Quo Vadis Psychiatry? Why It Is Time to Endorse Evolutionary Theory

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Abstract: In recent decades, psychiatry and the neurosciences have made little progress in terms of preventing, diagnosing, classifying, or treating mental disorders. Here we argue that the dilemma of psychiatry and the neurosciences is, in part, based on fundamental misconceptions about the human mind, including misdirected nature-nurture debates, the lack of definitional concepts of "normalcy," distinguishing defense from defect, disregarding life history theory, evolutionarily uninformed genetic and epigenetic research, the "disconnection" of the brain from the rest of the body, and lack of attention to actual behavior in real-world interactions. All these conceptual difficulties could potentially benefit from an approach that uses evolutionary theory to improve the understanding of causal mechanisms, gene-environment interaction, individual differences in behavioral ecology, interaction between the gut (and other organs) and the brain, as well as cross-cultural and across-species comparison. To foster this development would require reform of the curricula of medical schools.

Key Words: Psychiatry, life history theory, gene-environment interaction, "real-world" behavior, across-species comparison

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Psychiatry, it seems, has maneuvered into a cul-de-sac, both clinically and scientifically. Obviously, in the last two decades, little progress has been made in terms of preventing, diagnosing, classifying, and treating mental disorders. Instead, the discipline struggles with fuzzy boundaries between normal trait variation and disorder, whereas the term "disease" is almost entirely shunned in psychiatric terminology, except for neurodegenerative processes. Indeed, distinguishing "disease" from "disorder" is particularly difficult in psychiatry, because specific causes and characteristic symptoms are known for only a small fraction of psychiatric conditions (*i.e.*, the prerequisites for justifying the term "disease" are not fulfilled for most conditions), which has led some scholars to suggest avoiding the term "disease" in psychiatric discourse unless it is completely justified (*e.g.*, Cooper, 2004). In addition, neither the introduction of *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (*DSM-5*) nor the introduction of research domain criteria has led to substantial improvements in defining more reliable syndromal entities or in identifying transsyndromal entities of clinical utility; these frameworks still hinge on concepts developed in Western Europe and North America some 100 years ago. Moreover, a global perspective suggests dramatic increases in prevalence of noncommunicable diseases, including depression and other psychiatric conditions, with no clue how prevention programs could reduce the burden on health, commonly measured in years lived with disability (Murray et al., 2012). Finally, ground-breaking psychopharmacological innovations are lacking for all psychiatric conditions (Cressey, 2011). An exception to this situation is psychotherapy, a field that has advanced considerably over the last few decades, especially those methods with direct or indirect ties to attachment theory (Fricchione, 2018).

This critique of psychiatry's current state of affairs is not a list of bold and unsupported statements about the current crisis of the field. Instead, it is a slightly more detailed description of what one of the leading authorities in mental health, Thomas Insel, expressed some time ago after resigning as the director of the National Institute of Mental Health (NIMH) in the following words: "I spent 13 years at NIMH really pushing on the neuroscience and genetics of mental disorders, and when I look back on that I realize that while I think I succeeded at getting lots of really cool papers published by cool scientists at fairly large costs—I think $20 billion—I don't think we moved the needle in reducing suicide, reducing hospitalizations, improving recovery for the tens of millions of people who have mental illness. I hold myself accountable for that."

Succinctly put, Insel's allegations not only admit the failure of a whole discipline, but also completely lack envisioning solutions to the list of dilemmas.

Here, we propose that the crisis of psychiatry is grounded, in large part, in misconceptions about the human mind, particularly in relation to interactions between the environment and biological systems, as well as in incomplete theoretical frameworks in relation to biopsychosocial explanations for psychopathology. To resolve these conceptual shortcomings, we contend that it is necessary to endorse evolutionary theory as an overarching framework to improve understanding of causal mechanisms involved in the etiology of psychiatric conditions, which includes hitherto underrecognized insights concerning gene-environment interaction, individual differences in behavioral ecology, the interaction between the brain and the rest of the body, and the appreciation of a comparative approach.

CLAIM 1: PSYCHIATRY'S PROBLEMATIC PREMISES

Since its implementation as a branch of medicine in the late 19th century, psychiatry has struggled to anchor itself as a biological and as a social science (Engel, 1977). Initially, in the early 20th century, with the rediscovery of the rules of genetic inheritance, psychiatric research has largely disregarded the contribution of environmental contingencies to the etiology of mental disorders, particularly the experience of adversity, such that poverty, traumatization, abuse, and neglect were ascribed to the biological concept of degeneration (Roelcke, 1997). After World War II, the pendulum swung in the opposite direction, claiming, for instance, that poor mothering could be "schizophrenogenic." Amidst this "nature versus nurture" debate, an important discovery was made that has prevailed over the decades to follow for reasons discussed below: attachment theory (Bowlby, 1969). Nowadays, psychiatry is again back on the biological (neuroscience-dominated) track, one-sidedly focusing on putative brain abnormalities (structural or functional) or genetic factors (discussed below). These new trends largely disregard alternative

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interpretations, including ones suggesting that functional or structural brain differences from a statistical norm may reflect complex adaptations to stressful environmental conditions, not deficits per se (Teicher et al., 2003).

The relationship of psychiatry to psychology is also poorly elaborated. This leads to the bizarre situation that psychiatry, unlike all other medical disciplines, has just implicit, but no explicit understanding of the physiological nature of the human mind. It is, as if a cardiologist's knowledge about hearts was solely based on the analysis of cardiac failure, oblivious of how a healthy heart works; or to believe that tachycardia can only be caused by the action of accessory atrioventricular bundles, but overlooking the fact that tachycardia could be part of a fight or flight response. Put another way, psychiatry has conceptual difficulties in distinguishing defense from disorder or disease. Cough and fever are well-known examples of how bodies guard themselves against unwanted intruders; these physiological responses helped organisms to survive (although these defenses can be unpleasant), and thus, it is generally not recommended to suppress these reactions right from the start. By comparison, the situation with low mood is entirely different. One of the most far-reaching misleading presumptions in psychiatry is that low mood always reflects disorder. Low mood states are unpleasant, they are often elicited by the experience of loss, conflict or entrapment, and hence communicate important messages (Gilbert, 2001).

