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Diagnostic Brain Imaging in Psychiatry: Current Uses and Future Prospects

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Psychiatric Diagnosis and Brain Imaging

The biological revolution in psychiatry, which started in the 1960s, has so thoroughly transformed the field that the phrase "biological psychiatry" now seems redundant. A huge literature exists on the biological correlates of psychiatric illness, including thousands of published research studies using functional neuroimaging methods such as SPECT, PET, and fMRI. In addition, most psychiatric treatment is biological in that it directly affects the brain through medication, stimulation, or surgery. Even "talking therapies" are now understood to change the brain in ways that have been visualized by neuroimaging [1].

Diagnoses in psychiatry, however, are based entirely on behavioral, not biological, criteria [2]. Depression is diagnosed by asking patients how they feel and whether their sleeping, eating, and other behaviors have changed. Attention deficit hyperactivity disorder (ADHD) is diagnosed by asking the patient, family members, and others about the patient's tendency to get distracted, act impulsively, and so on. For these and all other psychiatric illnesses described by the *Diagnostic and Statistical Manual* of the American Psychiatric Association, findings from brain imaging do not appear among the diagnostic criteria. Aside from its use to rule out potential physical causes of a patient's condition, for example a brain tumor, neuroimaging is not used in the process of psychiatric diagnosis.

In this article we review the current status of brain imaging for psychiatric diagnosis. Among the questions to be addressed are: why has diagnostic neuroimaging not yet found a place in psychiatric practice? What are its near-term and longer-term prospects? What obstacles block the use of such methods? The answers to these questions involve the nature of imaging studies and of psychiatric diagnosis.

Sensitivity, specificity and standardization in psychiatric brain imaging. The vast majority of psychiatric neuroimaging studies aggregate data from groups of subjects for analysis, whereas diagnosis must be made for individuals, not groups. Structural and functional studies reveal a high degree of variability within groups of healthy and ill subjects, often with considerable overlap between the distributions of the two groups [3]. In the language of diagnostic tests, imaging studies are generally not highly *sensitive* to the difference between illness and health.

Another current limitation concerns the *specificity* of candidate diagnostic markers from imaging. Most psychiatric imaging studies involve subjects from only two

categories—patients from a single diagnostic category and people without any psychiatric diagnosis. The most that can be learned from such a study is how brain activation in those with a particular disorder differs from brain activation in those without a disorder. The dilemma faced by a diagnosing clinician, on the other hand, is rarely "Does this person have disorder X or is she healthy?" Rather, it is typically "Does this person have disorder X, Y, or Z?" The pattern that distinguishes people with disorder X from healthy people may not be unique to X but shared with a whole alphabet of other disorders.

Indeed, there is considerable similarity in the abnormalities noted in brain activation across different diagnoses. A meta-analysis of neuroimaging studies of anxiety disorders reported common areas of activation (amygdala, insula) across posttraumatic stress disorder, social phobia, and specific phobia—suggesting that neuroimaging has yet to reveal patterns of neural activity that are unique to specific anxiety disorders [4]. Abnormalities of amygdala activation also have been reported consistently in neuroimaging studies of depression [5], bipolar disorder [6], schizophrenia (a disorder primarily of thought rather than of mood) [7], and psychopathy (which shares features with the *DSM* diagnosis of antisocial personality disorder) [8].

More sophisticated methods of image analysis may hold promise for discerning the underlying differences among the many disorders that feature similar regional abnormalities, including the "usual suspects," limbic hyperactivity and prefrontal hypoactivity. In addition, new multivariate statistical approaches to image analysis make it possible to discover spatial and temporal patterns that correspond to performance of specific tasks and specific diagnoses [9]. These methods have only begun to be applied to clinical disorders but show promise for increasing the specificity of brain imaging markers for psychiatric illness [10, 11].

Standardization is relevant in light of the many ways in which protocols differ from study to study, particularly among functional imaging studies. The patterns of activation obtained in studies of psychiatric patients depend strongly on the tasks performed by the subjects and the statistical comparisons examined by the researchers afterwards. Although the results of psychiatric imaging research are often summarized by stating that certain regions are under- or overactive or more or less functionally connected, such summaries are fundamentally incomplete unless they include information about what task evoked the activation in question: were the patients resting, processing emotional stimuli, trying not to process emotional stimuli, or engaged in effortful cognition? The fact that any imaging study's conclusions are relative to the tasks performed adds further complexity to the problem of seeking consistently discriminating patterns of activation for healthy and ill subjects.

