness implications, whereas combinations of specific levels of each did have differential fitness results.

Is this just a resurrection of the "non-additivity" alternative that K&M reject? To some extent, but their comments on non-additivity seem to me the most thinly supported within their argumentational juggernaut, leaving this perhaps a viable direction for exploration. Moreover, some balancing selection or other constraints may be at work at various levels of the genetic "watershed," *not* directly selecting for the disordered combination of traits but rather exerting selective force to keep the variations on individual traits (e.g., low conscientiousness,

high thrill seeking) in the population. Consideration of which such scenarios yield susceptibility alleles "invisible" to or ineliminable by natural selection seems a promising direction in which to look for viable alternatives to K&M's mutation-selection balance thesis for some disorders.

Multiple timescales of evolution

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Abstract: Keller & Miller's (K&M's) treatment of disorders usefully avoids diagnostic minutiae; but it needs more real-world constraints. Classifying processes by their evolutionary age helps to clarify both evolution and current function. Evolutionarily old, optimised, normative processes deserve special recognition, because they can be studied in animals and computers, and because they provide the machinery through which disorder-related polymorphisms act.

Introduction: Dimensions of the task. Keller & Miller (K&M) see evolution as a continuous series of mutations, competing for selection in a distant, rather abstract world. Other scholars focus on brain developments that were taking place at the moment in prehistory when a disorder became recognisable (e.g., Crow 1995b). Yet others reduce evolution to a "final cause" or purpose for each disorder (e.g., Jensen et al. 1997; McGuire et al. 1992).

These authors each address just one aspect of causation, and neglect the whole (see Killeen & Nash 2003; Pearl 2000). The causal networks underlying the appearance of a disorder in an individual at a particular point in time are more complex than any river (contrast K&M's Fig. 3 with Kendler et al. 2002, Ramus 2004, and Sonuga-Barke 2005).

Crucially, causes of normal function must be included *within* these causal networks, not in the "mutual" relationship K&M suggest. Addressing mental disorder without normal function is like practicing medicine without physiology (Nesse 1991; cf. Dayan & Williams 2006). Not only are many mental disorders "expressed through the structural medium of normal brain function" (David & Halligan 2000, p. 509), many are distortions of normal function. Normal functions such as learning (Moore 2004), language (Elman 2005), and walking upright (Gregory 1928) – as well as, doubtless, emotion and cognition – do not arrive along a tidy trajectory: they arise and change through many stages, and persist or fail for many interacting reasons; and many abnormal functions must be as complicated. K&M cut through this complexity, offering the long-accepted principles of polygenicity, mutation, and selection as the basis for all common mental disorders; but differences between disorders are the real issue, and linking evolution to the remarkable recent progress in psychiatric genetics requires considering genes not as abstractions but as having specific neural roles in bodies interacting with real environments.

K&M mention optimization in their first sentence, but do not consider its ramifications. A behavioural response that is optimal in one environment may be disastrous in another; and occasionally organisms need to make mistakes in order to see whether the optimum has changed (Williams & Taylor 2006). Such mistakes are a form of entropy, which K&M distrust, stating that "entropy erodes functional complexity" (sect. 1.3, para. 3), but entropy is also a prerequisite for genetic and social evolution (Williams 2005). Regulation of this entropy, a *meta-optimisation*, is seen in lower animals, which have sophisticated mechanisms "specifically to increase the rate of mutation in localized parts of the genome" (Metzgar & Wills 2000, p. 584) – as do humans (Chuang & Li 2004). Such careful regulation hardly merits the term "inevitable mutational load."

An organising heuristic. Some of these problems can be avoided by classifying brain processes by their approximate time of evolutionary appearance. Putting measurements into broad time bins is a standard heuristic for disentangling complex biological causation (Samoilov et al. 2001; Wen et al. 1998). Boxes in Figure 1 contain causes characterized by duration, but also correlated with prevalence, manipulability, study methods, and the level to which they have been subjected to mutation and selection (optimisation). The stacking of boxes indicates the accumulation of influences from bottom to top, with each layer grounded, like sediment, on the layer below it. Hence, mutations unique to an individual (f) generally exert their influence via long-evolved systems of which they are part (b and d).

The suggested categories are:

a. Universal experiences, available even to primitive animals. These include the clustering of signals in the environment, the reduction in signals from distant sources, gravity, and diurnal rhythm (Campbell 1974).

b. Normative neural processes (which K&M call "universal features of human nature"; sect. 5.1, para. 1) acquired due to category (a), such as primitive learning and regulation of exploration. Pragmatically, these deserve to be distinguished from K&M's abstract "inevitable mutational load" because they are highly conserved (Campbell 1974; McAdams & Pals 2006; Moore 2004) so can be studied in animals and can be presumed present in humans even if submerged or distorted; also they can be presumed to be largely optimised so predictions from optimised mathematical processes can be used to reverse engineer them (e.g., see Gadanho 2003; Montague et al. 1996).

c. Species-specific experiences, and common differences in experience, such as between hot and cold climates or wealth and poverty, or experience of social parasitism (discussed by K&M in sects. 5.6 and 5.8).

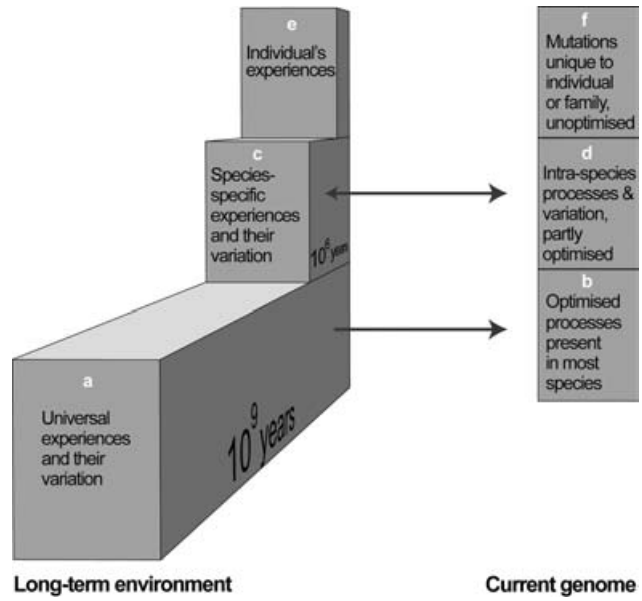

Figure 1 (Williams). Some broad categories of influences on an individual's current cognition and behaviour. Factors common to all mammals can be included in layers **a & b**. Additional layers could be added within layers **c & d** for nested groups such as primates or human subgroups. Adaptations within a lifetime have important effects on disorders (Sonuga-Barke 2005) and even on the genome (Hinton 1987), as do consecutive adaptations in an individual species (Richerson & Boyd 2004); these are excluded for simplicity.

d. Species-specific processes (e.g., language) and common intra-species genetic variations. Several factors control these, including non-harmfulness (discussed by K&M sects. 3.3, 4.3), environmental differences (c), and benefits of population diversity (Williams & Taylor 2006). Optimality is generally impossible to ascertain here, unlike (b).

e. An individual's experiences, both shared and unshared. These are biological, psychological, and social; K&M mention illicit drugs in section 4.4. As another example of the complexity of causation of disorder, anti–basal ganglia antibodies induced by *Streptococcus* are found in 50% of children in some clinics (Dale & Heyman 2002).

f. Each human contains about 175 new mutations (Nachman & Crowell 2000). Most of these are obviously not significant clinically, but the proportion of disorder attributable to them is a major unknown.

Normative processes (b) are a crucial tool in our teasing apart disorders into conceptually coherent components. Some instances of a disorder are fully appropriate to recent life events (i.e. determined by normative processes: e+b in Fig. 1). Others are the inevitable outcome of rare, functionally obvious, mutations, which must nonetheless act through normative processes (f+b). The majority are more complicated, and many of these appear to result from common polymorphisms superimposed on normative processes (e+d+b), summarised in the following paragraphs.

Depressive disorders. Conserving energy at non-propitious times is useful to animals (a&b), and to robots during exploration (Gadanho 2003). Such studies clarify the evolutionary origins of mood, clearly relevant to the evolution of mood *disorder* (see also Keller & Nesse 2005). So *learned helplessness* is a handle for studying the neuroscience of such normative responses that would produce much less interpretable results if applied to abnormal animals, or indeed to humans diagnosed with depression. Criticisms of such models as being unlike human disorder are factually correct but almost irrelevant to this process-based approach.

Adverse life events certainly contribute to depression, but the 31% of the population homozygous for long 5HTT-LPR appear to be protected from this effect (Caspi et al. 2003). This and the social importance of depression (e.g., its possible role in honest signalling; Watson & Andrews 2002) suggest modification in humans of the much longer-term mechanism (b).

Depression and anxiety are largely due to the same genetic factors (b&d), yet depression tends to follow loss events (e), whereas anxiety follows threat (Eley & Stevenson 2000; Kendler et al. 1987). This shows a limitation of K&M's confessed environment-light approach. Furthermore, a full account of depression clearly needs to describe why some people are genetically predisposed to encounter more adverse events than others.

Attention-deficit/hyperactivity disorder (ADHD). Punishment, threat, and reward regulate activity and attention in all organisms, as alluded to previously. Other control systems regulate our exposure to new information, via alertness, boredom, and attentional control (a&b). It appears that many of the deficits associated with ADHD can be attributed to aberrations of these normative control systems (Williams & Taylor 2004) or of the similarly ancient neural mechanisms of decision-making (Williams & Dayan 2005).

On the surface, ADHD is a family of genetically determined *deficiencies* with the fractions attributable to particular alleles (mainly dopaminergic to date) ranging from 8% to 20% (Daly et al. 1999; Faraone et al. 2001, 2005). However, there is evidence that one of its susceptibility genes is positively selected for (Ding et al. 2002) and it now seems likely that, despite disadvantages for the individual, ADHD conveys subtle benefits for the group (Williams & Taylor 2006). These include genetic *exploration* which is closely related to K&M's thesis, and group risk minimisation during behavioural exploration, which is not.

Schizophrenia. Despite this disorder being relatively rare, disabling, and characteristically human, its causation clearly involves long-evolved processes (b) including synaptic pruning, fear, emotion regulation, sensory filtering, causal attribution, and the increased focussing of attention when anxious (Cosmides & Tooby 1987; Luce et al. 1997).

Schizophrenia also involves recently evolved human characteristics (d) such as cerebral lateralisation and language (Crow 1995b). Similarly, cognitive dissonance probably contributes to delusional mood, delusions, and hallucinations (Brabban & Turkington 2002), but is less important in nonhumans (Armus 2001).

The *developmental instability* hypothesis (Yeo et al. 1999) suggests that schizophrenia and other neurodevelopmental disorders result from an individual's reduced ability to "buffer" developmental insults. The deficiency preferentially affects males, who have four times the nucleotide mutation rate (Nachman & Crowell 2000) and a similar excess of neurodevelopmental disorders. This sex difference is a key aspect of the evolution of mental disorder (see Williams & Taylor 2006) without which a model as abstract as K&M's appears impoverished.

