A biocultural approach to psychiatric illnesses

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Abstract

Rationale As a species, humans are vulnerable to numerous mental disorders, including depression and schizophrenia. This susceptibility may be due to the evolution of our large, complex brains, or perhaps because these illnesses counterintuitively confer some adaptive advantage. Additionally, cultural and biological factors may contribute to susceptibility and variation in mental illness experience and expression. Taking a holistic perspective could strengthen our understanding of these illnesses in diverse cultural contexts.

Objectives This paper reviews some of these potential factors and contextualizes mental disorders within a biocultural framework.

Results There is growing evidence that suggests cultural norms may influence inflammation, neurotransmitters, and neurobiology, as well as the illness experience. Specific examples include variation in schizophrenia delusions between countries, differences in links between inflammation and emotion between the United States and Japan, and differences in brain activity between Caucasian and Asian participants indicating that cultural values may moderate cognitive processes related to social cognition and interoception.

Conclusions Research agendas that are grounded in an appreciation of biocultural diversity as it relates to psychiatric illness represent key areas for truly interdisciplinary research that can result in culturally sensitive treatments and highlight possible biological variation affecting medical treatment.

Keywords Biocultural · Depression · Schizophrenia · Culture · Neuroinflammation · Evolutionary medicine

Introduction

This paper argues that psychiatric illness is best understood as a biocultural phenomenon grounded in our species’ evolutionary history. Although we share key physiological mechanisms that influence stress and affect with other animals, including glucocorticoid and neuroinflammatory responses, and conditions similar to Alzheimer’s and anxiety have been described in non-human primates (Kummrow and Brüne 2018; Nash et al. 1999; Botero et al. 2013; Brüne et al. 2006), psychiatric illnesses in humans seem to be unique in their scope and impact. Large, complex brains and complex, meaningful social lives are central to humanity’s success as a species but appear to have left us particularly vulnerable to mental illness. Researchers grounded in evolutionary theory have offered potential explanations for how this vulnerability arose and why it persists (Williams and Nesse 1991), and neuroscience and allied fields have outlined the proximate mechanisms that contribute to these illnesses. What is sometimes missing from these perspectives, however, is an appreciation of context and variation in affecting psychiatric illness. For instance, genetic variation affecting neurotransmitters, inflammatory factors, or hormones that contribute to schizophrenia, depression, and other illnesses could influence disease susceptibility and severity. Research in psychoneuroimmunology, psychosomatic health, and cultural neuroscience highlights the connections between the social and biological domains, raising the likelihood that our cultural context(s) further influence the shape of these illnesses.

My primary aim is to highlight potential avenues for novel, interdisciplinary research with the ultimate goal of strengthening clinical approaches to understanding and treating these disorders. For instance, an appreciation of
the role that social environments and, more broadly, culture can play in shaping the behavioral symptoms of psychiatric illness could theoretically contribute to individualized diagnoses and treatments. Contextualizing these conditions within an evolutionary framework could de-stigmatize some diagnoses, highlight novel genomic regions of interest, and point toward potential alternative treatment modalities.

The ubiquity of psychiatric illness: an evolutionary legacy?

Psychiatric illness is certainly not new to humans. Hippocrates described depression in terms recognizable to us today (Horowitz et al. 2016); schizophrenia and perhaps anxiety disorders are similarly present in the historical record (Jablensky et al. 1992; Jablensky 2010; Crocq 2015). Combined with the comparative animal research mentioned above, this suggests widespread susceptibility to psychiatric illness and allows us to ask intriguing questions as to why we should remain so vulnerable to conditions that demonstrably reduce our quality of life and can affect our ability to successfully reproduce and sometimes shorten our lifespan, the key aspects of evolutionary fitness.

Evolutionary approaches to health and medicine (“evolutionary” or “Darwinian” medicine) concern themselves with understanding the evolutionary forces that might explain the presence of pathologies across our species (Nesse 2006). Within this framework, several hypotheses have been proposed to explain our vulnerability to somatic and psychiatric disease, including mismatches between our current environments and the conditions in which our species evolved, imperfect adaptations, and the adaptive benefit of some “diseases.”

As an example of this latter category, depression has been theorized as: an adaptive trait that prevents or minimizes wasting energy and time on potentially risky activities or lost causes (Klinger 1975; Andrews and Thompson 2009); a signal of distress that elicits assistance and care from others (Hagen 2003; Steinkopf 2017); and part of an evolved behavioral defense against infectious disease that encourages social withdrawal thereby decreasing transmission risk (Raison and Miller 2013; Anders et al. 2013). In each case, depression is beneficial in short bouts but pathological if it persists longer than is necessary to readjust motivational priorities, gain assistance, or avoid infection. In other words, pathological depression represents a flaw in an otherwise healthy defense mechanism, much like chronic pain (Nesse 1999).

Schizophrenia, too, may be an unintended consequence of a human adaptation, in this case our cognitive evolution. Crow (1997) proposed that susceptibility to schizophrenia may be the cost associated with language, creativity, and intelligence. There is evidence that genes related to schizophrenia have undergone positive selection (Crespi et al. 2007) and are more likely to be found in genomic regions that demonstrate evolutionary divergence from Neanderthals (Srinivasan et al. 2016). In a recent examination of the human “connectome” (i.e., the network of neural connections) via mathematical simulations, Gollo et al. (2018) found that areas of network fragility overlap with areas of gray matter reduction as occurs in schizophrenia. Vulnerable areas include the prefrontal cortex, central to many human cognitive traits (Teffer and Semendeferi 2012). Susceptibility of the connectome to connective perturbations may be a result of its overall complexity, which is due to the competing demands of minimizing brain size to reduce metabolic demands and the need to undertake complex, rapid cognition (Gollo et al. 2018).

