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The Puzzle of Neuroimaging and Psychiatric Diagnosis: Technology and Nosology in an Evolving Discipline

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The Puzzle of Neuroimaging and Psychiatric Diagnosis: Technology and Nosology in an Evolving Discipline

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Abstract

Brain imaging provides ever more sensitive measures of structure and function relevant to human psychology and has revealed correlates for virtually every psychiatric disorder. Yet it plays no accepted role in psychiatric diagnosis beyond ruling out medical factors such as tumors or traumatic brain injuries. Why is brain imaging not used in the diagnosis of primary psychiatric disorders, such as depression, bipolar disease, schizophrenia, and ADHD? The present article addresses this question. It reviews the state of the art in psychiatric imaging, including diagnostic and other applications, and explains the nonutility of diagnostic imaging in terms of aspects of both the current state of imaging and the current nature of psychiatric nosology. The likely future path by which imaging-based diagnoses will be incorporated into psychiatry is also discussed. By reviewing one well-known attempt to use SPECT-scanning in psychiatric diagnosis, the article examines a real-world practice that illustrates several related points: the appeal of the idea of image-assisted diagnosis for physicians, patients and families, despite a lack of proven effectiveness, and the mismatch between the categories and dimensions of current nosology and those suggested by imaging.

Brain imaging has enabled tremendous progress in the basic science of human cognition and affect, as well as finding useful application in medical research and practice. However, as a growing literature points out, the appeal of imaging goes beyond its demonstrated capabilities (e.g., McCabe & Castell, 2007). Important goals for neuroethics include distinguishing between appropriate and inappropriate uses of brain imaging, explaining the persistence of inappropriate uses and assessing the ethical, legal and societal impact of inappropriate uses. These issues have been addressed in relation to neuromarketing, neuroeducation and brain-based lie detection (e.g., Fisher, Chin & Klitzman, 2010; Hardiman et al., 2011; Wolpe, Foster & Langleben, 2005). In contrast, relatively little analysis has been directed toward the use of neuroimaging in psychiatry. The status of imaging for psychiatric diagnosis is particularly difficult to understand because of the greater prima facie relevance of neuroimaging to psychiatry compared with other areas such as marketing, education or lie detection and the more advanced state of imaging research in psychiatry compared to these other fields.

The puzzle of diagnostic neuroimaging in psychiatry

"Psychiatrists remain the only medical specialists that never look at the organ they treat." This statement, from the website of psychiatrist Daniel Amen (http://www.amenclinics.com/amenclinics/clinics/information/about-us/[1]), highlights the puzzle with which this article is concerned. On the one hand, brain imaging technologies provide ever more sensitive measures of structure and function that are, in principle, relevant to cognitive and emotional functioning. Furthermore, the psychiatry research literature documents with image-based correlates for virtually every psychiatric disorder. On the other hand, notwithstanding a small number of practitioners (including Amen) who use functional brain imaging as a diagnostic tool, the established view in psychiatry is that brain imaging has no role to play in routine clinical care. Aside from its use to rule out potential medical causes of a patient's condition, for example a brain tumor, neuroimaging is not used in the process of psychiatric diagnosis.

[1] This and other online information cited here was accessed May 24, 2012.

Diagnoses in psychiatry are based entirely on behavioral, not biological, criteria. We diagnose depression by asking the patient how he feels and whether his sleeping, eating and other behaviors have changed. We diagnose attention deficit hyperactivity disorder (ADHD) 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 imaging do not appear among the diagnostic criteria. In the words of Kim, Schulz, Wilde and Yudofsky in *The American Psychiatric Publishing Textbook of Psychiatry* (5th Ed., 2008), "Neuroimaging does not yet play a diagnostic role for any of the primary psychiatric disorders."

Several questions are raised by this eschewal of diagnostic brain imaging by most psychiatrists and its endorsement by a few. The first question is the puzzle referred to in the title of this paper: Given that psychiatric disorders are brain disorders, and given the large literature on neuroimaging in psychiatry, why is imaging not useful for diagnosis? In addition, we can ask why some psychiatrists and other mental health professionals nevertheless maintain that neuroimaging does have a role to play in diagnosis. Indeed, for all the various stakeholders – practitioners, patients and patient families – we can ask what motivates them to pursue neuroimaging in this context. Another set of questions concerns how patients, their families and society stand to benefit or be harmed by the current use diagnostic neuroimaging in psychiatry. Finally, we can ask about the future prospects for neuroimaging in clinical psychiatry: How might diagnostic imaging eventually enter mainstream psychiatric practice? What is being done now to facilitate this transformation? And are there other more immediately promising applications of neuroimaging to clinical practice? Each of these questions is addressed below. We begin with a brief review of the role of neuroscience in contemporary psychiatry as a reminder of why imaging has prima facie relevance to diagnosis, and the some of the motivations for seeking imaging-based diagnosis.

