Advances in Functional Neuroimaging of Psychopathology:
A Response to: Conceptual Challenges in the Neuroimaging of Psychiatric Disorders

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In their paper “Conceptual Challenges in the Neuroimaging of Psychiatric Disorders,” authors Kanaan and McGuire review a number of methodological and analytical obstacles associated with the use of functional magnetic resonance imaging (fMRI) to study psychiatric disorders. While we agree that there are challenges and limitations to this end, it would be a shame for those without a background in neuroimaging to walk away from this article with the impression that such work is too daunting, and thus not worth pursuing. On the contrary, despite a number of challenges (which are an inevitable part of all research), fMRI has already contributed many important insights into the nature and mechanisms of psychopathology and has the potential to contribute many more. Therefore, in the interest of providing an argument for the expanded use of fMRI in clinical research, we would like to briefly review the benefits of fMRI and how it can contribute to our understanding of psychiatric disorders.

Functional MRI has revolutionized the study of human thought, emotion, and behavior. While lesion studies have provided and will continue to provide valuable insights into brain function, there are obvious limitations to its application that dramatically limit potential research populations and questions. As a non-invasive technology, fMRI gives us a relatively unique form of access to the human mind, in vivo.

As Kanaan & McGuire discussed in their paper, fMRI has a number of limitations, particularly when applied to psychiatric populations. Such limitations include the physical constraints of the scanning environment, the difficulties and complexities of trying to image “illness” per se, and the confounds of disorder heterogeneity and comorbidity. These are all important issues that certainly dictate (and thus limit) the tasks, study designs, and patient groups that realistically can be included in fMRI research. Thus, it is a fair conclusion that fMRI may not be the best tool with which to study all psychiatric disorders and all psychiatric research questions. Some disorders (e.g., anxiety, depression) are simply more conducive to fMRI research than others (e.g., ADHD, Tourette’s), and some designs (e.g., group-based comparisons) are more appropriate than others (e.g., single-subject diagnoses).

Nevertheless, there are many important clinically-focused questions that can be uniquely addressed with functional neuroimaging. In addition to allowing us to learn which neural structures are involved and impaired in psychopathology (i.e., the “where”), fMRI findings, when evaluated in the context of existing knowledge (as all results should be), can help us understand which neural processes are involved and impaired (i.e., the “how” and “why”). As such, fMRI can ultimately help us improve the assessment, prevention, and treatment of psychiatric illness. While it is true that there are limited direct clinical applications for fMRI currently, it is essential for us to push forward with clinically-based fMRI research in order to establish a solid foundation of knowledge from which many direct clinical applications can emerge in the not too distant future.

As the technology stands today, the most fruitful design approach for clinically-focused fMRI research has two general characteristics. First, it involves the investigation of groups of subjects, rather than single individuals. This approach may involve comparing patients to healthy matched controls, comparing patients with disorder X to patients with disorder...
‘Y’, or even examining individual differences within a group of patients with a common diagnosis. Second, instead of trying to capture episodes of “illness” in the scanner, fMRI tasks designed to index more basic cognitive, emotional, or behavioral processes that are predicted to be dysfunctional in certain disorders are used. This approach is similar to what Chris Frith has done in his research on schizophrenia, and obviates a dependence on the manifestation of patient symptoms during scanning sessions. As in all research, one must find an appropriate compromise between generalizability of the findings and rigorous control of the independent variables. In the earlier stages of a new field (such as fMRI), it is often more advantageous to lean towards rigorous control until the basic mechanisms are fairly well known.

The power provided by this group-based approach means that there will be sufficient signal to noise ratio (SNR) to find meaningful results with samples as small as N=16-20 (per group) and task lengths of a mere 20-30 minutes (e.g., Goldin, Manber, Hakimi, Canli, & Gross, 2009; McCabe, Cowen, & Harmer, 2009; or see Desmond & Glover, 2002; Mumford & Nichols, 2008). Given that behavioral studies often involve significantly larger samples and assessment times, fMRI research has the advantage in this regard. Following is a more detailed description of ways in which this approach can be used to advance our understanding of psychopathology.