Conclusion. Adding to previous examples, this *quantitatively* demonstrates that the multidimensional space of genetic possibilities is explored not indiscriminately, but by branching "tentacles" which incrementally, tentatively, and interactively reach up through the levels shown in Figure 1. In this metaphor, the two hypotheses dismissed by K&M probably describe *some* tentacular branchings. Their favoured hypothesis has few constraints beyond Watson and Crick's, and successfully places the octopus in a large bag. Now we need to get inside and study the octopus's normative processes.

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The evolution of evolutionary epidemiology: A defense of pluralistic epigenetic modes of transmission

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Abstract: First kudos, followed by some friendly badinage, and then renewed appreciation and a look ahead. This commentary is meant to clarify main arguments, redress incorrect attributions, and strengthen an excellent contribution that draws further attention to the importance of evolutionary epidemiology. Keller & Miller (K&M), despite significant errors, have done well to further systematize the evolutionary epidemiology of psychopathology.

The target article, which helps to reform evolutionary psychology, begins lucidly as Keller & Miller (K&M) re-emphasize three basic ways in which selection can operate on etiogenes associated with common, harmful, heritable mental disorders (MDs), for example, schizophrenia, bipolar disorder, phobias and mental retardation. The article later elegantly extends into a more robust evolutionary epidemiological framework, but then falters amid the murky mires of psychiatric genetics.

Still, the review is an impressive scholarly synthesis of many pertinent concepts and relevant information that, taken together, systematizes how to assess evolutionary epidemiology of major mental illnesses. It is a way forward as sufficient, necessary, and naturalistically valid data may accrue to really understand each epigenetic syndrome. But not only has nothing so much yet accrued, there are other problems.

Darwin saw valid taxonomy as absolutely essential to evolutionary cogency. Therefore, by way of first and strongest criticism, it must be said plainly that the main fulcrum of argument, "mental disorder," is a fallacious, intrinsically non-Linnaean pseudotaxon. This construct so broadly conflates distinct moieties – schizophrenia, depression, mania, diverse phobias, and even mental retardation – that it is ultimately without demonstrable naturalistic validity.

I, with others, have long held that the received diagnostic categories are often incompatible with genetic research, and I, with others, have urged more parsimonious nosology with better lumping of phenotypic equivalents. But this proffered straw man, "mental disorder," is – literally – chimerical and inadequate to the task. From this anheuristic notion, one simply cannot cobble together the diverse building blocks for any deep understanding of psychopathology in its wide remit. For example, most mental retardation is caused by chromosomal anomalies that have, strictly speaking, nothing to do with genetic mutation.

Similarly, the authors often over-argue to a preferred mechanism and, in so doing, misconstrue others' prior work. For instance, John Tooby and Leda Cosmides, as well as Linda Mealey, are incorrectly attributed to have believed that genetic variation in human psychology is the result only of neutral or balanced selection. Rather than the clumsy sweep wrongly ascribed to them, these researchers have noted this only with specific reference to a few traits of interest. No one (with the possible exception of Tim Crow and his "psychosis gene"; cf. Crow 1995a) has recently argued for a Mendelian single-locus model of schizophrenia, bipolar disorder, phobias, mental retardation, or much else.

My own work is likewise battered about on several occasions, and usually badly. For example, early on in the target article I, along with other psychiatrists interested in evolutionary explanations, am given the backhanded compliment that "clinicians more familiar with psychiatric hospitals, prisons, and detox centers were understandably skeptical . . . [of] Panglossian evolutionary ideas" of Darwinian psychiatrists (sect. 2, para. 2).

This would-be ad hominem is most amusing! I have spent my entire career in extremely active hospital care of persons suffering from psychoses, mania, depression, substance abuse, and nearly all else. Indeed, I have worked at the sharpest edges of hospital, public, and forensic psychiatry, having admitted in excess of 4,000 acute manics or psychotics at Harvard affiliated McLean Hospital (Belmont, MA) and later committed some 3,000 dangerous persons as medical director of Summit Behavioral Health Center in Cincinnati, the largest (and most poorly funded!) state hospital in Ohio.

So, too, Nesse, Price, McGuire, Gardner, Gilbert, Beahrs, Sherman, Pearce, Erickson, Sloman, Thompson, and others of Darwinian stripe are not naifish armchair psychiatrists befogged in Ivory Towers. Moreover, I, like most psychiatrists of Darwinian leaning, do not misunderstand selection-mutation nor espouse Panglossian adaptationism nor wallow in miscreance, as the authors so casually indict! Ah well, a side issue perhaps.

But no, as then again K&M totally invert my long-standing and oft-stated view that a great deal of, and perhaps most, psychopathology is the stochastic noise of mutation selection. Still later (sect. 5, para. 1), I am said to have implied that balanced selection is the only plausible explanation for prevalence of genes linked to common psychiatric disorders. I have only said that of highly prevalent quasi-Mendelian traits and meanwhile have always held that neutral evolution and mutation-selection balance presumably explain many other syndromes. Thereafter again, analogy is taken literally, as I am attributed to have stipulated that heterozygote advantage à la sickle cell is the sole mechanism that sustains epigenes for bipolar disorder (see sect. 5.4, para. 2). Oh dear!

Meanwhile, game theoretical analysis of clinical phenomenology is an important and valid corpus of evidence that the authors either dismiss or ignore, even though it is germane to resolving the possible paradox of common, harmful, heritable mental disorders. Perhaps it constitutes some of the "tortuous . . . frustratingly implausible" stuff referred to early on (sect. 1.1, para. 3). But game theoretical mathematics and the neuroethology of social rank and mood are not only the stuff of Nobel Prizes, they are also heuristics well beyond the capacity of the "mental disorder" construct to address with any fidelity or insight (Gardner & Price 1999). Oh dear, oh dear!

These broad-brush tarrings too often detract from K&M's otherwise elegant article. Though I cannot speak for others, these are strong misreadings of, if not liberties taken, with the main body of my work. This work has for some 20 years focused on the extended phenotypies of bipolar disorder as one of the rare psychiatric diagnoses that (1) approaches validity as a natural taxonomic unit; (2) plausibly transmits an adaptive endophenotype consistent with oligenic, kinship, and negative frequency-dependent selection; (3) clearly corresponds to social rank and stress biology phenotypies common to social mammals, including the limbic system and stress axis, especially in the anthropoid line; (4) is testable as specific game mathematical cost/benefit consequences of neuroethological variants in reptilian, paleomammalian, and neomammalian brain and behavioral repertoires; (5) entails a fascinating range of corollary traits of relevance to sexual selection and assortative mating, among many other ethological and sociobiological factors; and (6) may express more pathophenotypy amid the rampant mismatches and disruptive genomic reactivity of modern developmental environments.

The authors have done nothing to undermine this line of interpretation.

Yet all that is beyond the present scope, so then back to the other major flaws in the article beyond the untenable construct of "mental disorders." The further claim is made that these are mostly extreme points along axes of dimensional expression. This suggestion repeats a current fad among genomic researchers who, unable to easily replicate preliminary linkage studies, avow this failure can only mean traits in question are necessarily complex, polygenic, or even Gaussian in their distribution, and thereby without basis, presume these can only be extreme tips of normative dimensional traits.

Alternative interpretations are plausible and more accurate, although in the present state of genetic knowledge it must be plainly said that we simply do not know. Key issues such as mutation, fertility, homology, mismatch, and heterogeneity are almost entirely inferential. Indeed, the classical genetic studies of twins, adoptees, and families still inform more about several major psychiatric syndromes than does molecular work and these have long suggested prevalence about likely mutation rates (Wilson 1998).

Despite this absence of critical data there is also generally, and in the target article, an unfortunate tendency to terminologically assume what is not Mendelian is necessarily complex and dimensional. What of oligogenesis? What of endophenotypy? What of threshold trait expression? What of epistasis? What of the effects of major or even moderate genes admixed with a varying host of minor traits? What of the vast and uncharted realms of proteomic regulation? What of so much else?

Meanwhile, negative frequency-dependent selection is given short shrift even as it may sustain a number of human capacities, including several that are, in terms of possible genomic and sociocultural dynamics, akin to the bipolar extended phenotype, notably sociopathy (Mealey 1995), left-handedness (Brooks et al. 2004; Faurie & Raymond 2005), Tourette's (Pauls 2003), and homosexuality (Rahman 2005).

Negative frequency-dependent selection occurs in special situations such as in plant self-recognition, host–parasite relations, and mimetic species –in which a tasty butterfly has two alleles, each of which mimics a different poisonous butterfly. Here, rarity increases fitness. So, too, negative frequency-dependent

selection occurs in social competition (viz., what behavioral ecologists call pairwise contest and comparative ethologists call ritual agonistic encounter, that, by whatever name) clearly corresponds to clinical ego states of dominant or submissive mood, affect, and behavior. Choice of protagonist strategy depends on the strategy opted by the antagonist rival, and, in general, if there are two possible strategies, it pays to adopt the strategy not chosen by the rival. Handedness is a manifestation of this in the physical sphere – when fighting a right-hander, it can pay to be a left-hander.

As in the physical domain, so in the behavioral. The two main strategies are escalation (hawk) and de-escalation (dove). If the rival escalates, it may pay to de-escalate. Hence, agonistic social ranking is likely a key normative aspect of the endophenotype for bipolar disorder that is quite plausibly inherited as a negative frequency-dependent polymorphism (whatever the number of alleles!). The tendency to too readily over-escalate or de-escalate rises as novel developmental environs are encountered (i.e., mismatch). Yet the target article ignores such game mathematic analysis of frequency-dependent selection clinical phenomenology as well as its evolved social neurobiology consistent.

Perhaps most fundamentally unpersuasive is how the target article posits that there is (much less, that there must be) only one mechanism of genomic transmission for a wide variety of psychiatric syndromes – wrongly subsumed into a spurious category of "mental disorder." A glaringly obvious question, with an equally glaringly obvious answer, is: What do the phyloepigenetics of apples (e.g., mental retardation) have to do with oranges (e.g., mania)? This slap-dash Linnaeanism is a taxonomic house of cards.

Who presently can say that the clinical range of phobias derives from a single mechanism, much less that, depression, psychosis, or Tourette's – and all the rest in the panoply of psychopathology – necessarily spring from a single selective mode? As it is, improper taxonomics, notably poorly characterized endophenotypes, renders nearly all of psychiatric molecular genomics of little present help in understanding the epigenetics of major syndromes of psychopathology, much less their phylogeny.

It is entirely possible (and, as I have argued previously, likely) that a range of epigenetic mechanisms express diverse syndromes. It is also entirely possible (and, as I have also argued previously, most likely) that several major syndromes are composites of clinically homologous but genetically distinct variants. If there are variant strains of depressions or manias or psychoses, a few may well be Mendelian, others oligogenetic, still others major traits epistatically affected by a range of minor interacting genes, and yet others merely extremes of normal dimensions. Any such variation may explain much in the way of co-morbidity. It also would, and, as I have further mentioned previously, most surely continues to, play havoc with molecular linkage and related analyses.