Diagnostic Neuroimaging in Psychiatry: Plausibility and Promise. Most psychiatric treatment is "biological," in the sense of operating directly on the brain. This includes medication for depression, anxiety, psychosis and disorders of attention. It also includes such nonpharmacologic treatments as electroconvulsive therapy, neural

stimulation, biofeedback and surgery. Even talking psychotherapy such as cognitive and behavioral therapy is now understood to change the brain, in ways that have been visualized by neuroimaging (DeRubeis, Siegle & Hollon, 2008). In the light of the biological nature of psychiatric treatments, one would expect psychiatric diagnosis to be biological as well.

The idea of diagnostic brain imaging is all the more plausible given that psychiatric illnesses have biological correlates that are apparent in both structural and functional brain imaging. Functional brain imaging, in particular, has been widely used in psychiatry research. For example, Medline returns hundreds of hits each for searches pairing diagnostic categories such as depression and schizophrenia with imaging methods such as PET and fMRI. Given the ability of brain imaging to reveal biological correlates of psychiatric disorders, it seems plausible that imaging would play some role in psychiatric diagnosis.

The idea of imaging-based diagnosis is not only plausible; it also promises to increase the validity of psychiatric diagnoses as well as increasing the accuracy with which individual patients can be diagnosed. A valid category is one that, as Plato put it, "carves nature at its joints." According to this view, the task of science is to identify the ways in which potentially unique phenomena cluster into groups with underlying similarity in nature. Validity, in the context of psychiatric diagnosis, refers to many different ways in which a diagnostic category corresponds to the true clustering of psychiatric dysfunction in the world. Although debate continues as to whether the diagnostic categories of psychiatry can be drawn on the basis of purely biological factors or whether society's demands, beliefs and values also play a role (see, e.g., Wakefield, 1992; Horowitz & Wakefield, 2007), all of the following are viewed as potential indicators of the validity of diagnostic categories: covariance among symptoms within a category and not between categories, the sharing of underlying etiology, similar courses of illness over time, and relations with genetic and other biological traits of a patient and with their treatment response (see Andreasen, 1995; Kendell & Jablensky, 2003; Kendler, 2006).

One of the earliest explicit calls for biological testing was made by Robins and Guze (1970) in their seminal paper on the validation of psychiatric diagnoses. These authors laid out a broad range of criteria by which diagnostic categories could be validated: clinical

correlates, family history, treatment response, course, outcome and what they termed "laboratory studies." Neuroimaging per se was not mentioned simply because it was so rudimentary in those days. But on the assumption that psychiatric disorders are brain disorders, one could not wish for a better indication of the validity of a diagnostic category than a measure of brain function found in all and only patients with that diagnosis.

Better diagnostic methods would of course also improve the accuracy with which individual patients can be diagnosed and thereby result in more patients receiving effective treatment. By capturing information about the underlying pathophysiology believed to cause the disorder, rather than behaviors that are one causal step removed from that pathophysiology, brain imaging promises to deliver a more direct and therefore potentially more accurate diagnosis. For similar reasons, image-based diagnosis could also increase the power of research to develop better treatments, by reducing the number of inappropriate research subjects included in study samples.

The related problems of validity and accuracy of current DSM categories are most pressing for patients whose history and behavior seem equally consistent with more than one diagnosis. Researchers have long been aware of the potential contribution of neuroimaging in such cases. For example, in an early and influential PET study of depression, Schwartz et al. (1987) wrote that such findings "may have value ... as a tool for the differential diagnosis" of bipolar and unipolar depression (p. 1370). In a survey of possible uses for SPECT in psychiatry, O'Connell et al. (1989) judged it to be "a promising technique that appears to have potential in differential diagnosis" (p. 152). The hope that neuroimaging can assist in differential diagnosis lives on, as expressed more recently by Brotman et al. (2009) who suggest that functional neuroimaging will help us to distinguish between different disorders with similar presentations: "Determining the neural circuitry engaged in processing neutral faces may assist in the differential diagnosis of disorders with overlapping clinical features" (pp. 61-62). As these quotes make clear, none of these authors viewed imaging as applicable to current practice, but were instead expressing great hope for its future potential.

SPECT Clinics: Putting Neuroimaging to Work Now

Some practitioners are already using brain imaging for psychiatric diagnosis. We view this practice as premature at best, but also as potentially informative concerning the forces acting to promote and impede the eventual incorporation of neuroimaging into diagnostic practice. In this real-world example we can see the intersecting motivations of clinicians, patients and families. We can also see one nonhypothetical way in which diagnostic imaging affects nosology in practice,

The imaging method currently being used is Single Photon Emission Computed Tomography (SPECT), a functional imaging method by which regional cerebral blood flow is measured by a gamma-emitting tracer in the blood. From these regional blood flow measures a 3-dimensional, low-resolution image of brain activity is constructed.

