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Evolutionary Perspectives on Genetic and Environmental Risk Factors for Psychiatric Disorders

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Abstract

Evolutionary medicine uses evolutionary theory to help elucidate why humans are vulnerable to disease and disorders. I discuss two different types of evolutionary explanations that have been used to help understand human psychiatric disorders. First, a consistent finding is that psychiatric disorders are moderately to highly heritable, and many, such as schizophrenia, are also highly disabling and appear to decrease Darwinian fitness. Models used in evolutionary genetics to understand why genetic variation exists in fitness-related traits can be used to understand why risk alleles for psychiatric disorders persist in the population. The usual explanation for species-typical adaptations—natural selection—is less useful for understanding individual differences in genetic risk to disorders. Rather, two other types of models, mutation-selection-drift and balancing selection, offer frameworks for understanding why genetic variation in risk to psychiatric (and other) disorders exists, and each makes predictions that are now testable using whole-genome data. Second, species-typical capacities to mount reactions to negative events are likely to have been crafted by natural selection to minimize fitness loss. The pain reaction to tissue damage is almost certainly such an example, but it has been argued that the capacity to experience depressive symptoms such as sadness, anhedonia, crying, and fatigue in the face of adverse life

situations may have been crafted by natural selection as well. I review the rationale and strength of evidence for this hypothesis. Evolutionary hypotheses of psychiatric disorders are important not only for offering explanations for why psychiatric disorders exist, but also for generating new, testable hypotheses and understanding how best to design studies and analyze data.

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INTRODUCTION

Understanding the causes of human health and disease is the central goal of biomedical research, with the hope that such studies can lead to the treatment and prevention of disease. The empirical approach to this endeavor has been enormously successful over the past two hundred years, having led to a dramatic decline in infant mortality, the eradication or control of communicable diseases such as measles and smallpox, and the identification of behavioral health hazards such as smoking. This revolution in empirically guided biomedical research over the past century and a half has occurred in parallel with a similarly consequential theoretical revolution in the life sciences—that of evolutionary theory, which has become the central, unifying framework in biology and genetics. Until recently, biomedical research and the study of evolutionary theory largely existed in separate spheres. Increasingly, however, there is recognition of the potential for using evolutionary theory to understand the causes of human diseases and disorders, a pursuit termed evolutionary medicine (Nesse & Williams 1994, Williams & Nesse 1991).

Evolutionary medicine: a scientific discipline that uses evolutionary theory to understand the causes of human diseases and disorders

Balancing selection: an alternative model for explaining genetic variation in which natural selection actively maintains two or more alleles at a locus, usually because the selective benefits of the alleles are inversely related to their frequencies

Although both traditional and evolutionary approaches to medicine attempt to understand the causes of disease, they focus on different levels of explanation. Evolutionary medicine attempts to answer ultimate questions—how and why traits evolved in a way that makes humans vulnerable to disease—whereas biomedical research usually attempts to answer proximate questions about the mechanisms underlying disease. The two levels of explanation are not at odds with one another, and at best, both are understood and mutually consistent for a given phenomenon. For example, the ultimate explanation for the high rates of sickle cell disease among people whose ancestors evolved where malaria was endemic is that the risk variant was maintained by balancing selection (heterozygote advantage) at the hemoglobin-beta gene, whereas the proximate explanation has to do with the loss of red blood cell elasticity among individuals who inherit two risk variants. Both answer the question of why sickle cell anemia exists, and both are correct. This is not to say that an ultimate explanation is required for every proximate one or vice versa. A focus solely on proximate mechanism, for example, may be sufficient for understanding how to develop a new vaccine or to demonstrate an association between a genetic variant and a disease. Nevertheless, evolutionary

theory can supplement and deepen proximate explanations by providing satisfying explanations for disease vulnerability and by helping to generate new, testable hypotheses.

In this review, I present two types of explanations that offer alternative and potentially useful perspectives on psychiatric disorders, using depression and schizophrenia as examples. First, many of the differences between individuals' risks to disorders are due to differences in the genes they inherit. The ultimate explanations for genetic variation in traits related to fitness have been central pursuits in evolutionary genetics since its inception, and the models used in this field are increasingly used to understand and model the genetics underlying human disorders, including psychiatric disorders such as schizophrenia. Second, natural selection seems to have designed behavioral and somatic reactions to adverse environmental conditions—physical pain arising from tissue damage, for example. The capacity to mount reactions to such negative situations is itself adaptive and universal, but the phenomenological experience of these reactions is unpleasant, and extreme forms of them have been deemed disorders. Considering psychological anguish as a potential expression of such facultative defenses may help answer ultimate questions about why humans are vulnerable to depression.

The evolutionary explanations I focus on are far from exhaustive. For example, I discuss neither evolutionary explanations of age-related cognitive decline that may be caused by genes that benefit the young at the expense of the old nor evolutionary explanations for disorders such as drug abuse that may occur due to mismatches between modern and ancestral environments. Similarly, for brevity and focus, I review only two disorders, discussing explanations for the genetic variation in schizophrenia and for the environmental variation in depression. This of course is not to deny the importance of genetic and environmental factors in both. Despite the necessarily brief and incomplete treatment of the topic, the types of explanations discussed here provide a sense of the ways in which scientists are using evolutionary theory to try to better understand and model the risk to psychiatric disorders.

INDIVIDUAL DIFFERENCES IN GENETIC RISK TO SCHIZOPHRENIA

The lifetime prevalence of psychiatric disorders is extremely high. Approximately half of the US population will at some point surpass diagnostic thresholds for at least one psychiatric disorder (Kessler et al. 2005). More than half of this burden is from clinical depression, and as argued below, many of these cases may be normal reactions to highly adverse situations. Other common disorders, such as attention deficit hyperactive disorder, may be deemed dysfunctional only in the context of evolutionary novel situations—those requiring extended focus and little physical activity, for example—and the neurobehavioral underpinnings that give rise to symptoms of such disorders in modern environments may not have been dysfunctional in ancestral environments (Jensen et al. 1997). Similarly, ancestral environments likely did not have highly purified psychoactive drugs available that now hijack reward and pleasure systems (Nesse & Berridge 1997), and so substance abuse is unlikely to have existed ancestrally as it does today. Thus, much of the burden of psychiatric disorders may represent normally functioning mechanisms that find themselves in adverse or evolutionarily novel situations. According to some evolutionary psychologists, such cases of diagnosed psychiatric disorders should not be considered disorders at all because the mechanisms underlying them work as designed by natural selection (Wakefield 1992, 1999). Thus, the true burden of psychiatric disorders, as defined by dysfunctional neural mechanisms, may be substantially lower than that suggested by epidemiological statistics.

Nevertheless, this argument for the high levels of apparent psychiatric dysfunction in the population only goes so far. Highly debilitating psychiatric disorders such as bipolar disorder, schizophrenia, autism, and obsessive compulsive disorder seem fundamentally different. They are

not obviously reactions to negative or evolutionarily novel situations, and the capacity to develop them does not appear universal—most people would not develop these disorders, regardless of the environment. Rather, studies consistently show that individual differences in their liabilities are mostly genetic in nature. Given their high heritabilities, any evolutionary models attempting to explain the existence of highly disabling psychiatric disorders must grapple with the existence of the genes that predispose to them. This section focuses on evolutionary explanations for the genetic variation underlying perhaps the most disabling of these disorders, schizophrenia, although the explanations can be applied to the genetic risk underlying any disorder or trait that reduces fitness.

