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.

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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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