The paradox – if it is paradoxical – of common, harmful, heritable mental disorders is not resolved. K&M's belief that nearly all psychopathology has a single mode of phylogeny – simple stochastic noise – is but one possible resolution. Does a whiff of over-enthusiastic, prematurely conclusory triumphalism detract? Time will tell. Meanwhile, despite a number of substantive limitations, the target article has many useful implications for psychology, psychiatry, and genetics, among other means to study human behavior. It is especially welcome for more clearly conceptualizing how future progress can be made in evolutionary epidemiological analyses of psychopathology.

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Authors' Response

An evolutionary framework for mental disorders: Integrating adaptationist and evolutionary genetic models

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Abstract: This response (a) integrates non-equilibrium evolutionary genetic models, such as coevolutionary arms-races and recent selective sweeps, into a framework for understanding common, harmful, heritable mental disorders; (b) discusses the forms of ancestral neutrality or balancing selection that may explain some portion of mental disorder risk; and (c) emphasizes that normally functioning psychological adaptations work against a backdrop of mutational and environmental noise.

R1. Introduction

We thank the authors of the 23 commentaries for their generous comments, valuable insights, and helpful suggestions. We are especially grateful to those contributors who expanded our framework in promising new directions. As a parallel to our target article, we organize our response to the comments according to the different types of evolutionary genetic explanations that can help make clear the central paradox of our target article: What explains the evolutionary persistence of susceptibility alleles that increase the risk of common, harmful mental disorders? The commentaries can be separated into those that suggested processes that did not receive enough attention in the target article (sect. R2), those that advocated neutral evolution or balancing selection mechanisms as viable alternatives to a mutation-selection model (sects. R3 and R4), those that called into question the evidence we marshaled in favor of mutation-selection explaining some portion of the mental disorder risk (sect. R5), and, finally, those that made specific new points or that pushed our thinking in new directions (sect. R6). As an antidote to our "whiff of over-enthusiastic, prematurely conclusory triumphalism" (**Wilson**), we also emphasize our omissions, errors, and confusions, where appropriate. By necessity, some good points made by individual commentators – especially those that we agreed with and therefore felt less impelled to respond to – must go unaddressed.

R1.1. The goal of our response

Our target article had two main goals. First, we wanted to promote more consilience among behavioral/psychiatric geneticists, evolutionary psychologists/Darwinian psychiatrists, and evolutionary geneticists. Second, we wanted to review the models that can explain the persistence of susceptibility alleles, understand the predictions

those models make, and review relevant empirical evidence. In writing the target article, we came to realize that the best-supported model, both theoretically and empirically, was a balance between individually rare, harmful mutations arising at the thousands of loci that must underlie complex human behaviors, and their eventual removal, due to natural selection. Although several commentators called into question the evidence supporting a role of mutation-selection in the genetic risk of mental disorders, we did not find these arguments particularly compelling or well supported by the data (sect. R5).

If mutation-selection explains some portion of susceptibility alleles for a given disorder, then this has a couple of important consequences. First, it means that no other single explanation (viruses, sexual conflict, heterozygote advantage, etc.) can be the *sole* explanation for that mental disorder. When we say in our response that some process is unlikely to be "a general resolution to the paradox," this is all we mean: that it appears insufficient for explaining *fully* the existence of a disorder's susceptibility alleles, not that the process is unlikely to explain a portion of that risk. Contra several commentators, our point has never been to argue that a single mechanism explained all mental disorders (sects. 4.4, 5.8, 7.6, 8, and R5.2). Second, as we argue in this response, we think that a mutation-selection explanation is mutually incompatible with only two evolutionary models of mental disorders: (a) that mental disorders are affected by only a few genes, or that they are byproducts of "genes that made us human" that have already fixated in the population (sect. R2.2), and (b) that mental disorders are themselves complex adaptations (sect. R4.1). Other than these two models, evidence for a mutational role in mental disorder risks is perfectly compatible with other types of evolutionary explanations, and with a general adaptationist perspective (R5.4).

A major point in our response is to argue for theoretical pluralism. This does not mean that we have to believe that each hypothesis has equal explanatory weight; the evidence should be allowed to clarify their relative importance. As we did in our target article, in our reply we try to generate discriminating empirical predictions for each type of process, and, when possible, we bring whatever data that we are aware of to bear on the question. Ultimately, the validity of these models is going to be quantitative, not qualitative. So, for example, 35% of the risk of some given mental disorder may stem from deleterious mutations, 20% from environmental insults, 15% from alleles in host-parasite conflict, 10% as a side-effect of balancing selection on other traits, and 8% as a side-effect of alleles sweeping to fixation or extinction (ignoring obvious complicating factors that certainly occur, such as interactions between these processes). For other disorders, such as those that have greatly increased in incidence since ancestral conditions (R3.2), the mix might be much different. Nevertheless, as things stand, we believe that current empirical evidence best supports a mutation-selection balance model for the types of serious, common mental disorders that we focused on in our target article (sect. 1.3). Time will tell whether the weight of current evidence reflects the true etiological mix.

R2. Evolutionary genetic processes that did not receive enough attention in the target article

In attempting to resolve the paradox of common, harmful, heritable mental disorders, our target article focused on neutral evolution, balancing selection, and mutation-selection balance, which are the three principal models used by evolutionary geneticists to explain genetic variation in nature. These models are useful for understanding gene frequencies that are roughly at equilibrium (stable and unchanging) in the population. **Gangestad & Yeo**, **Crespi**, and **McGrath** suggest two non-equilibrium models that may also be relevant to understanding genetic variation in mental disorder risk: antagonistic coevolutionary arms-races and recent selective sweeps. We agree that both models deserve more thorough discussion. As pointed out by Gangestad & Yeo, equilibrium and non-equilibrium evolutionary genetic processes are in no way mutually exclusive – both classes of processes must occur simultaneously. In this section, we consider the two non-equilibrium evolutionary genetic models in turn, although, for clarity of presentation, we distinguish two classes of coevolutionary arms-races: those that occur between hosts and parasites (R2.1.1) and those that occur between genes within the same species (R2.1.2).

R2.1. Antagonistic coevolutionary arms-races

R2.1.1. Antagonistic coevolutionary arms-races between hosts and parasites. Gangestad & Yeo and **Crespi** discuss situations where the human genome is not in evolutionary equilibrium because of ongoing coevolutionary arms-races between hosts and parasites. We also mentioned this mechanism as a possible candidate for explaining some mental disorder risk (sect. 5.8), although we are somewhat perplexed that we did not discuss its relevance in more detail, given our previous work on it (Cliff & Miller 2006; Miller 1997).

Although host–parasite coevolution can be powerful at maintaining genetic variation at loci concerned with antipathogen defense (Hull et al. 2001; Tooby 1982), such as the major histocompatibility complex (MHC) loci, we argued in the target article that it is unlikely to cause much maladaptive variation in psychological traits as a side-effect (sect. 5.8). This is because only a small minority of loci are directly involved in pathogen defense (Venter et al. 2001), and because natural selection should favor minimum overlap between the highly variable defense system loci (in which mutation and crossover rates may be adaptively higher; Metzgar & Wills 2000; Nachman 2002) and the tightly regulated loci that are involved more centrally in neurodevelopment. Indeed, as one might expect, most disorders that stem from defective genes in the defense system are related to failures of pathogen defenses – anomalies in immune response, pathogen susceptibilities, failures to distinguish between self and foreign antigens, allergies, and so forth (F. Vogel & Motulsky 1997) – rather than to neurological or behavioral disorders.

However, host–parasite coevolution might maintain behavioral genetic variation in more subtle, and interesting, ways than we discussed. How this might occur requires some explanation. The starting place is

appreciating that viruses, protozoa, bacteria, and other parasites can cause long-term dysfunction that might otherwise appear as congenital or developmental disorders (Cochran et al. 2000). The classic medical example concerns stomach ulcers, which used to be classified as maladaptive stress responses, but which turned out to be caused by infection by *Helicobacter pylori* (Marshall et al. 1988). Some human mental disorders may be similar, as in the hypotheses that the protozoan *Toxoplasma gondii* (Ledgerwood et al. 2003) and in utero viral infections (Brown & Susser 2002) increase schizophrenia risk. As noted by **McGrath** and **Nettle**, this evidence is perfectly consistent with a model whereby neurodevelopmental disruptions from many different sources, including mutations, cause schizophrenia (see also Gangestad & Yeo 1997).

The dysfunction wreaked by parasites may not simply be an unfortunate by-product; parasites might actively manipulate hosts to produce apparently bizarre behavior for their own benefit. For example, rabies makes dogs enraged so they bite more often, which spreads the rabies virus through saliva; the rage is harmful to the dog but adaptive to the virus (Klein 2003). Similarly, sexually transmitted parasites in humans might provoke promiscuity (Cochran et al. 2000), and contact-transmitted parasites might provoke not only sneezing and coughing, but also behavioral changes such as poor hygiene or indiscriminate social contact. If one is blind to these conflicts between hosts and parasites, one can easily mischaracterize a parasite's adaptation as a host's maladaptation. These specific ideas may be right or wrong, but parasite-manipulation explanations deserve more attention in Darwinian psychiatry.

Are such host–parasite coevolutionary models relevant to the central paradox of our target article? As already noted, parasites appear to have a modest effect on the risk of schizophrenia (and perhaps other mental disorders), but this risk could come from two different kinds of processes. First, if population differences in the risk of initial infection and/or subsequent suffering from it are *not* highly heritable, then parasite infections would be additive factors that increase schizophrenia risk, pushing already at-risk (e.g., high mutation load) individuals over the edge. Some people might describe this as a gene-by-environment (G–E) interaction, but it really is not, because the environmental agent (the parasite) merely *adds* risk to whatever genetic and environmental risk an individual already has. This mechanism is not a resolution to the paradox because an individual's genetic risk (e.g., mutation load) still requires an explanation, which could come from any of the evolutionary genetic models we have reviewed.

The second process, however, can provide an alternative explanation for the persistence of susceptibility alleles. If differences in the risk of being infected and/or suffering from infections *are* highly heritable, then parasite infections and susceptibility alleles would be interactive factors increasing schizophrenia risk. In this case, individuals unlucky enough both to be infected and to have the predisposing alleles would be at higher risk of developing schizophrenia. Individuals carrying the predisposing alleles would also pass these "susceptibility alleles" on to their offspring. This is a plausible G–E interaction scenario: Susceptibility alleles are maladaptive only (or mostly) in environments where the parasites are endemic. This process can also explain the high heritability of mental disorders, because alleles that are adaptive at one time point become maladaptive later, as the parasite evolves new ways to circumvent old defenses. Under this scenario, susceptibility alleles can be at high frequencies, similar to alleles governed by balancing selection (indeed, host–parasite coevolution is often considered a type of balancing selection).

