# The promise of evolutionary psychiatry

In this issue of the journal[1], R.M. Nesse – one of evolutionary psychiatry's most intellectually fertile theorists – provides a primer of the field's accomplishments and makes a compelling argument for evolutionary psychiatry as a foundational science for psychiatry. He portrays a rapidly maturing field bursting with fresh insights and provocative hypotheses. Using innovative methodologies – ranging from genetic analysis of natural-selection histories of specific alleles to studies of nomadic human groups living in conditions similar to our human evolutionary environment – evolutionary psychiatry has moved from heuristic speculation to scientifically fruitful empirical testing of rival hypotheses. Nonetheless, the promise of this field has thus far largely lain dormant.

This is a good time to examine the strengths and limitations of evolutionary psychiatry. Psychiatric nosologists are currently grappling with the failed aspirations of the DSM-III revolution and disputing what, if anything, should replace it, whether symptom dimensionalization (e.g., Hierarchical Taxonomy of Psychopathology, HiTOP)[2], network theory[3], biologicalism (e.g., Research Domain Criteria, RDoC)[4], or something else. Each competitor for psychiatry's nosological mantle characterizes itself as a "paradigm shift". How does evolutionary psychiatry fit into this dispute about psychiatry's future?

The most fundamental contribution of evolutionary psychiatry is that, by studying distal natural-selective processes that explain the existence and functional architecture of psychological mechanisms, it illuminates evolved human biological design and thus the nature of normality. It provides the functions relative to which we can identify the "dysfunctions" referred to in DSM's and ICD's definitions of mental disorder[5]. It can thereby help us to refine disorder categories to be more valid. For example, evolutionary psychiatry can clarify why social deviance and other problematic mismatches between individuals' natures and current social demands are not necessarily mental disorders, and reveal the importance of context in recognizing normal emotional functioning.

The "smoke detector" explanatory heuristic mentioned by Nesse illustrates such novel insights into normality. It reminds us that the organism's defense systems are often designed to react vigorously even to modestly probable threats, because failing to defend when the threat is real (a "false negative") can be fatal or highly costly, whereas an overreaction (a "false positive") is not too costly. Thus, many biologically designed defensive responses, from fever to anxiety, sometimes occur at levels disproportionate to actual threat.

Evolutionary psychiatry usefully resists the tendency to reify superficial symptom syndromes into disorders with presumed single etiologies. There are multiple reasons why a function may fail, and what seem like disorders may be normal reactions to extreme environmental conditions. To extend an analogy used by Nesse, if one's automobile does not start, a trouble-shooting manual will provide a dozen possible breakdown etiologies, but also note that you may simply be out of gas. From an evolutionary perspective, some current DSM symptom syndromes are best construed as entries in a "trouble shooting guide" for the mind that point to sets of potential explanations, both normal and pathological, for the problematic condition. Throughout his review, Nesse emphasizes that natural selection explains *vulnerability* to disorder (because by definition disorder is not naturally selected). Vulnerability is risk, and risk for disorder may transform into disorder for multiple reasons.

The importance of the normal/disorder demarcation is not only conceptual/nosological (distinguishing disorder from problems in living) or sociopolitical (answering anti-psychiatric critics who argue that psychiatry is about social control). It also underlies a distinctive and powerful medical strategy of discovery. Biological design's extraordinary complexity often eludes full understanding at the causal-mechanism level. However, shared intuitions about biologically designed functioning offer a background explanatory framework that allows identification of manifest design failures, and etiological or curative factors can then be sought despite gross ignorance of internal mechanisms. I call this the "wrench in the gears" strategy because, as with the gears of a machine, one can see that there is a failure of designed functioning and find a way to fix it without ever understanding what a machine does or how it works. This strategy worked well in physical medicine. Evolutionary psychiatric insights could translate into more powerful use of traditional medical strategies of disorder identification and treatment discovery.

A major contribution of evolutionary psychiatry is that it can help to resolve the current impasse between dimensional and categorical views of mental disorder. Sometimes problematic extremes on symptom dimensions are due to mutations that constitute clear categorical dysfunctions. For example, many known mutations cause intelligence to fall within the disorder of intellectual disability. Recent research suggests that mutational dysfunctions define normal/disordered boundaries on continuous symptomatic dimensions between premenstrual syndrome and premenstrual dysphoric disorder[6], and between morning sickness during pregnancy and the disorder of hyperemesis gravidarum[7].

Moreover, independent of mutations, evolutionary psychiatry can provide normal/disordered boundaries based on the presence or absence of natural selective pressure – what I call the "overshoot" problem. The distribution of alleles across genetic loci contributing to a multigenic selected trait commonly forms a normal curve with regard to strength of the trait, with the mean and some interval around it being naturally selected. However, one or both tails of the distribution may not confer the trait at a naturally selected level. Some instances of intellectual disability appear to be due not to mutations but to non-selected distributions of alleles at intelligence-relevant genetic loci. For emotions, one can imagine that both tails, too little and too much, might be non-selected.

