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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