We can therefore look to our species’ past to better understand why we remain vulnerable to psychiatric conditions like depression and schizophrenia. This evolutionary approach goes beyond simple academic interest, however. Approaching depression as an adaptive trait can refocus research and treatment on the causes and consequences of its dysregulation rather than treating the mechanisms of depression (e.g., neurotransmitter imbalances or inflammation) (Nesse 1999). A focus on the genetic differences between Homo sapiens and Neanderthals can indicate new genomic regions of interest in schizophrenia research beyond what may have been apparent in studying humans alone. However, constraining analysis to biological factors only, whether proximate or evolutionary, arguably risks discounting the contribution of social context.

5-HTTLPR: stress, depression, evolutionary history, and social contexts

The serotonin transporter protein 5-HTT is crucial in terminating the actions of serotonin through synapse reuptake. The short (s) allele of the 5-HTTLPR serotonin transporter polymorphic region results in less transcriptional activity and reduced serotonin uptake, and has been associated with lower levels of emotional resilience (Stein et al. 2009), depression (Caspi et al. 2003), and increased cortisol reactivity to social stressors (Way and Taylor 2010) relative to carriers of the long (l) allele. Non-human primates show similar polymorphisms, suggesting that these variants arose after the divergence of the Primates order and that multiple independent evolutionary events contribute to observed allele patterns across primate species (Dobson and Brent 2013). Treating the s allele as entirely detrimental cannot adequately explain its relatively high frequency across populations examined to date (Chiao and Blizinsky 2010). Instead, the effects of the s allele appear to be dependent on social contexts.
Dobson and Brent (2013) suggested that the s allele and other low-expressing genotypes evolved in primate species characterized by short-term fluctuating rates of intra-group competition. During periods of high competition and social threats, individuals who are more attuned to social environments and who respond in a risk-averse manner, as is characteristic of the s allele in humans, are better able to cope. On the other hand, during periods of lower competition, long allele carriers should be favored, in part because they do not experience the potential costs of hypervigilance such as disproportionate responses to minor stressors, lost foraging and feeding time, and so on.

These alleles may also influence behavioral phenotypes during early life. Rhesus macaque (Macaca mulatta) juveniles carrying the s allele and who experience higher maternal protection in the first 12 weeks of life are more likely to engage in social play, whereas l allele carriers were generally insensitive to their childhood environment and showed no effect of maternal behavior (Madrid et al. 2018). Because social play is associated with social competence and predictive of social networks and stable social bonds in later life, the benefits of the s allele in combination with positive maternal environments may outweigh potential costs, including those in low-competition environments.

Belsky and colleagues have outlined the differential susceptibility hypothesis (Belsky 1997, 2005), which states that individuals vary in their responsivity to the same environmental influences, thereby explaining the continued presence of “vulnerability” genes in spite of their evolutionary disadvantages (van IJzendoorn et al. 2012). Belsky (1997, 2005) suggested that this differential susceptibility is evolutionarily adaptive as a form of “bet hedging” against uncertain environmental conditions (Belsky and Pluess 2009). Belsky’s original formulation of the hypothesis, focusing on child susceptibility to parenting cues, has been complemented by Boyce and Ellis (2005) who argued that maintenance of high levels of stress reactivity in children is beneficial in highly positive or highly negative developmental environments (Belsky and Pluess 2009). In positive circumstances, a child would benefit from maximizing the degree to which this environment contributed to his or her development, whereas in adverse circumstances, a child would benefit from heightened threat vigilance (Boyce and Ellis 2005; Belsky and Pluess 2009). In either case, greater sensitivity to the surrounding social and physical environment would be selected for. In the differential susceptibility framework, carriers of the 5-HTTLPR s allele are more sensitive to both positive and negative environmental cues, as in the previous example of rhesus macaques and in parallel with Dobson and Brent (2013). Caspi et al.’s (2003) widely cited longitudinal study found that the s allele predisposed individuals to increased depression after exposure to stressful life events. However, risk of depressive symptoms was reduced in s/s homozygotes if their early social environments were supportive, a relationship not found in individuals carrying the long (l) variant (Taylor et al. 2006). Similar results have been described for neuroticism (Pluess et al. 2010). A meta-analysis has shown additional support for the differential susceptibility hypothesis, with s allele carriers developing poorly in adverse environments but more positively than l allele carriers in beneficial circumstances (van IJzendoorn et al. 2012). Hence, it is better to think of 5-HTTLPR as a “plasticity” allele rather than a “vulnerability” allele (Madrid et al. 2018). In a large sample of African-Americans, carrying two such plasticity alleles, including 5-HTTLPR-s, interacted with exposure to adverse environments to predict chronic anger and aggression (Simons et al. 2011). However, these same individuals scored lower in aggression, anger, and similar traits than individuals with other genotypes when they had experienced positive environments (ibid.). Suomi (2006) has even proposed that the presence of the 5-HTTLPR polymorphism in humans and macaques contributes to these species’ resilience across a wide variety of environments and subsequent evolutionary success. By adopting an evolutionary perspective, Belsky and colleagues have highlighted shortcomings in a widely held theoretical model (the diathesis-stress model; Belsky and Pluess 2009) and posed fascinating questions about the intersections of social environments and biology and the ability of both to shape psychological health.

We might further extend this framework of susceptibility and resilience by considering culture as a key component of our social environment. Culture, discussed in detail below, is a shared framework for experiencing and explaining the world and therefore shapes our social environments. Exploring the reasons why some, but not all, disadvantaged African-Americans adopt the “code of the street” (i.e., a culture of opposition to social rules, distrust of others, retribution against disrespect), Simons et al. (2012) found that 5-HTTLPR, dopamine, and monoamine oxidase A (MAOA) plasticity polymorphisms interacted with adversity to predict adherence to this code, but that carriers of these same alleles were less likely to adhere to the code when adversity was minimal.