The best known of the SPECT clinics are the Amen Clinics, founded by the psychiatrist and self-help author Daniel Amen, who was quoted at the outset of the article. There are now four Amen Clinics operating in the US, the first of which opened in 1989, and plans for another two clinics in major US cities have been announced (http://70.32.73.82/blog/5534/changing-the-world-one-brain-at-a-time/). Other clinics offering SPECT-guided psychiatric diagnosis and treatment include Cerescan, Pathfinder Brain SPECT, Silicon Valley Brain SPECT Imaging Center, Dr. Spect Scan and MindMatters of Texas. The use of brain imaging appears to be a selling point for these clinics; their web sites all feature brain images prominently and the names of the first four leave no doubt about the emphasis they place on imaging for attracting patients (Chancellor & Chatterjee, 2011; Farah, 2009).

These clinics promise to diagnose and treat a wide range of psychiatric disorders in children and adults, and base their diagnoses on patient history and examination along with the results of SPECT scans. We will focus our discussion of SPECT-assisted psychiatric diagnosis on the Amen Clinics, because their website and publications offer much more information concerning their diagnostic procedures, diagnostic categories and patient care philosophy than is publicly available from other clinics.

SPECT-Assisted Diagnosis. At the Amen Clinics, patients are typically scanned twice: once at rest and once performing cognitive tasks. The clinics do not rely solely on brain imaging for diagnosis but combine imaging with more conventional diagnostic

methods. They "use brain SPECT imaging, in addition to clinical interviews, diagnostic checklists and laboratory studies when appropriate."

The Amen Clinics use a system of diagnoses that does not correspond to the standard system defined by the Diagnostic and Statistical Manual of the American Psychiatric Association. For example, anxiety and depression are combined into a single superordinate category and 7 subtypes, with names such as "Temporal Lobe Anxiety and Depression" and "Overfocused Anxiety and Depression." Attention deficit hyperactivity disorder is also reconceptualized as having 6 subtypes, with names such as "Limbic ADD" and "Ring of Fire ADD." The use of new diagnostic categories in conjunction with diagnostic brain imaging is not coincidental. The mutual influence of diagnostic tests and the categories to which patients are assigned by those tests is discussed later in this article.

The images are also used to identify certain dimensions of functioning that cut across diagnostic categories, associated with seven specific brain regions: Prefrontal Cortex, Anterior Cingulate Gyrus, Basal Ganglia, Deep Limbic Thalamus, Temporal Lobes, Parietal Lobes and Cerebellum. In a section of the website for professionals (http://www.amenclinics.net/clinics/professionals/how-we-can-help/), Amen explains that "Once we know the brain system or systems that are not functioning optimally, we can then target treatment to the system that needs help." The same section of the website includes the proposed diagnostic significance of these different systems and implications for therapy. Taking the basal ganglia system as an example: "Increased basal ganglia activity is often associated with anxiety (left sided problems are often associated with irritability, right sided problems more often associated with inwardly directed anxiety). Often, we have seen increased activity in this part of the brain in our normal population as well. We have seen increased activity associated here with increased motivation. Clinical correlation is needed. We have seen relaxation therapies, such as biofeedback and hypnosis, and cognitive therapies help calm this part of the brain. If clinically indicated, too much activity here may be helped by antianxiety medications, such as buspirone. Sometimes, if the finding is focal in nature (more one side than the other), anticonvulsant medications can also he helpful" (http://www.amenclinics.net/clinics/professionals/how-we-can-help/brain-science/basal-ganglia-system-bgs/).

Evidence of usefulness. The Amen Clinics website states that they have performed almost 50,000 scans (http://www.amenclinics.com/clinics/patients/18-ways-spect-can-help-you/), a huge number which, with associated clinical data and analyzed appropriately, 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 to widespread condemnation of diagnostic SPECT as premature and unproven.

In 2005 the American Psychiatric Association Council on Children, Adolescents, and Their Families issued a white paper that concluded, "At the present time, the available evidence does not support the use brain imaging for clinical diagnosis or treatment of psychiatric disorders in children and adolescents" (APACCA, 2005). In a review of one of Amen's popular books, appearing in the American Journal of Psychiatry, Leuchter (2009) writes, "it is not clear how the SPECT image provides reliable information that informs clinical decisions… There is also no evidence presented to justify exposing patients to the radiation of a SPECT scan and to support the considerable expense to patients, families and their insurers…." It was recently reported that the Brain Imaging Council of the Society of Nuclear Medicine proposed a test of Amen's methods by asking him to interpret a set of blinded SPECT scans, but the offer was declined (Adinoff & Devous, 2010). Amen (2010) has countered that the Society did not "formally" approach him with this proposal.