By comparing patients to healthy, matched controls, we can elucidate neural regions and processes that seem to ‘malfunction’ in a disorder and then use this information to optimize treatment. For example, a number of researchers have found that individuals with anxiety disorders exhibited heightened amygdala activity in response to threat cues relative to healthy, matched controls (for a review, see Rauch, Shin, & Wright, 2003). In and of itself, this research reveals an important neural underpinning of the threat sensitivity/excessive fear that is a hallmark of anxiety disorders. Taking these findings one step further, Goldin and colleagues (2009) used fMRI to examine how individuals with anxiety disorders self-regulated such threat or fear responses. Specifically, they had participants with social anxiety disorder (SAD) (1) passively view fear-relevant stimuli and then (2) view the stimuli while using a cognitive reappraisal technique whereby they re-evaluated the stimuli in less threatening terms. (Cognitive reappraisal is a central component of cognitive behavioral therapy, CBT, an established, effective treatment for anxiety disorders.) While the patients showed significantly greater amygdala activity during the passive viewing condition compared to the controls (replicating previous work), there were no differences in the extent to which the amygdala activity was dampened when participants used the cognitive reappraisal technique. Behavioral data corroborated these findings such that self-reported levels of distress in the passive viewing condition relative to the cognitive reappraisal condition were reduced equivalently in patients and controls. In other words, individuals with SAD were able to use the cognitive reappraisal strategy to reduce amygdala activity and self-reported distress as effectively as the healthy controls when they were instructed to do so; that is, patients and controls exhibited an equivalent capacity for emotion regulation. It was not the case that healthy controls were ‘better’ at using this strategy than the patients. An alternate explanation for the impaired emotion regulation associated with SAD may be that these individuals exhibit a decreased tendency to spontaneously utilize such regulatory processes. Thus, treatments that teach patients how to employ this strategy in everyday situations (i.e., increase their tendency to use the strategy) may be more effective than treatments that focus on simply how to use this
strategy (i.e., improve their capacity to use the strategy). This is a subtle difference, but an important one. (For additional discussion of this difference, see Berkman & Lieberman, 2009).

One might suggest that it is possible to simply rely on the self-report data to come to this conclusion and save the expense of fMRI scanning. However, self-report alone paints an incomplete picture both because it can be biased, particularly in patient populations vulnerable to demand characteristics and concerns of social desirability (Crowne & Marlowe, 1960) and because there are processes in our minds to which we simply do not have introspective access. Thus, it is essential to use alternate methods in order to verify, complement, and extend what we can obtain with self-report. In particular, it is likely that there are neural signals that fMRI can detect that provide important information beyond what self-report can yield. Furthermore, fMRI can uniquely reveal whether there are actual underlying neural ‘impairments’ associated with disorders or whether more upstream inputs are to blame. For example, as mentioned above, excessive anxiety and fear is associated with heightened amygdala activity. This heightened amygdala activity may be the result of (among other things) a dysfunctional amygdala that is inherently hyperactive, poor control from regulatory regions in the prefrontal cortex (PFC), or both. While the outcome of these possible scenarios is the same neurally, behaviorally, and emotionally, the mechanism is different. Accordingly, the optimal treatment approach would likely vary, depending on which mechanism is at play. Using an analogy from medicine to clarify this point, obesity can be caused by both (1) a sedentary lifestyle and poor diet, or (2) hypothyroidism. In the latter case, an underlying ‘dysfunction’ is at work, whereas in the former, the body is ostensibly functioning normally given the context. Although the presentation is the same (i.e., obesity), the treatment approach for the two scenarios would likely have both common and distinct elements (i.e., exercise vs. thyroid hormone). Similarly, amygdala sensitivity resulting from an innately hyperactive amygdala vs. poor regulatory control may suggest different targets for optimal treatment.

In addition to comparing patients to healthy controls, a group-based approach can also be used to compare patients with different diagnoses to uncover common and distinct underlying neural patterns. Blair and colleagues (2008) used fMRI to examine whether two often-comorbid disorders, generalized social phobia (GSP) and generalized anxiety disorder (GAD), represent distinct disorders or different presentations of a single underlying pathology. They scanned patients and healthy controls while they viewed fearful faces, a common, reliable elicitor of amygdala responses. They found that while patients with GSP exhibited greater amygdala activity to fearful faces compared to healthy controls, patients with GAD exhibited the opposite pattern. They also found that symptom severity correlated with amygdala responses to the fearful faces in the GSP group, but not in the GAD group. This study suggests that while fear and anxiety constitute a core component of both GSP and GAD (and all anxiety disorders), one of the key neural structures involved in fear processing, the amygdala, is not uniformly hyperactive in these disorders. This suggests a fundamental difference between GSP and GAD. In fact, some have suggested that GAD may be better characterized as a depression-spectrum disorder rather than an anxiety disorder (Lecrubier, 2008). Supporting this idea, Kendler and colleagues (2007) found evidence of genetic overlap between major depressive disorder
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Overall, this type of research can help to refine or even redefine diagnostic categories or spectrums, thereby facilitating assessment and treatment.