As Darwin expressed it: "Pain or suffering of any kind, if long continued, causes depression and lessens the power of action, yet it is well adapted to make a creature guard itself against any great or sudden evil" (Darwin and Darwin, 1887, pp 51–52).

Accordingly, like fever and cough, it is not always wise to suppress low mood states from the outset (Nesse, 2009) nor is it helpful to assign bereavement the status of disorder (as was debated for the revision of the *DSM*; discussed in Nemeroff et al., 2013).

We assert that there is only one scientifically sound solution to these problems: to provide psychiatry with an integrative understanding of human nature, including our species-typical cognitions, emotions, and behavioral repertoire, shaped by biological as well as socioenvironmental factors in the past and the present. This integrative framework for psychiatry would then be endowed with tools needed to answer four essential questions about mechanism, ontogeny, phylogeny, and adaptive (or in the case of disease, maladaptive) properties of any given trait, originally proposed by Tinbergen (1963) for the study of ethology, and later on, suggested as a conceptual agenda for the study of psychiatric conditions (Brüne, 2014; Medicus, 2015; Nesse, 2013).

CLAIM 2: CONCEPTUAL DIFFICULTIES

In finding solutions to overcome the shortcomings of simplistic biomedical models of psychiatric conditions, George Engel (1960, 1977) and Horacio Fabrega Jr (1975) have pleaded for a biopsychosocial approach, which integrates "illness" and "patienthood" in a culture-sensitive context that gives credit to all three aspects and discards the primacy of biological factors as the sole explanation of disorder or disease. This was a great conceptual leap forward for psychiatry and medicine as a whole, yet the biopsychosocial model seems to suggest that the three dimensions have additive value in explaining the nature of disorder and disease, but are not necessarily causally related to one another. So, psychiatry still struggles with the question at what point in the diagnostic or therapeutic stage the "bio" or the "psycho" or the "social" has more weight than the other two in any individual patient (Fabrega and Brüne, 2017). Accordingly, as exemplified by depression, one can find in the literature evidence for any position suggesting that biological treatment (*i.e.*, medication) works better than psychotherapy, psychotherapy better than medication, that a combination of the two works best, and even for harmful effects of antidepressants on depressive symptoms (*e.g.*, Margraf and Schneider, 2016).

We propose that, instead of looking at potential additive effects of biological, psychological, and social aspects of disorder and disease, the biopsychosocial model needs to be updated and refined based on behavioral ecology. As we will argue, this approach puts forth a causal model where environmental contingencies, foremost social factors at early ontogenetic stages, have predictive value for an individual's psychological and biological development throughout the lifespan. The behavioral ecological perspective is therefore a particularly powerful tool for both research and the clinics.

Behavioral ecology is defined as the study of behavior in the context of its ecological setting and evolutionary basis; it explains how and why differences in growth and reproduction depend on environmental preconditions. Central to behavioral ecology is life history theory (LHT), which describes how environmental contingencies impact an organism's differential allocation of resources to either physical growth or reproduction. Put differently, an organism's capacity to invest energy in somatic growth is counter-balanced against its capacity to invest in reproductive activity. Accordingly, growth rate, body size, timing of sexual maturation, investment in mating versus investment in number and size of offspring, mortality rate, longevity, and so on are predictable biological traits expressing different life history strategies (LHSs; Stearns, 1992).

The concept of LHT was originally designed to account for between-species differences in growth and reproduction, with growing evidence for within-species differences in LHS. This ground-breaking discovery, hitherto largely disregarded by psychiatry and the neurosciences, suggests that ecological (environmental) conditions (interacting with genetic factors) determine whether an individual adopts a "faster" or "slower" LHS. One of the most interesting aspects of LHT is that future resource availability is estimated on the basis of observable cues or prior experience acquired in early developmental stages (Ellis et al., 2009). Accordingly, early experiences shape an organism's "decision" over the pursuit of a faster or slower LHS, or "pace of life." This kind of decision-making entails the timing of biological maturation, current versus future reproduction, quality versus quantity of offspring, and quality versus quantity of parental care in offspring and mating, whereby the terms "strategy" or "decision-making" by no means imply conscious reflection or intentional action (Ellis et al., 2011).

Abundant research has shown that the principles of LHT apply to humans in the same way as to any other organism. Specifically, the quality of parenting profoundly impacts the way individuals develop "inner working models" about safety, emotional availability of significant others, trustworthiness, and future resources (*e.g.*, Murray et al., 2009; Petterson and Albers, 2001). In this regard, LHT is entirely consistent with attachment theory and the predictions that derive from this developmental perspective. For example, children who grow up in an emotionally secure and stable familial environment are more likely to develop trustworthy interpersonal relationships with peers and partners, and to expect sufficient amounts of social and material resources in the future, such that investment in mating is relatively intense and reproduction is delayed, relative to children who grow up in conditions of financial, social, or emotional uncertainty (Chisholm et al., 2005). In line with predictions from LHT, securely attached individuals tend to sexually mature later, form stable long-term intimate relationships, and are generally risk averse. They are also cooperative, empathetic, less aggressive, and have good inhibitory control over impulses. In terms of personality traits, they score high on conscientiousness and agreeableness. In contrast, individuals who are exposed to early adversity such as harsh parenting, violence, poverty, or other sources of danger are more likely to develop inner working models, suggesting that future resource availability is unpredictable. Such a biographical background more likely shifts an individual's pace of life toward the faster end, which includes earlier biological maturation, sexual activity, and earlier reproduction with less investment in enduring relationships and parenting. A faster LHS is thus more often associated with increased delay discounting, greater impulsivity, larger numbers of sexual partners, and lack of reciprocity (Belsky et al., 1991).