In recent writings Amen and coauthors have argued for the value of SPECT in psychiatry by emphasizing its usefulness in complex and treatment-refractory cases (Amen, Trujillo, Newberg, Willeumier, Tarzwell, Wu & Chaitin, 2011; Amen, Willeumier & Johnson, 2012). They offer case studies ranging from failed marriage therapy to compulsive eating in which SPECT studies revealed evidence of previous head injury, toxin exposure, seizure disorder or normal pressure hydrocephalus. Patients improved after appropriate treatment of these (neurological, by conventional terms) problems. Such peer-reviewed reports of individual cases do represent empirical evidence that is relevant to the usefulness of SPECT in psychiatry, but the role they support for neuroimaging is already recognized in mainstream psychiatry: the identification of medical causes for psychiatric symptoms. As case reports they are essentially existence proofs that SPECT can sometimes be useful, but do not tell us how often SPECT would be expected to yield diagnostically

useful information for any given category of psychiatric patients. Furthermore, they do not address the more fundamental issue surrounding SPECT-assisted diagnosis: whether, and to what extent, SPECT can aid in the diagnosis of primary psychiatric disorders including DSM Axis-I disorders such as depression, bipolar disorder, anxiety, and ADHD.

At present we have no evidence that would allow us to estimate the value added to psychiatric diagnosis by SPECT imaging. It is possible that SPECT scans are helpful in diagnosing some or most patients; alternatively it is possible that the scans add nothing to the accuracy of diagnosis. It is even possible that that the scans add a red herring to the diagnostic process, leading physicians to less accurate diagnoses or less helpful treatment plans.

Although we lack information about the "benefit" side of the risk-benefit calculation for SPECT-aided diagnosis in psychiatry, we do know something about the risks, specifically the small but non-negligible risks of radiation exposure from SPECT scanning (see, e.g., Amis et al., 2007). Incidental findings and false negatives could also be viewed as risks. An additional consideration for individuals seeking such a procedure is the cost: depending on the location of the Amen Clinic, a complete work-up including the two SPECT scans costs $3,575-$4,125 (http://www.amenclinics.com/clinics/patients/). Patients and their families typically pay out of pocket for SPECT scans, as insurers will not pay for unproven methods of diagnostic testing.

Appeal of diagnostic neuroimaging to practitioners, patients and families.

The vast majority of psychiatrists and psychologists do not use SPECT imaging when they diagnose patients. What might account for the small fraction who do? The list of possible answers includes a desire to practice a more biologically based form of psychiatry, despite the current prematurity of diagnostic imaging; the potential for brain scans to motivate patient compliance with treatment plans (http://www.amenclinics.net/clinics/professionals/how-we-can-help/direct-benefits-for-patients-and-families/), and the ability to attract patients who pay directly (as opposed to third-party payment) for the procedure and follow-up.

Why would patients and their families pay large sums of their own money for an unproven method? The answer is that most patients are unaware that diagnostic SPECT scanning in psychiatry lacks empirical support. In addition, Amen has become a familiar

and trusted figure thanks to his numerous best-selling books and TV shows broadcast on Public Broadcasting Service stations (which are not PBS productions but self-produced shows that some have called "infomercials" for Amen's products and clinics; see Burton, 2008). Amen's positive image, coupled with the intuitively sensible notion that physicians should look at the organ they plan to treat, draws many patients.

If prospective patients come across criticisms of SPECT scanning for psychiatric diagnosis online or from a healthcare provider, they may be reassured by carefully composed statements from the Amen Clinics such as the following, from the Brain SPECT Informed Consent Form (available online at http://www.markkosinsmd.com/PatientPortal/MyPractice.aspx?UCID={85CB5B0E-51C8-468B-AE34-174650EE240F}&TabID={4}) in answer to the question "Is the use of brain SPECT imaging accepted in the medical community?": "Brain SPECT studies are widely recognized as an effective tool for evaluating brain function in seizures, strokes, dementia and head trauma." In addition to sidestepping the question of SPECT for psychiatric diagnosis, the answer continues by discounting criticism as rooted in ignorance: "As with many new technologies or new applications of existing technologies, many physicians do not fully understand the application of SPECT imaging." The answer concludes with the statement that "Psychiatric SPECT imaging is used in the academic setting in many centers in the US and abroad," which is only true if it refers to research uses of SPECT rather than the diagnostic purpose for which patients are giving consent. The Amen Clinics website also invokes the authority of Thomas Insel, Director of the National Institute of Mental Health, quoting from a lecture in which he said "Brain imaging in clinical practice is the next major advance in psychiatry." Although Insel's statement was clearly about the future of imaging in clinical practice, and therefore might be taken as implying that imaging is not currently useful, it is quoted under the heading "The Future is Now" (http://www.amenclinics.com/clinics/patients/18-ways-spect-can-help-you/).

There are many reasons that patients and families may seek diagnostic SPECT scanning for psychiatric problems, beyond the claims just reviewed. 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 in imaging's visual proof that psychological problems have a

physical cause. The Amen Clinics cite several ways in which patients and their families may find this helpful.

First, the images can reduce feelings of stigma and guilt. Brain imaging provides a concrete reminder that psychiatric disorders are disorders of brain function. As the Clinic website states, "SPECT scans help patients better understand their problems, decreasing shame, guilt, stigma and self-loathing." By demonstrating, visually, that patients' psychological problems are associated with brain dysfunction, imaging may help them feel less responsible for their illness or less personally stigmatized by it; they can believe that "It's not me, it's my brain" (see Dumit, 2003).

