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

## Multiple timescales of evolution

Jonathan Williams

*Department of Child and Adolescent Psychiatry, Institute of Psychiatry, London SE5 8AF, United Kingdom.*

**johwilliams@gmail.com** **http://folk.uio.no/jonathaw/**

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

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

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

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

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

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

The suggested categories are:

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

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

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

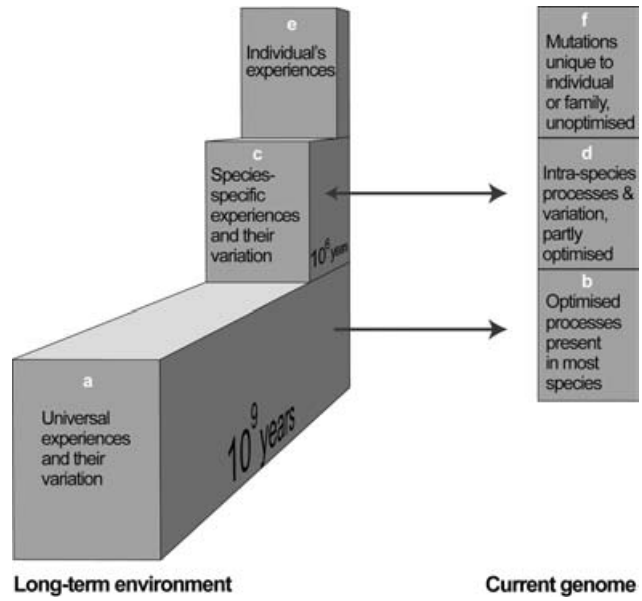



Figure 1 (Williams). Some broad categories of influences on an individual's current cognition and behaviour. Factors common to all mammals can be included in layers **a & b**. Additional layers could be added within layers **c & d** for nested groups such as primates or human subgroups. Adaptations within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



https://doi.org/10.1017/S0140525X06439091 Published online by Cambridge University Press

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

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

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

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

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

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

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

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

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

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

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

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

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

ACKNOWLEDGMENTS

I thank Peter Dayan, Peter Killeen, Michael Moutoussis, and Eric Taylor for helpful comments on a draft of this commentary.

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

Daniel R. Wilson

*Departments of Psychiatry and Anthropology, Creighton University, Omaha, NE 68131.*

**wilson@creighton.edu** **http://cp.waittdesign.com/**

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

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

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



https://doi.org/10.1017/S0140525X06439091 Published online by Cambridge University Press