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Evolutionary Explanations, Psychiatric Genetics, Media and the Cultural Imagination

National Public Radio science blogger Barbara J. King recently reported on the 42nd of Discover Magazine's 100 "top science stories of 2012" titled "The Myth of Choosey Women, Promiscuous Men". This year, evolutionary biologists repeated A.J. Bateman's 1948 touchstone study on fruitfly mating that demonstrated male reproductive success relies on mating with many females, while female reproductive success demands selective partner choice. The original Bateman study, conducted before the invention of DNA analysis methods, used "heritable, dramatic, and phenotypically obvious genetic mutations to identify the parents of offspring in small, replicated trial populations": progeny could have a single-dose mutation from the mother or father, or a double dose mutation from both parents, allowing lineage to be traced and mating methods determined. The crucial mistake? Those double-dose mutations drastically increased offspring mortality, a key data effect that was unaccounted for in Bateman's conclusions. Modern researchers also found that there must have been some critical discrepancy in data collection (or perhaps in trait penetration), as inexplicably Bateman's results revealed more single-mutant offspring with the father's single mutation than with the mother's.

King argues that the implications of this faulty finding permeated throughout the natural and social sciences, as well as into popular culture and the social psyche of generations. She describes how the bias in Bateman's work, after being cited in Robert Trivers' 1972 paper on parental investment, altered investigations in her own field of

primate behavior, and notes that even after extensive social anthropology data that seemed to debunk the myth (most notably in anthropologist Sarah Hurdy's 1981 book *The Woman That Never Evolved*), this theory thrived. In other words, when society's vanguards of objectivity failed to successfully and systematically challenge faulty and outdated methodology, the double standard of gendered sexual behavior was consecrated into a culture primed to intuitively accept such sexism as biologically valid. Now that the original mating research has been debunked, how and when this fresh perspective will be integrated into the American public's social conscience is unknown. The prospects aren't good; even the most basic and immediate scientific education in this country is failing, as evidenced by the paltry 12% of Americans with proficient health literacy according to the Office of Disease Prevention and Health Promotion (Mika, 2005). Studies indicate that most of the U.S. population uses popular media outlets as the primary source of their genetics education, indicating that the onus is on news distributers to provide informed, critical, and accessible information on genetic research (Lanie, 2004).

The field of psychiatric genetics presents unique challenges and opportunities for this kind of responsible journalism. Mental illness, with its pervasive but not intuitively advantageous characteristics, challenges the core assumption that modern peoples represent the apex of our historical species. It is not difficult to trace this intellectual inheritance back to Darwin's *Origin of the Species*, which devotes a significant portion of its five hundred plus pages to drawing parallels (ostensibly for the sake of improving relatability and authorial credibility) between artificial selection and natural selection. "Nature" is often personified, and the active decision-making of characters such as the English pigeon breeders is implicitly transferred to this "Nature". The western world's

introduction to evolution via heritability espoused an explanatory mechanism that codified the wild chaos of the natural environment in anthropomorphic terms. In a human world that operates on the scale of actors and actions, with the ability to understand motivations, wills, and desires considered essential to productive living, it is not unexpected that the dominant paradigm of understanding evolution embraces causality and goal-oriented thinking. While this paradigm may be intellectually convenient, I hope to demonstrate through an analysis of popular media's use of psychiatric genetics that it is also destructive to the progress of scientific disciplines and to the consumer population as a whole.

In October 2012 *The Atlantic* published an article titled "The Evolutionary Advantage of Depression," which detailed the results and implications of a paper, "The Evolutionary Significance of Depression in Pathogen Host Defense" by Dr. Andrew Miller and Dr. Charles Raison. The article begins by describing the increasing effects of suicide in America, suicide being the most devastating and clearly maladaptive byproduct of depression and other mood disorders. The author then pivots to the true hook of his piece, revealing that new genetic evidence implies that depression "was actually adaptive (helpful) to our ancestors." This evidence asserts that certain alleles that increase the risk for depression also enhance immune response to infections. The author's original assumption that the human genome can draw sound conclusions about ancient civilizations is reinforced by a quote from one of the study's authors, Dr. Raison, who states, "The basic idea is that depression and the genes that promote it were very adaptive for helping people—especially young children—to not die of infection in the ancestral