Another important prediction from LHT is that individuals pursuing a faster pace of life also invest less in body maintenance. In other words, the accumulation of stress-associated allostatic load (McEwen, 2000) and thus somatic disease is more likely to occur in those following a fast LHS compared with individuals with a slow LHS, referred to as the "disposable soma hypothesis" (first described by Kirkwood and Rose, 1991). This has now clearly been demonstrated for people with severe personality disorders (Otto et al., 2021), thus opening new avenues for preventive medicine.

Together, LHT is a powerful tool from which empirically testable predictions can be derived, not just at population level, but, in fact, for individual lives. No other biological, psychological, or social theory has anything comparable to offer. That said, our enthusiasm for LHT as a framework for the understanding of psychopathological condition by no means excludes other approaches such as Bayesian analyses of cognition, emotion, decision-making, and behavior. Instead, we strongly believe that, for instance, decision-making based on Bayesian inference principles such as prediction error are adaptive properties of species that can explain how brains work. Indeed, elsewhere we have proposed that humans possess a "social predictive brain" comprising many properties that are relevant in social decision-making (Brown and Brüne, 2012). Therefore, Bayesian principles are, in our view, fully compatible with LHT approaches.

Psychiatry's conceptual difficulties are further illustrated by the lack of acknowledgment of important biological mechanisms that are widespread in nature, including the concept of the "extended phenotype" (Dawkins, 1982). A speculative, although consistent with the existing evidence, example suggests considering the possibility that human behavior could be influenced by the manipulatory action of intracellular parasites such as *Toxoplasma gondii*. *T. gondii* has a complex reproductive lifecycle, with felines being its definitive host for sexual reproduction. Many species of mammals and birds are intermediate hosts. They usually ingest oocytes orally. Different cellular stages travel via the bloodstream preferentially to the liver, the heart, and the brain where they build residential tissue cysts. The reproductive life cycle of *T. gondii* closes when affected animals succumb to feline predators (Webster et al., 2013). Interestingly, the behavior of intermediate hosts is actively manipulated by *T. gondii*. Infected rodents, for example, loose their innate aversion of cat urine odor, and display more "risky" behavior that increases the likelihood of predation. Human carriers of *T. gondii* antibodies are significantly at greater risk of developing psychopathological conditions compared with noncarriers. In particular, the risk for schizophrenia is 2.7-fold elevated, which by far exceeds any single genetic contribution to the disorder (Torrey et al., 2007). Similarly, suicidal behavior and traffic accidents have also been associated with a latent *T. gondii* infection (Sutterland et al., 2019). It has been estimated that up to a third of cases diagnosed with schizophrenia are etiologically linked to *T. gondii* infection (Ewald and Swain Ewald, 2019). Clinically, a bird's-eye view is compatible with the assumption that the manifold alterations of cognition, emotions, self-awareness, and social behaviors associated with the disorder could be the result of the manipulatory action of *T. gondii*, ultimately promoting social exclusion from the community. In "environments of evolutionary adaptedness" (EEA; a term coined by Bowlby, 1969), this would certainly have led to an increased risk of succumbing to a large feline predator—to the parasite's reproductive benefit (Brüne, 2020). So, instead of discarding biological phenomena as "unthinkable" in regard of human beings, such hitherto underappreciated approaches could contribute to develop innovative treatment options for psychosis and other conditions (Brüne and Theiss, 2020).

CLAIM 3: INCOMPLETE VIEWS ON PSYCHIATRIC GENETICS AND BLIND SPOTS IN EPIGENETICS

The human genome comprises about 3.5 billion base pairs. It contains a surprisingly low number of fewer than 24.000 functional genes, whereby some 97% of DNA is noncoding. It has been estimated that in humans approximately 55% of coding DNA is expressed in the brain, suggesting that the majority of mutations affect brain function. Single nucleotide polymorphisms occur about every 1500 bases, yet the DNA of two randomly chosen humans is to a large degree identical, even across populations (Witherspoon et al., 2007). These issues are relevant for genetic research, especially because the explanatory power of genetics with regard to disorder and disease seems overestimated.

Genome-wide association studies (GWASs), for example, have become feasible due to enormous technological advancements that make large data analyses not only possible, but also affordable. It is therefore tempting to search for the needle in the haystack. Problems with GWAS arise from the fact that huge numbers of individuals need to be recruited that are likely phenotypically not well characterized. Nevertheless, GWAS usually produce replicable findings, yet the conclusions drawn from this approach sometimes seem trivial. Wherever one looks, the common message is that any trait is influenced by many genes, perhaps in the hundreds or thousands, with largely unknown epistatic effects (Tam et al., 2019).

In sharp contrast to the limitation of GWAS, some researchers have declared that the search for candidate genes was obsolete (Duncan et al., 2019), in part, because this genetic approach is often fraught with poor replicability of findings. Although the latter is certainly true, the main problem of psychiatric genetics resides, aside from statistical limitations, in a lack of hypotheses-driven research, one that is grounded in evolutionary theory (Uricchio, 2020).

For example, the most widely accepted genetic framework for psychopathological conditions, known as the "diathesis-stress" model (Monroe and Simons, 1991), proposes that carriers of a certain risk allele or alleles are vulnerable to developing a psychiatric disorder, especially when exposed to adverse environmental conditions in either early ontogeny or in the form of adverse events at some point over the lifespan. In contrast, individuals who do not carry such "vulnerability" genes are less susceptible to adversity or even resilient (Feder et al., 2009).