What types of evidence would support this latter possibility as an important explanation for the evolutionary persistence of schizophrenia susceptibility alleles? First, this type of process predicts not only interaction effects on schizophrenia risk, but also main effects both for parasite infections and for alleles that cause susceptibility to those infections. While the infection-schizophrenia link is quite strong (Sullivan 2005), there is little evidence for genes of major effect in schizophrenia, as described in the target article (sects. 7.6 and R2.3). This is not necessarily damning evidence because it might indicate that such G–E interactions are only partial explanations, but it weighs more strongly in favor of the additive than the interactive hypothesis. Second, we should also expect that likely schizophrenia susceptibility alleles will tend to cluster in genome regions associated with pathogen defense, but we are aware of no reliable supporting evidence (Sullivan 2005; Wright et al. 2001). Thus, for the moment, we find the hypothesis that parasite infection is one of many additive risk factors in schizophrenia most compelling, while acknowledging that interactions between parasites and host's genes could also play some as yet to be determined role.

R2.1.2. Antagonistic coevolutionary arms-races between genes within the same species. Coevolutionary arms-races can occur anytime genes have conflicting goals, both between and within species. **Gangestad & Yeo** and **Crespi** argue that antagonistic coevolution between genes within the same species might help explain some portion of mental disorder risk. Although it can take several forms (between siblings, between sexes, etc.), here we focus on antagonistic coevolution between maternal and paternal genes within an offspring (Gangestad 2003; Rice & Holland 1997). The optimal amount of maternal investment from the perspective of paternal genes is higher than the optimal amount from the perspective of maternal genes. This is because each maternal gene is guaranteed to have a 50% chance of being represented in the mother's future offspring, whereas paternal genes have less than a 50% chance of being represented in her future offspring (because she might mate with a different male).

The fact that the effects of genes can depend on whether they were inherited from the mother or the father, called *genetic imprinting*, sets up the means by which differences in optimal strategies between maternal and paternal genes can turn into coevolutionary arms-races. For example, paternally expressed genes might cause infants to take a bit more milk than they did before, which would provoke a counter-response in maternally expressed genes, causing infants to take a bit less. Never mind that neither side is likely to get ahead for long in such a race – evolution is blind to the future – what matters is that evolution can grotesquely exaggerate

what initially began as a relatively minor difference. As a real-world example, female mice that lack a paternally expressed gene called *Peg3* make poor mothers, investing little effort in their pups (Li et al. 1999).

Genetic imprinting may play a role in human mental disorders. Badcock and Crespi (2006) suggested that the "extreme male brain" of autistics is caused by a disrupted balance between male and female expressed genes. This fascinating hypothesis could very well explain much about autism, but a central question remains: Why have autism susceptibility alleles (alleles that alter the balance between imprinted genes) persisted in the population? We discuss two possibilities. Mutation-selection is a potential explanation for this, given the data we reviewed in our target article that these disorders are associated with mutation loads (sect. 7). Because mutation-selection maintains substantial variation only in polygenic phenotypes, this hypothesis requires that many genes are imprinted and/or regulate imprinted genes.

Gangestad & Yeo provide an alternative possibility: Alleles that were adapted to a previous counter-adaptation become maladaptive in the context of a newer counter-adaptation. At any given time, some portion of alleles should be increasing or decreasing in the population, driven by a futile, but nevertheless consequential, arms-race between maternal and paternal genes. Such constant flux would maintain some level of maladaptive genetic variation in the population (Gangestad 2003; Gangestad & Yeo 1997). In section R2.3, we review some predictions and evidence that might help distinguish between these mechanisms.

R2.2. Recent selective sweeps

Alleles can be increasing or decreasing in the population for any number of reasons, not just due to coevolutionary arms races. **Crespi** (see also **McGrath**) suggests that mental disorders may be, in part, harmful side-effects of such alleles that have positive or negative net fitness effects. Of course, it is important to point out that such alleles cannot have fixated or gone extinct; otherwise, no genetic variation would result. Human molecular genetics is revealing several examples of recent selective sweeps (Cochran et al., in press; Evans et al. 2005), and it is possible that such alleles affect mental disorder risk.

As **Crespi** acknowledges, "strong selection leads to maladaptive, more or less transient by-products." The question is, how transient is transient? In our view, selective sweeps seem most relevant to explaining population-specific concentrations of disorders that reflect alleles no more than a thousand generations (20,000 years) old (e.g., Cochran et al., in press). Such a time frame would be consistent with **McGrath's** comment: Relative to the other models (with the exception of G–E interactions), recent selective sweeps predict variation in prevalence rates between populations. Selective sweeps that began further back in time would be increasingly unlikely to result in polymorphisms today, because even minor fitness effects drive alleles to fixation or extinction over such time periods (target article, sect. 4.3). Therefore, we are highly skeptical of the psychiatric relevance of selective sweeps that occurred before humans split into several lineages, such as those concerning the evolution of schizophrenia, as proposed by T. J. Crow (2000), Horrobin (2002), or Burns (2004). These earlier selective sweeps, which ostensibly began before the human lineage split (50,000–200,000 ago), could have had two effects (see also sect. 5.1 of the target article). First, they could have brought the susceptibility allele to fixation or extinction – hence, no genetic variation. Second, the susceptibility allele could have been hitchhiking nearby an adaptive allele but become unlinked in the course of evolution, in which case the time clock begins when the alleles became unlinked. Again, if this was much longer than a thousand generations ago, no genetic variation would result. Until someone can offer a reasonable explanation of why 100,000-year-old susceptibility alleles under directional selection are still polymorphic, such "genes that make us human" hypotheses cannot be considered viable explanations for the genetic variation in risk of any mental disorder (Keller 2005).

R2.3. Predictions of non-equilibrium processes

Each of the non-equilibrium models require that previously adaptive alleles that are now sweeping toward extinction (or currently adaptive alleles sweeping toward fixation) have side-effects that increase mental disorder risk. Given that, at some point in their evolution, these alleles were an adaptive part of a genome that made a fully functioning individual, it is not clear why this would often be the case, but it is certainly possible. We need empirical predictions that can discriminate between equilibrium and non-equilibrium evolutionary processes.

Perhaps the strongest prediction, common to all of the non-equilibrium evolutionary genetic processes that we have reviewed, is that susceptibility alleles could be at any frequency at a given time within a population. This is similar to the prediction of high-frequency alleles governed by balancing selection, but at a molecular genetic level, the two processes can be distinguished (Bamshad & Wooding 2003). Non-equilibrium processes can be even more easily distinguished from a mutation-selection balance. Although both might yield predictions that are similar (the possibility of population-specific susceptibility alleles), other predictions are quite different (alleles sweeping to fixation/extinction could be at much higher frequencies than harmful mutations would reach, and the sweeping alleles would not cause any of the indicators of mutation load reviewed in sect. 7). Because they are more likely to be common, we should expect that alleles governed by non-equilibrium processes will be relatively easy to find in gene-mapping studies, although, to date, there is little evidence that genes of major effect exist for any of the common mental disorders that are the focus of our target article. This may simply mean that such alleles have minor effects, or that they are population specific. Moreover, some common susceptibility alleles of importance may yet emerge, and **Gangestad & Yeo's** observation that imprinted genes appear over-represented among possible susceptibility alleles is provocative.

Of course, as **Crespi** notes, the most direct evidence in favor of a selective-sweep hypothesis of mental disorder alleles would come from (a) finding alleles that are reliably associated with mental disorders, and (b) demonstrating that these alleles have been under directional selection. **Crespi** cites 20 papers covering 12 different genes in defense of his assertion that bipolar disorder and

schizophrenia susceptibility alleles have been under positive selection in the human genome. Eleven of these citations purport to show that certain of these alleles have been under positive selection, whereas the rest are primary research publications showing various levels of support for associations between these alleles and schizophrenia or bipolar disorder. However, if the last 15 years of gene-mapping studies have taught us anything, it should be that conclusions based on a handful of association or linkage findings in primary research are nearly worthless. The chances of Type I errors (the associations are not real) and Type II errors (many associations were missed because of small effect sizes) in individual findings from primary research are almost certain (Sullivan 2005).

Meta-analyses are not free from problems either, but they are preferable to primary research. We conducted a *PubMed* search on each of the 12 genes listed by **Crespi** by using keywords "meta-analysis," the name of the gene in question, and "schizophrenia" or "bipolar." If multiple meta-analyses were found, we report the most recent. We found no meta-analyses for seven of the genes (APOL1, FOXP-2, GRM3, HOPA, IMPA2, MAOB, and SYNJ1), indicating that not enough research had been accumulated about them to warrant one. The results of three meta-analyses were negative (for the schizophrenia links with APOE [Xu et al. 2006] and with DRD4 [Glatt et al. 2003] and the bipolar link with DRD4 [Lopez Leon et al. 2005]) and three were positive (for the schizophrenia links with SLC6A4 [Cho et al. 2005] and NRG1 [Li et al. 2006] and for the bipolar link with MAOA [Preisig et al. 2005]). The effect sizes for the positive findings were quite small (odds-ratios less than 1.25), about the sizes discussed in our target article (sect. 7.6). These studies do not provide persuasive evidence that these genes, individually or together, explain much of the population risk in bipolar disorder or schizophrenia. Nevertheless, meta-analyses are typically conducted by averaging results that come from different evolutionary lineages, and it is possible that these genes increase mental disorder risk in only certain populations, depending upon different genetic or environmental backgrounds.

R3. Responses to arguments favoring neutral explanations for mental disorders

R3.1. Are mental disorders beneficial?

Gernsbacher, Dawson, & Mottron [**Gernsbacher et al.**] persuasively argue that autism confers specific cognitive benefits in certain individuals. However, from an evolutionary genetic perspective, fitness effects of mental disorder must be defined in terms of evolutionarily relevant benefits or costs to oneself and ones' relatives (inclusive fitness), not just advantages in certain domains of modern-day functioning (see also sect. R4.2). In fact, most people with autism have extreme difficulty attracting and retaining sexual partners, so autism is likely to be *evolutionarily* harmful. Of course, whether or not a mental disorder (or any other trait) is evolutionarily maladaptive says nothing about whether that trait should be considered "wrong" or "maladaptive," in the way that the words are used (interchangeably) in everyday parlance. Adoption of genetically unrelated offspring may decrease inclusive fitness, but we hope no one concludes from this that adoption is wrong!

R3.2. Does the possibility of gene-by-environment (G–E) interactions suggest that mental disorders were benign or extremely rare in ancestral environments?