Purifying selection: removes alleles with lower fitness in favor of one or more alternative alleles with higher fitness

Heritability: the proportion of trait variation that can be attributed to genetic factors

Alleles: alternative versions of genetic variants at a given locus

Risk allele: an allele that increases risk for a disorder or disease

Schizophrenia has a heritability of ∼.80 and affects approximately 7 people in 1,000 over the lifetime in industrialized countries, and slightly fewer (∼5.5 people in 1,000) in less developed countries (Saha et al. 2005). Schizophrenia results in profound impairment, and individuals who suffer from it have fewer than half the number of offspring compared to the unaffected population (Bundy et al. 2011). The observation of disorders that are highly heritable and highly debilitating is not at all uncommon. There are thousands of so-called Mendelian diseases like this, for example Apert's syndrome, Achondroplasia, Niemann-Pick disease, and Zlotogora-Ogur syndrome, but such disorders typically have a very simple genetic basis, and although cumulatively common (∼2%; Sankaranarayanan 2001), they are individually exceedingly rare. The evolutionary explanation for fitness-reducing, highly heritable, rare disorders has been well-understood for a century: Mutation-selection balance, which involves deleterious mutations arising in the population at some rate and being subsequently purged from the population by purifying selection at another rate—given the balance between these two forces—results in a (very low) prevalence of the deleterious mutations that cause these disorders. However, highly heritable yet fitness-reducing complex disorders such as schizophrenia are approximately 1,000 times more prevalent than most fitness-reducing Mendelian disorders. Unlike disorders associated with cognitive decline, they strike before or during peak reproductive years. They typically follow a lifelong course and lead to profound social and cognitive impairment. And such highly debilitating disorders have a cumulative lifetime prevalence of approximately 4%). What is the evolutionary explanation for these disorders? If these disorders reduced fitness ancestrally, selection seemingly should have removed the alleles that predispose to them, so why do such risk alleles persist in the population? We have termed this the paradox of common, harmful, heritable psychiatric disorders (Keller & Miller 2006).

Evolutionary Genetic Models for Genetic Variation in Fitness-Related Traits

The questions above parallel a long-standing focus in evolutionary genetics: What causes genetic variation in traits related to fitness? Surprisingly, given that natural selection tends to decrease the genetic variation in traits (Fisher 1930), fitness-related traits studied in natural (typically nonhuman) populations, such as larval survival or number of surviving offspring, tend to show a high level of genetic variation when properly standardized (Charlesworth & Hughes 1999, Houle 1992, 1998). This observation prompted extensive research into why genetic variation persists despite selection. The models used to explain the existence of genetic variation underlying fitness-related psychiatric disorders should reasonably be drawn from the range of models already developed in evolutionary genetics, and should profit from the empirical and theoretical insight derived from them.

To simplify, two basic classes of models have been used to explain genetic variation in fitness-related traits at equilibrium: mutation-selection and balancing selection. Mutation-selection was described above and might seem an unlikely possibility because deleterious mutations are typically kept rare by selection and therefore do not individually contribute much to genetic variation.

However, although it is true that mutations with catastrophic phenotypic effects, such as those that cause many Mendelian disorders, are exceedingly rare, the vast majority of deleterious mutations segregating in a population have very small effects on fitness. Indeed, the effects of many deleterious mutations are likely to be so small that they "drift," by chance, to high frequencies (>1%), especially in small populations, and can even fixate (reach 100% frequency) despite their negative effects (Ohta 1973). Thus, for highly polygenic traits influenced by numerous alleles that individually have small effects on fitness, random processes (drift) in addition to selection play a crucial role in governing allele frequencies; hence, mutation-selection is better conceptualized as mutation-selection-drift.

Mutation-selection-drift: a model that explains genetic variation as a function of the loss of deleterious alleles via selection, the gain of new ones via mutation, and chance events causing some deleterious alleles to drift to high frequencies

Although some deleterious mutations drift to high frequencies, most eventually go extinct, but their numbers are constantly replenished through new mutations introduced into the population via DNA copying errors in reproductive cells, leading to equilibrium between their "arrival" into the gene pool via mutation and their removal via purifying selection. It is likely that, by virtue of needing to integrate so many upstream mechanisms to successfully survive and reproduce, fitness-related traits have enormous mutational target sizes (Charlesworth 1987; Houle 1992, 1998; Price & Schluter 1991) and are therefore perturbed by the action of deleterious mutations in a huge number of genes. Individually, none of these mutations contribute much to the genetic variation of fitness-related traits, but collectively, the variation can be large. Thus, the importance of mutation-selection-drift on any given trait depends crucially on how polygenic the trait is. More genetic variation is predicted for more polygenic traits because the mutational target size is larger and because, by spreading the fitness effect across so many loci, the per-locus selection coefficient may often be lower. Although there continues to be debate in the evolutionary genetic community about whether mutation-selection-drift is sufficient for explaining the genetic variation underlying fitness-related traits, it is now widely accepted that it creates a substantial amount of fitness-related genetic variation and that it serves as a good null model that should first be eliminated before resorting to other, "more interesting" explanations for genetic variation (Charlesworth 2015).

The second major model used to explain genetic variation in fitness-related traits is balancing selection, which occurs when the effects of two (or more) alternative alleles at a given locus have countervailing effects on fitness that cancel each other out. For such a scenario to lead to persistent genetic variation, there must be some mechanism that ensures that one of the alternative, equally fit alleles does not drift by chance to fixation, eliminating genetic variance contributed by the locus. The most commonly invoked possibility is that the fitness effects of alleles are inversely related to their frequencies, which can lead to a stable polymorphism in the population. The advantage of individuals heterozygous at the hemoglobin-beta gene, described at the beginning of this review, is such an example. As the risk allele for sickle cell anemia becomes more common, it more often finds itself paired (homozygous) with other sickle cell risk alleles, decreasing the fitness of its host and therefore the fitness of the risk allele. However, as it becomes rarer, the risk allele more often finds itself paired with the nonrisk allele (heterozygous), conferring valuable immunity to malaria without the risk of sickle cell anemia. The same dynamic occurs for the alternative allele too, because homozygosity of the nonrisk allele is suboptimal due to lack of malarial resistance. The end result is not so much an oscillation as a stable equilibrium in allele frequencies at loci under balancing selection. There are other types of such balancing selection as well—for example, frequency-dependent selection at the phenotypic level, where the fitness effects of alternative, heritable morphs in the population are inversely related to their frequencies. The differentiation of male and female morphs within species is likely to have arisen anciently via balancing selection in this way (Hamilton 1967). And although male or female is now determined randomly, resulting in roughly equal proportions of morphs, balancing selection tends to maintain the frequencies of morphs or genotypes that lead to equal fitness effects. The risk allele for sickle

cell anemia, for example, has a frequency of 10% to 40% in sub-Saharan populations, where malaria is endemic because the effect of sickle cell disease decreases fitness more than lacking immunity to malaria (Piel et al. 2010). Because alleles maintained by balancing selection tend to exist at high frequencies, a small number of loci can maintain a large amount of genetic variation.

A third explanation for genetic variation, although not a focus of equilibrium models of genetic variation, can contribute to our understanding of evolutionarily transient genetic variation. Directional selection tends to increase the frequency of the fittest allele, and once that allele reaches fixation, the locus no longer contributes to genetic variation. Thus, the types of arguments used to explain adaptations, including universal capacities for disorders (detailed below for depression), are typically irrelevant to understanding genetic variation in the liability to developing a disorder. For example, explanations that anorexia is an adaptive response to fleeing famine ancestrally (Guisinger 2003) or that schizophrenia is a side effect of language evolution (Crow 2000) may or may not provide insight into universal susceptibilities to these disorders, but because positive selection tends to fixate alleles, they do not explain individual differences in their risk. There is one important exception: For any given snapshot of evolution, there are likely to be multiple alleles across the genome that are under positive selection and are rising in frequency but have not yet fixated. During the period when the alleles have yet to fixate, they will contribute to genetic variation. For example, the T_13910 allele, which regulates expression of the *LCT* gene, arose ~7,000 years ago and has been sweeping toward fixation in European populations, ostensibly due to its effect of allowing noninfants to digest dairy (Holden & Mace 1997, Tishkoff et al. 2007). However, *LCT* has not yet fixated in the population and therefore contributes to genetic variation in lactose (in)tolerance. Overall, the amount of genetic variation contributed by alleles sweeping toward fixation is thought to be a minor contributor to standing genetic variation in traits (Huber et al. 2016, Vitti et al. 2013).