In this case, our species’ evolutionary legacy, in the form of these plasticity alleles that can influence stress and depression, interact with social environment quality to predict adherence to specific cultural values, but additional evidence suggests that culture could shape psychiatric illness either directly or through interactions with biological factors. For instance, cultural neuroscience research has been able to offer some direct evidence of how culture is “embrained,” noting that the brain itself can be affected by interaction with culture (Kitayama and Salvador 2017). Holistic answers to questions about
human health and behavior must address both biology and culture, sooner or later, and recognize the possibility that both cultural and biological variation within and between populations can shape susceptibility to illness and perhaps the illness itself. Applying this biocultural framework to psychiatric conditions requires us to pursue research beyond the so-called WEIRD (Western, Educated, Industrialized, Rich, and Democratic) populations (Henrich et al. 2010) and to ultimately arrive at a more nuanced understanding of culture than has generally been used in the health literature.

**What is culture?**

There have been many different definitions of culture through the years. An NIH Expert Panel on culture and health provided an excellent definition: “an internalized and shared framework […] through which both the individual and the collective experience the world [and] is created by, exists in, and adapts to the cognitive, emotion, and material resources and constraints of the group’s ecologic system to ensure the survival and well-being of its members, and to provide individual and communal meaning for, and in, life” (Kagawa Singer et al. 2016). Additionally, many current approaches in the social sciences recognize that individuals or groups differentially engage with and contest received cultural patterns. Intersectionality theory also challenges simplistic notions of cultural influences on health by noting that multiple culturally constructed identities (e.g., gender, class, race/ethnicity) often interact to shape health outcomes depending on context (Dhamoon and Hankivsky 2011; Hankivsky 2012). Finally, historical and modern diffusion of cultural norms through globalizing processes such as migration, the internet, and media complicates notions of cultures as independent entities, something that should be accounted for during study design and analysis (Borgerhoff Mulder 2001; Eisenberg and Hayes 2011).

Unfortunately, the culture concept is often misapplied in many health disciplines. Broad ethnic or national categories (e.g., Hispanic/Latinx, Chinese, East Asian) are often conflated with individual “cultures.” This is understandable, at least to a degree, as these categories have considerable historic inertia and are often reinforced in governmental census categories and similar data. These groups may also represent some amount of shared genetic ancestry, experience, and interpretive frameworks and characteristics important for health outcomes, such as discrimination or concentration of populations in underserved areas. However, ethnicity, nationality, and biology are not culture per se, and treating them as such replaces dynamic, complex cultures with static proxy constructs. As Kirmayer and Ryder (2016, p. 143) have stated, “it has become increasingly difficult to justify research or clinical practice that typifies people simply in terms of membership in broad ethnic groups.” Considering differences between these coarse proxies (as this paper is constrained to do) is certainly a useful first step toward improved understandings of disease and has already been a productive line of inquiry, but their conflation is inaccurate and, in the end, may hamper our attempts at improving health disparities and associated goals.

In spite of these methodological challenges, medicine and psychiatry have much to gain by taking a biocultural perspective. Culture informs our beliefs about, and approaches to, illness and health, thereby shaping risk factors, treatment seeking, and other domains. Culture affects our perceptions and cognition as well as their underlying neurobiology (Denkhaus and Bös 2012). The extent to which culture can mold our biology—that is, “get under the skin,” to use a fashionable phrase—is a fascinating and exciting question with implications for any field interested in mind, behavior, and health. A useful next step toward this goal is to expand research outside of WEIRD populations to begin exploring mental health in diverse groups.

**The problem of weird populations**

The use of WEIRD participants in behavioral and psychological research is widespread. From 2003 to 2007, 68% of samples in the flagship journals of the American Psychological Association (APA) were from the USA, while approximately 95% of samples were from the USA, Europe, Canada, Australia, and New Zealand (Arnett 2008). A propensity to use undergraduate students as subjects compounds this sampling problem, leading to concerns about generalizability and replicability.

Henrich et al. (2010) noted that several aspects of psychology, cognition, and perception vary significantly when comparing WEIRD with non-WEIRD individuals. For instance, San foragers from the Kalahari did not perceive the Müller-Lyer illusion (that the same line appears longer when tipped with outward facing diagonals, i.e., \( > < \) vs. \( < > \)) that reliably “fooled” Western participants (Segall et al. 1966). Similar results have been found with the Tsimane of Bolivia (Gurven 2018), who do not provide as much infant-directed speech as other populations (Cristia et al. 2017), have no apparent mid-life crises (Stieglicz et al. 2015), no sex differences in dead reckoning navigation (Trumble et al. 2016), and in whom the Big Five personality construct does not fully replicate (Gurven et al. 2013). Importantly, each of these has been proposed as a human norm or universal (Gurven 2018). Differences in physical and built environments may underlie some of these differences. For instance, Segall et al. (1966)
and Henrich (2008) speculate that perception of the Müller-Lyer illusion is dependent on the presence of “carpentered corners” during an individual’s development, which is a relatively recent invention and not shared by all cultural groups. Based on existing data, males tend to use large-scale topographic features to help orient themselves in the environment, but these types of features are lacking in the Tsimane habitat and so might contribute to the lack of sex differences in dead reckoning (Trumble et al. 2016). Language too may help shape between group variance in spatial cognition, depending on whether the language uses an egocentric system (i.e., relative to the self, characteristic of English and other Indo-European languages) when locating objects, or an allocentric system, in which items are described in terms of cardinal directions or in relation to other objects (Henrich et al. 2010).