Mayo & Leach, **Polimeni**, and **Wakefield** rightly point out that the paradox of our target article depends on harmful fitness effects and high prevalence rates of mental disorders in the ancestral past, a point we also made in the article (sects. 3.3 and 4). We argued that the likely ancestral fitness costs of particular disorders could be inferred to some degree from the current dysfunctions they impose, and the current social and sexual stigmatization they evoke. If mental disorders existed in the past as they do today, then at some level of abnormality, they almost certainly lowered ancestral fitness. Of course, they may not have existed in the past as they do now. Mayo & Leach critique an argument, attributed to us, that large G–E interactions were implausible (sect 4.2), and point out that such interactions have been observed, for example, in diabetes and possibly in depression. However, we should point out that we have never doubted that large G–E interactions were possible, but only that strict neutrality, whereby maladaptive alleles today were completely neutral ancestrally, was implausible. Nevertheless, Mayo & Leach's point is perfectly valid: large G–E interactions cannot be ruled out a priori.

Strictly speaking, therefore, the central paradox of the target article may not exist, but is this likely? The short answer is no. We very much doubt **Polimeni's** suggestion, echoing Michel Foucault, that mental disorders may have been socially unimportant before the eighteenth century. It would be incredible if people living in ancestral environments were all intelligent, emotionally stable, cheerful, and sane – in other words, free from mental disorders – just as it would be incredible if they were all healthy and attractive. Given that this was not the case, scientists need good, testable hypotheses for *why* heritable traits subjected to continual natural selection nevertheless can be maladaptive.

Furthermore, writings from ancient sources up through the Middle Ages describe symptoms consistent with modern diagnoses of schizophrenia, mental retardation, depression, bipolar disorder, and anxiety disorders (Draguns 1982; Jeste et al. 1985; Willerman & Cohen 1990). In modern times, schizophrenia has been found in investigations of 46 different countries, including underdeveloped, emerging, and developed countries (Saha et al. 2005). We did not discuss the historical evidence in our target article because the evidence is contestable, suffering from obvious methodological shortcomings, but taken together with modern prevalence estimates, it casts further doubt on suggestions that mental disorders are purely modern phenomena.

In our target article, we argued that G–E interactions can be inferred from highly variable mental disorder prevalence rates over time or location (e.g., 1% versus 20%), plausible interacting environmental agents, and the possibility of very high prevalence rates. Some mental disorders, especially depression, follow these patterns, but the most serious mental disorders – mental

retardation, schizophrenia, and bipolar disorder – do not, or do to a much lesser degree. Here, we offer one additional empirical statistic that might help weigh whether G–E interactions explain high prevalence rates of a given mental disorder: its *minimum* prevalence rate across cultures. The minimum rate suggests how low its rate could have been in ancestral environments, barring the unlikely event that all cultures worldwide have already gone through the same relevant environmental shifts. If reliable estimates of the minimum rate across cultures approach zero, then ancestral neutrality of susceptibility alleles is a plausible hypothesis. However, so long as the cross-cultural minimum is non-negligible (>50 per hundred thousand), its prevalence requires an explanation.

Finally, commentators who advocated ancestral neutrality and strong G–E interactions failed to grapple with some of our key theoretical and empirical objections to this explanation. For example, ancestral neutrality predicts that any prevalence rates, from 0% to 100% across mental disorders, should be observed, rather than those (<5%) typically observed (sect. 4.3). Perhaps most importantly, evidence that inbreeding increases mental disorder risk is seriously damaging to explanations that disorders were ancestrally neutral or adaptive, because the direction in which traits move following inbreeding clarifies the direction of low fitness in *ancestral* environments (contra **Sherman**, who thinks that inbreeding provides information on modern fitness effects).

For these reasons, we do not think that widespread and large G–E interactions can fully explain the high prevalence rates of some of the most serious mental disorders, but we do think it is a plausible model for some of them (sect. 4.4). What are severely needed, but lacking, are good data on the prevalence rates of mental disorders from traditional societies, whose lifestyles are probably more representative of ancestral conditions. We think that one of the highest priorities for Darwinian psychiatry should be to enlist the help of anthropology collaborators to carry out such research.

R4. Responses to arguments favoring balancing selection explanations for mental disorders

Not surprisingly, many of the commentators most critical of our target article were those who have invested the most in balancing selection arguments (**Klimkeit & Bradshaw**, **Polimeni**, **Preti & Miotto**, **Price**, **Sherman**, **Wilson**), which posit overt or hidden adaptive benefits to certain mental disorders or their susceptibility alleles. Other commentators developed more nuanced arguments that balancing selection plays a larger role than we suggested (e.g., **Allen & Badcock**, **Easton**, **Schipper, & Shackelford** [**Easton et al.**], **Crespi**). In this section, we respond to commentators who argued for the viability of balancing selection explanations.

R4.1. Are mental disorders complex adaptations?

We welcome several commentators' efforts to question whether particular mental disorders are truly harmful (**Gernsbacher et al.**, **Easton et al.**, **Klimkeit & Bradshaw**, **Polimeni**). As we stated, such questioning is an important counterbalance to the prevailing assumption that all mental disorders are dysfunctional. Indeed, the authors themselves have proposed adaptive functions for states considered disorders in mainstream psychiatry – depressive symptoms in response to losses or threats (Keller & Nesse 2006), and female vaginismus or anorgasmia in response to low-quality sexual partners (Jenkins & Miller 2005; Miller 2005). Natural selection should optimize facultative (environmentally responsive) adaptations which are reliably triggered in all humans in certain situations. However, the identification of adaptive benefits for a putative disorder does not imply that balancing selection maintains the alleles that cause the *genetic variation* of that disorder (see also sects. 1.2 and R4.2).

As **Troisi** points out, adaptationist hypotheses are easy to create but hard to falsify, although this problem is not unique to adaptationist hypotheses (Andrews et al. 2002). Researchers forwarding hypotheses that mental disorders are adaptive should be eager to find empirical avenues that would help falsify their favored hypotheses. We identified several such avenues in our original target article. Here, we offer another.

Hypotheses that mental disorders are themselves complex adaptations, maintained by balancing selection (**Polimeni**, **Price**, **Sherman**), are some of the only evolutionary hypotheses of mental disorders that are *not* consistent with any degree of mutation-selection explaining susceptibility alleles. This is because it is absurdly improbable that mutations (and other developmental insults) would lead to full-fledged, complex adaptations by chance. No commentator has rebutted this point. We believe that we have made a compelling case that mutations are responsible for at least some, and we think much, of the genetic variation in mental disorder risk (sects. 7 and R5.7). Such evidence is devastating to hypotheses positing that bipolar disorder, schizophrenia, autism, and the like, are themselves complex adaptations.

R4.2. Are demonstrations of benefits among those with mental disorders or their relatives (e.g., creativity) sufficient evidence for balancing selection?

Crespi, **Klimkeit & Bradshaw**, and **Nettle** point out that the empirical evidence of links between creativity–schizotypy and creativity–bipolar disorder are actually quite robust. We cede the point – there appears to be a stronger mental disorder–creativity link than we acknowledged – but we disagree that this, or any other supposed benefit of mental disorders, constitutes sufficient evidence for balancing selection. If nothing else, we hope that our target article highlights the additional types of evidence required to make a case for various types of evolutionary explanations of genetic polymorphisms. An argument for balancing selection also entails: (a) explaining why the net fitness effect of the susceptibility allele is equal to the fitness effect of the non-susceptibility allele; (b) explaining why one of these alleles doesn't fixate by chance (which probably entails explaining how its fitness depends on its frequency); and, critically, (c) presenting data that support predictions from balancing selection hypotheses.

Our point is that simply positing a putative benefit of a mental disorder is not at all convincing evidence that the mental disorder is maintained by natural selection.

Creativity may be one advantage (among many disadvantages) of bipolar or schizophrenia susceptibility alleles. However, genes typically have many effects (pleiotropy). Mutations or the disorders they cause that have a net fitness-reducing effect nevertheless may have apparently beneficial effects in particular domains. For example, those with Down syndrome have high self-esteem (Glenn & Cunningham 2001) and are described as being cheerful, happy, and helpful (Meyers & Pueschel 1991). If true, would this imply that Down syndrome has been maintained by balancing selection? Likewise, a congenital inability to feel pain could yield such benefits as higher bravery and risk seeking, but its net effect on fitness is certainly negative because it usually results in early death (Sternbach 1963). If one looks hard enough, positive side-effects could be posited or demonstrated for practically any disorder. Depression saves energy in the winter, whereas mania boosts it in the spring (**Sherman**); schizophrenia alleles increase creativity in relatives (**Crespi**), or lead to group dispersal (**Price**), or increase the chance that one becomes a shaman (**Polimeni**), and so forth.

However, the question is *not* whether susceptibility alleles for bipolar disorder, autism, and schizophrenia – or for a congenital inability to feel pain, or for Down syndrome for that matter – have positive effects in particular life domains. The question is whether the net fitness effects of these susceptibility alleles, summed across all relevant life domains and across all possible genomes that they might find themselves in, are positive, negative, or (as required by balancing selection) exactly zero. It seems likely to us that the benefits of increased creativity do not compensate for the increased risk of mental disorders, especially given that there are probably many ways to be creative without having an increased risk of mental disorders. Of course, this is a plausibility argument, as are the arguments by commentators who suggested that the mental disorder–creativity link was evidence of balancing selection. What predictions distinguish these possibilities?

Balancing selection arguments typically imply strong, discriminating predictions at the genetic level, which their advocates failed to discuss. A whole host of evolutionary genetic models predict that balancing selection maintains just a few polymorphic loci (though see sect. 7.6 of the target article) harboring a few (usually just two) common alleles at each locus (Barton & Keightley 2002; Mani et al. 1990; Roff 1997). (Contra **Wilson**, the number of common alleles *does* matter, and provides evidence as to which evolutionary processes explain them.) Such alleles should be easy to find by using current gene-hunting methods, and continued lack of progress in finding them would augur poorly for such a hypothesis (sect. R5.8). The strong evidence (sects. 7 and R5.7) that harmful mutations play at least some role (and probably an important one) in mental disorder risk also casts doubt on balancing selection being a general resolution to the paradox.

How, then, is one to reconcile evidence of the mental disorder–creativity link in light of evidence that mutations play an important etiological role? One obvious answer is that no reconciliation is necessary; as we just described, not every facet of a disorder need be negative for its net effect to be negative. An alternative explanation is provided by **Nettle**. The normal range of creativity may be nearly neutral (or under balancing selection). Most of the genetic risk of mental disorders comes from harmful mutations. High creativity has negative effects on fitness when coupled with a high mutation background because it increases the risk of mental disorders, but it has positive effects when in a low mutation background. Similarly, creativity could be a sexually selected signal, designed to partially reveal one's mutation load: only those with a low mutation load can afford the cost of being creative. By this view, mental disorders are the result of being too creative in the context of a high mutation load (Shaner et al. 2004). In neither scenario are mental disorders directly maintained by balancing selection, and they each demonstrate how mutation explanations can be consistent with certain forms of balancing selection or neutral evolution acting on other traits. Of course, such explanations also must explain the variation in creativity or in mismatches, and both must make empirically tractable predictions before being accepted.

R4.3. Does increased fertility in relatives of those with mental disorders indicate heterozygote advantage?