Although abundant research has supported the diathesis-stress model—as, for instance, the landmark studies about the association of risk for antisocial personality with the low-activity variant of the monoamine oxidase A (MAO-A) enzyme, particularly in individuals who grew up under adverse environmental conditions (Caspi et al., 2002), or the association of s-allele of the serotonin transporter gene (5-HTTLPR) with depression (Caspi et al., 2003)—the diathesis-stress model has overlooked that carriers of the same alleles may have a lower-than-average risk for psychopathology when growing up under favorable conditions such as positive parenting (*e.g.*, Belsky and Pluess, 2009). In fact, the diathesis-stress model falls short of explanations why "vulnerability" alleles exist at all in the genepool of a population and have not been eliminated via natural selection. Moreover, the model does not account for recent positive selection of "risk" alleles in largely unrelated (or at best distantly related) human populations. From an evolutionary point of view, it is simply implausible to assume that natural selection has favored allelic variants that increase vulnerability to adversity, particularly when considering that the EEA was probably fraught with adverse life events throughout the lifespan. Instead, these genetic variants must also convey hitherto undetected beneficial effects with regard to reproductive fitness (which is not necessarily the same as subjective well-being or mental health; Ellis et al., 2011).

A few examples may illustrate these important ramifications for psychiatry. Cross-cultural studies suggest that the 7-repeat variant of the *DRD4* gene emerged some 50,000 years ago, with the 4-repeat variant being the ancestral form (Ding et al., 2002). Interestingly, the long variant seems to be more prevalent in migratory, as opposed to sedentary, populations (Chen et al., 1999). Consistent with these findings, the 7-repeat allele has been associated with the personality trait "novelty seeking," which arguably may have conferred a reproductive advantage in human history, particularly for migrating populations (Matthews and Butler,

2011; Reist et al., 2007). The 7-repeat variation has also been linked to an increased risk for attention deficit hyperactivity disorder (ADHD), yet children carrying the 7-repeat variant of the *DRD4* gene develop ADHD and externalizing problems less than average if their mothers are responsive to their children's emotional needs (Bakermans-Kranenburg and van Ijzendoorn, 2006).

This astonishing discovery suggests that a particular genetic variation can predispose to psychopathology if associated with early adversity (*i.e.*, diathesis-stress) but can have protective effects when developmental contingencies are more supportive, referred to as "differential susceptibility" or "plasticity" (Belsky, 1997; Boyce et al., 1995). Consistent with the "differential susceptibility" model, it has been shown that the low-activity MAO-A variant is associated with lower than average prevalence of antisocial personality when children grow up in supportive environments (Widom and Brzustowicz, 2006). Similarly, the s-allele of the 5-HTTLPR confers lower risk for depression under favorable environmental conditions (Taylor et al., 2006).

Together, this line of research strongly suggests that genetic variation involved in dopamine and serotonin turnover confer differential susceptibility to environmental conditions, possibly via differential responsivity to reward and punishment (Bakermans-Kranenburg and van Ijzendoorn, 2007; Ellis et al., 2011). GWASs can be helpful in discovering new candidates for this effect, but it is not hypothesis-driven in itself nor is GWAS helpful in predicting individual phenotypes. Contrary to mainstream views, we propose that candidate gene studies are not obsolete or superfluous. Instead, "differential susceptibility" models are not only consistent with testable predictions, they are also compatible with evolutionary explanations of why these alleles have been preserved in human genepools (Boyce and Ellis, 2005).

Aside from sidelining evolutionary aspects in psychiatric genetics, a similar case can be made for studies in epigenetics. Current epigenetic research in psychiatry is mainly concerned with studies of early developmental adversity such as abuse or neglect on methylation patterns (*e.g.*, Jones, 2012). Another line of research focuses on telomere shortening in relation to stressful life events (Young, 2018). Both threads make total sense in an evolutionary perspective, especially if linked to testable hypotheses derived from LHT, including the "disposable soma hypothesis" (van den Heuvel et al., 2016; Young, 2018).

By comparison, the impact of environmental toxins on human behavior, including disorder and disease, has been relatively underresearched. However, mounting evidence suggests that environmental chemicals in water, air, and food may disrupt normal development and may be causally linked to the worldwide increase of neuropsychiatric disorders, including neurodevelopmental and neurodegenerative diseases (Chin-Chan et al., 2015; Colborn, 2004; Grandjean and Landrigan, 2014; Heindel et al., 2017). Indeed, pregnancy and early postnatal development are highly sensitive and plastic periods for the long-term modulation of neural, immune, reproductive, and metabolic function (Brucker-Davis et al., 2010; Colborn et al., 1994; Crews and McLachlan, 2006; Hanson and Gluckman, 2015; Heindel et al., 2015).

Many man-made environmental neurotoxic compounds act as endocrine disruptors (EDs), interfering with, imitating, or antagonizing the normal function and/or the production of hormones. Animal studies have shown that prenatal and/or neonatal exposure to EDs produces postnatal adverse effects on multiple tissues and functions, including the brain, and have postulated multiple potent pathways by which EDs alter the hormonal milieu during development to cause endocrine-dependent diseases, including epigenetic changes (Barker, 2004; Schug et al., 2016). Consistently, human epidemiological studies have highlighted an association between EDs and reproductive, metabolic, and neurobehavioral disorders (reviewed in Braun, 2017; Street et al., 2018). In a variety of mammalian species, including humans, strong evidence exists that behavior is a sensitive target of endocrine disruption (Palanza et al., 2016).