What do these various models of genetic variation in fitness-related traits tell us about the genetic variation in psychiatric disorders? Ten years ago, there was little information to go on, but the intervening period has seen an explosion of information on the genetic architecture of psychiatric disorders, and these findings are beginning to clarify evolutionary explanations of the genetic variation underlying these disorders. I first provide a brief overview of what has been learned about the genetic architecture of schizophrenia over the past ten years and then discuss how this informs ultimate questions about the existence of its risk alleles.

Adaptations: species-typical behaviors or structures designed by natural selection to solve a particular problem that was recurrent ancestrally

Single nucleotide polymorphism (SNP): a single nucleotide position that is variable in the population; most SNPs have no phenotypic effect but can be correlated with risk alleles

Minor allele frequency (MAF): frequency of the least common allele at a locus; by convention, loci where MAF > 0.01 are common and are otherwise rare

Whole-genome arrays: provide data for a subset (e.g., ~10%) of common SNPs across the genome

The Genetic Architecture of Schizophrenia

Early approaches to understanding the genetics of schizophrenia relied on candidate genes, where particular alleles within particular genes, such as *COMT*, *DRD2*, and *DISC*, were chosen based on biological hypotheses and plausibility. Although much was learned about the biology and signaling cascades of these genes themselves, attempts to associate them with specific disorders led to a large and confusing literature and a checkered history of replication. Since 2007, an alternative, hypothesis-free approach, the genome-wide association (GWA) study, has led to a great deal more clarity. GWA studies measure a large number (~1 million) of single nucleotide polymorphisms (SNPs) across the genome, and the trait is regressed on each SNP in a series of linear models. Given the large number of tests performed, SNPs must pass a stringent threshold ($p < 5x10^{-8}$) to be deemed "genome-wide" significant. Although only a fraction (e.g., ~10%) of all common SNPs [those with minor allele frequencies (MAF) of more than approximately one-half of one percent] that exist in a given population are actually measured on modern whole-genome arrays, the effects of almost all common variants, including most common repeat polymorphisms, are captured because common SNPs tend to be correlated (or in linkage disequilibrium) with

multiple other nearby common SNPs. Indeed, most modern GWA analyses use the correlation structure between SNPs in large sequence reference panels to impute with high fidelity the status of nearly all the common variants in the genome into a sample that was measured only on a whole-genome array, and then regress the trait on these imputed variants. Thus, GWA studies provide a test of the importance of nearly all common variants in the genome on a trait.

The use of very large consortium datasets and field-wise agreement on proper analytic procedures has been remarkably successful, leading to ~10,000 robust associations with disease and quantitative traits to date (Visscher et al. 2017). Importantly, whole-genome SNP data can be used for more than just association analyses. A growing class of methods (e.g., genomic-relatedness based restricted maximum likelihood (GREML) as instantiated in the GCTA package; Yang et al. 2010) uses all SNPs simultaneously to estimate the total genetic variation of a trait caused by all variants tagged by SNPs and estimates the relative importance of different types of genetic annotations (e.g., variants in genes versus those not in genes; Bulik-Sullivan et al. 2015b, Yang et al. 2010). Recently, these methods have been used to estimate parameters that are directly related to the selection coefficients of risk alleles. Importantly, these methods rely on neither knowing which variants are truly associated nor reliable estimations of the effect sizes of individual SNPs. Rather, by modeling all variants together and estimating a small number of parameters, these methods derive unbiased estimates that provide our first true insight into the genetic architecture of complex traits, including schizophrenia.

The lessons of the GWA era for schizophrenia can be summarized briefly. With few exceptions, these lessons apply to all complex traits studied to date. First, no common genetic variant explains much schizophrenia risk. GWA studies tend to first find the SNPs that explain the most variation—the low-hanging fruit—and no SNP explains more than one-twentieth of one percent of the variation in the liability of schizophrenia (Gratten et al. 2014). Enormous sample sizes are therefore required to identify even the largest-effect SNPs. The most recent GWA consortium study of schizophrenia had 37,000 cases and 113,000 controls, and identified 108 SNPs that together explain approximately 3.5% of the variance in schizophrenia liability in independent samples (Ripke et al. 2014). This same pattern applies to rare variants that are associated with schizophrenia as well. Because rare copy number variants (CNVs) can be measured from SNP panels and can therefore be analyzed using the very large GWA datasets, whereas measuring rare SNPs requires much more expensive sequencing data, all individual rare variants reliably associated with schizophrenia to date have been CNVs. This should not be misinterpreted as saying that rare CNVs are particularly relevant to schizophrenia risk or that rare SNPs are not—it is likely that many associations with rare SNPs will be discovered once large sequence datasets are available. It is just that CNVs have been the only class of rare variant amenable to investigation with large datasets to date, and so the observation of schizophrenia being associated with rare CNVs and common SNPs has occurred for technical, not interesting, reasons. **Figure 1*a*** shows the relationship between MAF of genome-wide-significant variants (common SNPs and rare CNVs) and their effect sizes (log odds ratios). Even though the largest-effect rare variants (CNVs) greatly increase the risk for individuals who carry them (e.g., odds ratios >10), they are so rare that they explain very little population variation in liability—approximately the same amount of variation as the largest-effect common SNP variants, which have miniscule odds ratios (<1.2).

The second lesson learned about schizophrenia in the GWA era is that the number of loci that affect schizophrenia is enormous. GWAS results suggest that there are likely to be thousands of common variants that influence schizophrenia risk, and there are almost certainly many more rare than common variants that influence schizophrenia risk. Third, variants associated with schizophrenia are not randomly distributed across the genome, but rather are disproportionately found in biologically meaningful categories that scientists are only beginning to catalog and