environment." The article argues that some modern patients with major depressive disorder are likely to have the form of a mutated version of the gene coding for Neuropeptide Y, which allegedly decreases one's tolerance for stress in comparison to the normal gene version, and simultaneously enhances immunity. Further speculations on the relationship between immune function and major depression discuss behavioral characteristics of depression. Drs. Raison and Miller postulate that some symptoms of depression including social withdrawal and lethargy once increased survival by conserving the body's energy reserves and decreasing the likelihood of encountering an infectious agent.

Miller and Raison's original article published in *Molecular Psychiatry* examines a broad set of single-nucleotide polymorphisms (SNPs) with immune/host defense functions that were associated with major depression based on the largest available meta-analysis of genome-wide association studies conducted on major depression. The researchers' core argument is that "knowing the effects of depressogenic alleles on outcomes following infection with specific pathogens may cast light on the relative importance of each pathogen for driving human evolution, because the high price imposed by depressogenic alleles mandates a compensatory high payoff in terms of pathogen defense" (13). Not all SNPs associated with major depression had a function in the immune system, though the paper includes discussions of even those with potential related functions, as in SEL1L2 which belongs to a wider sel1 gene family with another protein that is important for IgM production and limiting the infectious capacity of key viruses. The ten identified risk alleles for depression were each evaluated in the context of immune responses to infection that the researchers deemed likely to enhance survival

in the ancestral environment. The overall conclusion of Raison and Miller was that a regular association between these alleles and immune response was established. The foundational hypotheses criteria for this conclusion are summarized here:

Table 1 Pathogen Host Defense (PATHOS-D) theory of depression: foundational hypotheses

(1) Depression should be associated with increased inflammation and inflammatory activation should induce depression.
(2) Allelic variants that increase the risk for major depressive disorder (MDD) should enhance host defense mechanisms in general and innate immune inflammatory responses in particular.
(3) Environmental risk factors for MDD should be associated with increased risk of infection and attendant inflammatory activation.
(4) On the whole, patterns of increased immune activity associated with MDD should have decreased mortality from infection in ancestral environments.
(5) Depressive symptoms should enhance survival in the context of acute infection and in situations in which risk of infection from wounding is high.

Each allele-immunity interaction is evaluated through these foundational hypotheses. Though Miller and Raison conclude through a "weight of evidence" approach that the overall association is strong, the individual arguments based on scientific evidence accumulated for each allele in question often seem weak and speculative. Take for example one depression risk SNP, rs1006737, which is in the CACNA1C gene that codes for a subunit of one kind of voltage-gated calcium channel. The depression risk role of the SNP seems valid enough (carriers of the risk A allele present brain function and morphology changes consistent with changes seen in MDD patients), and the calcium voltage channel is essential to many immune cell types, including dendritic cells, CD4+/CD8+ T cells, mast cells, and macrophages. As predicted the depressogenic A allele is associated with reduced activation of an anti-inflammatory messenger (i.e. overall leads to increased inflammation). However, Timothy Syndrome, a rare gain-of-function variant in the voltage-gated calcium channels, is associated with increased infection risk, and activation of these channels actually impeded host defense, at least in the case of M. tuberculosis. In their article the authors recognize that this SNP and many elements of other SNP effects and pathways do challenge the pathogen host defense hypothesis, but their eventual conclusions (and statements in popular media) seem to overlook such complexities. The second branch of reasoning in PATHOS-D argues that depressive symptoms play a valuable role in the intricate drama of pathogen host defense. Common depressive symptoms that fit this bill include hyperthermia, reduced bodily iron stores, conservation/withdrawal behavior, hypervigilance, and anorexia. Each of these symptoms can be reasonably attributed to increased survival in the face of infection. For example, many depressives seem to experience a state of "conservation withdrawal" that

can be induced by proinflammatory cytokines. This behavioral state characterized by depressed mood, anhedonia, psychomotor retardation, social avoidance and anorexia may be valuable when the body's limited resources must be directed to the metabolically demanding tasks of immune activation, fever generation, and tissue repair.