However, not all differences in cognition and information processing are entirely due to ontogeny or environment. Evidence suggests that at least some group differences in perception and emotion processing are attributable to differences in brain function, possibly as a result of differing cultural values. One of the most common putative cultural distinctions in the literature is between “collectivistic” and “individualistic” societies (e.g., Triandis 1995). In the former, individuals subsume personal goals in order to foster the goals of a larger group, whether a family, tribe, or other in-group, and behaviors are driven by perceived duties and obligations. In the latter, personal goals are favored, although individuals certainly still belong to various in-groups, and behaviors are driven by attitudes and other internal processes (Triandis 1995; Singelis et al. 1995, but see Voronov and Singer 2002 for a critical review of this construct). In general, (East) Asian cultures have been characterized as collectivistic or interdependent (Markus and Kitayama 1991) and situated against the individualistic American culture. Other researchers have expanded on the individualistic/collectivistic dichotomy. For instance, Gelfand et al. (2011) distinguished between “tight” (i.e., having strong norms and low tolerance of deviant behavior) and “loose” cultures with higher tolerance for deviant behavior and weaker norms. These differences in self-construal and adherence to group goals can shape emotional expression and internalized ideal emotional states (Tsai et al. 2006; Kitayama et al. 2006; Kitayama and Park 2017). Whereas emotional expression is valued (or at least not discouraged) in the West, calmness and serenity are often described as desired traits in Asia, perhaps due to Confucian traditions that see strong emotions as a threat to social harmony and order (Murata et al. 2013; Kitayama et al. 2006). Emotions appear to be linked with body responses and sensations through anterior insula (AI) activity, which is activated when individuals experience emotion and which also plays a role in generating mental images of one’s physical state (i.e., interoception) (Craig 2002; Immordino-Yang et al. 2014). A comparative fMRI study of Chinese, non-Asian Americans, and second-generation East Asian-Americans found that while basic interoceptive processing, as measured by AI activity, did not differ between the three groups, subjective strength of emotion was associated with different areas of the AI between the groups (Immordino-Yang et al. 2014). In both the Chinese and non-Asian American participants, emotional strength was largely associated with dorsal AI activation, whereas in the Chinese subjects, the ventral AI was more active. Immordino-Yang et al. (2014) speculate that differences in the contribution of the dorsal or ventral AI to subjective emotional strength between Chinese and American participants (notably, Asian-American participants showed an intermediate patterns of activation) indicate that different types of somatic information are used when constructing subjective emotional states. Chinese participants relied on a brain region associated with changes in autonomic modulation, the ventral AI, whereas European American participants relied on dorsal AI somatosensory cues. Similarly, Murata et al. (2013) found that electroencephalographic indicators of emotional processing in the parietal region were decreased to a marked degree in Asians, but not Caucasians, when participants were asked to suppress their emotions in response to emotion-eliciting pictures. The authors suggest that these data indicate a true dampening of emotions at a neurological level in Asian participants, but because emotional suppression is generally counter to cultural norms in Caucasians, they were unable to suppress their emotions to the same degree.

Similar results have shown differences in information processing related to social norm violations. Although experimental social norm violations elicited N400 EEG responses (a marker of unexpected stimuli and incongruent information) in the central and parietal regions of the brain in American and Chinese participants, the Chinese participants exhibited an additional response in the frontal and temporal regions as well (Mu et al. 2015). The authors speculate that this additional brain activity in Chinese participants may indicate inferences as to the mental state of the norm violator, given the relationship between the frontal N400 and brain regions associated with mentalizing/theory of mind, although other regions, like the right temporoparietal junction, may be more important in theory of mind (Saxe and Wexler 2005). Other differences in brain activity between Westerners and East Asians include variation in medial prefrontal cortex (PFC) activity when thinking of themselves (Zhu et al. 2007); activation of frontal and parietal regions when engaging in culturally preferred judgment tasks (Hedden et al. 2008); and differences in amygdala activation in response to threatening faces (Chiao et al. 2008). Additionally, a recent meta-analysis of 35 publications has reinforced the evidence for activation of different neural networks between East Asian and Western individuals (Han and Ma 2014).

Variation in neural activity may lead to morphologically different brain structures. Chee et al. (2011) found a significant difference in cortical thickness in multiple regions
associated with the polymodal association cortex between European Americans and East Asians, which the authors surmise may be connected to differences in information processing between the two groups. East Asian individuals tend to process information holistically by integrating context more so than Westerners, who attend to individual objects independent of their contexts (Nisbett and Miyamoto 2005). Based on Chee et al.’s findings, which have since been replicated (Yu et al. 2018), further research has explored the role of cultural norms in explaining this difference. In a large (n = 265) study of Chinese students from Beijing, greater self-reported independence was associated with increased gray matter volume in the ventromedial prefrontal cortex (vmPFC), the dorsolateral PFC (DLPFC), and the right rostrolateral PFC (RLPFC), while interdependent self-construal was associated with reduced gray matter volume in the mPFC (Wang et al. 2017a; but see Kitayama et al. 2017, which raises questions about the stringency of statistical thresholds with voxel-based images). Enlargement of a brain region is typically associated with greater proficiency in that given domain, and the vmPFC, DLPFC, and RLPFC are linked with a variety of functions related to the self, including self-referential thinking, personal agency, and memory (ibid.). On the other hand, the mPFC is associated with the development of personal self-identity (Yu et al. 2018). In a similar study with Japanese participants, Kitayama et al. (2017) found negative correlations between interdependent self-construal (i.e., the degree to which an individual places their social group(s) above their own needs and self-interest) and gray matter volume in the orbitofrontal cortex (OFC), a brain region the authors hypothesize may be important in promoting and maintaining self-interest given its established role in establishing consistent personal preferences and the calculation of rewards based on social contexts and other external cues. Similar associations were also found in the right fusiform gyrus and left inferior temporal gyrus, among others. The OFC findings were moderated by attunement to the external environment, such that individuals who were better able to create vivid mental images had lower OFC volumes than their counterparts without this ability (Kitayama et al. 2017). Importantly, these studies examine variation in cultural beliefs within a putative cultural group, allowing the authors avoid or minimize possible bias from differences in other cultural values, environment, genetics, and other sources. Extending this work, Yu et al. (2018) found that European Americans had greater OFC and mPFC gray matter volume than East Asians, and that the 7- and 2-varying number tandem repeat (VNTR) polymorphisms of the dopamine receptor gene DRD4 interacted with culture, such that individuals carrying the rare 7/2 VNTR polymorphisms showed a greater cultural difference in OFC volume than did non-carriers. A similar interaction was also found in the mPFC, albeit at marginal significance. Dopamine is involved in reward processing, and the 7- and 2-repeat polymorphisms have been associated with greater dopamine signaling capabilities and a greater sensitivity to environmental cues (Yu et al. 2018). The authors suggest that these variants sensitize their carriers to cultural influences; hence, attending to these cues could lead to positive reinforcement and the strengthening of neural connections in associated brain regions. These and similar findings further speak to potential hidden heterogeneity in the culture-brain nexus. As 90% of neuroimaging studies involve Western samples (Chiao 2009), additional differences are sure to be uncovered in research using diverse groups. This is not to argue that all aspects of cognition, brain activity, or other physiological systems vary between or within groups, but there are intriguing differences that highlight the necessity of including non-WEIRD populations in our research in order to better explore the effects of biological and cultural variation. If the healthy brain/mind can demonstrate such variability, as outlined above, then we can plausibly expect differences in pathologies as well.