Given that endocrine function during development as well as brain and behavior and virtually every aspect of physiology differs in males and females, long-term effects of ED exposure are expected to vary in relation to sex. Current evidence emerging from animal models and human studies indicates altered sex differences in behavioral development in response to early exposure to EDs. For example, there is strong evidence that bisphenol A (BPA), one of the most widely prevalent EDs, is a neuroendocrine disruptor at environmentally relevant "low" doses and can interfere with normal sexual differentiation processes (Palanza et al., 2008; Palanza et al., 2021; Vandenberg et al., 2013). In fact, one of the most consistent and robust findings across several mammalian species including humans is that sex is a fundamental variable in accounting for BPA effects on behavior (Gioiosa et al., 2007; Gioiosa et al., 2013; Laviola et al., 2005). Specifically, research in rodents has shown that low-dose exposure to BPA in utero or early postnatal life disrupts the development of normal sexually differentiated behaviors, including anxiety, exploration, social interaction, play behavior, reward sensitivity, spatial learning and memory, and sexual and parental behavior (reviewed in Arambula and Patisaul, 2018; Gore et al., 2019; Palanza et al., 2016, 2021; Rosenfeld and Trainor, 2014). Human epidemiological studies have linked sex-specific effects of maternal BPA levels to increased externalizing behaviors in girls (Braun et al., 2011; Harley et al., 2013) and increased emotional responses, internalizing behaviors, anxiety, and aggression in boys (Braun et al., 2017; Harley et al., 2013; Perera et al., 2012; Roen et al., 2015). Moreover, another study reports an association between childhood BPA exposure and risk for ADHD in boys but not in girls (Casas et al., 2015).

Together, BPA and other EDs can disrupt normal steroid programming of the brain, which has profound consequences for sexually selected traits. In addition, male and female organisms seem to respond differently to early exposure to EDs. The functional interplay among biological, psychological, and environmental factors differs in males and females, and the same is true for their impact on the crosstalk of homeostatic networks required for health and disrupted in disease. These aspects need to be taken into account when considering the impact of early adversity on development.

CLAIM 4: PROBLEMS ARISING FROM THE CONCEPTUAL ISOLATION OF THE BRAIN FROM THE REST OF THE BODY

The human brain contains an estimated number of 86 billion neurons and at least the same number of glia cells with hundreds of trillions of synapses connecting neurons and nonneuronal cells (Azevedo et al., 2009). These shear unimaginable figures render the brain as the most complex organ that ever evolved. So, it is understandable that psychiatry and neuroscience have focused on unveiling those brain mechanisms involved in dysfunction and disorder. For most of the research, however, this endeavor has put the brain in isolation from the rest of the body. In other words, the impact of other organs or organ systems on brain function has, until quite recently, received less attention than it should have. Now, we have only begun to understand that brain function interacts with immunological processes, and that a healthy brain critically depends on the metabolism of alien cells residing in the human guts, in the respiratory tract, and on the skin, referred to as the "microbiota." Foreign cells are about as abundant in the human body as own cells are, together amounting to a mass that roughly matches the average weight of a human brain (Sender et al., 2016). Unraveling the complex interactions between the microbiota (and their genes, the so-called microbiome) with immune function and the brain is in its infancy (Dinan and Cryan, 2017), although accumulating evidence from animal studies suggests that the absence of a functional gut microbiome can be (causally?) associated with immature brain immunity and aberrant myelination of prefrontal neurons (Fung et al., 2017). Moreover, the gut microbiota seems to be involved in a wide range of pathological brain conditions, including stroke, autoimmune processes, and neuropsychiatric

disorders such as anxiety disorders, depression, and dementia (Fung et al., 2017). Seen this way, humans (like all other complex organisms) are holobionts or ecosystems (Furness and Bravo, 2015), and as such need to be explored multidimensionally.

Along the same lines, inflammation profoundly impacts human social behavior and vice versa. That is, a proinflammatory state promotes defense mechanisms including increased sensitivity to rejection and social exclusion. Conversely, social stressors such as separation distress, bereavement, or social competition can produce proinflammatory states, which are highly relevant for the understanding of a diverse range of psychiatric disorders, as these stressors are common across populations (Eisenberger et al., 2017).

Indeed, one common behavioral pathway across species is sickness behavior (SB). SB usually occurs after exposure to pathogens or toxic substances. It is characterized by fatigue, heightened body temperature, loss of appetite and drive, psychomotor retardation, and social withdrawal. This helps conserve energy and avoid continuous exposure to toxic or infectious substances. Moreover, SB reduces the risk of being attacked in times of enhanced vulnerability. From a clinical point of view, SB resembles states of depression. This view is corroborated by immunological theories, suggesting that aberrant priming of the immune system could be part of an explanation for the "depression pandemic" (Anders et al., 2013; Raison and Miller, 2017; Rook et al., 2017). Moreover, one of the first clinical observations likening immunologically induced SB with depression was that people receiving interferon beta often developed SB or even clinical depression (Felger et al., 2016).

Together, these two examples illustrate (in our view) that brain function is tightly linked with other organs in reciprocal ways, and that evolutionary processes are involved, as changes to the microbiota and the immune system reflect selective-adaptive responses observable in live organisms.

CLAIM 5: DIAGNOSTIC PROCEDURES UNDERAPPRECIATE ACTUAL BEHAVIOR

Psychiatric assessment serves several purposes: first, to understand signs and symptoms in terms of their (maladaptive) meaning; second, to ascertain a (preliminary) diagnosis, which includes differential diagnostic considerations; and third, to initiate treatment. Current procedures very much rely on subjective report, often aided by the application of standardized rating scales. Although there is nothing wrong with standardized assessments, the risk is to forego essential information from nonverbal ("what is expressed") and paraverbal ("how something is expressed") behavior. Moreover, as the clinical interviewer's resonance is an important diagnostic tool, too, meticulous perception and reflection of one's own responses (both psychological and somatic) to patients' expressions is mandatory. Good rapport is essential for the formation of a trustful relationship, particularly, because many individuals with psychological problems or psychiatric disorders are susceptible to misinterpreting the interviewer's behavior as rejecting; others are highly sensitive to dominance hierarchies, such that the interviewer's body language ought not to force the patient into an inappropriately submissive position or provoke hostility.