For similar reasons the families of patients may also feel relieved by brain imaging. This is especially true for parents, who may worry that their child's illness was caused by their own behavior toward the child, for example their absence from the home, too much TV or inadequate discipline. An abnormal brain scan can be seen as proof that the child's brain, and not his or her upbringing, is responsible for the psychiatric disorder. Of course, the alternatives of brain and upbringing are not mutually exclusive. Any behavioral trait must have a basis in the brain whether its causes are genetic or environmental. Nevertheless, insofar as images depict the biological basis of mental illness, they shift the attention toward a more physical, deterministic understanding of the disorders and away from responsibility, blame and other moral concepts that add to the burden on patients and families. Amen points this out as a benefit when he states that "A SPECT scan can help families understand the underlying medical reasons for a problem, which helps decrease shame, self blame and conflict" (http://www.amenclinics.com/clinics/patients/18-ways-spect-can-help-you/).

Patients and families may also appreciate the similar role played by SPECT scans in legal contexts, "helping judges and juries understand difficult behavior." (http://www.amenclinics.com/clinics/patients/18-ways-spect-can-help-you/). Functional neuroimaging has been introduced as evidence in a variety of roles in the US and other legal systems, most often as evidence of brain injury in tort cases but also by the defense in criminal trials (Patel et al., 2007). In the latter case it is most often used for mitigation in the sentencing phase of criminal trials, where it can provide concrete, visual evidence of a person's abnormal or diminished faculties (Hughes, 2010).

Prospects for Diagnosing Psychiatric Illness With Neuroimaging

Current and foreseeable diagnostic practices. At the time of writing, psychiatric illnesses are currently classified according to one of two similar systems, the 4th Edition, "Text Revised," of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) and the 10th edition of the International Classification of Diseases (ICD-10). Psychiatric diagnosis is poised for change, however, with the revision of the DSM. New disorders defined by new constellations of signs and symptoms are being considered for addition to the DSM-5, scheduled for release in May 2013. Some disorders already covered by previous editions may be subdivided differently or merged in the DSM-5. For each diagnostic category, criteria for inclusion and exclusion are being reviewed and updated in light of current knowledge. In relation to this last change, the incorporation of genetic and neurobiological measures has been considered (Regier, Narrow, Kuhl & Kupfer, 2009).

Why will brain imaging not figure in these new diagnostic criteria? The consensus answer is that, despite the value of brain imaging in understanding mental disorders, it would be premature to include brain imaging among diagnostic criteria for the next DSM (Agarwal et al., 2010; Hyman, 2007; Miller, 2010; Miller & Holden, 2010). Whereas biological evidence will figure more prominently in the DSM-5 than in any previous edition, its role is expected to be in the validation of the categories themselves rather than in the criteria for diagnosing an individual patient (Hyman, 2010).

Current obstacles to diagnostic neuroimaging. Why has diagnostic neuroimaging not yet found a place in psychiatric practice? Generic answers such as "psychiatric neuroimaging is in an early stage of development" or "medicine is a conservative field" contain kernels of truth but do not adequately address the question. After all, psychiatry research has made use of neuroimaging for three decades, and psychiatry has eagerly pursued new treatment technologies, including transcranial, deep brain and vagal nerve stimulation as well as drugs borrowed from specialties as diverse as epilepsy (Yatham, 2004) and sleep medicine (Ballon & Feifel, 2006). How, then, can we explain the lack of a role for neuroimaging in psychiatric diagnosis? What obstacles currently lie on the path to the use of such methods? The answer involves the nature of imaging as well as the nature of psychiatric diagnosis itself.

Limitations related to imaging. The vast majority of current neuroimaging research in psychiatry compares two groups of subjects, those with an illness and healthy control subjects. For functional neuroimaging studies the subjects may be resting or performing a task involving cognitive or emotional processing. The words "two," "groups" and "task," above, each represent important limitations on the ability to translate such research into diagnostic tests, related to *specificity*, *sensitivity* and *standardization*, respectively.

We will start by examining the *sensitivity* of imaging studies of psychiatric patients. Although the accuracy and reliability of individual subject scans has increased since the early days of brain imaging with PET, SPECT and fMRI due to improvements in image acquisition methods as well as data analysis, the vast majority of psychiatric neuroimaging studies aggregate data from groups of subjects for analysis. In contrast, diagnosis must be applied to individuals, not groups. When structural and functional findings from individual subjects are examined, a high degree of variability is observed, even within groups of healthy and ill subjects. More problematic for diagnostic purposes, the distributions of healthy and ill subjects generally overlap (see Gillihan & Parens, 2011). In the language of diagnostic tests, imaging studies are generally not highly sensitive to the difference between illness and health.