### Biocultural sources of variation in psychiatric illness

Schizophrenia exemplifies the ways that culture can potentially affect the experience and expression of psychiatric illness. Although the global prevalence of schizophrenia appears to be relatively stable (0.5–1.0%, Doi et al. 2009; Koelkebeck and Wilhelm 2014), there are intriguing differences in symptoms. In “collectivistic” societies, delusions that are centered around bringing shame to someone or being a burden to others seem to be more common, whereas delusions of persecution are more common in Western, “individualistic” societies (Koelkebeck and Wilhelm 2014). In one study, individuals experiencing delusions and hallucinations in the USA, India, and Ghana were interviewed about the voices they heard. Participants in all three countries reported hearing both good and bad voices and had conversations with these voices, but the experience was much more negative and stressful, and the voices more violent, in the USA, where hearing voices was more likely to be attributed to brain disease2 (Luhmann et al. 2015).

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2 Cultural differences in psychiatric disorder epidemiology, etiology, etc. raise the question of the universality of emotional expression and interpretation in humans. Depression and schizophrenia, for instance, are diagnosed in part based on the presence of inappropriate emotional states. It is certainly reasonable to think that inappropriate emotional responses are shaped by culture, meaning that a pattern of behavior may be considered pathological in one cultural context but not another. A lengthy discussion of the universality of human emotions is beyond the scope of this paper, but data suggest that at least some facial and vocal expressions are uniformly recognized between cultures (e.g., anger, grief) but also that there may be emotional dialects, i.e., subtle differences in emotional expressions, that hinder identification in members of an out-group (for review see Scherer et al. 2011). Commendably, the DSM-V has addressed the role of cultural norms in the diagnosis of some psychiatric illnesses (Table 2 in Paniagua 2018).
The effect of migration status on schizophrenia symptoms further demonstrates the power of culture in shaping mental illness. Pakistani individuals living in Britain (17 years duration, on average) were significantly different in their delusions compared to both Pakistanis from Lahore and Caucasian Britons (Suhail and Cochrane 2002), perhaps as a result of acculturation. For instance, both Caucasian and Pakistani Britons believed that others were talking about them at a similar frequency while both groups of Pakistanis were more apt to believe they were being persecuted (ibid.).

Psychological distress can also manifest as physical symptoms (i.e., somatization), and there is a large literature describing differences between populations. Kirmayer and co-authors (Kirmayer and Young 1998; Kirmayer and Ryder, 2016) have critiqued simplistic, though frequent, claims that non-Western populations are more prone to somatization, highlighting some of the methodological and conceptual problems in that body of work. For instance, while some authors attribute differences in somatization to cultural differences in the relative value placed on individualism or collectivism (Varela et al. 2004; Weiss et al. 2009), a possible alternative explanation is that differences in culturally appropriate health-seeking behaviors or, relatedly, symptom interpretation may be responsible. In a clinical sample of Thai children with psychiatric symptoms seeking treatment, rates of somatization were higher than in comparative US children, as well as healthy US and Thai children (Weiss et al. 2009). In the Thai cultural context, somatic symptoms may be perceived as more dangerous or may be a more socially acceptable reason to seek treatment than psychological symptoms (ibid.). Somatization may also be condition-specific. For instance, both Mexican-American and Chinese adults (both immigrants to Western countries and those living in Asia) report more physical symptoms of depression than do Caucasians (Escobar 1987; Ryder et al. 2008), but North Americans with anxiety are more likely to present with somatic complaints than individuals in China (Dere et al. 2013). Beyond differences in symptom characteristics, expression, and interpretation, cultural and biological variation may also interact to shape mental illness at a more fundamental level.

**Inflammatory and immunological variation**

One of the core findings of psychoneuroimmunology and allied fields is the inflammatory basis of some neurodegenerative and psychiatric conditions (Skaper et al. 2018). The immune system is, of course, central to survival and has even been called a sixth sense due to its interactions with the nervous system (Blalock 2005). However, there is evidence that immune and inflammatory responses are not necessarily universal (beyond differences due to age, sex, nutritional status, etc.), which may have implications for neuroinflammatory conditions. For instance, studies using the bacille Calmette-Guerin (BCG) vaccine have found that T cells from Malawian and Gambian infants show strong Th1 responses dominated by interferon-γ (IFN-γ), while Indonesian infants show additional IL-5 and IL-13 responses to the vaccine that are not seen in Malawian, Gambian, South African, or British children (Dujuardi et al. 2010; Lalor et al. 2011). Similar differences in immunogenicity, antibody titers, and antibody duration have also been found for *Haemophilus influenza b* (Hib) (e.g., Siber et al. 1990), hepatitis B (Asturias et al. 2009), and tetanus vaccines (Gergen et al. 1995), among others (see Kollmann 2013 for an extensive review). Some of these differences are independent of nutritional status but could be explained by differences in prenatal environments, previous exposure to infectious disease, or genetic variation (Kollmann 2013), perhaps due to selective pressures of local disease ecologies.