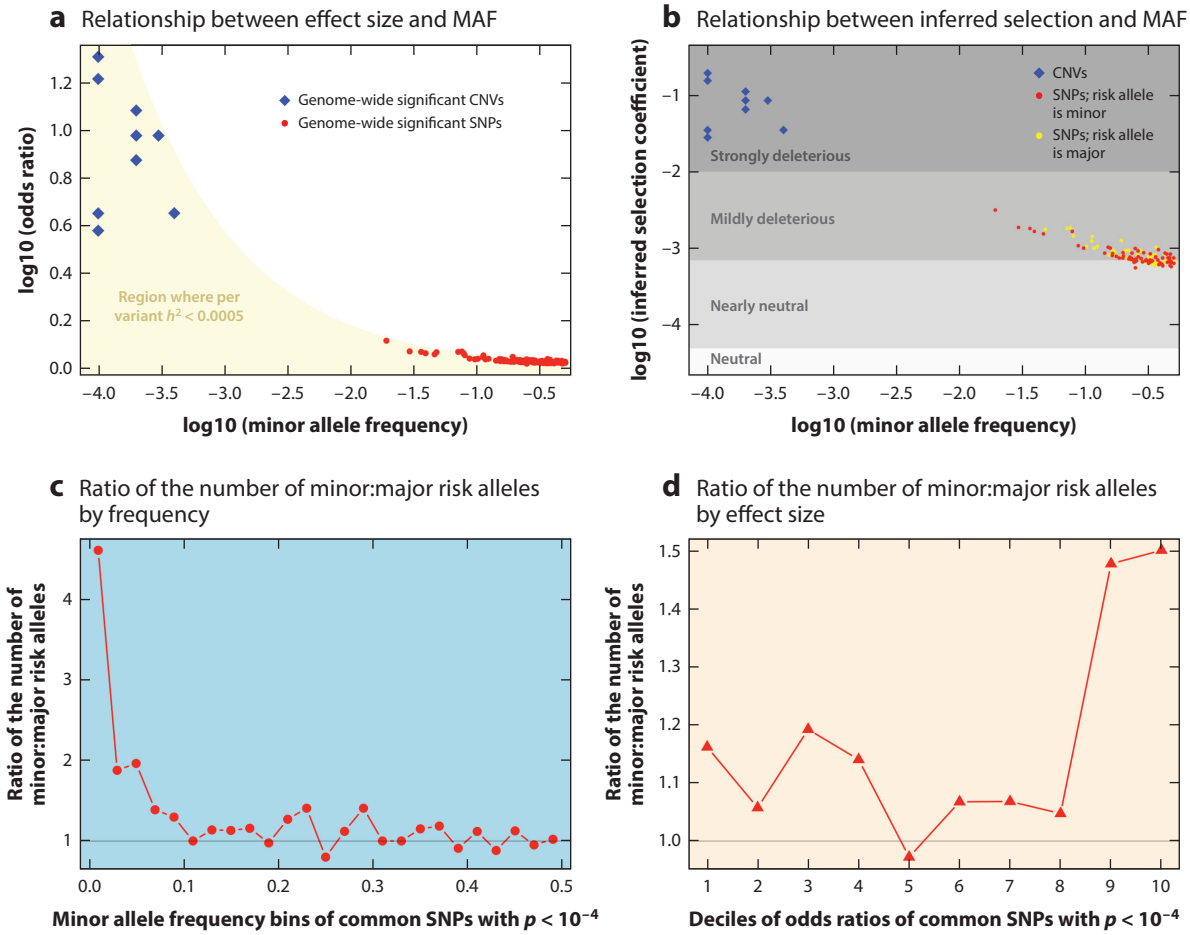

Figure 1

(*a*) There is a clear relationship between effect size and MAF of 108 genome-wide-significant SNPs and 9 genome-wide-significant CNVs for schizophrenia. This is suggestive of purifying selection because large effect variants are kept rare by strong selection whereas small effect ones can drift up to appreciable frequencies. The shaded region is defined as all combinations of effect size and MAF where the variance explained (h^2) is less than 0.0005 assuming a 1% prevalence of schizophrenia. No common CNVs have been found that are significantly associated with schizophrenia. There is adequate statistical power to detect only variants near the top of the shaded region. Rare SNPs (MAF < 0.005) have not yet been assessed with large enough samples to meet stringent genome-wide significance levels, hence the lack of rare SNP associations. Presumably the entire shaded region is populated with schizophrenia risk alleles. (*b*) This shows the same data as **Figure 1*a***, but with the effect sizes converted to inferred selection coefficients, $s = \lambda p(RR - 1)$, where λ is the fitness of those with the disease relative to those without it (assumed to be 0.5), p is the disease prevalence (1%), and RR is the risk ratio of each variant. Note that for all CNVs significantly associated with schizophrenia, the risk allele is the minor allele. (*c*) The ratio of the number of minor to major schizophrenia risk alleles is higher for low-MAF SNPs, as expected under purifying selection. Data are based on 2,148 SNPs (MAF > 0.005), with $p < 10^{-4}$ from the second PGC schizophrenia mega-analysis (Ripke et al. 2014) that were independent of one another (choosing the most associated SNP within each LD block). The higher p-value threshold increased the number of SNPs in the analysis, thereby reducing sampling variance compared to analyzing only genome-wide-significant ($p < 5\text{x}10^{-8}$) SNPs. Although some included SNPs are likely to be type-I errors, as a group they should be highly enriched for true associations. (*d*) On the basis of the same data as those for **Figure 1*c***, this shows that among SNPs with the largest effects on schizophrenia risk (in the highest two deciles of odds ratios), the alleles increasing risk are more likely to be the minor alleles, as expected under purifying selection. Abbreviations: CNV, copy number variants; LD; linkage disequilibrium; MAF, minor allele frequency; PGC Psychiatric Genomics Consortium; SNP, single nucleotide polymorphism.

understand, such as in genes that encode voltage-gated calcium channel subunits or that are involved in glutamatergic neurotransmission (Ripke et al. 2014). Fourth, GREML and related methods indicate that approximately one-third to one-half of the genetic variation in schizophrenia liability is due to the additive effects of common (MAF > 1%) risk alleles (Lee et al. 2012, Bulik-Sullivan et al. 2015b, Pardiñas et al. 2016). The rest may be due to the effects of rarer risk alleles or to nonadditive genetic effects. Fifth, pleiotropy (the same allele affecting multiple traits) is widespread. Schizophrenia is genetically correlated at ∼.80 with bipolar disorder, ∼.50 with major depression, and ∼.2 with anorexia, autism, and attention deficit hyperactive disorder (Bulik-Sullivan et al. 2015a). However, it is essentially genetically unrelated to both smoking and IQ, of interest because schizophrenia patients tend to smoke and score lower on IQ tests (Bulik-Sullivan et al. 2015a).

These insights into the genetic architecture of schizophrenia are relevant to ultimate questions about its genetic variation, but before turning to this, I highlight an issue relevant to interpretation of the past literature on the genetics of schizophrenia. Each schizophrenia risk variant explains no more than a tiny proportion of the variance (<0.05%) in schizophrenia liability. Thus, candidate gene studies, which have typically employed small (n < 5,000) sample sizes, have been extremely underpowered to detect real effects. Moreover, the most commonly studied candidate genes appear about as related to schizophrenia as random collections of control genes when investigated directly in very large GWA datasets (Farrell et al. 2015, Johnson et al. 2017). Thus, evolutionary explanations for schizophrenia genetics that are based on one or a handful of candidate genes (Belsky & Hartman 2014, Carrera et al. 2009, Crespi et al. 2007) are unlikely to be illuminating. Rather, to be applicable to the overall genetic variation underlying schizophrenia, tests of evolutionary hypotheses need to be based on conglomerate results from all SNPs together. Next, I turn to recent studies attempting to do this.

A Mutation-Selection-Drift Model of Schizophrenia Risk Alleles

It is crucial to recognize (and often misunderstood) that a mutation-selection-drift hypothesis is not a hypothesis that de novo mutations account for all, or even much, of the genetic variation for a trait. Rather, mutation-selection-drift should be understood as a model of purifying selection against deleterious alleles (old mutations) that contribute to the trait variation. At equilibrium, the number of deleterious alleles lost to selection each generation are balanced by the number of new deleterious mutations arising each generation. Unless selection per locus is extreme, as it is with most Mendelian disorders, standing variation in a population is typically due to old, segregating deleterious alleles that by chance have increased in frequency.

The number of segregating deleterious alleles affecting fitness in the typical human genome is thought to be very high. A typical human genome may contain ∼1,000 deleterious to slightly deleterious alleles in genes (Chun & Fay 2009), and probably many more thousands of such variants in nongenic regions, given that genes only make up approximately 1% of the genome but ∼8% of the genome is under purifying selection (Rands et al. 2014). Estimating these quantities is difficult, and they are sensitive to assumptions, so they should not be taken too literally; however, it seems clear that human genomes are awash in alleles that disrupt optimal functioning.