Reliability and validity of current diagnostic categories. Other reasons why progress toward diagnostic imaging in psychiatry has been slow stem from the nature of the diagnostic categories themselves. The categories of the *DSM* are intended to be both

reliable and *valid*. That is, they are intended to be usable in consistent ways by any appropriately trained clinician, so that different diagnosticians arrive at the same diagnosis for each patient (reliability) and to correspond to the true categories of psychiatric illness found in the population, that is, to reflect the underlying psychological and biological commonalities and differences among different disorders (validity). Good, or at least improved, reliability was one of the signal achievements of the *DSM-III*, and was carried over to *DSM-IV*. Unfortunately, validity continues to be more difficult to achieve.

As an illustration of how far from being necessarily valid our current diagnostic categories are, consider the criteria for one of the more common serious psychiatric conditions, major depressive disorder. According to the *DSM-IV-TR*, patients must report either depressed mood or anhedonia and at least four of eight additional symptoms. It is therefore possible for two patients who do not share a single symptom to both receive a diagnosis of major depressive disorder. There are also commonalities of symptoms between categories. For example, impulsivity, emotional lability, and difficulty with concentration each occurs in more than one disorder. To the extent that our psychiatric categories do not correspond to "natural kinds," we should probably not expect correspondence with brain physiology as revealed by imaging. Taken together, the fact that (a) different exemplars of a category can share no symptoms and (b) exemplars of two different categories may share common symptoms raises questions about the validity of the current diagnostic categories.

The Present and Future of Diagnostic Brain Imaging in Psychiatry

A defiant minority now use brain imaging for psychiatric diagnosis. Despite the challenges just reviewed, a small number of psychiatrists offer diagnostic neuroimaging to patients in their clinics. The imaging method used is single photon emission computed tomography (SPECT), which measures regional cerebral blood flow by detecting a gamma-emitting tracer in the blood. The best known of these clinics are the four Amen Clinics, founded by the psychiatrist and self-help author Daniel Amen. Others include the Clements Clinic, Cerescan, Pathfinder Brain SPECT, and Dr. Spect Scan. The use of brain imaging appears to be a selling point for these clinics; their websites generally feature brain images prominently and the names of the last three leave no doubt about the emphasis they place on imaging.

These clinics promise to diagnose and treat a wide range of psychiatric disorders in children and adults based on patient history and examination along with the results of SPECT scans. The Amen Clinics use a system of diagnosis that does not correspond to the standard diagnostic categories defined by the American Psychiatric Association's *Diagnostic and Statistical Manual*. For example, anxiety and depression are combined into a single superordinate category and then divided into 7 subtypes with names such as "temporal lobe anxiety and depression" and "overfocused anxiety and depression" [12]. Attention deficit hyperactivity disorder is also reconceptualized as having 6 subtypes, with names such as "limbic ADD" and "ring of fire ADD" [13].

The Amen Clinics website states that they have performed almost 50,000 scans [14], a huge number that, combined with associated clinical data including outcomes, could provide important evidence on the value of SPECT scanning in diagnosis and the efficacy of Amen's approach to psychiatric care. Unfortunately, no such studies have been reported. The lack of empirical validation has led many to condemn the use of diagnostic SPECT as premature and unproven [15-18].

Why do people pay for an unproven, even dubious, diagnostic test? Brain imaging has a high-tech allure that suggests advanced medical care. People may assume that the treatments available at these clinics, as well as the diagnostic methods, are cutting-edge. In addition, there is a strong allure to the idea that imaging can give visual proof that psychological problems have a physical cause. The Amen Clinics cite several ways in which patients and their families may find this evidence helpful, including the reduction of stigma and guilt [14]. Of course, these considerations do not address the question of whether diagnosis is improved by the use of SPECT scans.

