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Representing Human Cultural and Biological Diversity in Neuropsychiatry: Why and How

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Abstract

Over the past decade, findings from cultural neuroscience have demonstrated that functional neural processes vary significantly across populations. These findings add a new dimension to the well-established literature describing cultural differences in human behavior. Although these findings are informative for understanding complex relationships between social and neurobiological processes, they also have significant implications for psychiatric research. Neuropsychiatry already co-considers the relationship between brain and social world; however, its research findings notoriously underrepresent diverse cultural, ethnic, and gender groups. Considering that psychiatric patients across cultures exhibit different behavioral presentations and symptom distributions, they may exhibit equally different functional neural processes as well. Increasing representation of diverse patient groups in neuropsychiatric research would allow potential differences to be investigated and understood. Although cross-cultural comparisons may be the most direct means of accomplishing this goal, such studies must be carefully constructed to avoid reinforcing stigmas or stereotypes when working with sensitive patient populations. For example, hypotheses and inclusion criteria must avoid reliance on stereotypes or conflation of geographic boundaries with cultural boundaries. These pitfalls point to deeper problems with current approaches to culture-brain research, which lack operational definitions of 'culture' more generally. After outlining these issues, solutions to these methodological problems will be presented and an operational definition of culture for neuropsychiatry will be proposed.

Introduction

Population biases in current neuropsychiatric research

When it comes to the studying of culture in psychiatry, most researchers roughly fit into one of two groups: those who study the effects of culture and social context on disorders, and those who don't. Most researchers who study culture and disorder focus on behavioral variations of the disorder, cultural meanings, and developing clinical tools; while few employ methods from eye tracking, neuroimaging, or genetics.

Outside of these targeted cultural-clinical studies, most mainstream psychiatric research, including neuropsychiatry, comes from Western Europe and North America (Patel & Sumathipala, 2001). A majority of participants within these leading research countries are Caucasian (Henrich, *et al.*, 2010; Isamah *et al.*, 2010; O'Brien *et al.*, 2006; Gogolin, 2002). As a result, evidence supporting prominent treatments is dominated by specific subpopulations within a handful of countries, many of which share political borders or genetic pools. Experimental findings have as much cultural and ethnic bias as the

studies they are based on. This implies that relatively large and systematic knowledge gaps surround human neural and genetic diversity, which pertain to the study of psychiatric disorders.

Research findings from cultural psychiatry and the non-clinical field of cultural neuroscience suggest that this knowledge gap may be significant. Over the past fifty years, culture has become clearly established as a significant contributor to psychiatric disorders. For example, characteristics of disorders vary across cultures. While patients in North America are more likely to report digestive problems as expressions of stress or anxiety, in India many experience burning sensations (Escobar & Gureje, 2007; Kirmayer, 2001). Likewise, patients with schizophrenia in India are more likely to report hearing positive or playful voices; whereas patients in the U.S. or Canada usually report voices that are menacing or threatening (Luhrmann *et al*., 2014). Culture-bound syndromes are perhaps the most salient examples of the strong influence culture has. Culture-bound syndromes are disorders that are unique to a single country or global region. Latah, for example, is a condition specific to Southeast Asia where a frightening stimulus causes a trance-like state that appears dissociative or catatonic in nature (American Psychological Association, 2000). Kufungisisa, on the other hand, is specific to Zimbabwe and has a combination of symptoms overlapping with anxiety, depression, and panic disorders; the cause of the disorder is attributed to ruminating (American Psychological Association, 2013). These and other culture-specific disorders have been added to the DSM and ICD to facilitate work with foreign patients (Gone & Kirmayer, 2010).

Over the past decade and a half, non-clinical studies from cultural neuroscience have demonstrated robust differences in neural network activity across cultural backgrounds (*e.g.*, Goh, Leshikar, & Sutton, 2010; Gutchess *et al*., 2010; Kitayama & Park, 2010; Chiao *et al*., 2008; Hedden, Ketay, Aron, Markus, & Gabrieli, 2008). Many of these studies have focused on differences in neural pathways used for language or self-knowledge processes, while others show differential activity in regions like the hippocampus and amygdala that are associated with memory and emotion – all of which are commonly associated with features of many psychiatric disorders (see Table; Carmichael *et al*., 2012; Liemburg *et al*., 2012; Lombardo *et al*., 2010). For example, the high variability of amygdalar responses to certain events or stimuli may have implications for anxiety patients with diverse backgrounds (Sotres-Bayon, Corcoran, Peters, & Sierra-Mercado, 2008). At the very least, these studies suggest that the brain activity of healthy control populations may vary across cultures, potentially resulting in different outcomes when compared with patient groups. However, given the frequency of cultural variations in mental disorders, it seems much more likely the neural processes in patient groups vary across cultures too.