The group-based approach can also be used to examine individual differences within a common diagnosis; that is, it can reveal how certain individual difference factors (e.g., disorder severity, specific symptom severity, etc.) correlate with neural activity across participants. For these analyses, rather than comparing the neural activity between two separate groups of participants, a regression analysis is used to examine the relationship between an individual difference measure and a neural region of interest. For example, previous research has shown that the level of amygdala activity in patients with anxiety disorders correlated with disorder severity (Evans et al., 2008; Phan et al., 2006) and predicted clinical outcomes a year after treatment conclusion (Furmark et al., 2002). This suggests that amygdala reactivity in individual subjects may be a potential marker of not only disorder severity, but also treatment response. Additionally, this approach allows us to examine whether a particular neural “dysfunction” is essentially the extreme end of normal functioning, or else represents a categorical difference.

In addition to examining neural activity that is associated with a particular patient group or individual difference measure, fMRI can also provide important insights into the functional connectivity of multiple brain regions in psychopathology. In group-wise connectivity analyses, we are able to see whether two neural regions are more or less correlated in one group vs. another. For example, amygdala hyperactivity in anxiety disorders may be a function of an inefficient relationship between the amygdala and prefrontal regulatory regions, instead of or in addition to impairments in the amygdala and PFC themselves.

Recent advances have also allowed us to examine individual differences in functional connectivity using psychophysiological interaction (PPI) analyses. This approach allows us to calculate an index of the functional correlation between two regions for each individual during a specific task, thereby allowing us to examine how the functional relationship between two neural regions is moderated by disorder severity, symptom severity, etc.

In each of the studies mentioned above, the researchers used fMRI tasks that targeted specific processes known to be dysfunctional in the disorder in question. Specifically, since these studies focused on anxiety disorders, the researchers presented the patients with fear-relevant stimuli known to engage fear-related neural regions. Although viewing fearful faces or other threat-related cues is clearly a different experience for the patients than a real life anxiety-provoking situation, it still allows us to investigate the underlying mechanisms of fear-processing, and actually constitutes a more rigorous test of the hypotheses. Furthermore, it allows us to examine potential impairments at the most basic level, thereby minimizing confounding variables.

Similarly, given the role of anhedonia in MDD, McCabe and colleagues (2009) used a reward processing task to compare unmedicated, recovered MDD patients with healthy controls, in an effort to determine if impaired reward processing represented an endophenotype for depression. They had patients and controls simply view and taste chocolate (i.e., a rewarding experience). Despite the subtly of the task, the absence of depression symptoms in all participants, and equivalent self-reported ratings of the stimuli,
the recovered MDD patients exhibited decreased neural activity in ventral striatum, a region involved in reward processing. These fMRI results suggest an underlying abnormality and vulnerability in the recovered MDD patients in reward processing that was not evident through other means. Although such tasks may seem “artificial” and far removed from the experience of psychopathology, they allow us to test the same mechanisms that underlie more complex, realistic situations. To use another analogy, one can certainly check the breaks on a car in the comfort of a garage instead of just slamming on the breaks at top speeds to avoid running a red light.

In summary, there are a number of ways in which fMRI can be used to improve our understanding of psychiatric disorders. Through an iterative approach and in conjunction with other modalities of research, fMRI has the potential for many important clinical applications, including: (1) revealing important psychological processes to emphasize in psychological interventions, (2) pinpointing novel targets for psychopharmacological interventions, (3) helping to redefine clinical diagnoses on a less subjective, biological basis, and (4) clarifying the heterogeneity and comorbidity of many diagnoses (e.g., a particular clinical presentation may be the result of impairments in alternate components of a complex process). Thus, while fMRI cannot provide all the answers regarding psychopathology, it can make an invaluable contribution.
References