Common elements of interpersonal behavior include frequency and duration of eye contact, as well as nonverbal signals of affiliative, submission, flight, assertiveness, ambivalence, and relaxation (Troisi, 1999). Typical elements pertaining to these categories are part of our species-typical behavioral repertoire (Grant, 1968). Because nonverbal behavior is under less conscious control than verbal report (Burgoon, 1985), it is considered more reliable with regard to an individual's emotional state, and subtle nonverbal cues may even help distinguish between deception and truth telling (Troisi, 1999; Yu et al., 2014). Thus, the analysis of nonverbal behavior may also help identify discrepancies between a patient's verbally given information (*e.g.*, denying suicidal ideation) and behavioral signals of distress such as motivational ambivalence (*i.e.*, "displacement activities"), and may hence help detect deterioration of even prevent suicide attempts (Schelde, 1998; Troisi, 2002). Similarly, patients who intentionally try to hide their emotions or intentions may be unable to show a genuine smile (referred to as "Duchenne smile"). The Duchenne smile is characterized by the activation of the muscles surrounding the eyes (orbicularis oculi muscle), which are not under voluntary control. Thus, an individual trying to mimic a smile (consciously or unconsciously) is less well able to activate the orbicularis oculi muscle, and hence displays a "false" smile (Ekman, 1982, 2003). It requires a lot of training, however, to uncover such subtleties of nonverbal expressions.

Despite the important messages conveyed by nonverbal communicative signals, the scientific background necessary for the analysis of nonverbal interaction is barely taught in medical schools. Historically, a comparative evolutionary approach to the study of behavior was initiated by Charles Darwin (1872). The foundations of ethological research were, however, laid down much later by Nicolaas Tinbergen and Konrad Lorenz.

Basically, ethology posits that the behavior of any species is hierarchically organized. Elements of behavior may or may not share a common causal factor and a common (biological) function. Put differently, elements of behavior that occur in the same context but not in others are assumed to share a similar cause related to that context. Moreover, behavioral elements that produce a similar effect are assumed to be functionally homologous. In addition, nonverbal behavior serves the achievement of biological goals (*e.g.*, reproduction, territorial behavior, social behavior, etc.). Observation and registration of behavior allow the description of ethograms. Ethograms are catalogs of discrete elements of behavior that make part of the behavioral repertoire of the species under study (Eibl-Eibesfeldt, 1995).

In psychiatry and the neurosciences (with few exceptions, as for example in neuroethology; Ploog, 1988), no ethograms exist for clinical use, and the abundance of questionnaires for all kinds of disorders aiming at quantifying syndrome severity largely disregard nonverbal aspects of behavior (Troisi, 1999). An additional feature of ethological methods is that it implies a low inference; the observer does not influence at any extent the behavior under observation and does not make any kind of interpretation while observing it, thus minimizing subjectivity. Such a detailed and objective description of the behavior in a naturalistic setting may contribute to an objective assessment of behavioral alterations associated with mental disorders. Although ethological observation requires practice and careful determination about category formation and data-collection strategies, it provides information about the form and ecological function of behavior and its functional impairment in persons with psychiatric symptoms (Burgoon, 1985; Troisi, 1999).

The omission of nonverbal interaction in psychiatry is, however, not only prevalent in clinical practice. It is already evident at the theoretical level. For example, the *DSM* is entirely unconnected to any theory of human behavior (Nesse and Jackson, 2006). A consequence of this omission is that psychiatric disorders are dealt with as if they were diseases. Moreover, the *DSM* approach disregards contextual factors, yet no behavior, emotion, or cognitive process is independent of context. As Nesse and Jackson (2006) succinctly put it, the *DSM* "does not differentiate whether a panic disorder initially started in a grocery store or a prison." Thus, although real-world observation of behavior is marginalized in clinical psychiatry, it is direly needed, because of the highly artificial nature of hospital wards and consultation rooms.

Conversely, what ethology can offer to clinical psychiatry is not only the quantitative analysis of patients' nonverbal behavior. In addition, ethology developed as the study of behavior in natural settings, as opposed to experimental psychology that consisted in analyzing a few behavioral patterns in settings that lack environmental and social complexity. Current methods of clinical psychiatry resemble more the approach of experimental psychology than that of ethology (Troisi,

2020). These artificial settings are likely to give a very limited and distorted view of what patients do when they interact with their relatives, romantic partners, or work colleagues in their "natural" environments. An evolutionary perpective suggests to renew the GOAL for psychiatric diagnosis: give less weight to symptoms; observe and measure behavior; assess functional capacities; and leave your office (Troisi, 2012).

CLAIM 6: ETHNOCENTRISM AND ANTHROPOCENTRISM

Approximately 10 years ago, Henrich et al. (2010) published a seminal review addressing a major problem of psychological research. According to the authors, behavioral scientists routinely publish broad claims about human psychology and behavior based on samples drawn entirely from WEIRD (Western, educated, industrialized, rich, and democratic) societies. They concluded "we need to be less cavalier in addressing questions of human nature on the basis of data drawn from this particularly thin, and rather unusual, slice of humanity" (p 61).