While many researchers have welcomed this hypothetical solution to the pressing psychiatric puzzle regarding the prevalence of disorders like major depressive disorder, others have voiced concerns about Raison and Miller's narrative. Maes et al., 2012 emphasizes the distinction between clinical depression and sickness behavior; it is sickness behavior that Raison and Miller describe (the behavioral complex induced by infections and immune trauma), and this paradigm excludes key markers of major depression such as feelings of guilt or worthlessness. The phenomenological similarity between these two states alone does not demonstrate a causal genetic or pathway-dependent common foundation. Additionally, the clinical diagnosis of major depressive disorder is currently based on whether patients meet the threshold of displaying a somewhat arbitrary number among a wider set of symptoms. Many researchers believe that in the future diagnostic buckets like "depression" will be more finely defined into sub-categories of illness based on molecular and genetic indicators. This kind of nuanced thinking is conspicuously absent from Miller and Raison's general conclusions, though their work might very well gain more significance if focused on a subset of depressives whose symptoms perfectly align with "sickness behavior" or may have a greater susceptibility to depressive episodes when fighting infection. Instead, Miller and Raison ruthlessly advocate for parsimonious explanations of depression prevalence despite

multiple logical gaps, and though there is no evidence that such an explanation must exist.

It is only in its final sentences that the *Atlantic* article acknowledges "individuals with major depressive disorder and elevated levels of inflammation may represent a subset of individuals with depression," a statement that undermines the sweeping title declaration that implies these findings are pertinent to all major depression sufferers. Surely many evolutionary biologists and geneticists are frustrated by this category of just-so stories that popular media often extrapolates from scientific articles. The argument implicit in this article posits that because mental illness persists in our population and that only genes that confer advantages to host survival and reproduction are retained through evolution, there must be a survival benefit to mental illness. Even those (such as the author of *Atlantic* piece) who have been appropriately trained to understand scientific writing seem to fall into this trap, shying away from any depiction of natural selection as a flawed, arbitrary process that is not driven to be efficacious or direct.

Mental illness is particularly vulnerable to the seduction of just-so stories. When individuals speculate on the evolutionary advantages of mental illness, they are also speculating on what exactly drives the mentally ill to act in such "irrational" or non-socially sanctioned ways. The impenetrable mystery of the individual experience of mental illness in part drives the mystery of the genetic conservation predisposing such illness across evolutionary time. When the social withdrawal of a depressed individual is not initially understood by a healthy colleague, the just-so narrative that interprets their behavior in terms of a deterministic and outdated method of self-preservation has the power to "explain away" what could be a cry for help, or indication of environmental

stress, etc. Popular media narratives explaining modern phenomenon in terms of ancient adaptation not only jeopardize the integrity and confound the actual implications of a given study, but also endanger the fragile curiosity that offers the potential to bridge worlds between the healthy and the sick.

Genetics can serve a very positive role in the stigma and novel therapeutic techniques of those with mental illness. For example, the aggressive stance taken by Miller and Raison to promote the Pathogen Host Defense Hypothesis may ultimately lead to the identification of a subset of MDD patients who can benefit from immunology-driven interventions. But there is nothing positive about twisting data to reinforce preexisting ideological constructs, as can be remembered from the heyday of the eugenics movement. Many mental health advocates have embraced and promoted several other "just so" stories about the advantages conferred by depression, anxiety, bipolar disorder, and schizophrenia. The historical prevalence of successful artists with depression and other mood disorders has been well documented, as in Kay Redfield Jamison's book *Touched With Fire*, and many studies have attempted to draw some genetic or biological relationship between "creativity and madness" with limited success (some have suggested that the connection can be attributed to the incredible perseverance and resilience required to live with mental illness, which is also necessary to complete any great work of art). The director of recent film *Melancholia* used his own experience with depression to craft a story that implies the advantage of depression is that in crisis, people with low emotional reactivity and affect are able to maintain their rational perspective and undergo a role reversal, becoming empowered rather than victimized. Stanford biologist Robert