Standardization might appear to be a premature concern for an approach to diagnosis that is nowhere near ready for widespread clinical use. In the context of diagnostic testing, the term "standardization" often refers to the specification of all details of the protocol that might vary from lab to lab and could influence the results. Here we refer to a broader but related issue, namely the many obvious and fundamental ways in which protocols differ between imaging studies, in particular 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 this seems obvious when applied to cognitive neuroscience studies of normal subjects, it is easier to lose sight of when considering studies of psychiatric patients, where results may be summarized by stating that certain regions are under- or over-active, or more or less functionally connected, in particular patient groups. Of course such summaries are fundamentally incomplete unless they

include information about what task evoked the activation in question: were the patients resting, processing emotional stimuli (eg, fearful faces), trying not to process emotional stimuli (eg, emotional Stroop task) or engaged in effortful cognition (eg, task switching)? 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 control subjects and patients with different disorders.

Another limitation imposed by imaging concerns *specificity*. When researchers compare subjects from only two categories -- patients from a single diagnostic category to healthy subjects -- the most that they can learn is how brain activation in a single illness differs from healthy brain activation. Of course, the dilemma faced by a diagnosing clinician is rarely "Does this person have disorder X or is he healthy?" Rather, it is typically "Does this person have disorder X, Y or Z?" For all we know, the pattern that distinguishes people with disorder X from healthy people is not unique to X but is shared with a whole alphabet of other disorders. It might be nothing more than a sign of psychopathology per se, and thus provide less specificity for diagnosis than a brief clinical exam. Because few imaging studies directly compare brain activation across multiple disorders, or use sufficiently standardized methods that their results can be directly compared with the results of other studies, we lack good evidence on the likely specificity of brain imaging for diagnosis.

The best we can do, at present, is to compare the results of brain imaging across studies, with admittedly different tasks and methods of analysis, in order to assess specificity. On the face of things, there is considerable similarity of imaging results across different diagnoses. For example, a meta-analysis of neuroimaging studies of anxiety disorders reported common areas of activation (amygdala, insula) across PTSD, social phobia, and specific phobia—suggesting that neuroimaging has yet to reveal patterns of neural activity that are unique to specific anxiety disorders (Etkin & Wager, 2007). Abnormalities of amygdala activation also have been reported consistently in neuroimaging studies of depression. For example, Gotlib and Hamilton (2008) reviewed the literature on neuroimaging of depression and concluded that "… most consistently, the amygdala and subgenual [anterior cingulate cortex] appear to be overactive in [major depressive disorder], and the [dorsolateral prefrontal cortex] underactive" (p. 160). A

similar pattern of results has been reported in bipolar disorder; Keener and Phillips (2007) summarized the relevant neuroimaging results as showing increased activity in emotion processing regions (including the amygdala) and decreased activity in executive regions (e.g., dorsolateral prefrontal cortex). In schizophrenia, a disorder primarily of thought rather than of mood, amygdala hyperactivity is again often observed, along with lower dorsolateral prefrontal activity (Berman & Meyer-Lindenberg, 2004). Psychopathy (which shares features with the *DSM* diagnosis of Antisocial Personality Disorder) has been associated with similar neural patterns; in their recent review, Wahlund and Kristiansson (2009) stated that "a dysfunctional amygdala has been suggested as one of the core neural correlates of psychopathy…. Aside from the amygdala, frontal lobe dysfunction has been suggested in psychopaths" (p. 267).

More sophisticated methods of image analysis may hold promise for discerning the underlying differences among the many disorders that feature similar regional abnormalities. By taking into account the nature of the task used to evoke brain activity and functional relationships among different activated or resting brain areas, we may be able to revise the initial impression that all imaging of psychopathology involves the "usual suspects" such as limbic hyperactivity and prefrontal hypoactivity. In addition, new multivariate statistical approaches to image analysis enable the discovery of spatial and temporal patterns within brain images that distinguish between task conditions or types of subject more effectively than traditional statistical methods (Haynes & Rees, 2006). 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 (Bray et al., 2009; Calhoun et al., 2008).

Finally, as methods of acquiring and analyzing brain images continue to develop, it bears remembering that imaging will never measure all aspects of brain function. There is no guarantee that it will be able to capture those aspects most characteristic or defining of the psychiatric disorders. Regional differences in brain activity measured on a spatial scale discernible through current functional imaging methods, or neurochemical differences discernible through PET or SPECT are not the only ways in which disordered brains can differ from healthy brains. Although neuroimaging research has demonstrated differences among brain activity in different psychiatric disorders, it is an open empirical question

whether current or future imaging methods will reveal sufficiently sensitive and specific features of brain function to ever serve as diagnostic tests.

Limitations related to current diagnostic categories. Another set of reasons why progress toward diagnostic imaging in psychiatry has been slow concerns the nature of the diagnostic categories themselves. The categories of DSM are intended to be both valid and reliable. As discussed earlier, validity refers to the correspondence between diagnostic categories and the ways in which psychiatric disorders are truly structured in nature. Reliability refers to the degree to which the categories' criteria can be used consistently by any appropriately trained clinician, so that different diagnosticians will arrive at the same diagnosis for each patient.