Table 1

Brain regions with know cultural and clinical variations

Brain Region	Cross-Cultural Comparisons	Associated Neuropsychiatric Conditions
Medial prefrontal cortex	Different activity patterns during social tasks (*e.g.*, self-affiliation)[1]	Autism[2], schizophrenia[3], bipolar disorder[4], general anxiety disorder[5], major depressive disorder[6]
Rostral anterior cingulate cortex	Different activity patterns during social tasks (*e.g.*, self-other representation)[7]	Autism[8], schizophrenia[9], bipolar disorder[10], social anxiety disorder[11], major depressive disorder[12]
Left inferior parietal lobe	Different activity patterns during perceptual tasks (*e.g.*, visual attention control)[13]	Autism[14], schizophrenia[15]
Amygdala	Different activity patterns depending on socio-cultural meaning of stimuli (*e.g.*, in-group/out-group)[16]	Autism[17], schizophrenia[18], bipolar disorder[19], general anxiety disorder[20], major depressive disorder[21], social anxiety disorder[22]

Note. Examples of regional brain activity and processes that vary across cultures and disorders, according to cultural neuroscience and neuropsychiatry respectively. Each study used slightly different paradigms. Citations indicated by superscript: [1]Chiao *et al*., 2009; [2]Gilbert *et al*., 2008; [3]Pomarol-Clotet *et al*., 2010; [4]Keener *et al*., 2013; [5]Kim *et al*., 2011; [6]Murray *et al*., 2011; [7]Ray *et al*., 2010; [8]Chan *et al*., 2011; [9]Pedersen *et al*., 2012; [10]Wang *et al*., 2009; [11]Klumpp *et al*., 2013; [12]Alexander *et al*., 2011; [13]Hedden *et al*., 2008; [14]Koshino *et al*., 2005; [15]Torrey *et al*., 2007; [16]Derntl *et al*., 2012; [17]Kleinhans *et al*., 2010; [18]Mukherjee *et al*., 2013; [19]Brotman *et al*., 2010; [20]Ressler *et al*., 2010; [21]Suslow *et al*., 2010; [22]Sladky *et al*., 2012.

In the past few years, genetic studies from cultural neuroscience have begun to emerge that may also have clinical relevance. For example, Kitayama *et al*. (2014) found that carriers of the dopamine D4 receptor of gene DRD4 showed stronger cultural learning than non-carriers in both European Americans and Asian-born Asians. Reduced social and cultural learning and flexibility are key impairments in many psychiatric disorders, and the dopamine D4 receptor may be one biomarker of these impairments in some patient groups (for further examples, see also Chiao & Blizinsky, 2010; Eisenberg & Hayes, 2010; Kim *et al*., 2010). This hypothesis would, of course, have to be rigorously tested; however, this finding points to a possible clinical application of genetic research from cultural neuroscience.

A couple of recent studies have directly investigated neuropsychiatric questions in cultural genetics. For example, Crafa and Warfa (2014) evaluated global rates of autism, reporting that children born after their mothers migrated to a new country were more than twice as likely to have autism (Crafa & Warfa, 2014). This finding was equally true for Caucasian children who had immigrated (usually from European or Scandinavian countries) as for children of most of the other ethnicities considered by the study. These findings, alongside other epigenetic research, suggest that the act of immigrating may impose a stress on the mother that initiates key epigenetic changes that have been impli-

cated in the emergence of autism in offspring. These findings agree with a large body of other research on the impact of stress on epigenetic processes (*e.g.*, Glover, 2011).

This study also found that the social environment after migration might have protective effects against autism; Hispanic families who were part of large social communities had lower rates of second-generation autism, even compared to the rates observed in the general population of families that had never migrated (Crafa & Warfa, 2014; cf., Thoits, 2011). Such findings are echoed by multiple other studies suggesting similar protective effects of Hispanic culture on birthing conditions typically associated with epigenetic changes, as well as other studies demonstrating that non-Hispanic immigrants were more likely to report dissatisfaction or discrimination after immigrating (*e.g.*, Acevedo-Garcia *et al*., 2005; Fuentes-Afflick & Lurie, 1997; Collins & Shay, 1994). These findings may be specific to other cultural groups too; however, they have not been studied in the current literature.