Another example of discontinuity along dimensions is the "cliff-edge" phenomenon noted by Nesse. This occurs when selective

forces have pushed us to a genetic sweet spot regarding a certain trait that does not tail off gradually but, with relatively minor changes in the allele distribution, suddenly transforms into disorder. Many psychological traits may need to stay within narrow bounds to enable adaptive social interaction, so small variations may yield cliff-edge disorder vulnerability.

Emergent properties of specific allele combinations may exist for other unexpected reasons. For example, a recent study found that certain combinations of positively selected alleles yielding cognitive advantage increased risk for autism spectrum disorder[8]. Moreover, beyond alleles, at the trait level, there can be dysfunction-causing combinations of individually selected positive traits (e.g., certain combinations of individually selected personality traits can yield personality disorders such as psychopathy). All of this goes to show that it is not dimensionality *per se* but the way selective processes operated on various elements on a dimension that determines normality and disorder.

Evolutionary psychiatry's role thus transcends the current dispute over psychiatry's nosological future. Whichever proposal triumphs, psychiatry's status as a medical discipline requires distinguishing normal variation from mental disorder, which rests on understanding human psychobiological design. Symptom networks, extremes on symptom dimensions, and intense brain circuitry activations can be normal or abnormal depending on context. These proposals, whatever their merits, rearrange the symptomatic deck chairs on our nosological Titanic without addressing the root problem: i.e., that DSM psychiatric nosology is sinking due to lack of attention to the evolved nature of human normality, yielding invalid normal/disorder demarcations[9]. Only evolutionary psychiatry provides a scientifically defensible answer to the fundamental nosological normal/disorder "demarcation" problem.

Because the way people are biologically designed does not always fit social values and ideals, evolutionary psychiatry treads on potentially controversial ground. There is a tension between social idealizations – what we want to believe about ourselves and demand of our society's members – versus the scientific reality of human nature. M. Foucault correctly observed that a society's view of human nature tends to be distorted and permeated by its values and biases, rationalizing its efforts at social control. If psychiatry is to make scientific progress, it must understand the truth of human nature that lies beyond cultural preconceptions as a basis for valid diagnostic concepts that support psychiatric science. The promise of evolutionary psychiatry is that it is the one subdiscipline of psychiatry devoted to realizing this foundational goal.

Jerome C. Wakefield
Center for Bioethics, School of Global Public Health, and Silver School of Social Work, New York University, New York, NY, USA

1. Nesse RM. World Psychiatry 2023;22:177-202.
2. Kotov R, Krueger RF, Watson D et al. J Abnorm Psychol 2017;126:454-77.
3. Borsboom D. World Psychiatry 2017;16:5-13.
4. Insel TR, Cuthbert B, Garvey M et al. Am J Psychiatry 2010;167:748-51.
5. Spitzer RL. J Abnorm Psychol 1999;108:430-2.
6. Dubey N, Hoffman JF, Schuebel K et al. Mol Psychiatry 2017;22:1172-84.
7. Fejzo MS, Sazonova OV, Sathirapongsasuti JF et al. Nat Commun 2018;9:1178.
8. Polimanti R, Gelernter J. PLoS Genet 2017;13:e1006618.
9. Wakefield JC. World Psychiatry 2022;21:4-25.

DOI:10.1002/wps.21070

# Biomarkers in psychiatric disorders: status quo, impediments and facilitators

As probes of the beating heart of a disorder, few research domains match both the promise and complexity of biomarkers. From monoamines to cortisol, inflammatory markers, neuroimaging and cognition, serial waves of enthusiasm have broken concerning biological markers in psychiatry only to dissipate feebly on the shores of research validation, but research is still very active in this area. Biomarkers have diverse potential roles: there may be biomarkers of risk, of diagnosis/trait, of state or acuity, of stage, of treatment response, and of prognosis[1]. This classification is not arcane; a marker might succeed in one domain but fail in others – there are multiple examples in general medicine that this is indeed the case.

In this issue of the journal, Abi-Dargham et al[2] explore the most promising candidate biomarkers in major mental disorders. They highlight an electroencephalographic event-related brain potential, the N170 signal, for autism spectrum disorder; striatal resting-state functional magnetic resonance imaging (fMRI) measures for schizophrenia; an electrophysiological metric, error-related negativity, for predicting the onset of generalized anxiety disorder; and resting-state and structural brain connectomics for social anxiety disorder. All of these candidate biomarkers await confirmation by definitive and replicated studies.

There are multiple hurdles to be cleared in the race to the finishing line of clinical translation of biomarkers. One of the most significant ones is related to current diagnostic classifications. It is implausible that symptom-based classifications can cleave the biology of nature at its joints, yet they remain the reference point against which biomarkers are indexed. Most psychiatric disorders are extremely heterogeneous and at the same time overlap extensively with other disorders. Comorbidity, with other psychiatric disorders and with non-communicable physical disorders, is the rule, and both can influence any exploratory marker. There are also extensive interactions between any potential marker and a plethora of variables, including early life experiences, genetics and epigenetics, current stressors, medications and other therapies, environmental and lifestyle risk factors, stage of illness trajectory, age, as well as secondary biological adaptations to these variables.

A frequent stumbling block is power, with most biomarker