Good, or at least improved, reliability was one of the signal achievements of the DSM-III, and has carried over to DSM-IV. Unfortunately, validity continues to be more difficult to achieve. This is not surprising given how closely validity is related to scientific understanding, and how complex and poorly understood psychiatric illness continues to be (Robert, 2007). To the extent that our psychiatric categories do not correspond to "natural kinds" (Quine, 1969), we should probably not expect perfect correspondence with brain physiology as revealed by imaging.

As an illustration of how far from being natural kinds our current diagnostic categories are, consider the diagnostic criteria for one of the more common serious disorders, Major Depressive Disorder. According to the DSM-IV-TR, patients must report at least one of the two symptoms of depressed mood or anhedonia and at least four of an additional eight symptoms. It is therefore possible for two patients who do not share a single symptom to both receive a diagnosis of Major Depressive Disorder. In addition to heterogeneity within the diagnostic categories of psychiatry, there are also commonalities of symptoms between categories. For example, impulsivity, emotional lability and difficulty with concentration each occur in multiple disorders.

The present and future of brain imaging in psychiatry

Co-evolution of science, diagnostic tests and diagnostic categories. We are currently far from being able to use brain imaging for psychiatric diagnosis. Yet all of the

limitations of imaging and diagnosis just reviewed may eventually be overcome. By what path might this occur?

Imaging markers of diagnostic categories may emerge from basic research on psychopathology and prove to be highly diagnostic. Alternatively, it is possible that 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 promises to be a lengthy and expensive process, which could easily fill the interval between two or more editions of the DSM.

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. Brain imaging may succeed in delineating categories of patients based on abnormalities in brain function, but these categories may not be the same as the categories of the DSM. Indeed, given the heterogeneity within diagnostic categories and the overlap between categories just noted, it seems likely that our nosology will be forced 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.

More revolutionary change is also possible. Psychiatrists do not view DSM categories as ground truth and the validity of the current system of categories has been widely questioned (e.g., Radden, 1994). The potential for imaging research to disrupt the gradual, iterative approach to nosological change was anticipated by First and Kendler (2010), who wrote "the iterative model assumes continuity over time in … the methods used to determine validity…. What happens if dramatic technical breakthroughs in genetics, imaging or neuroscience cast the problems of psychiatric nosology in an entirely new light? The application of such new methods to our nosology would likely disrupt the smooth evolutionary approach of the iterative model" (p. 263). If a new nosology based on imaging is proven to have clinical utility, for example enabling better treatment decisions, then imaging may prompt a radical reconceptualization of psychiatric diagnosis and entirely new diagnostic categories may emerge. Indeed, the existence of categories per se

has been questioned, with some experts proposing to characterize patients in terms of where they fall on different dimensions of psychological functioning, which may be more or less severely impaired, rather than assigning them to discrete categories. This system may better capture the ways in which patients differ from one another and from healthy people (Krueger, Watson & Barlow, 2005).

It is interesting to note that both the emergence of new diagnostic categories and the use of dimensional classification schemes are presaged by the uses of SPECT just reviewed. Although SPECT-aided psychiatric diagnosis has no basis in evidence and is regarded with extreme skepticism by most experts, it nevertheless reveals the tension that can be expected between the DSM's system of categories, on the one hand, and the kinds of diagnoses that are more naturally built on functional brain imaging results, on the other.

Recall that the Amen Clinics' diagnostic system includes entirely new types of diagnoses such as "Overfocused Anxiety and Depression" and "Ring of Fire ADD," which do not correspond to anything in the DSM. They are instead based on a combination of behavioral observations and SPECT findings. Examples of the latter include "increased anterior cingulate gyrus activity and increased basal ganglia and/or deep limbic activity at rest and during concentration" for the "Overfocused Anxiety and Depression" (http://www.amenclinics.net/conditions/Anxiety_Issues/) and "marked overall increased activity across the cortex, may or may not have low prefrontal cortex activity" for "Ring of Fire ADD"(http://www.amenclinics.net/conditions/ADHD/). Although the validity and clinical utility of these categories is far from clear, given the absence of any peer-reviewed evidence supporting them, they demonstrate in a concrete way how the inclusion of neuroimaging data in the diagnostic process can change not only that process but the diagnoses themselves. Imagine that patients sharing some features of a conventional diagnosis, without meeting all criteria, are found to group into distinct categories according to their patterns of brain activation. It would be reasonable to consider these new groupings good candidates for new and more valid diagnostic categories.

Similarly, in the Amen Clinics' approach we also see the use of dimensions of functioning that cut across diagnostic categories, in the form of the seven different anatomically defined systems described earlier (Prefrontal Cortex, Anterior Cingulate Cortex, Basal Ganglia System, Deep Limbic System Thalamus, Temporal Lobes, Parietal

Lobes and Cerebellum; see http://www.amenclinics.net/clinics/professionals/how-we-can-help/). Setting aside the question of the validity of these systems, it is apparent that the organization of the brain into functionally and anatomically distinct systems, combined with the graded nature of activation in those systems, fits naturally with a dimensional rather than categorical system for characterizing patients.