Psychiatry, we claim, suffers from the same weaknesses as noted by Henrich et al. (2010) for psychology. It is dubious to what extent data collected in WEIRD societies on the epidemiology, etiology, prognosis, and treatment of mental disorders are generalizable to people living in other socioecological contexts. Intraspecific differences, adaptation to different ecological niches, and individual phenotypes as a result of gene-environment interactions are central concepts in evolutionary biology. We suggest that the adoption of a comparative perspective inspired by evolutionary reasoning is likely to minimize the ethnocentric and anthropocentric biases afflicting contemporary psychiatry.

Ideally, research and clinical psychiatrists should have access to an extensive database based on studies of psychopathological symptoms and syndromes in contemporary human populations living in different socioecological conditions. These clinical data should be combined with findings from paleoanthropological and primatological studies. Clearly, such a database does not exist, and some of its data are difficult to collect (*i.e.*, psychiatric disorders in hominin species; Brüne et al., 2004; Brüne et al., 2006). However, the few data that are currently available suggest that the mental disorders listed in major nosographic systems (*e.g.*, *DSM* and *ICD*) are not necessarily human pathologies invariant over time and across environments.

A question addressed by the comparative perspective is if the type and frequency of mental disorders found in WEIRD populations are the same found among other human societies. Unlike transcultural psychiatry and its emphasis on cultural relativism, the evolutionary approach focuses on socioecological differences and their possible role in causing mental disorders. Much of the environment WEIRD populations inhabit is increasingly out of the optimal range for which our body's physiological and psychological mechanisms were generated by the processes of evolution (the mismatch hypothesis; Gluckman and Hanson, 2006). Many aspects of the physical and social environment have been dramatically altered by human action particularly in our recent past (Gluckman and Hanson, 2006). It is likely that the prevalence of those mental disorders that depend largely from risk factors common in modern environments may be lower in human populations still living in socioecological conditions matching ancestral environments. A possible example is postpartum depression.

Postpartum depression consists of a depressive episode that begins after delivery. Its prevalence varies widely with the levels of social and affective support given to new mothers. In traditional societies, mothers caring for newborns and infants enjoy extended family and community support. In these societies, the prevalence of postpartum depression is low, as shown by the "Latina paradox" (Campos et al., 2008). Mothers who emigrate from Mexico to the United States have lower rates of postpartum depression than White mothers, although immigrant mothers are relatively disadvantaged economically and are more often unmarried. The factor thought to explain this paradox is the high degree of family and community support experienced by Latina women, compared with richer but more isolated White women.

There is evidence that, throughout human evolution, shared child care was a major feature of social organization (Burkart et al., 2009). It is plausible that the shift from multigenerational families to smaller nuclear families impacted women's ability to cope with the demands of motherhood and increased the risk for postpartum depression (Hahn-Holbrook and Haselton, 2014). Support for the hypothesis that postpartum depression reflects a "disease of civilization" comes from anthropological studies of contemporary hunter-gatherer populations. During his long-term study of the Eipo hunter-gatherers, the German physician and anthropologist Wulf Schiefenhövel never observed a case of postpartum depression (personal communication, July 12, 2006). Hunter-gatherer families typically live in kin groups in which grandparents, aunts and uncles, and older siblings assist mothers and fathers with their young children. In contrast, in WEIRD societies, nuclear families often live far away from close kin and have fewer children spaced closer together in age, simultaneously making it less likely that older siblings will be available to help with child care and more likely that mothers will need to simultaneously care for multiple very young children.

A better knowledge of which mental disorders are caused mainly by a mismatch between modern and ancestral environments would offer preventive psychiatry the conceptual background for targeting modifiable environmental risk factors.

Another question addressed by the comparative perspective is the phylogenetic emergence of mental disorders. A recent study (Srinivasan et al., 2016) hypothesized that schizophrenia is a by-product of the complex evolution of the human brain and a compromise for humans' language, creative thinking, and cognitive abilities. The authors arrived at such a conclusion by applying a polygenic statistical approach and analyzing data from recent large GWAS. They found that gene loci associated with schizophrenia are significantly more prevalent in genomic regions that are likely to have undergone recent positive selection in humans. The measure used to assess recent positive selection was the Neanderthal selective sweep score, which is a likelihood index of phylogenetic divergence between modern humans and Neanderthals. Two implications of this study are worth discussing (Troisi, 2020). First, the results go exactly in the opposite direction of the cliché often applied in the past to characterize the evolutionary approach to psychiatric disorders (*i.e.*, that mental illness reflects a condition of phylogenetic regression and atavism). The evolution of novel cognitive abilities, not the regression to a more primitive stage, seems to be the evolutionary reason for the existence of psychosis. Second, the results are an excellent demonstration of how the biology of proximate questions can integrate profitably with the biology of ultimate questions. The identification of the genes predisposing to schizophrenia belongs to the realm of functional biology (*i.e.*, the study of biological mechanisms), but the explanation of their persistence in contemporary populations is a task for evolutionary biologists.

Partial insight on the phylogenetic emergence of mental disorders could profit from studies of our nonhuman living relatives: apes and monkeys. At a first sight, spontaneous (nonexperimentally induced) psychopathology seems to be much more frequent in human beings than in nonhuman primates. For example, McGuire et al. (1983) wrote: "[we] have probably spent over 20,000 hours observing vervet monkeys in quasi-natural environments, and we have never seen behavior suggestive of schizophrenia, mania, agitated depression, or involutional depression" (p 324). It is possible that the expression of psychopathology requires cognitive and emotional capacities that are unique to human beings or that the etiology of human psychiatric disorders involves genetic and environmental contributions for which there are no well-established counterparts among nonhuman primates. However, the role of diagnostic criteria should not be overlooked. An experienced clinical psychiatrist who spent 20,000 hours observing the nonverbal

behavior of human subjects interacting in their natural environments (*e.g.*, home, at work) would be able to identify only a minority of those individuals who are affected by psychiatric disorders, as defined by current diagnostic criteria. If the diagnostic criteria for different types of psychiatric disorders could be reformulated in ethological terms, the same or similar criteria could be applied in naturalistic primate studies and the detection of psychopathology in nonhuman primates might then become more feasible (Troisi, 2003).