Given that approximately one-half of genes are expressed in the brain (Naumova et al. 2013), alleles that affect fitness may do so in part through their influences on behavior. According to several theorists (Keller & Miller 2006, Uher 2009, van Dongen & Boomsma 2013, Yeo et al. 1999, Zietsch et al. 2015), psychiatric disorders (as well as individual differences in other quantitative behavioral traits) are, in part, behavioral manifestations of accumulated disruptions arising from these deleterious alleles. Such alleles individually cause minor disruptions in the normal upstream

Selection coefficient (*s*): quantifies the strength of selection against deleterious alleles; ranges from 1 (lethal) to 0 (neutral)

mechanisms (or endophenotypes) that underlie human behavior (Cannon & Keller 2006). Humans do not, of course, directly perceive variation in these upstream mechanisms, but rather variation in behavior, which is some complex function integrating different networks of mechanisms. Individuals at the extremes of behavioral dimensions carry a high load of deleterious alleles in genomic regions that affect particular constellations of these mechanisms, and psychiatrists and laymen have given these individuals diagnostic labels. Thus, according to mutation-selection-drift models, schizophrenia and several other psychiatric disorders are likely to be heterogeneous groups of dysfunctions in mechanisms whose final common pathways lead to similar behavioral symptoms. Of course, for the variation of a particular trait to be explicable in terms of mutation-selection-drift, a very large number of genes must influence it. It has been estimated that approximately three-fourths of the ~3,000 megabase (million base pair) segments in the genome contain at least one variant influencing schizophrenia risk (Loh et al. 2015), implying a large mutational target size of schizophrenia.

There are now several lines of evidence that suggest that, on average, schizophrenia risk alleles are under various strengths of purifying selection. First, there is a clear relationship between the MAF at loci known to be associated with schizophrenia (Ripke et al. 2014) and their effect sizes (**Figure 1*a***). The frequencies of alleles under negative selection are largely governed by their selection coefficients: Selection tends to keep alleles with large fitness effects rarer than those with small effects, which can drift by chance to appreciable frequencies. Such a relationship between effect size and frequency is not expected under a balancing selection or purely neutral model. If such a trade-off between effect size and frequency occurs across all the loci that affect a trait, then the maximum amount of variance explained by any one locus should be fairly constant across the range of MAF. This is because an allele's frequency and its effect size have opposing effects on the variance explained by the locus, which is proportional to $2p(1-p)\ln(OR)^2$, where p is the frequency of the risk allele and $\ln(OR)$ is the natural log of its odds ratio (Wray et al. 2011). Loci harboring alleles with large *OR* will have low p, whereas those with small *OR* can drift to higher frequencies (have high p). Empirically, the proportion of variance explained in schizophrenia liability (h^2) by individual SNPs and CNVs is <0.0005 (shaded region in **Figure 1*a***). For a given sample size, the statistical power to detect a variant is primarily governed by its h^2, which is why significant variants tend to cluster along the top of this shaded region. However, it is virtually certain that the entire shaded region is populated with risk variants not yet discovered due to lack of power. Because common SNPs with the largest h^2 have probably already been found, it is unlikely that any common SNP explains more than this amount, and it is reasonable to assume this will hold true for rare SNPs (once they are discovered) in the same way that it holds for rare CNVs.

Under a simple model, **Figure 1*b*** converts each variant's effect size into an inferred selection coefficient per variant, s, based on the variant's odds ratio and a presumed fitness disadvantage of schizophrenia of 50% (Bundy et al. 2011). As alleles' fitness effects become small, random chance becomes an increasingly important factor governing their frequencies. This occurs for the same reason that variability of a sample mean is greater in small samples. Alleles that would be driven to a quick extinction in large populations may, by chance, reach appreciable frequencies in small ones. Given what is known about ancestral human population sizes, the frequencies of alleles that decrease fitness by less than ~0.005% ($s < 0.00005$) should be governed mostly by random chance and can drift to high levels, whereas the frequencies of alleles with $s > 0.00075$ (mildly to strongly deleterious) should be low and dominated by selection. Alleles with selection coefficients between these values ($0.00005 < s < 0.00075$) are termed nearly neutral, and, although rare as a group, many nevertheless drift to high frequencies, even fixating by chance (Ohta 1973). **Figure 1*b*** shows that, based on inferred selection coefficients, the most common schizophrenia risk alleles appear

to be on the cusp between nearly neutral and mildly deleterious. By virtue of having been detected in GWA analyses, however, these SNPs are not likely to be representative of the vast majority of other SNPs truly associated with schizophrenia. Out of the thousands of risk alleles in the population, the ones most likely to be detected are those that drifted to frequencies higher than would be expected based on their effects on risk, because such SNPs explain the most variation ($\propto 2p(1-p)\ln(OR)^2$). The vast majority of common schizophrenia risk alleles must explain less heritability (and have smaller effects on risk given their frequencies) than those discovered to date, and thus are likely to be in the nearly neutral range of selection coefficients. Moreover, recent modeling demonstrates that, even for traits under mutation-selection-drift where all variants are mildly deleterious (e.g., $s = 0.0005$), much—potentially the majority—of the genetic variation of the trait can result from common variants due to the drift of nearly/mildly deleterious variants to high frequencies (Simons et al. 2014). Thus, observations that approximately one-third to one-half of the variation of schizophrenia liability is due to common risk alleles and that genome-wide-significant variants appear to have slightly larger effects than would be expected from their frequencies are not inconsistent with a mutation-selection-drift model (Bulik-Sullivan et al. 2015b, Pardiñas et al. 2016). Finally, a strong prediction of all purifying selection models is that the frequency distribution of variants is skewed, such that variants that decrease fitness are more often the minor alleles. This should be especially evident when MAF is low and/or when the absolute effect size (odds ratio) is large. Consistent with this, schizophrenia risk alleles are more likely to be the minor alleles among low MAF SNPs (**Figure 1*c***) and among SNPs with the biggest effects on risk (**Figure 1*d***).

Minor allele: an allele that is less common in the population; for SNPs, there are almost always exactly two alleles

The evidence shown in **Figure 1** is consistent with a mutation-selection-drift model, such that schizophrenia risk alleles are, on average, selected against. However, this evidence draws inference from a small subset of schizophrenia risk variants—those that explain the most variance and are therefore individually detectable in GWAS studies. There are several methods being developed that allow investigators to make conclusions about parameters of interest that are based on all common SNPs that influence schizophrenia risk, including SNPs that have extremely small influences on schizophrenia risk and are not individually detectable in GWAS. For example, modeling 58 different functional annotations using linkage disequilibrium (LD) score regression across a large number of disease traits, Gazal et al. (2017) found that the youngest 20% of common SNPs explained ~4 times more heritability than the oldest 20% ($p = 2.38 \times 10^{-104}$), and this difference was even more stark for psychiatric disorders. This is a strong signal of purifying selection because deleterious variants tend to be younger, even if they reach high frequencies (Kiezun et al. 2013). Contrary to the Gazal et al. (2017) conclusion, however, two other studies found that regions enriched with schizophrenia risk variants are more likely to show signatures of positive selection (Srinivasan et al. 2016, Xu et al. 2015), perhaps suggesting that many schizophrenia risk and/or protective variants are sweeping toward fixation. However, purifying selection can mimic signatures of positive selection because it tends to remove entire haplotypes from a region of the genome, reducing the effective population size at that genomic region and making local genetic drift much stronger (Comeron et al. 2008). After controlling for this effect, Pardiñas et al. (2016) found that positively selected regions were less, not more, likely to harbor schizophrenia risk alleles, and that weak purifying selection on schizophrenia risk alleles appeared to be pervasive.