Epidemiological or cross-sectional studies generally find ethnic differences in pro-inflammatory cytokines, namely higher basal levels of IL-6 in individuals of African descent relative to those of European ancestry (Steffen et al. 2012; Paalani et al. 2011). Importantly for experimental studies, these patterns in basal levels may not carry over during immune challenge. Although Ferguson et al. (2013) replicated these baseline findings in a large sample of Americans, African descended participants showed an attenuated cytokine/inflammatory response to lipopolysaccharide (LPS). Peak levels of tumor necrosis factor-α (TNF-α), IL-6, IL-1 receptor antagonist (IL-1ra), C-reactive protein (CRP), and serum amyloid A (SAA) were all lower (albeit to a modest degree) in these participants, although only CRP and IL-1ra achieved statistical significance. On the other hand, a recent genetic analysis linked the degree of African ancestry in African-Americans with an increase in transcriptional response in macrophages to in vitro exposure to Gram-positive and Gram-negative bacteria (Nédélec et al. 2016), relative to European Americans. Genes involved included many related to cytokine production, inflammation, and leukocyte activation. This increased inflammatory activity contributed to improved bacterial clearance but may come at the cost of elevated risk of autoimmune and inflammatory diseases like rheumatoid arthritis, ulcerative colitis, and others (ibid.). Whether these differences in immune-related genes contribute to variation in neuroinflammation and/or psychiatric conditions is unexplored. However, evidence from cytokine promoter region single nucleotide polymorphisms (SNPs) is suggestive.

Two such SNPs (IL6-174G [rs1800795] and TNF-308A [rs1800629]) have received considerable attention due to their ability to increase circulating cytokine levels, though the magnitude of effect appears to be limited in the absence of an inflammatory stimulus (Amaral et al. 2015). These alleles have also shown relationships with mood. IL6-174C homozygous individuals (a low IL-6-producing genotype) reported fewer depressive symptoms during IFN-α and ribavirin
treatment for hepatitis C (Bull et al. 2009), and the high-producing -174G allele has been linked with greater mood disturbances during viral infections (Piraino et al. 2012). On the other hand, Tarrett et al. (2015) report that C/C homozygosity interacted with chronic interpersonal stress, leading to higher levels of depression. The TNF-308G/G genotype (normal TNF production) has been associated with increased fatigue ratings in chronic fatigue syndrome, cancer-related fatigue, and fatigue due to other diseases (Wang et al. 2017b). Perhaps this or similar alleles can affect somatic symptoms of depression.

While research on the global distribution of SNPs like these is still in its infancy, studies have generally found that non-Caucasian/European samples have higher frequencies of the IL-6-174G allele than Caucasians, though the latter tend to have higher frequencies of TNF-308A/A and -308G/A genotypes, both associated with higher TNF production (Abraham and Kroeger 1999; Allen 1999; Shattuck and Muehlenbein 2015). There are also some intriguing preliminary data suggesting that these polymorphisms may interact with ethnicity to affect symptom expression. IL-6-174G/G predicted moderate/severe pain, fatigue, and other symptoms in non-Caucasian/European samples have higher frequencies of TNF-308A/A and -308G/A genotypes, both associated with higher TNF production (Abraham and Kroeger 1999; Allen 1999; Shattuck and Muehlenbein 2015). Further research is needed to contextualize these SNP frequencies within cultural contexts. For instance, while high frequencies of the IL-6-174G/G genotype have been reported in Japan (e.g., Watanabe et al. 2005), large studies have found low levels of circulating IL-6, albeit in non-clinical samples (Coe et al. 2011). In addition to an absence of inflammatory challenge during sample collection, factors such as diet and social norms could potentially explain this discrepancy, as discussed later.

Genetic variation can also affect cytokine receptor levels. Multiple polymorphisms, including rs4537545 and rs1892284 (now rs2228145), affect production of the soluble IL-6 receptor (sIL-6r) (Amaral et al. 2015; Rafiq et al. 2007; Reich et al. 2007). Individuals homozygous for the minor rs4537545 allele exhibited nearly double the amount of serum sIL-6r than their common allele homozygous counterparts (Rafiq et al. 2007). Interestingly, this same polymorphism was associated with increased IL-6, albeit at modest levels (ibid.). Admixture analysis has shown a significant association between European ancestry and increased sIL-6r levels due to the C allele at the rs2228145 SNP (Reich et al. 2007). This SNP is also associated with elevated IL-6 levels. More research is clearly needed to clarify the effects of these and other immune-related alleles on both (neuro)inflammation and psychiatric disorders, as well as their global distribution, but early work is promising. Inter- and intra-population variation in their effects (e.g., Shi et al. 2015) are particularly worth exploring, as it may highlight individuals and groups at elevated risk of disease.