Chiao and Blizinsky (2013) found that S serotonin alleles associated with 5-HTTLPR, a serotonin transport gene commonly implicated in mood disorders varied, across cultures as a function of 'individualist' versus 'collectivist' cultural values (for critical discussion of these terms see Crafa & Nagel, 2014b). Although the presence of 1-2 S alleles is a strong predictor of depression and anxiety in individualist cultures, these disorders emerge at lower rates in collectivist cultures despite its prevalence. This appears to be due to the protective effects of collectivist cultures, which promote community and strong social connections. These findings emerge despite that the S allele reportedly appears to be selected for in collectivist cultures and is theorized to contribute to collectivist traits (Chiao & Blizinsky, 2013; Mrazek *et al*., 2013).

Heterogeneity in neuropsychiatry

In addition to potentially filling the knowledge gap in neuropsychiatry, deliberate and careful pursuit of cross-cultural (and arguably sub-cultural) research comparisons may help clarify broader problems in neuropsychiatry. Neuropsychiatric research findings are often heterogeneous and highly contingent on the samples and paradigms being studied (Crafa & Nagel, 2014a). This heterogeneity is pronounced enough that it has arguably led to a recent reworking of the approach to disorders taken in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM; Kirmayer & Crafa, 2014; cf. American Psychiatric Association 2000, 2013). The contributions of socio-cultural background may partially explain some of the heterogeneity in neuropsychiatric literature. Striving to better understand the relationship between human psychobiological and cultural differences, both in patients and control populations, may lead to more precise understandings of psychiatric disorders and their variations (Crafa & Nagel, 2014a).

How to Consider Human Cultural and Biological Diversity in Neuropsychiatry

One of the biggest challenges researchers face is how to create an operational definition of 'culture,' which is a nebulous human construct that can be difficult to reify according to any objective terms (Crafa & Nagel, 2014a, 2014b; Choudhury & Kirmayer, 2009). The current working definition in cultural neuroscience appears to center broadly around dichotomies, such as east versus west (*e.g.*, European-Americans compared with Asian-born Asians; Kitayama *et al.*, 2014) and values of individualism versus collectivism within those dichotomies. Such approaches are helpful for laying groundwork for a challenging new direction in research, but are too broad and ill defined to adequately address issues of heterogeneity in clinical populations.

Crafa and Nagel (2014b) propose a statistical definition of culture in a Culture-Brain-Behavior Interaction Model (CBB Model) suggesting that common cultural traits are presumably normally distributed across people who live in a common region or self-identify with a predefined group. Closer examination of regional subcultures should, in theory, show different distributions of these traits compared to their region's dominant culture:

> Subcultures are influenced by mainstream behaviors common to a region, but may also have a subset of statistically common behaviors that are unique to the specific, and usually self-identified, group (cf. Choudhury & Kirmayer, 2009). For example, Hispanic culture in Southern California differs in many ways from Hispanic culture anywhere else in the world, and the 1960s hippie movement in California was uniquely progressive even for its time. Both examples identify subcultures that are distinct from the dominant culture, but still uniquely situated within it. In theory, observational and self-report measures can be used to isolate statistical commonalities and help describe various socio-cultural similarities and differences between groups (*ibid.*). (Crafa & Nagel, 2014b)

Applying this framework to psychiatric disorders, Crafa & Nagel (2014b) suggest that maladaptive features of psychiatric disorders can be interpreted as statistical outliers of their cultural group:

> From a statistical perspective, patients with different psychiatric disorders can be thought of as forming their own subcultures, which are simultaneously culturally contingent and distinct. While certain behaviors associated with individual disorders may be statistically uncommon relative to the general population, they are statistically common among other patients with the same disorder and may also be geographically or temporally unique. These definitions are useful for neuroscientific inquiries into the effects of 'culture,' because they suggest a framework for defining idioms, symptoms, behaviors, or neural events as common to a certain group within a certain culture and compared to groups across cultures. For example, dissociations are experienced by people across cultures and may have different culture-specific explanations and different associated disorders or symptoms (Seligman & Kirmayer, 2008). By using a statistical framework, we can evaluate the

neural events that may be statistically common for one group of patients with dissociations but statistically uncommon for another. This has the potential to lead to a more diverse and nuanced understanding of neural events associated with different conditions.