In summary, possibly the most important discovery in genetics in the GWA era has been the realization of how massively polygenic complex traits are (Boyle et al. 2017). This realization has forced evolutionary geneticists to update their ideas about typical mutational target sizes and the likely effect sizes of alleles that influence fitness-related traits. Whereas ten years ago, it was thought that mutation-selection-drift implied that the majority of genetic variation would be caused by rare variants (which was a core prediction we got wrong in our paper on the topic; Keller & Miller 2006),

the consensus on this view has eroded considerably in light of how massively polygenic complex traits are and how small individual allele effect sizes typically are (Kiezun et al. 2013, Simons et al. 2014, Zuk et al. 2014). Rather, the degree to which variants are rare or common depends crucially on the selection coefficients per allele, which in turn depends on the strength of selection against the trait and its polygenicity, as well as other factors (e.g., the typical degree of dominance of the alleles, the demographic history of the population, typical recombination rates around risk alleles, etc.). Much evidence is broadly consistent with the idea that schizophrenia risk alleles have been, on average, under weak to strong purifying selection. The strength of this evidence is compelling but tentative, and subject to change with improved methods or new insights. Nevertheless, it seems likely that the types of data and analyses now being done will lead to increasing consensus on this question in the foreseeable future. A mutation-selection-drift model of genetic variation can be extended, of course, to understanding the genetic variation in other disorders. Even disorders that may be explicable in terms of facultative defenses, such as depression, or in terms of mismatches between ancestral and modern environments, such as substance abuse, show substantial genetic variation, with heritability estimates of ~35% and 50%, respectively (Kendler et al. 2003), and the types of evolutionary genetic explanations discussed here may apply to this genetic variation as well. However, even if mutation-selection-drift turns out to be the most important process maintaining genetic variation underlying disorders, this would not invalidate the potential role of other mechanisms. They are not mutually exclusive. I turn next to balancing selection models for understanding schizophrenia genetic variation.

A Balancing Selection Model of Schizophrenia Risk Alleles

Under balancing selection, natural selection actively maintains two or more alleles at relatively high frequencies for potentially long periods of time, and as such leads to higher levels of variation per locus, and higher average MAF of risk alleles, than observed for loci drifting neutrally or that are subject to purifying selection. Thus, patterns of genetic variation around such loci are distorted, and genomic scans can, in principle, detect signatures of balancing selection. There are several well-known examples of balancing selection detected in the human genome, including at the hemoglobin-beta gene described above, at the ABO blood group locus, and throughout the human leukocyte antigen (HLA) immunity related genes. Despite considerable searching, however, only a handful of additional instances of it have been discovered (Bubb et al. 2006, Mitchell-Olds et al. 2007, Siewert & Voight 2017). However, absence of evidence is not evidence of absence, and the power to detect balancing selection might often be low (Siewert & Voight 2017).

Two of the strongest associations with schizophrenia occur for SNPs in the HLA region (Ripke et al. 2014, Sekar et al. 2016), and so it is not unlikely that at least some portion of genetic variation in schizophrenia liability is maintained as a side effect of the balancing selection at these HLA loci. Although there are many other hypothesized instances of schizophrenia risk loci being under balancing selection (reviewed in Taub & Page 2016), these have been conducted on traditional candidate genes that appear to be no more related to schizophrenia than genes chosen at random (Farrell et al. 2015, Johnson et al. 2017). Thus, outside of HLA, there is little evidence in the molecular genetic literature for an important role of balancing selection maintaining schizophrenia risk alleles.

Several theorists have posited or tested a mechanism related to balancing selection, antagonistic pleiotropy, which occurs when alleles increase fitness payoff of one trait while simultaneously reducing it for another. Many evolutionary geneticists do not consider antagonistic pleiotropy on its own a type of balancing selection because there is no homeostatic mechanism that ensures that one or the other allele does not fixate. In other words, antagonistic pleiotropy on its own does not lead to genetic variation—one of the alternative alleles will tend to eventually fixate, either

because one allele is slightly more fit than the other, or due to drift if the opposing fitness effects are extremely close in strength. Nevertheless, antagonistic pleiotropy is a worthwhile possibility to consider because it may explain why some schizophrenia risk alleles have drifted to frequencies higher than would be expected based on their apparent fitness effects (**Figure 1*b***). A commonly invoked idea with regard to schizophrenia is that some of its risk alleles may increase fitness by increasing creativity among carriers, but this fitness increase is counter-balanced due to (slight) increases in risk to schizophrenia or bipolar disorder (Barrantes-Vidal 2004, Karlsson 1974, Nettle 2001). Consistent with this, it appears that schizotypal personality traits, a personality dimension predictive of schizophrenia, is associated with artistic creativity and number of mating partners, at least in males, which is probably a more ecologically valid measure of reproductive success than number of offspring in societies where birth control is easily available (Nettle & Clegg 2006, Beaussart et al. 2012). There is also good evidence that first-degree relatives of people with schizophrenia are over-represented in creative professions (Kyaga et al. 2011), and that people who harbor more schizophrenia risk alleles are more likely to be in creative professions (Power 2015). This evidence suggests that creativity is pleiotropically related to at least a modest proportion of common schizophrenia risk alleles. Although there is little evidence that relatives of people with schizophrenia have more offspring in a way that might compensate for the negative fitness of schizophrenia (Haukka et al. 2003, Power 2015), modern fertility may not be a good way to gauge the ancestral fitness effects of alleles, and it is these ancestral fitness effects that are relevant to modern allele frequencies. On balance, it seems plausible that some proportion of schizophrenia risk alleles increase, on average, creativity in a way that might have increased fitness ancestrally. This might in turn suggest that the net fitness of these risk alleles is closer to neutrality than would be expected based on their effect on schizophrenia risk. This is different than positing that schizophrenia risk alleles are advantageous—which would also be paradoxical, because they should then fixate—or saying that they are maintained by balancing selection per se.

In summary, there is intriguing evidence that schizophrenia risk alleles might confer some advantages to their carriers that partially offset their negative fitness effects due to increasing risk of the disorder, and it seems likely that some of its risk alleles are maintained by balancing selection on immunity-related traits. However, it seems unlikely that balancing selection or antagonistic pleiotropy are general mechanisms that maintain the genetic variation in the liability to schizophrenia. Rather, given the evidence that schizophrenia risk alleles are rarer and younger than nonrisk alleles (Gazal et al. 2017), mutation-selection-drift is likely to be a more general explanation for the patterns observed in the data.

DEPRESSIVE SYMPTOMS AS ADAPTIVE DEFENSES TO BAD SITUATIONS

Pain is an unpleasant subjective reaction, typically to physical stimuli that risk causing tissue damage. There is little doubt that the capacity to experience pain, when expressed in the appropriate contexts, is vital to survival. People with congenital insensitivity to pain, a rare condition in which the person cannot feel physical pain, often die early through untreated infections, burns, and wounds and find it very difficult to avoid the types of activities that cause such harm (Danziger & Willer 2009). This disorder highlights the two likely adaptive functions of the normal pain reaction: It causes reflexive retraction from damaging stimuli, such as a hot surface, and its aversiveness motivates avoidance of such damaging stimuli in the future (Nesse & Williams 1994).