Crespi and **Polimeni** both say that there is good evidence for heterozygote advantage in mental disorders. Because Polimeni provides no support for this, we will focus on Crespi's claim, which argues that we were too quick to dismiss three previous "positive" studies (Avila et al. 2001; Fananás & Bertranpetit 1995; Srinivasan & Padmavati 1997) that found higher reproductive success in first-degree relatives of schizophrenics in favor of a single study (Haukka et al. 2003) that did not. We want to make four points regarding these studies and their implications. First, several other studies have also failed to find an increase in reproductive success among first-degree relatives of schizophrenics (Bassett et al. 1996; Buck et al. 1975; Rimmer & Jacobsen 1976; H. P. Vogel 1979). Second, the Haukka et al. (2003) study is important not only because it was so much larger than previous ones (11,000 schizophrenics versus fewer than 200 in previous studies), but, more importantly, because it was the best controlled of all the studies. The three previous "positive" studies ascertained schizophrenic patients from psychiatric research hospitals, and (for example) the types of families that admit their relatives to psychiatric research hospitals might not be representative of the families of all schizophrenics. The Haukka et al. (2003) study, on the other hand, was conducted on hospitalization data from every individual born in Finland from 1950 to 1959, and thus the chance of unforeseen biases (e.g., the types of patients ascertained) was negligible. Third, modern fertility has an unknown relationship to ancestral fertility (sects. 3.3, 4, and 7.1). More persuasive evidence for heterozygote advantage would come from data showing some type of credible benefits among unaffected relatives, such as creativity, but such evidence would be only one piece of the puzzle (sect. R4.2).

Last, and echoing our remonstrations from section R4.2, higher reproductive success in relatives – or any other putative benefits among them – is *not* itself evidence for heterozygote advantage; it is merely one explanation consistent with such a hypothesis. So, too, would **Nettle**'s or Shaner et al.'s (2004) hypotheses provide an explanation for such findings. We need discriminating predictions

based on evolutionary genetic theory, not just a collection of interesting findings that can be cobbled together to form a plausible story. For example, heterozygote advantage predicts very high dominance variation in particular (Falconer & Mackay 1996), in addition to high non-additive genetic variation in general. Do we see this for schizophrenia, or for bipolar disorder for that matter? If the genetic variation in these disorders is due to dominance variation, parent and offspring risk ratios should be quite low, whereas sibling risk ratios should be higher. The relative risk for schizophrenia is 6 for parents of schizophrenics and 13 for offspring of schizophrenics, whereas the sibling risk is 9 (Gottesman 1991). (Parents had the lowest rate because schizophrenics are less likely than non-affected individuals to have children [Haverkamp et al. 1982]). Similarly, no consistent differences between risks in parents, offspring, and siblings for bipolar disorder have been observed in the literature (Craddock & Jones 1999). The genetic action involved in these disorders appears to be due to additive and/or epistatic genetic action, but probably not to genetic dominance. If one hypothesizes that heterozygote advantage maintains these mental disorders, one must explain this inconsistency. Otherwise, it may be time to jettison the hypothesis.

R4.4. Can antagonistic pleiotropy explain mental disorder susceptibility alleles?

Several commentators forwarded the idea that normal variants might come together in rare, toxic combinations to produce mental disorders (**Allen & Badcock**, **Wakefield**, **Williams**). Wakefield and Allen & Badcock both state that the Eaves et al. (1990) study – which found higher fertility among those with (a) high neuroticism and low extraversion and (b) low neuroticism and high extraversion – suggested a mechanism by which susceptibility alleles might be maintained in the population. Leaving aside the important issue of whether modern fertility can be used to infer ancestral fertility (sects. 3.3, 4, and 7.1), these are arguments for antagonistic pleiotropy of susceptibility alleles – they have positive fitness effects against some genetic backgrounds and negative fitness effects against others. Wakefield is not necessarily wrong, however, when he says this situation is related to non-additive genetic variation. In many cases, such as this one, antagonistic pleiotropy and non-additive genetic variation are completely intertwined. Theoretical work (Curtisinger et al. 1994; Hedrick 1999; Prout 1999) has shown that antagonistic pleiotropy maintains genetic variation only if it is caused by heterozygote advantage at just one or a few loci, in which case almost all the genetic variation would be non-additive (dominance) variation. Therefore, the lack of empirical evidence for heterozygote advantage (sects. 5.4 and R4.3) is also relevant here.

The example of mental disorders being caused by toxic combinations of normal variants is instructive, because it illustrates why previous evolutionary genetic models have found that antagonistic pleiotropy is unlikely to maintain genetic variation in any trait in any species (see also sect. 5.5). Consider a hypothetical locus that affects neuroticism: the allele *N1* at this locus increases neuroticism and the allele *n1* decreases it. Assume that there are also lots of alleles at different loci that also increase or decrease neuroticism (*N2* and *n2*, *N3* and *n3*, etc.) and extraversion (*E1* and *e1*, *E2* and *e2*, etc.). *N1* increases fitness when it finds itself in a body with lots of *e* alleles in its DNA, and decreases fitness when it finds itself in a body with lots of *E* alleles in its DNA (this is true irrespective of the number of other *N* alleles in the DNA). The opposite happens for *n1*.

The question is: Will this process itself maintain both *N1* and *n1* in the population? The answer is: It will not. The reason is that the fitness of *N1* is very unlikely to be equal to the fitness of *n1*. If there are more *E* alleles than *e* alleles in the population, *N1* will, across all the bodies it finds itself in, have a negative fitness effect *on average*. It will go extinct, and *n1* will fixate. If there are more *e* alleles in the population, *n1* will go extinct, and *N1* will fixate. In either case, variation at the locus is not maintained. The exact same dynamic is also working at all the other loci harboring the other *N*/*n* alleles and *E*/*e* alleles. Eventually, they should all fixate in favor of one combination or the other: either all people will be highly neurotic introverts, or they will all be non-neurotic extraverts. Even in the unlikely situation where the balance of *E*/*e* and *N*/*n* alleles is such that the fitness of *N1* and *n1* are exactly the same, the mechanism is not stable to perturbations due to random genetic drift. If *E* alleles happen to get a little more common by chance, *N1* decreases, which fuels a further increase in *E* alleles, and so forth. Unlike frequency-dependent selection or heterozygote advantage, antagonistic pleiotropy offers no homeostatic mechanism that maintains alternative alleles in the population (Curtisinger et al. 1994; Hedrick 1999; Prout 1999).

R4.5. Is morbid jealousy an adaptation maintained by balancing selection?

We place our response to **Easton et al.**'s commentary separately because it raises an interesting issue. Jealousy is a facultative response (a response to environmental cues), and there is good reason to believe that it serves an adaptive mate-guarding function (Buss 2000). Easton et al.'s balancing selection model sees morbid jealousy as a potentially adaptive extreme of normal sexual jealousy. Before continuing, we would like to note two caveats regarding this hypothesis. First, such a hypothesis requires the types of support outlined in sections R4.2 and R4.3 – demonstrations of putative benefits are not enough. Second, it seems likely that one could focus on the extreme end of *any* behavioral dimension and ask why "it" has been maintained in the population. Thus, we agree with Easton et al. that it is important to understand if morbid jealousy is discrete or part of a continuum.

A slight modification of **Easton et al.**'s model would make it parallel to our model of depressive responses: Some morbid jealousy might be a normal and adaptive reaction to highly jealousy-provoking situations, whereas other instances of it might be side-effects of developmental and mutation noise (e.g., Yeo et al. 1999) in the neurodevelopmental system. Here's where things get complicated in explaining facultative mechanisms: Where does the error in the neurodevelopmental system come from? One answer, given in our target article (sect. 1.2), is that it is a side-effect of environmentally and genetically induced error that disrupts setting the appropriate threshold for sexual jealousy. Alternatively, this

error might not directly affect the jealousy system at all, but rather might be a reflection of overall mutation load (P. Andrews, personal communication, April 10, 2006). Individuals with a high mutation load might have a reduced ability to retain mates and deter rivals, and might thereby adaptively lower their jealousy threshold. This latter explanation would also predict that genetic inbreeding, paternal age, and environmental perturbations would increase morbid jealousy – not because of disruptions in the jealousy system, but because of lower general mate value. Morbid jealousy would be common, harmful, and heritable because low mate value is common, harmful, and heritable.

A similar explanation might account for some of the genetic variation of several other disorders that are extremes of facultative responses. For example, people who are less able to function in the world, perhaps because of a high mutation load, may be more likely to suffer from normal depressive symptoms. Consistent with this hypothesis, exposure to stressful life events is itself heritable, and this appears to contribute to the genetic liability for depression (Kendler & Karkowski-Shurman 1997; Silberg et al. 1999).

Ultimately, however, it should be realized that these two explanations of the source of error in facultative systems are alternative descriptions of *how* developmental errors and mutations affect mental disorders, but they are not conflicting. They are important to consider because they force one to think more deeply about the varied pathways that connect genes to phenotypes.

R5. Response to concerns over the polygenic mutation-selection balance model

R5.1. Does the watershed model fail to explain how different mutations lead to a structured set of mental disorders?

Whether this concern is a strength or a weakness of our model depends on how much structure one thinks there is to psychopathology. **Behrendt**, **Polimeni**, **Price**, **Voracek**, **Williams**, and **Wilson** suggest or imply that certain current diagnostic categories are real and distinct. On the other hand, **Airey & Shelton**, **Allen & Badcock**, **Buss**, **Campbell, Osipova, & Kähkönen** [**Campbell et al.**], **Easton et al.**, **Gangestad & Yeo**, **Klimkeit & Bradshaw**, **McGrath**, and **Troisi** suggest or imply that current diagnostic categories are dimensional, heterogeneous, and ultimately somewhat arbitrary.

This is the fundamental question in psychiatric nosology (Krueger & Piasecki 2002; Widiger & Samuel 2005) and a key issue in Darwinian psychiatry (Troisi & McGuire 2002; Wakefield 1992): Are mental disorders natural kinds best described as discrete categories, or are they arbitrarily divided symptom sets that may have a hierarchical or dimensional structure? Several recent models of mental disorders based on multivariate genetic studies or exhaustive symptom-structure studies of community samples (Clark 2005; Kendler et al. 2003; Krueger & Piasecki 2002) support a hierarchical or dimensional structure of mental disorder categories. Such findings suggest that the same gene affects multiple disorders, and that the same disorder is affect by many genes, and are consistent with the watershed model.

Gangestad & Yeo's developmental instability theory offers a useful clarification of our watershed model. Mutations and other insults perturb finely tuned developmental processes. Owing to the nature of neurodevelopment, certain processes channel along the same pathways. The disruption of different developmental processes can thereby lead to common outcomes (see also **McGrath**). Our failure to cite their seminal papers (Yeo & Gangestad 1993; Yeo et al. 1999) in our target article is like a fish not noticing the water in which it swims. We have been so influenced by that model, that we overlooked the obvious: Developmental instability can help explain how mutations and other developmental errors manifest as mental disorders.