In sum, there are a priori reasons to expect our diagnostic system to change as imaging data are incorporated. There is also the illustrative, if not adequately-evaluated, example of SPECT-aided psychiatric diagnosis, where the use of imaging has led to redrawn categories and cross-cutting dimensional classifications of patients. Although changes to our diagnostic systems may well be inevitable as neuroimaging provides new information linking brain function with psychiatric symptoms, and those changes can be expected to improve validity and clinical utility, these changes will likely come slowly. Where diagnoses are concerned there are strong arguments for conservatism.

The current system of categories is valuable in part simply because we have used it for so long and therefore much of our clinical knowledge is relative to this system (e.g., First & Kendler, 2010). As Hyman (2002) put it, "We should not tinker with existing diagnoses without a very high threshold because even small changes in diagnostic criteria may have negative consequences. They may alter the apparent prevalence of disorders, confound family and longitudinal studies, alter treatment development by affecting regulatory agencies…"(p. 6). For these reasons it is appropriate for the influence of brain imaging on psychiatric diagnosis to be more evolutionary than revolutionary. In keeping with this approach, 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 minority being subdivided, merged, added and eliminated in the light of new research findings.

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 US 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" (Insel et al., 2010). The RDoC system, still under construction at the time of

writing (see http://www.nimh.nih.gov/research-funding/rdoc/nimh-research-domain-criteria-rdoc.shtml), is organized into five domains: negative valence, positive valence, cognitive processes, social processes, and arousal/regulatory processes. Within the domains are more specific functions related to known neural circuits, which vary dimensionally from normal levels of function to abnormal. Examples include Fear, in the Negative Valence domain, associated with "amygdala, hippocampus, interactions with ventromedial PFC" and Working Memory, in the Cognitive Processes domain, associated with "dorsolateral PFC, other areas in PFC." The use of RDoC across research labs, in parallel with DSM categories, may ultimately lead to the development of a new diagnostic system that would both be more valid and also possibly more consistent with the use of imaging as a diagnostic test.

Nondiagnostic uses of imaging in clinical psychiatry

We have seen that, for reasons to do with both the nature of neuroimaging and the nature of psychiatric diagnosis, imaging is far from providing useful diagnostic information in psychiatry. However, neither is it without immediate clinical promise. Here we summarize several promising roles for imaging other than diagnosis.

New treatments can be suggested by imaging research, exemplified by the use of deep brain stimulation (DBS) in area 25 for the treatment of depression. Based on findings from functional and structural neuroimaging studies, Mayberg and colleagues developed a neural model of major depressive disorder that included the influence of hyperactivity in the subgenual cingulate cortex on other regions important for mood. The initial test of this model in a treatment setting used electrodes implanted in this region of the brain in six individuals with treatment refractory depression. Four of the six patients in this group achieved remission of their depression (Mayberg et al., 2005). Subsequent work with a larger group of patients confirmed the efficacy of DBS for treatment resistant depression (Lozano et al., 2008). Imaging is also being used to assess the effectiveness of this technique and personalize the placement of electrodes (Hamani et al., 2009).

Another potential application of imaging to clinical care involves the prediction of treatment response. Treatments for some psychiatric disorders take weeks or months to produce a therapeutic effect, and not all treatments are equally effective for all patients.

The ability to predict a patient's response to a given treatment can therefore save considerable time and suffering. Although not currently part of clinical care, there is reason for optimism concerning its feasibility in several different disorders (Evans, Pollack & Rauch, 2006). In addition to the prediction of treatment response in those already diagnosed with an illness, imaging can aid prediction of disease onset in asymptomatic individuals. For example, research has shown that structural MRI can predict first episodes of schizophrenia in individuals who are at genetically increased risk (McIntosh et al., 2010), enabling early or even preventive treatment to be offered to those most likely to benefit from it.

Finally, functional neuroimaging can be used as a treatment itself, by providing patients with a real time measure of regional brain activity to use in biofeedback training (deCharms, 2008). This technique has been used to enhance pain control in chronic pain patients by deCharms and colleagues (2005). DeCharms (2008) has also noted the potential of the method for treating depression and addiction.

Neuroimaging will be likely to enter clinical use with the applications just reviewed before it finds a general role in diagnosis. Nevertheless, attempts to diagnose with the help of imaging will undoubtedly continue. Practitioners have a financial incentive to offer this service and patients are attracted by the promise of more scientific diagnosis and treatment, as well as relief from blame and stigma. Neuroimaging has strong prima facie relevance to psychiatric diagnosis that can only be dispelled by careful reflection on the technical limitations of imaging and the historical and pragmatic nature of psychiatric nosology.

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