Although the evidence for psychiatric disorders among apes and monkeys is scanty, some reports show that nonhuman primates can suffer from symptoms that resemble those of human patients. Goodall (1986) described in detail the severe effects of death of the mother on wild chimpanzees of the Gombe Stream Reserve. Being nutritionally independent, juvenile chimpanzees (aged 5–7 years) generally survive to the death of their mother. Yet, in response to the traumatic event, they show evident symptoms of emotional distress that, in some cases, can leave lasting scars. All orphaned chimpanzees initially become listless and show the typical signs of depression including huddled posture, sad facial expression, withdrawal from social activities, and a marked reduction of social play. In most cases, these orphaned youngsters are adopted by elder siblings or adult females, and their depression gradually decreases in the following 4 to 8 months. However, recovery from loss may be more problematic for some individuals (depending on their individual vulnerability and life history). Goodall observed a variety of long-lasting disorders following death of the mother including development of abnormal behaviors, such as rocking and plucking out one's own hair, growth retardation, and increased vulnerability to infectious diseases.

Another class of psychiatric disorders that may occur spontaneously in nonhuman primates is somatization disorders. The essential feature of these disorders is the conscious or unconscious production of physical symptoms that lack an organic basis. Patients diagnosed with these disorders present to their doctors with somatic complaints or objective signs of disease for which there are no demonstrable organic findings. Caine and Reite (1983) reported that one macaque female in their colony "showed signs of what could possibly be called 'hysterical paralysis' or malingering. Whenever she was placed in her social group, she limped badly, although, upon examination, no evidence of injury or disease was found. Furthermore, the limping disappeared when the animal was housed alone" (p 25). Along similar lines, De Waal (1998) described a case of disease simulation by an adult male chimpanzee deliberately displayed in front of the new alpha male by whom he was defeated in a fight, whereas being entirely normal when out of sight of the new alpha male (De Waal, 1998).

Interestingly, the nonhuman primate data reported above are in line with the evolutionary hypothesis that somatoform symptoms may be a manifestation of complex strategies of social manipulation (Troisi, 2011). More generally, they suggest that the most useful contribution of nonhuman primate studies to clinical psychiatry is that psychiatric symptoms are distributed across a continuum ranging from adaptive reactions to dysfunctional manifestations.

CONCLUSIONS

In this article, we aimed to discuss several aspects of contemporary psychiatry and the neurosciences in terms of their conceptual shortcomings, and of the need of a scientific framework that is useful for both research and the clinics. We assert that progress in terms of prevention, diagnosis, and treatment of psychiatric disorders cannot be made without acknowledging evolutionary theory with all its facets as the basic science for psychiatry and possibly medicine as a whole. We have tried to reinforce this statement by exemplifying current conceptual shortcomings that cannot be resolved without an evolutionary approach. Contemporary concepts that need refinement comprise—at least—the distinction between defense and defect, the complex interaction between genes and the environment, the interaction between the brain and the rest of the body, and the recognition of patient behavior outside the consultation room. What is perhaps most relevant for psychiatry is the necessity to acknowledge LHT as a framework that has the power to span and integrate a huge bundle of issues, ranging from global health care to the tailoring of individual treatment including psychotherapy.

As regards global mental health care, for example, LHT predicts that poverty, homelessness, environmental destruction, exposure to pathogens and toxins, and so on contribute to the adoption of a "fast" LHS, that is, riskier lifestyle. Conversely, if policy would take appropriate action, less exploitation of developing countries by developed countries, improving living conditions in economically unstable societies, and providing access to health care and health education would almost certainly help people slow down their "pace of life"; this would also predictably reduce the burden of disease, number of offspring in developing countries, and reduce the rising numbers of depression (Brüne and Schiefenhövel, 2019). The same logic applies to individual therapy. Preventing child abuse and neglect and ameliorating social inequality would also downscale the pressure to assume a "fast" LHS. Even in individual psychotherapy, it could make sense to include LHT issues, because most of the processes determining one's pace of life are unconscious, but of course accessible and open to change (Brüne, 2016a). Attachment theory-related approaches are highly compatible with such a proposition, last, but not least, because attachment theory is currently the only framework in psychiatry and the neurosciences that is unequivocally embedded in evolutionary theory (Fricchione, 2018).

Moreover, as pointed out previously, a comparative perspective (both cross-cultural and across-species) can greatly advance the difficult distinctions between nature and nurture, as well as among the social, psychological, and biological factors involved in the etiology of mental disorders. In this perspective, Tinbergen's four questions (Tinbergen, 1963) considering both proximal (mechanisms and ontogeny) and ultimate (adaptive significance and phylogeny) mechanisms of animal behavior can and should be applied to the study of functional and dysfunctional human behavior.

All this needs to be taught in psychiatric training, if not earlier as part of curricula at medical schools. We (Brüne, 2016b; McGuire and Troisi, 1998; Palanza and Parmigiani, 2016) and others (*e.g.*, Nesse et al., 2010) have published quite a few articles, book chapters, and monographs (*e.g.*, Gilbert and Bailey, 2000; Nesse, 2019) to highlight the relevance of an evolutionary approach to psychiatry and neuroscience. It is essential that this endeavor be taken further and elaborated (Nesse et al., 2010). Considering Thomas Insel's lament on the practical benefits of past funding, we suggest that $20 billion would be well spent on projects that explicitly endorse evolution as a basic science for psychiatry and the neurosciences.

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DISCLOSURE

The authors declare no conflict of interest.

The authors declare that the manuscript is written in full consideration of the Declaration of Helsinki.

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