Behrendt offers a different, though not necessarily inconsistent, hypothesis for how diverse perturbations of a system can lead to an apparently singular disorder. He suggests that schizophrenia might seem like a semi-coherent category, not because there is some final common pathway in the neurogenetic watershed, but rather because developmental errors undermine individuals' capacities for normal social interactions. In response to the complex social dynamics that characterize human life, vulnerable individuals develop symptoms which we define as schizophrenia.

R5.2. Are mental disorders too diverse to be explained by a single evolutionary genetic model?

Several commentators are skeptical of a mutation-selection model on the grounds of epistemic humility. **Preti & Miotto** caution against "a 'theory of everything' which explains everything and nothing" (suggesting that a mutation-selection model does not generate testable predictions). **Wilson** and **Polimeni** are unconvinced that one evolutionary genetic mechanism could explain mental disorder susceptibility alleles. **Allen & Badcock** warn that premature commitment to a single model runs the risk of neglecting equally viable ones.

Epistemic humility is sometimes a virtue, but not always. It is simply false to claim that a single hypothesis cannot explain many diverse phenomena. Newton's theory of gravitation and Darwin's theory of natural selection successfully explained rather broad classes of phenomena. A mutation-selection model has already been shown to explain parsimoniously thousands of phenotypically diverse Mendelian disorders (sects. 1.3 and 7.6). There is no good philosophy-of-science reason to think that it cannot do likewise for the sundry symptoms of mental disorders. All else being equal, the more a hypothesis explains, the better. Given the evidence reviewed in this response and in our target article, we continue to find the theoretical and empirical arguments strongest for a mutation-selection explanation for some, and probably much, of the genetic variation behind most serious mental disorders.

That said, we never claimed that mutation-selection was the only mechanism responsible for the evolutionary persistence of susceptibility alleles, or that balancing selection played no role in maintaining them (this was explicitly stated in sects. 4.4, 5.8, 7.6, and 8). Mutation-selection explanations for susceptibility alleles are perfectly consistent with other evolutionary processes – near-ancestral neutrality, maladaptive by-products of balancing selection,

coevolutionary arms-races, selective sweeps, and so forth. We fully expect that each of these processes will explain the existence of some portion of susceptibility alleles.

We also agree that, in future research, it may sometimes be best to compare evolutionary genetic models one disorder at a time, given the different prevalence rates, heritabilities, genetic correlations, environmental triggers, symptoms, and fitness effects of different disorders. However, we worry that disorder-by-disorder research reifies DSM or ICD categories in ways that have inhibited big-picture thinking in Darwinian psychiatry. In particular, researchers who focus on one disorder at a time tend to miss the genetic correlations and phenotypic comorbidities among disorders that may be generated by a polygenic mutation-selection balance, or that may reflect balancing selection on general personality traits.

R5.3. Is the mutation-selection explanation pessimistic?

Brüne and **Airey & Shelton** worry that, to the degree that mutation-selection explains mental disorder risk, the search for susceptibility alleles could be a fruitless endeavor. It is true that evidence for a major role of mutations in the etiology of mental disorders should cause dismay to those psychiatric gene-hunters who expect that susceptibility alleles have large effects that replicate across populations. However, even if most of the mental disorder genetic variation is caused by mutation-selection (which is far from certain), this would not mean that psychiatric gene hunting is doomed (sects. 7.6 and 8). It would, however, mean that the quest to find susceptibility alleles will be much slower than originally anticipated, and that alternative gene-hunting methods will need to be implemented (Wright et al. 2003). For example, Airey & Shelton, **Campbell et al.**, and **McGrath** argue that empirical support for a mutation model has made current drives to simplify the genetic structure of mental disorders (through finding and using endophenotypes) all the more imperative. Similarly, Campbell et al. argue that small regional subisolate populations could be a gene-hunting gold mine, because each population may contain different susceptibility alleles at fairly high prevalence rates due to bottlenecks and genetic drift.

R5.4. Is the mutation-selection explanation anti-adaptationist?

Some commentators have drawn a distinction between adaptationist approaches to understanding susceptibility alleles (by which they seem to mean balancing selection models) and a mutation-selection model. We think this is a false distinction. We are ourselves ardent adaptationists who fully appreciate the value of evolutionary psychology in characterizing species-typical psychological adaptations (e.g., see Keller & Nesse 2006; Miller 2005). We agree with **Brüne** and **Troisi** that evolutionary insights are crucial for understanding mental disorders, which must be understood against the background of normally functioning psychological adaptations. As an example, Troisi has forwarded that lifetime prevalence rates of mental disorders that are approaching 50% suggest that current definitions fail to distinguish true disorders from adaptive responses to difficult situations. Current psychiatric definitions are driven by corporate interests for profit, as well as individual interests to not suffer, but evolutionarily informed definitions would be much more scientifically useful (Troisi & McGuire 2002; Wakefield 1992).

As **Troisi** skillfully points out, our target article was not arguing against adaptationism as a general research strategy. It was arguing against a particular type of Darwinian psychiatry that immediately reaches into the adaptationist toolbox to understand genetic variation – usually this means either balancing selection, or, worse (because it doesn't explain adaptive genetic polymorphisms), directional selection. Our mutation-selection watershed model is indeed not adaptationist, but neither is it *anti-adaptationist*. Our model is perfectly compatible with adaptationism; indeed, for it to have much explanatory power, it requires the extraordinary complexity and polygenic basis of biological adaptations. If human consciousness could arise from a simple brain built by a small set of genes, it would be wonderfully mutation-resistant. Alas, we think human consciousness can only arise in a brain of gargantuan complexity built by thousands of genes and that has a vast mutation target size. *In our view, mental disorders are side-effects of adaptive complexity, not arguments against adaptive complexity.*

We think that balancing selection is conceptually attractive to some commentators because it promises to bridge the gap between human universals (as studied by evolutionary psychology) and individual differences (as studied by personality researchers and psychiatrists) – and to do so within a behavioral ecology framework that embraces optimality modeling and evolutionary game theory. Mutation-selection models are anathema to a narrow view of behavioral ecology because they undermine the rational-agent assumptions of optimality modeling. In a perfect world with no phenotypic disruptions and no behavioral errors, balancing selection is the only force that can make sense of individual differences. Fundamentally, our point is that adaptationists do not have to believe that we live in this perfect world. Mutations and other developmental errors happen, and they mess us up.

This is absolutely not to say that most Darwinian psychiatry has been a waste of time. We are convinced, for example, that depression has some close relationship to normal sadness, grief, and transient low mood, and that these states have ancestrally adaptive functions (Keller & Nesse 2006), as several Darwinian psychiatrists have theorized before (Gilbert 1992; Hagen 1999; Nesse 2000; Price et al. 1994; Watson & Andrews 2002). Our question is: Are these adaptive mood states – complex, finely tuned, and polygenic as they are claimed to be – immune to disruption? The same question applies to the many plausible hypotheses about adaptive functions of personality disorders, sexual disorders, and so forth. We can probably keep many of the insights from such work, as long as we bear in mind the likelihood that any complex psychological adaptation, by necessity, is susceptible to breakdowns induced by environmental and genetic insults.

R5.5. Do mutations during spermatogenesis fail to explain the paternal age effects observed for schizophrenia?

Crespi has cited five studies (Farrer et al. 1992; Malaspina et al. 2001; Reik et al. 1993; Sipos et al. 2004;

Tiemann-Boege et al. 2002) that, he says, show that genomic imprinting effects provide a persuasive alternative hypothesis for paternal age effects on schizophrenia risk. However, three of these citations (Farrer et al. 1992; Reik et al. 1993; Tiemann-Boege et al. 2002) regard Huntington's disease and achondroplasia, Mendelian disorders with much simpler modes of inheritance than any complex mental disorder. These studies are therefore not relevant to judging whether the paternal age effects in complex mental disorders have anything to do with genomic imprinting. On the other hand, the Sipos et al. (2004) and Malaspina et al. (2001) studies are indeed relevant to the issue, but they support a mutational explanation over an imprinting one. Malaspina et al. (2001) stated only that genomic imprinting might explain the effect, not that it was likely. Malaspina later followed up her study in order to test which explanation was correct, and concluded that mutations, not genetic imprinting, explained the paternal age effects, because the effect was due solely to sporadic (non-familial) cases (Malaspina et al. 2002). Similarly, in a better-controlled, population-based cohort study, Sipos et al. (2004) also found that the paternal age–schizophrenia link existed only among sporadic cases. Contra Crespi, the evidence strongly supports the hypothesis that the link between paternal age and schizophrenia (and perhaps other mental disorders [sect. 7.3]) exists because older fathers are more likely to pass on new, deleterious mutations to their offspring, who are thereby more likely to develop schizophrenia.

R5.6. Are mutation rates adaptively modulated, and does this imply that mutations are not harmful?

Williams appears to suggest that, because mutation rates are adaptively higher in certain restricted regions of the genome (Metzgar & Wills 2000), the consequent entropy stemming from them is not generally deleterious. However, no evolutionary geneticist that we are aware of subscribes to the notion that mutations are not generally deleterious, or that mutation loads are not real. Besides the extensive evidence from mutation-accumulation experiments that species do suffer from mutation loads (e.g., see García-Dorado et al. 2004), it should be proof enough to note the extraordinary adaptations within cell nuclei that minimize the rate or effects of mutations: copying enzymes, proofreading enzymes, repair enzymes, cell suicide mechanisms; indeed, DNA itself is probably an improvement over its progenitor, RNA, because DNA is less likely to mutate (Ridley 2000). It is true that mutation rates differ across the genome, and some of this difference is probably adaptive, but this only signifies that, in certain areas of the genome where molecular variation is adaptive (e.g., the MHC region), selection against mutations is much reduced.

R5.7. Are chromosomal abnormalities fundamentally different from mutations?

As briefly mentioned in the target article (sect. 8), chromosomal abnormalities (translocations, inversions, and so forth) sometimes cause behavioral syndromes that are otherwise identical to bipolar disorder, autism, schizophrenia, depression, anxiety disorders, and mental retardation (Bassett et al. 2000; Blackwood et al. 2001; Inoue & Lupski 2003; MacIntyre et al. 2003). Contra **Wilson**, there is no theoretically important distinction to be made between such chromosomal abnormalities and point mutations – they are all different types of mutations that affect the phenotype because they disrupt proper gene functioning. Of course, chromosomal abnormalities tend to disrupt many genes at once, and so are phenotypically easier to detect and study in pedigree studies. The fact that major mutations (chromosomal abnormalities) can cause mental disorders strongly suggests that minor ones do, too. An additional piece of evidence that we have learned more about since writing the target article is that ionizing radiation, which can cause both germ-line and somatic mutations, increases the risk of mental retardation and schizophrenia (Loganovsky & Loganovskaja 2000; Otake 1996). Both pieces of evidence strongly implicate a role for harmful mutations in mental disorder risk. A perusal of the results from an academic search engine (e.g., *PubMed*) with keywords "schizophrenia," "bipolar disorder," "autism," or "mental retardation" and "inversion," "translocation," "chromosomal abnormality," or "ionizing radiation" should make sober reading for anyone who posits that these disorders are themselves adaptations (sect. R4.1).