Implementing this definition of 'culture' in neuropsychiatric research can imply measuring cultural traits using questionnaires that target specific qualities. In addition to assessing individualist and collectivist values, these questionnaires may include the relevant behaviors, beliefs, and expectations surrounding the study questions. For example, an experiment studying eye contact behaviors in autistic children in Italy (where eye contact is culturally encouraged) and Japan (where eye contact is culturally discouraged) may ask parents whether they believe they encourage/discourage eye contact in their children, whether they think it is important to make/avoid eye contact, and etc.[1] Asking related questions, such as whether the families value social hierarchy or respect authority, may also be useful here. Such questionnaires provide a framework for interpreting the socio-cultural differences when asking sophisticated cultural questions. These suggestions are useful for neuroimaging and genetic research alike, to ensure that research findings are sufficiently nuanced and avoid design problems, such as type 1 or type 2 statistical errors, due to poor sample definition.

Avoiding stereotypes and stigma when studying sensitive patient populations

Crafa & Nagel (2014b) propose the CBB Model as a framework that avoids risks of reifying stereotypes and stigmas that pose additional challenges when using neuroscience to investigate cultural-clinical differences. Many ethnic and cultural groups have long histories of discrimination, as do 'foreigners' and immigrant groups more generally. Psychiatric patients also have long histories of stigma, and many struggle for acceptance in today's society. This may be especially apparent in the case of genetic projects that co-consider ethnicity and culture. Race-based genetic discrimination and the horrific hypotheses of eugenics are not very far in the past; likewise, discrimination by insurance companies threaten to increase coverage rates for people based on genetic generalizations in the future (Fisher & McCarthy, 2013). However, neuroreductive claims can be equally damaging for mental health, especially if they essentialize socio-cultural traits as being "all in the brain" or immutable.

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[1]This example is taken from an ongoing research project led by D. Crafa, and provides an opportunity for further discussion of potential ways to solve conflicts between culture and experimental design. In the case of this autism study such questions about parenting were not permitted by one of the two cultural groups. The investigators worked around this by anecdotally asking employees and students affiliated with the hosting lab who were not aware of the specific project about their beliefs regarding eye contact and whether their parents taught or discouraged certain behaviors. This approach was more anthropological in method and qualitative in nature, but still provided some confirmation that the hypothesized differences in eye contact behaviors reflected the beliefs and values of cultural natives rather than relying on stereotype.

Careful construction of research questions and thorough considerations of findings can promote nuance and prevent cultural generalizations. In the above example of autism across cultures, the research question is based on the 'cultural domain' of eye contact behaviors (Choudhury & Kirmayer, 2009). This approach is more flexible and nuanced than discussion of east versus west, collectivism versus individualism. It also empowers the researcher to design more clinically relevant questions: As in the example above, eye contact is a key sign of autism and its variation across cultures could help identify, for example, whether ethnic and minority children are misdiagnosed with autism due to misunderstood cultural differences in body language, as has been suggested by previous literature (Fountain, King, Bearman, 2011; Mandell *et al*., 2009). This question could improve diagnoses of Japanese immigrant children. It could also help us understand whether or not autism and control groups vary across cultures in culturally relative ways, or whether larger differences between autism and control groups emerge in cultures where controls are making more eye contact compared to cultures where controls make less eye contact.

When studying patient groups across cultures, one must also tread lightly and consider the moral and sociopolitical implications of research questions. For example, in many (but not all) countries, immigrants have higher rates of psychiatric disorders and may experience high rates of discrimination in their new country (*e.g.*, Bhui *et al*., 2005). Studying, for example, whether immigrants experience more severe forms of schizophrenia compared to native-born controls may be an experiment developed with the good intentions of wanting to help immigrant patients. However, reporting that immigrants have more severe schizophrenia could have the double edge of confirming prejudices about immigrants. This hypothesis needs reworking to form a responsible research question. For example, some non-clinical studies have shown that cultural exposure can improve social skills like perspective taking, and some immigrants can be more socially adaptable than native-born residents (Wu & Keysar, 2007). Considering this research, an alternative hypothesis can be formed: That immigrants with schizophrenia may be more severely impaired on social measures compared with native-born immigrants while control immigrants perform better on social measures compared with native-born controls. When the findings do not support such hypotheses, another way to avoid reinforcing stigma is to clearly discuss the fact that this finding may be culture-specific and tied to discrimination (as much previous research suggests; *e.g.*, Gee *et al*., 2007; Veling *et al*., 2007; Liebkind & Jasinskaja-Lahti, 2000).

Toward a cultural neuropsychiatry

Neuropsychiatry could greatly benefit from considering biological diversity across cultures and individuals. Carefully defining 'culture' and constructing nuanced experiments can help optimize the value and applicability of research. The CBB Model offers a framework for tackling these problems, and for interpreting the complex relationships between culture and biology (Crafa & Nagel, 2014b). This model can be expanded to

include the relationship between genetics and epigenetics. These applications may help lead to sophisticated insights for neuropsychiatry.

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