The example of pain as an adaptation is illuminating for several reasons. First, it makes clear that adaptations are designed to maximize fitness, not personal comfort or well-being. Second, people often assume that defenses such as pain, coughing, fever, and nausea are the problems

Adaptive defense systems: types of adaptations reliably activated in fitness-threatening situations in order to minimize fitness loss

themselves because their expression coincides with negative situations, such as illness, disease, and injury (Nesse 2005). An understandable and historically prevalent response is to treat the symptoms as a means to reduce suffering and aid recovery. However, the recognition that these reactions are likely bodily defenses raises the issue of unintended consequences of suppressing them, and indeed there is some evidence that blocking fever (Kluger et al. 1996) and pain (van Esch et al. 2013) can worsen outcomes. Third, overlaid across normally functioning pain mechanisms is a good deal of individual variation, in pain thresholds for example, and much of this variation is genetic in nature (Nielsen et al. 2008). Such genetic variation probably requires fundamentally different types of explanations, as discussed in the previous section. Finally, it is the capacity to experience pain, not pain itself, that is adaptive. The focus of ultimate explanations for defensive reactions should be on why selection favored their universal capacities. It is a fool's errand to attempt to explain the adaptive benefit for every particular instance of pain—it is sometimes expressed inappropriately or disproportionately. Even though the capacity to experience pain is almost certainly the product of fine-tuning from millions of years of natural selection, the system is not immune to disruption and inappropriate expression. Approximately one-fifth of people in modern industrialized environments experience chronic pain (Breivik et al. 2006). Many of these cases are normal reactions to bad situations, such as pain arising from arthritis, cancer, or herniated disks. Here, the pain system itself is probably functioning as designed; the dysfunction has to do with what caused the pain. However, in some unknown percentage of chronic pain cases, it is probable that the pain is disproportionate to the injury, and indeed, no cause can be identified in roughly ten percent of them (Breivik et al. 2006). Thus, to posit an adaptive explanation for pain is not to argue that all instances of it are adaptive.

The parallels between pain and depression are obvious, but before turning to evolutionary explanations for depression, one must first identify the unit of analysis. As with pain, it is probably more useful to focus first on understanding the capacity to experience depressive reactions rather than on clinical depression itself. Here, I define "depressive reactions" as the cluster of symptoms—sadness, anhedonia (inability to feel pleasure), pessimism, fatigue, changes in sleeping and eating behavior, and guilt—that probably occur in all normal people following certain types of negative situations such as deaths of loved ones, failures at life goals, romantic breakups, etc., without reference to the intensity or duration of the symptoms. Thus, depressive reaction and clinical depression are by design not synonymous here, because understanding normal reactions is a first step to understanding more severe ones. Unfortunately, the vast majority of the research on depressive symptoms is in the context of clinical depression. Nevertheless, insight into normal depressive reactions can be gained by such work, because it is likely that many episodes of clinical depression emanate from normally functioning mechanisms that find themselves in particularly adverse situations.

A hallmark of adaptive defense systems is that they are species-typical (Tooby & Cosmides 1990) and reliably activated in situations that were likely to harm fitness over evolutionary history (Janzen 1981). Depressive reactions appear consistent with these aspects of an adaptive defense system. Evidence suggests that depressive reactions to adverse life situations are the norm, not the exception. Brown & Harris' (1978) study as well as nine subsequent studies (reviewed in Brown & Harris 1986) found that on average 83% of depressive episodes were preceded by one or more severe negative life event, even though only approximately half of people facing severe life events crossed the threshold to clinical depression. A reanalysis of Brown & Harris' original (1978) data found that the depressogenic effects of severe negative life events was cumulative: 50% of the people exposed to one severe life event became depressed, 73% exposed to two severe life events became depressed, and 100% exposed to three severe life events became depressed (Monroe & Simons 1991). Much research supports the basic finding that depressive episodes are typically

not spontaneous, but are involuntary reactions to recent negative life events (Cassano et al. 1989; Kendler et al. 2000, 2002; Perris 1984).

If the capacity to have some sort of depressive reaction (regardless of whether it crosses an arbitrary threshold of clinical severity) following a negative life event is normal rather than pathological, why might such a capacity exist evolutionarily? According to several theorists, depressive symptoms are fundamentally about goal regulation, and depressive symptoms such as anhedonia, pessimism, fatigue, and sadness force one to withdraw and move on from failing goals (Carver & Scheier 2001, Nesse 2000, Nettle & Bateson 2012, Watson & Andrews 2002). Much research is consistent with this idea. For example, infertility treatment failure is predictive of depression, especially among people unable to let go of the goal of becoming pregnant despite repeated failure (Maroufizadeh et al. 2015, Salmela-Aro & Suikkari 2008). Similarly, longitudinal data showed that adolescent girls with higher levels of baseline depressive symptoms showed increased ability to disengage from failing goals, and such disengagement was subsequently associated with decreased levels of depressive symptoms (Wrosch & Miller 2009). Other theories posit that depressive reactions evolved to signal submissiveness following defeat (Price 1967, Price et al. 1994) or to coerce social partners to increase investment (Hagen 1999, Watson & Andrews 2002). There is evidence consistent with all of these hypotheses, showing that failures at goals, social defeat, and low social investment are sufficient causes of depression, but the evidence also shows that these are not necessary conditions—many different types of adverse life events precipitate depression. Thus, it is possible that each of these theories captures important elements of the depressive reaction without explaining the totality of it.

An alternative is that depressive reactions were designed to solve more general and multifaceted adaptive problems, and were useful in a wide variety of negative life situations where depressive reactions might minimize fitness loss. This requires consideration of the potential functions of specific depressive symptoms (Keller & Nesse 2006). We argued that, analogous to physical pain, sadness motivates avoidance of fitness-reducing situations. Given that people can anticipate their reactions to future actions, sadness can be adaptive preemptively, without the situation having ever occurred. Fatigue, pessimism, and anhedonia might serve to reduce goal pursuit and conserve resources when future effort is unlikely to succeed. Rumination and the depressive realism cognitive style may aid in sustained analysis of complex problems (Andrews & Thomson 2009). Crying may be a signal to others for social or emotional support. One prediction of the hypothesis that different depressive symptoms serve different functions is that precipitants should give rise to symptom patterns well matched to the adaptive challenges of each situation. This prediction has some support: Failures at goals are associated with symptoms such as fatigue and pessimism that should decrease future goal pursuit, whereas social losses are most strongly associated with sadness and crying and relatively low levels of pessimism or fatigue (Cramer et al. 2012; Keller & Nesse 2005, 2006; Keller et al. 2007). The main problem with these results is that they rely on self-reports of both depressive symptoms and their causes. The situations people report as the causes could be distorted by the symptoms and vice-versa, or the situations may themselves result from risk factors shared with depression (Kendler et al. 2011).

Another prediction of the hypothesis that different depressive symptoms serve different functions is that the symptoms should accomplish the hypothesized functions and that blocking them, via antidepressants, for example, might retard long-term well-being or adjustment. Investigating these predictions is difficult, however. For one, depressive symptoms occur in the context of negative situations where the prospects of positive outcomes are inherently diminished. Secondly, existing studies typically define successful outcomes in terms of depression remission rather than the solving of the problems that gave rise to the symptoms. This is clearly an area in need of more study and one in which evolutionary thinking raises many testable hypotheses waiting to be investigated.

Given that many depressive symptoms are hypothesized to be related to energy conservation and reduction of goal pursuit, it is telling that the typical behavioral symptoms induced by acute infections overlap highly with depressive symptoms (Maes et al. 2012). Carefully controlled experiments, quasi-experiments, and observational studies (Capuron et al. 2000, 2004; Meyers 1999; Wright et al. 2005; Yirmiya et al. 2000) show that the body's own defense response—specifically, proteins secreted by cells of the immune system called cytokines—cause this depressive reaction. That the body's defense against illness also causes depressive reactions is consistent with the hypothesis that the depressive reaction is a behavioral defense to specific adverse conditions. However, contrary to prediction about the specificity of depressive symptoms depending on the precipitant, at least two studies have found that all depressive symptoms, and not just those related to energy conservation (e.g., fatigue, pessimism, anhedonia), are elevated following infection (Bremmer et al. 2008, Stieglitz et al. 2015).