R5.8. Is the lack of progress in finding susceptibility alleles evidence for the common disease, rare variant hypothesis?

Although this issue was not raised by any reviewer or commentator, we end this section on mutation-selection by amending a point we made in our target article. In section 7.6, we stated that to the degree mutation-selection explains mental disorder susceptibility alleles, the common disease, rare variant (CDRV) hypothesis should be true, and if so, mental disorder susceptibility alleles will be difficult to detect using modern gene hunting methods. Both statements are correct. We followed this, however, by stating that the current lack of progress in finding genes made the CDRV more likely. Here we probably overstated our case. While the lack of progress in finding mental disorder susceptibility alleles does suggest that mental disorders are highly polygenic (itself a prediction of the mutation-selection hypothesis), it does not necessarily imply that the susceptibility alleles at these polygenic loci are individually rare (i.e., that the CDRV hypothesis is true). The reason is that most published gene hunting studies have used two approaches (linkage and candidate gene association) that provide little and/or imperfect information on the validity of the CDRV hypothesis. Whole genome association tests, on the other hand, can provide such information, but few such tests have been conducted to date. This state of affairs is set to change over the next five years. Instead of being framed as corroborating evidence, therefore, our point in this section should have been framed as a prediction: to the degree that mutation-selection explains the existence of mental disorder susceptibility alleles, forthcoming whole genome association tests will not be the silver bullet that they are hoped to be.

R6. Responses to particular points raised by commentators

R6.1. Do mental disorders require different explanations than other types of disorders?

Mayo & Leach argue that the explanations we provide for understanding the evolutionary maintenance of genetic variation are not unique to mental disorders, and that other types of disorders, such as diabetes, asthma, heart disease, and endometriosis, can be understood by using these same principles. We completely agree with this important point (briefly alluded to in sects. 2 and 8). The distinction between mental and physical disorders is, from a biological perspective, an arbitrary one. We think that the polygenic mutation-selection model applies to most organic dysfunction across all species, as many biologists have argued before us. It was a pragmatic decision not to extend our discussion to other harmful, heritable physical disorders or to other species.

R6.2. Do Keller & Miller understate the role of the environment?

Allen & Badcock assert that our target article understated the role of complex G–E interactions in phenotypic development. We agree that normal human development depends on complex interactions among genes, organisms, and the environment to produce psychological adaptations. However, in referring to the study by Caspi et al. (2003), Allen & Badcock (see also **Voracek**) stated that strong G–E interactions are the rule rather than the exception. Care must be taken in placing such findings in the proper context. G–E interactions that are relevant to understanding the prevalence of mental disorders are those with respect to *ancestral versus modern environments*, not necessarily with respect to the environmental factors (stressful life events) studied by Caspi et al. (2003). If the environmental factors identified in such G–E interaction research were also present in ancestral environments, even if only occasionally, then the susceptibility alleles would still require explanation.

R6.3. Does it make a difference whether alternative adaptive strategies are environmentally or genetically determined?

Price makes the point that behavioral ecology is an important tool for understanding psychiatry (we agree), but he also states that it makes no difference whether alternative adaptive strategies are environmentally or genetically determined, which is a point we emphatically disagree with. It simply does make a difference. If alternative strategies are environmentally determined, such that organisms adaptively shift strategies depending on the situation, the genes affecting this shifting behavior would be at fixation. In this case, straightforward directional selection arguments apply (the fittest alleles fixate in the population). If an adaptive behavioral polymorphism is genetically determined, on the other hand, then the only mechanism that could explain its existence is balancing selection, which we discussed in detail, and which makes specific, testable predictions. A central point in our target article was that the type of process used to explain most adaptations – directional selection – *cannot* explain an adaptive genetic polymorphism (sects. 5.1 and R2.2).

R6.4. Did Keller & Miller misrepresent the work of Wilson?

We feel impelled to reply to **Wilson's** statement that we engaged in ad hominem attacks and misrepresented his work. Clearly, we intended neither of these. The "would-be ad hominem" that **Wilson** describes was intended to draw attention to the fact that many psychiatrists, both researchers and clinicians, hold a dim view of what they consider to be Panglossian perspectives of mental disorders held by many Darwinian psychiatrists (see also **Troisi's** point in this regard). We did not mean to imply that Darwinian psychiatrists are "befogged in the Ivory Towers." Indeed, we consider ourselves ardent Darwinian psychiatrists, and we freely admit to having no experience working in psychiatric hospitals. Our wording should have been more careful.

We disagree, however, that we misrepresented the papers of **Wilson** that we cited, which were forceful deductive arguments that balancing selection maintains bipolar disorder, depression, and certain other common mental disorders. For example, Wilson (1998, p. 381) states that,

> Several important psychiatric conditions (manic depression, sociopathy, obsessive-compulsivity, anxiety, and even drug abuse and some disorders of personality) are so common and so strongly epigenetic that their epidemiological frequencies surpass even quite conservative thresholds of evolutionary selection. The deduction follows that such frequency thresholds were surpassed due to the Darwinian selection of genes advantageous over the course of evolution.

Wilson goes on to demonstrate how much more common bipolar disorder is than expected under a single-gene mutation-selection model, with the implication being that the disorder is so preposterously prevalent compared to what it would be under a mutation-selection balance that it must be maintained by natural selection (Wilson 1998, p. 390). Similarly, in a letter to the editor of *Archives of General Psychiatry*, he states, "It is clear … that some underlying genotypy of depression is altogether too common to not have been selected" (Wilson 2001, p. 1086). It seemed clear to us from these writings that Wilson portrayed balancing selection as the only viable option for explaining the very high prevalence rates of bipolar disorder, depression, and certain other mental disorders.

R6.5. Sex differences in mental disorders require explanations

We agree with **Brüne** that Darwinian psychiatry can and should help explain why males and females differ in the way mental disorders are manifested. Although a mutation-selection model alone does not explain sex differences in mental disorders, it can be easily integrated into an adaptationist framework to do so. We expect that the neurogenetic watershed will be sex differentiated, because human brain development and behavioral development are sex differentiated. The effects of mutation load will be overlaid on the background of a normal

psychology, and mutations that disrupt the sex-specific watersheds will tend to have sex-specific effects. The result may be that, for example, some of the same mutations that increase the risk of sociopathy in males increase the risk of borderline personality disorder in females.

R6.6. Does mutation-selection explain the genetic variation in personality?

We find it more likely that balancing selection explains the genetic variation in personality traits than that it explains the genetic variation in mental disorder risk. Personality traits are relatively orthogonal to one another, are not associated with the same levels of dysfunction as mental disorders, and have plausibly balanced fitness costs and benefits. Several personality traits are positively correlated with indexes of genetic or phenotypic quality (such as intelligence, health, attractiveness, and body symmetry), but these tend to be much lower in magnitude than these relationships among mental disorders. In these respects, personality traits are quite different from mental disorders, and are better candidates for balancing selection explanations.

As **Buss** pointed out, however, one could make the opposite argument: If mutation-selection explains most mental disorder susceptibility alleles, and if mental disorders are continuous with normal personality variation (Benjamin et al. 2002), then mutation-selection should explain the genetic variation of normal personality, as well. This viewpoint has intuitive appeal: Everyone harbors hundreds of deleterious mutations, but most people never develop a mental disorder. How are all those susceptibility alleles expressed in the non-disordered population? In support of this view, Buss noted that one end of each personality dimension is usually more socially and sexually attractive than the other end (e.g., openness vs. rigidity, emotional stability vs. neuroticism, etc.). Buss also emphasized other aspects of personality traits that are consistent with a mutation-selection model, including their non-additive genetic variance; their mild assortative mating coefficients; their social, sexual, and reproductive payoffs; and their salience in person perception as potential indicators of mutation load. We add that the lack of progress in finding genes of major effect in personality (Munafo et al. 2003) is also consistent with this hypothesis.

We offer two possible addenda to **Buss**'s insights. First, in discussing the mutation-selection model of mental disorders, we implicitly focused on directional selection: Selection should disfavor alleles that increase mental disorder risk. But mutation-selection models can also maintain variation in traits under stabilizing selection, and it seems possible to us that some midpoint in personality is optimal, with both extremes being suboptimal (perhaps leading to very different types of mental disorders). This doesn't seem to square with evidence that Buss discussed that one end of each dimension is more attractive than the other; but it is possible that the population average is to the left or the right of the most-fit midpoint, such that a linear effect would exist in addition to a quadratic one in personality attractiveness. Second, mutations might affect personality directly, as disruptions in behavioral mechanisms, but they might also do so indirectly if personality levels are facultative and adaptive (see also sect. R4.5). For example, if extraversion levels are adaptively set based, in part, on self-perceived mating quality (say), then extraversion would indeed be affected by mutations, but indirectly, because mutations degrade mating quality.

In any case, the variation in personality must be explained, and along with **Buss**, we find a mutational explanation plausible, if not likely. If mutations explain the genetic variation in personality, we should expect that personality (perhaps measured in absolute deviation units from the mean, if it is under stabilizing selection) is associated with all the empirical consequences of mutation-selection (sect. 7).

Wakefield was skeptical of any viewpoint that would "reduce much normal variation to mild biological dysfunction," but we do not see a priori why this is unlikely. Evidence from mutation-selection studies in biology suggests that maladaptation is ubiquitous, not just at the extreme ends of the distributions, but everywhere. Much of what we consider "normal" variation may indeed be mild dysfunction, even if too mild to be considered dysfunctional by any useful diagnostic system.

R7. Conclusion

Humans and other long-lived species are beset by mutational noise. Given the enormous complexity of human behavioral adaptations, it should come as no surprise that this maladaptive noise expresses itself behaviorally. We have argued that this provides a compelling explanation for the existence of some portion of mental disorder susceptibility alleles. A mutation-selection hypothesis for susceptibility alleles is not only testable, but a wealth of already available empirical data strongly support its role in maintaining some, and perhaps much, of the genetic risk of several common mental disorders. Nevertheless, as we have stressed throughout, such evidence does not preclude the roles of other evolutionary genetic mechanisms.

Each of the evolutionary processes we have reviewed makes discriminating predictions at the phenotypic, macro-genetic, and molecular genetic levels. The testing of different evolutionary genetic models is accelerating. Gene mapping is revolutionizing this endeavor because it provides a physical measure that partially reveals the history of genes, weighing in on the type of evolutionary process responsible for a given genetic polymorphism (Bamshad & Wooding 2003). **McGrath** says, "Let the data rule," and we could not agree more. It is exciting, and humbling, to realize that, within the next 50 years, we will probably know why alleles that predispose people to common, harmful, heritable mental disorders have persisted over evolutionary time.

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

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