The Midlife in the United States (MIDUS) and Midlife in Japan (MIDJA) studies have allowed researchers to explore group differences in relationships between inflammation and mood, which again appear to be modulated by cultural contexts. An examination of differences in inflammatory markers between the USA and Japan found that IL-6, soluble IL-6 receptor (sIL-6r), CRP, and fibrinogen levels were significantly lower in Japanese individuals than in Americans (Coe et al. 2011). While Coe and colleagues focus on differences in diet to explain these findings, they note that social integration and other emotional or stress-related processes can affect inflammatory markers. Other researchers have used the MIDUS/MIDJA datasets to explore differences in stress between the two countries. Curhan et al. (2014) found that although negative affect predicted poor health in both countries, the magnitude of the effect was much larger in the USA than in Japan. The authors suggested that this variability might be explained by differences in attribution of negative states; in the USA, negative affect is often interpreted as being due to a fault within the self, whereas it is often attributed to external forces in Japan. Similarly, a greater acceptance of negative emotions among Japanese than in the USA may prevent associated increases in IL-6 (Miyamoto et al. 2013). A similar pattern was found with expressions of anger (e.g., physically or verbally aggressive behavior) and “biological health risk,” as indexed by IL-6, CRP, systolic blood pressure, and cholesterol (Kitayama et al. 2015). Increased anger expression was associated with an increased health risk in Americans, while the opposite was true for Japanese participants. It may be that anger expression is a measure of accumulated stressors and annoyances in Americans, but in Japan, it is a marker of personal empowerment, whereby socially dominant (and ostensibly healthier) individuals are permitted to express anger (Kitayama et al. 2015). Similarly, differences in behavioral adjustment, the ability to modify one’s behavior to environmental circumstances, moderate the health effects of neuroticism in Japanese individuals, but not Americans (Kitayama et al. 2018). Kitayama and colleagues surmise that because Japanese culture is more interdependent than that of the USA, individuals have a higher degree of behavioral adjustment which can prepare them to meet the challenges that neuroticism (which reflects a heightened sensitivity to potential environmental threats) identifies. Subsequent feelings of empowerment at having overcome these challenges could lead to health benefits. On the other hand, individuals low in behavioral adjustment are unable or unwilling to change their behavioral patterns and therefore never gain these health benefits. This was the case in American individuals, who showed low behavioral adjustment capability and no significant relationships between neuroticism and health risk (Kitayama et al. 2018). This relationship between an ostensibly culturally dependent coping mechanism and sensitivity to the environment poses interesting research questions for psychological conditions like depression and obsessive-compulsive disorder (OCD). If, like neuroticism, these conditions are due to
heightened sensitivity to environmental and social threats—which some evolutionary approaches propose—they may be similarly affected by behavioral and psychological flexibility. Finally, variation in stress and biomarker relationships is not limited to Asia and America. Glei et al. (2013) reported that perceived stress was linked with markers of physiological dysregulation in male and female Russian participants, but only in American women, while there were no associations in Taiwanese women and an inverse relationship in Taiwanese men.

Hormonal and neurotransmitter variation

Additional sources of variation relevant to psychiatric conditions include hormones and neurotransmitters. Like 5-HTTLPR, glucocorticoid receptor (NR3C1) gene variants may play a role in resilience or vulnerability to stress. The *Th111I* (rs10052957) variant has been associated with higher basal levels of cortisol (though these effects may be due to associations with other receptor polymorphisms; Koper et al. 2014) and carriers of the N363S (rs56149945) and the *Bcl1* (rs41423247) polymorphisms have shown increased cortisol responses to the Trier Social Stress Test (TSST) (DeRijk 2009). These polymorphisms are also associated with variation in susceptibility to depression and post-traumatic stress disorder (PTSD) (Koper et al. 2014). Studies have reported that the N363S allele is virtually non-existent in Southeast Asians (Syed et al. 2004). In a large sample of Caucasian-, African-, and Asian-Brazilians, the 363S allele was not found at all in Asian-Brazilians and frequencies were comparable between Caucasian- and African-Brazilians (~3%), in accordance with frequencies in European samples (Souza et al. 2014). On the other hand, the rare allele of *Bcl1* had a frequency of 50% in Asian-Brazilians, but only 24–29% in the other two subpopulations (ibid.).

A new meta-analysis of 237 Trier Social Stress Test studies notes that while the TSST is a widely used and reliable tool to increase cortisol production in participants, there is heterogeneity in the strength of cortisol responses that, beyond random participant sampling, does not seem to be explained by known moderators (Miller and Kirschbaum 2019). Notably, TSST studies conducted in North America generally report smaller cortisol responses than do European studies. A meta-regression model that accounted for between-country heterogeneity captured an additional 25.5% of overall variance in cortisol levels after controlling for participant age and sex, and including multiple cultural value orientations in the regression revealed that the harmony-mastery cultural dimension was an important moderator of cortisol responses (Miller and Kirschbaum 2019). This dimension, from Schwartz (2006), tracks the degree to which a society values peace, environmental protection, and unity with nature (i.e., harmony) vs. social recognition, independence, ambition, and influence (i.e., mastery). Miller and Kirschbaum (2019) hypothesize that differences in cortisol reactivity between countries are a reflection of social environment, whereby individuals from highly competitive cultures with more potential socioec- onomic insecurity (e.g., the USA) are more habituated to psychoso- cial stress relative to their counterparts in countries (e.g., Scandinavia, Germany, Belgium) that promote social harmony and well-being. These results add support to the notion that cultural contexts can shape biological responses to environmental cues, but Miller and Kirschbaum also note that their analysis requires confirmation by studies that measure cultural value orientations at the participant, rather than national, level.

The 5-HTTLPR polymorphism, discussed earlier, has also received considerable attention. Short allele homozygotes demonstrated increased heart rate, cortisol, and IL-1β following acute stress in a small study of Japanese males (Yamakawa et al. 2015), and relationships between the s allele and elevated norepinephrine have also been reported (Otte et al. 2007). This genetic variant appears to sit at the nexus of inflammation, neurotransmission, and endocrinology and could contribute to differential susceptibility to depression, as discussed above. Notably, the early-life stresses that contribute to this vulnerability do not need to be extreme. Taylor and co-authors (Taylor et al. 2006) report that moderate household conflict/chaos and unaffectionate, disconnected behaviors were sufficient to increase risk of depression in s/s individuals.

Increased frequencies of the short allele have been found in Asian populations (e.g., Chiao and Blizinsky 2010) as well as in indigenous Amazonian populations (Bisso-Machado et al. 2013). These high frequencies suggest that there may be some evolutionary pressure maintaining the potentially deleterious allele. Chiao and Blizinsky (2010) sought to explain the high prevalence of the s allele in East Asia (70–80% vs. 40–45% in European samples) by noting potential connections between individualistic and collectivistic cultures and pathogen prevalence. Some research has shown correlations between current or historical pathogen prevalence and collectivism (e.g., Fincher et al. 2008, but see Ross and Winterhalder 2016 for a thorough critique), which is thought to buffer against disease transmission due to avoidance of out-group individuals. Short allele frequency mediated the relationship between historical pathogen prevalence and collectivism in data from 29 countries, suggesting that selection for this allele, perhaps due to associated cognitive biases favoring collectivistic values (or increased sensitivity to environmental cues in general, as discussed earlier), explains the relationship (Chiao and Blizinsky 2010).