What can adaptive explanations of normal depressive symptoms tell us about clinical depression itself? Clinical depression melds invisibly into subthreshold depression, which melds into the more common ranges of negative affect (Akiskal & Cassano 1997, Angst 1992, Kendler & Gardner 1998), making the distinction between clinical and subclinical depression necessarily definitional and, to some degree, arbitrary. Many evolutionary psychologists have been persuaded by Wakefield's (1992, 1999) harmful dysfunction model, which argues that disorders should be defined as failures of a mechanism's naturally selected functions. For example, the heart is a muscle designed by natural selection to pump blood. When it fails at this objective, this failure can reasonably be called a heart disorder. In their book, *The Loss of Sadness: How Psychiatry Transformed Normal Sorrow into Depressive Disorder*, Horwitz & Wakefield (2007) argue that definitions of clinical depression based on severity and duration do not distinguish dysfunctional from normal reactions. As with chronic pain, it is likely that many instances of clinical depression represent normal reactions to extremely adverse situations, and so it is crucial that the reaction be gauged relative to the adversity of the situation. Such an understanding of whether a reaction is dysfunctional given the situation requires a much better understanding of what the normal (adaptive) functions of the reaction are likely to be.

The harmful dysfunction model is important because it seeks to separate desires to avoid pain from dysfunction itself, potentially providing a conceptually sound foundation for defining depression. However, there are problems with implementing it in practice that go beyond simple resistance to evolutionary approaches in psychiatry. First, understanding the degree of abnormality of a depressive episode would require valid assessment of the severity of the situation, but such assessment is likely to be unreliable and potentially distorted because it must ultimately rely on self-report by the sufferer; objective reports or those from third parties cannot capture the subjective interpretation of events that is crucial to understanding individual reactions to events. Second, a definition based on dysfunction does little to clarify when depression should be treated (Nettle & Bateson 2012). Some evolutionarily nondysfunctional depressive episodes may nevertheless lead to real suffering in modern societies that could benefit from treatment (Kendler 2013). Finally, finding compelling evidence for ultimate explanations is inherently difficult—much more difficult, typically, than for proximate explanations. It is likely that an evolutionary understanding of why depressive reactions occur would be scientifically valuable, but it is not easy to conceive of real studies that would provide sufficiently compelling evidence to convince most researchers that depressive reactions have been shaped by natural selection.

Despite these difficulties, ultimate explanations of depressive symptoms serve important scientific functions. They provide a general explanation for why depressive symptoms exist, and they organize and explain observations in a theoretically coherent and unified manner. They also spur generation of novel hypotheses, most still awaiting tests. For example, if depressive

symptoms are adaptive, questions naturally arise surrounding the value of treating depression that would otherwise be ignored or rejected out of hand. Thus, evolutionary medicine offers a much different, and I would argue valuable, perspective on psychiatric disorders.

CONCLUSIONS

As Wakefield, Nesse, and others have argued, an evolutionary perspective can help build a more logical definition of dysfunction, highlight aspects of disorders that were not obvious from traditional perspectives, and suggest novel, testable hypotheses to investigate. It is probably true that proposed answers to ultimate questions will often be less conclusive than proposed answers to proximate ones, but this is intrinsic to focusing on different levels of explanations. Different fields have different levels of comfort with uncertainty as a consequence of the types of data that can be brought to bear on questions of interest. Behavioral scientists have a lower bar for certainty in their results than do molecular biologists, who in turn have a lower bar than physicists, but the questions asked across fields are no more or less worthy of study because of this. In the same way, evolutionary approaches can be useful, even if the level of certainty in their explanations is lower than the level of certainty in proximate investigations. Theories do not require conclusive evidence to be useful. Rather, they should provide satisfactory explanations for existing observations and make new, empirically testable, predictions, and evolutionary approaches to depression and other psychiatric disorders are beginning to do both.

The utility of evolutionary theory is becoming particularly apparent in the study of complex trait genetics. Different evolutionary processes leave different signatures in the genome that provide evidence for the evolutionary processes at work. Interpretation of this evidence does not require understanding ancestral conditions that cannot be observed. Furthermore, understanding the evolutionary processes responsible for maintaining genetic variation is not only a matter of satisfaction of curiosity—it is relevant to understanding how best to design studies and analyze data. For example, if risk alleles have been under purifying selection and are maintained by mutation, then methods that sum up the burden of minor alleles in functional regions of genes are more powerful than methods that allow either the minor or the major allele to be the risk variant (Lee et al. 2014). With the rapid growth of genetic data available to researchers, it is likely that the evolutionary forces that have maintained genetic variation in complex traits will be well understood within the next ten years.

SUMMARY POINTS

1. Evolutionary medicine and traditional biomedical research often attempt to explain the same phenomena, but at different levels. Evolutionary medicine typically focuses on ultimate explanations, whereas biomedical research typically focuses on proximate ones. These two levels of explanation are not competing, and at best can be mutually consistent and reinforcing.
2. Natural selection, central to understanding species-typical adaptations, is not typically a good explanation for the evolutionary causes of genetic variation in traits. Two basic types of evolutionary models—mutation-selection-drift and balancing selection—have been continuously developed over the past century to explain the existence of genetic variation underlying fitness-related traits, and these models can be used to understand genetic variation underlying psychiatric disorders.

3. Large whole-genome datasets in humans are beginning to clarify the genetic architecture of psychiatric disorders, including schizophrenia, and are now being used to test the predictions made by mutation-selection-drift and balancing selection models. Much of this evidence seems consistent with a simple mutation-selection-drift model, but this may change as more data and better models are developed in the coming years.
4. Natural selection crafts adaptations that maximize fitness, including reactions to negative events that can be subjectively unpleasant, such as pain, nausea, and sickness behavior. In a similar way, the universal capacity to experience depressive symptoms in unpropitious situations may be a behavioral defense crafted by natural selection to minimize fitness loss. This hypothesis serves only as an explanation for the environmental variation of depression, expressed as a function of the situation, and is not a good explanation for the genetic variation underlying depression.

FUTURE ISSUES

1. What is the genetic architecture of schizophrenia and other psychiatric disorders? This information can help us understand the likely evolutionary forces that acted on psychiatric disorder risk over evolutionary time, and can help in optimal design for genetic studies.
2. What are the typical selection coefficients for psychiatric disorder risk alleles? Adjustments to GREML methods (which model all SNPs simultaneously to estimate the total genetic variation of a trait caused by all variants tagged by SNPs) that are currently being developed will allow direct estimation of the average selection coefficients of risk alleles, which will provide information on whether they had, on average, positive, neutral, or negative fitness effects ancestrally.
3. Almost all scientific research on the liability underlying depression has been focused on the depressive end of the spectrum, but are there deficits among individuals at the other end of the spectrum who are highly resistant to becoming depressed? Evolutionary considerations predict that people incapable of experiencing depressive symptoms may persist in unreachable goals, be less able to learn from mistakes, and be at risk for losing valuable social connections.
4. What is the genetic architecture of depressive symptoms controlling for the severity of the situation that led to the depressive episode(s)? Major depression is a highly heterogeneous disorder, in part because some episodes of depression are normal reactions to extremely negative situations whereas others are extreme reactions to mildly negative situations. Controlling for the situation may simplify and/or change our understanding of the genetic architecture of major depression.

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