Diagnostic neuroimaging: prospects for the near-term and longer-term future. Few believe that brain imaging will play a role in psychiatric diagnosis any time soon. The forthcoming *DSM-5*, expected in May of 2013, will include reference to a variety of biomarkers for psychiatric disease, including those visible by brain imaging, but their role is expected to be in the validation of the categories themselves rather than in the criteria for diagnosing an individual patient [19].

In the long term, there is reason for optimism concerning the contribution of brain imaging to psychiatric diagnosis. This may happen first for differential diagnosis, particularly for diagnostic distinctions that are difficult to make on the basis of behavioral observations alone. In such cases potentially distinctive patterns of brain activation identified through imaging will be especially useful. For example, Brotman et al. have studied the patterns of brain activation evoked in the performing of various tasks with pictures of faces and found differences between the neural responses of children diagnosed with severe mood dysregulation and those with ADHD or bipolar disorder [20]. They and others [21] suggest that this finding could provide the basis for the future development of diagnostic imaging.

Diagnostic imaging in psychiatry could emerge from basic research on psychopathology, as in the example just cited. Alternatively, the relatively atheoretical multivariate statistical approach mentioned earlier could provide the first candidate neural signatures of psychiatric disorders. By whatever method the candidate neural signatures are identified, large-scale validation trials will be needed before they can enter routine clinical use. This process promises to be lengthy and expensive and could easily fill the interval between two or more editions of the *DSM*.

Coevolution of diagnostic methods and diagnostic categories. Whether the path to imaging-based diagnosis involves translation of newly discovered mechanisms of

pathophysiology, brute-force number crunching, or both, we cannot assume that it will preserve current nosology. Indeed, given the overlap of imaging findings between diagnostic categories and the heterogeneity within categories mentioned earlier, it seems likely the widespread incorporation of imaging into diagnostic criteria will force our nosology to change. If the mismatch between imaging markers and diagnostic categories is not drastic, the *DSM* categories may change incrementally, for example by revisions of individual diagnostic criteria for specific disorders. However, if brain imaging reveals a radically different pattern of "natural kinds," and if these kinds are proven to have clinical utility (e.g., enabling better treatment decisions), then imaging may prompt a radical reconceptualization of psychiatric diagnosis and entirely new diagnostic categories may emerge.

There are, however, strong arguments for conservatism. The current system of diagnostic categories is valuable in part simply because we have used it for so long and therefore much of our clinical knowledge is defined in relation to this system. *DSM* diagnoses have so far changed in a gradual and piecemeal manner through multiple editions of the manual, with most disorders retaining their defining criteria and a only minority being subdivided, merged, added, and eliminated in the light of new research findings. In keeping with this approach, the future influence of brain imaging on psychiatric diagnosis is likely to be more evolutionary than revolutionary.

An attempt to reconcile the need for consistency with the promise of more neurobiologically based classifications can be found in the Research Domain Criteria (RDoC) for psychiatry research proposed by the U.S. National Institute of Mental Health. This is "a long-term framework for research… [with] classifications based on genomics and neuroscience as well as clinical observation, with the goal of improving treatment outcomes" [22]. The RDoC system, still under construction at the time of writing [23], is meant to be used, in parallel with DSM categories, for research that may ultimately lead to more valid diagnostic categories, which might also be more consistent with the use of imaging as a diagnostic test.

Conclusions

Brain imaging will probably enter clinical use in other roles before it serves as a diagnostic laboratory test. For example, imaging has already guided clinical researchers in the development of new therapies [24] and in the customization of therapy for individual patients [25]; it shows promise as a predictor of vulnerability [26] and treatment response [27] and has even been used as a therapy itself [28].

While some physicians insist that they are able to use brain imaging now for psychiatric diagnosis, there is currently no reliable evidence supporting this view. On the contrary, there are many reasons to doubt that imaging will play a role in psychiatric diagnosis in the near future. As argued here, much psychiatric imaging research remains to be done to achieve sensitivity, specificity, and standardization of imaging protocols.

In addition, the nature of current psychiatric diagnosis may not even correspond to the categories of brain dysfunction that imaging reveals. Finally, the practical value of maintaining continuity in diagnostic classifications requires a cautious and incremental approach to redrawing diagnostic classifications on the basis of imaging research.

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