However, Eisenberg and Hayes (2011) re-analyzed these data and found no significant relationship between individualism-collectivism and 5-HTTLPR frequency when including a dummy variable for continent, and inconsistent and non-significant results for European and Asian data when analyzed separately. The authors raise critical methodological
considerations for the study of gene-culture relationships, namely that observations must be treated as non-independent due to genetic admixture between populations and possible cultural diffusion.

Another example of gene × environment (G×E) interactions comes from Brüne’s (2012) review of the SNP rs2254298 in the oxytocin receptor gene OXTR. Oxytocin, highly conserved across mammal species, influences lactation, parturition, and a number of pro-social behaviors, including affiliative and parenting behaviors (Brüne 2012; Campbell 2010). In terms of psychiatric disorders, oxytocin treatment is linked with improved social behavior in autism spectrum disorder (ASD) patients (Andari et al. 2010) whereas reduced serum/plasma oxytocin is associated with schizophrenia (Goldman et al. 2008), more severe schizophrenia symptoms (Rubin et al. 2010), and depression (Ozsoy et al. 2009). On the other hand, elevated oxytocin levels are related to social anxiety disorder symptom severity (Hoge et al. 2008).

The rs2254298 SNP encodes a guanine (G) to adenine (A) switch that is restricted to humans, being absent in other primates (Brüne 2012). Population genetics studies have demonstrated a high degree of allelic and genotypic variation across the globe. The A allele is extremely rare in samples with European ancestry (~7–17%, depending on sample), where most individuals are G/G homozygotes. Among Asian populations, the A allele appears much more frequently (~29–32%), and only about 40–50% of individuals are G/G homozygotes (Brüne 2012; Butovskaya et al. 2016). Frequencies of the A allele among Africans and African-Americans range from 19% to as high as 30% among the Datoga of Tanzania (Butovskaya et al. 2016). Interestingly, this SNP is associated with increased risk of psychiatric disorders, although specific effects vary between ethnicities. Thus, the A allele is linked with autism, but only in Chinese and Japanese samples, whereas the G allele is associated with autism risk in Caucasians. The G allele appears to be protective against depression in a non-clinical Japanese sample, but G/G homozygotes were over-represented in a sample of unipolar Italian patients; these homozygous patients also tended to exhibit avoidant attachment styles. Conversely, the presence of an A allele has been associated with higher rates of secure attachment styles in non-Caucasian children only (Brüne 2012).

One possible explanation of this heterogeneity is that phenotypic effects depend on developmental context (Brüne 2012), as with 5-HTTLPR and IL6-174C. In adolescent girls, A/G heterozygotes who had higher early-life adversity reported higher levels of symptoms of depression and anxiety than either high adversity G/G homozygotes or girls of either genotype who had experienced low adversity (Thompson et al. 2011).

Although not explicitly tested with rs2254298, another OXTR SNP, rs53576, seems to be modulated by cultural context. The G allele of this SNP has been linked with increased empathy, sensitive parenting styles, and reduced autism rates. During experimental psychosocial stress, American participants carrying the G allele increased their emotional support seeking relative to A carriers, whereas there was no such pattern observed in Korean participants (Kim et al. 2010). The authors attribute this difference to cultural differences in stress coping styles, noting that several studies have found that Asian individuals are less likely to seek emotional support during stressful events due to concern about how it might negatively impact their social relationships. In further support of this hypothesis, Korean-Americans in the study (genetically more similar to native Koreans, but culturally more similar to Americans) showed a similar response patterns to Americans (Kim et al. 2010).

The findings reviewed here highlight the intersections of biology and culture as they may relate to neuroinflammation and psychiatric conditions, and the types of novel research questions that can be brought to bear in a biocultural framework. For instance, what are the specific cultural factors that might sensitize or buffer individuals to psychological distress, and how do they interact with biological susceptibility to neuroinflammation or other components of mental illness? Kim et al.’s (2010) suggestion that the importance of social bonds affected responses to stress in Korean participants may reflect the proposed individualistic/collectivistic cultural dichotomy. The degree to which emotional expression is considered culturally appropriate, as discussed earlier, could also affect responses to stress. On the other hand, constructs like familismo, the purportedly stereotypical strong orientation to the family in Latinas/os, might mitigate some of the effects of stress due to perceived family support (e.g., Edwards and Lopez 2006). Finally, while “traits” like individualism/collectivism, stoicism, and familismo can serve as useful starting points to explore questions like these, researchers should bear in mind that these constructs can contain a gendered element (e.g., emotional expression and a family orientation might be expected more from women than men) and are not necessarily restricted to a given region, country, or culture as a result of increased global connectivity.

**Conclusion**

Studying psychiatric illness within a biocultural framework highlights the diverse sources of variation in these conditions. Depression, schizophrenia, and the like are shaped by evolution and biological variation and further molded by cultural values and norms. Approaching these conditions in primarily WEIRD populations will lead to an incomplete understanding of patient interpretations of symptoms and diagnoses, as well as any relevant biological variation that could affect treatment. For instance, variation in 5-HTTLPR may affect response to anti-depressants in an ethnicity-dependent fashion (Porcelli...
et al. 2012, but see Taylor et al. 2010). Including diverse participants in research and clinical studies, in line with recent calls from the NIH (e.g., the All Of Us program), can address some of these concerns. More ambitious, but no less necessary, is developing appropriate measures of “culture” that can account for inter- and intra-group variation. Finally, researchers interested in these topics should ensure that their methodological and statistical techniques adequately account for potential non-independence (Eisenberg and Hayes 2011), loss of information when individual-level surveys are aggregated to country-level (Ross and Winterhalder 2016), unequal sample sizes (ibid.), and problems of ecological fallacy (i.e., assuming that relationships observed at the group level hold true for individuals; Freedman 1999). In spite of these complications, this is fruitful ground for truly interdisciplinary collaborations and could greatly advance understandings of psychiatric illness.

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Compliance with ethical standards

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