Sapolsky is famous for a publicly distributed lecture that argues the evolutionary advantageous of schizophrenia through the heterozygote advantage that he believes is conferred to those with schizotypal personality disorders, the "half-crazy" among us who may have a kind of "metamagical thinking" that channels schizophrenic qualities into their proper contexts (Sapolsky lists historical examples of shamans, witch doctors, medicine-men, and religious founders to support his reasoning). These explanatory narratives and attempts to locate the logic underlying the prevalence of mental illness may be very interesting, but they have not led to advancements in the care and treatment of those with mental illness. At best, the increasing attribution of mental illness to genetic causes removes the blame from its victims and mediates the immense stigma they face.

For centuries philosophers have warned against those who worship science with the blind, explanatory faith that many primarily attribute to religion. Nietzsche's main argument in *On the Geneology of Morals* is that science has made us believe we are free thinkers, that we have finally progressed beyond the mystification of religion. Adorno and Horkheimer recapitulate this sentiment in the *Dialectic of Enlightenment* and other philosophers and social critics have taken up a similar stance: secular modernity's complete confidence in science is the only ideological anesthetic for the painful suffering of purposeless man. In Nietzsche's words:

> these hard, severe, abstemious, heroic spirits, who constitute the pride of our age, all these pale atheists, anti-Christians, […] these men in whom the intellectual conscience is alone embodied and dwells today—they believe themselves to be as free as possible from the ascetic ideal, these 'free, very free spirits': and yet, if I may reveal to them what they themselves cannot see—for they are too close to themselves—: this self-same ideal is their ideal too, they themselves are perhaps its sole representatives today, they themselves are its most spiritualized product, its most advanced party of warriors and scouts, its most insidious, most delicate, least tangible form of seduction—if I am in anything a solver of enigmas, then let me be so now with this proposition!… These men are far from free spirits: for they still believe in the truth! (126).

Josef Parvizi is a Stanford neurologist who wrote an article titled “Corticocentric Myopia: Old Bias in New Cognitive Sciences”. He argues that inherited notions of hierarchy and inhibition have created a corticocentric view of the brain (valuing the cortex as a center for study and advanced functions over subcortical structures) that permeates neuroscience research, limiting study design and justifying eugenics (which was based on the idea that humans have large frontal lobes because they evolved to control their lower subcortical structures/instinctual behavior, and thus measurements of different races’ frontal lobes could predict how “animalistic” that race was). This corticocentric perspective is “not rooted in the actual pattern of relationship between cortical and subcortical structures” but in Western history. Darwin wrote extensively on the voluntary and involuntary centers of the brain, and the suppression of animalistic tendencies through man’s will. Herbert Spencer, the founder of Social Darwinism considered social hierarchy as a sign of highly evolved societies, and claimed hierarchical governing structures and self-control saved England from the fate of revolutionary France. His friend and colleague John Hughlings-Jackson was inspired by the tenants of Social Darwinism to argue that the human brain must also be organized in a hierarchy, and through evolution there was the “adding on” of new structures that control and direct the sub-structures, much like the way a government controls and directs a nation. Spencer and Hughlings-Jackson lived in Queen Victoria’s time when dichotomies such as free will versus basic instinct framed morality and it was believed that humans should be able to “inhibit” sins. The value of this article is that it so clearly and persuasively traces the lineage of a steadfastly held 21st century “scientific” and “objective” framework. In other

words, the fancies of a few dead white men can truly alter the human course, even to the extent of whether a medication or discovery that could save your life one day will be developed.

My intent in this paper, using the case study of mental illness and the particular hypothesis of Pathogen Host Defense and inherited notions of human genetics, is to demonstrate how culturally acquired rather than scientifically validated, namely evolutionary, explanatory mechanisms may be limiting, both to the progress of science and to the public's understanding of important genetic advances.

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