Overdiagnosis in the Era of Neuropsychiatric Imaging

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New guidelines proposed by the National Institute of Mental Health are intended to transform the management of patients with psychiatric disorders. It is anticipated that neuroimaging and other biomarkers will play a more prominent role in diagnosis and prognosis, especially in the prodromal phase of illness. Earlier treatment of psychiatric disorders has the potential to improve outcomes significantly. However, diagnosis in the absence of symptoms can lead to overdiagnosis. Overdiagnosis is a problem in many fields of medicine but could pose additional problems in psychiatry because of the stigmatization that often accompanies a diagnosis of mental illness. This review discusses the magnetic resonance imaging methods that hold the most promise for evaluating neuropsychiatric disorders, the likelihood that they could lead to overdiagnosis, and opportunities to minimize the impact of overdiagnosis in psychiatric disorders.

Key Words: Neuroimaging; psychiatry; overdiagnosis.

NEW PARADIGMS IN NEUROPSYCHIATRY

In 2013, the American Psychiatric Association published the fifth edition of the Diagnostic and Statistical Manual (DSM-5) used for psychiatric diagnosis. It was generally regarded as an incremental change rather than a radical departure from the previous edition, published nearly twenty years earlier (1,2). Shortly thereafter, the National Institute of Mental Health (NIMH) rejected the DSM-5 and embraced a new framework for the study of neuropsychiatric disorders. This framework was based on the premise that genetic, cellular, and behavioral systems are responsible for mental health, and failure of these mechanisms constitutes mental illness (3). In doing so, the NIMH explicitly acknowledged that neuropsychiatric pathology may precede psychiatric symptoms. In contrast to the traditional approach taken by psychiatrists, the NIMH suggested that neuropsychiatric pathology may be treatable even before a diagnosis could be established with the DSM. Indeed, one of the primary motivations behind these changes was to encourage intervention in the prodromal phase of psychiatric disorders, with the aim of preventing progression (4). Support for this paradigm came partly from encouraging studies of early intervention in youth at risk of schizophrenia and other neuropsychiatric disorders (5–9). To identify patients who might benefit from intervention, the NIMH called for research into physiological biomarkers for psychiatric disease, particularly into neuroimaging biomarkers.

The evolution of neuropsychiatric therapy has mirrored the evolution of our understanding of neuropsychiatric disorders. Although pharmaceutical and behavioral interventions remain a mainstay of treatment, in some cases, clinicians have begun turning to direct stimulation of specific regions of the brain using implanted deep brain electrodes, as well as noninvasive transcranial techniques. Transcranial magnetic stimulation of dorsolateral prefrontal cortex has recently been approved by the Food and Drug Administration for use in patients with treatment-resistant major depressive disorder, with an average response rate of 29% (10). Long-term response rates of 64%–92% have been reported in depression after deep brain stimulation of subcortical targets (11). In obsessive–compulsive disorder (OCD), deep brain stimulation of the anterior limb of the internal capsule and/or striatum has been associated with symptom improvement in 60%–70% of treatment-resistant patients (12). Transcranial magnetic stimulation of dorsolateral prefrontal cortex, orbitofrontal cortex, and the supplemental motor area may also be effective in OCD (13). These and other regions of the brain are also under investigation as targets for transcranial stimulation in the treatment of neuropathic pain, anxiety, schizophrenia, addiction, and other diseases (10). As neuroscientists continue to advance their understanding of the relationship between brain structure and function, new targets are likely to emerge.

THE ERA OF NEUROPSYCHIATRIC IMAGING

Neuroimaging stands at the intersection of the evolution of neuropsychiatric diagnosis and the evolution of treatment. Meanwhile, neuroimaging itself is in the midst of a renaissance

Acad Radiol 2015; 22:995–999

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http://dx.doi.org/10.1016/j.acra.2015.02.004

driven by technological advancements in multiple complementary modalities. Currently, the most popular methods used to investigate neuropsychiatric disorders are functional magnetic resonance imaging, diffusion tensor imaging, and structural morphometry. Functional magnetic resonance imaging is used to localize neural activity on a time scale of seconds, usually by analyzing signal changes in blood related to the oxygenation state of hemoglobin (14). Diffusion tensor imaging is used to assess the integrity of white matter and anatomy of white matter tracts by tracking the movement of water during diffusion, which has a tendency to occur parallel to axons rather than across them (15). Structural morphometry is used to measure focal changes in brain volume, even when they are too subtle to detect visually, through the application of sophisticated registration techniques (16). These advances have produced a wealth of data regarding the imaging correlates of psychiatric disorders.

Schizophrenia, one of the first neuropsychiatric disorders to be studied with modern neuroimaging (17), has been associated with decreased volumes throughout the brain, particularly in the frontal and temporal lobes (18–21). Functional imaging studies of patients with schizophrenia have reported consistent hypoactivation of frontal circuits (22), some of which may be the result of genetic predisposition (23). Widespread white matter abnormalities have been reported as well (24). Neuroimaging studies have also explored the relationship between brain structure and individual disease course in schizophrenia. Hallucinations and other positive symptoms have been associated with distinct neuroimaging features, whereas different findings are associated with negative symptoms (25–27).

These same techniques have been applied to patients with other neuropsychiatric disorders. For example, autism has consistently been associated with increased brain volume in children (28). It has also been associated with abnormal microstructure in the corpus callosum and other regions of the white matter (28,29), as well as abnormal frontal and subcortical activity during tasks such as face processing (30,31). Functional connectivity, which is a measure of temporal synchronization of neural activity across different regions of the brain, may also be abnormal in autism (32–34). Posttraumatic stress disorder has been associated with abnormal activity in the amygdala as well as abnormal hippocampal and amygdala volumes (35–37). Depression has been associated with multiple structural and functional abnormalities (38). In keeping with the conceptual framework proposed by the NIMH, neuroimaging findings in these disorders have been shown to sometimes precede overt psychiatric symptoms (29,39–41).

THE CHALLENGES OF OVERDIAGNOSIS

The use of neuroimaging to identify disease represents a marked departure from the traditional practice of psychiatry. Unlike many other medical specialists, psychiatrists are often reluctant to treat people who lack symptoms. This philosophy is ingrained through the use of symptom-based checklists, emphasizing current impairment and distress, when making a diagnosis (42). Overdiagnosis, which by definition only occurs in the absence of symptoms, is a foreign concept to clinicians who must always attribute symptoms to their diagnosis. Much of the controversy regarding overdiagnosis has focused on the stress and anxiety resulting in patients who are assigned a diagnostic label in the absence of symptoms (43). For neuropsychiatric disorders, overdiagnosis could additionally lead to stigmatization, and fear of an unexpected diagnosis could accordingly reduce willingness to seek health care (44). Thus, it is worthwhile to consider the risk and benefits of neuropsychiatric imaging through the lens of overdiagnosis.

Imaging-related overdiagnosis is not an insignificant risk. Imaging findings in neuropsychiatric disorders tend to have relatively small effect sizes, which implies that normal states cannot always be distinguished from pathology. Nonspecificity is exacerbated by "the problem of reverse inference," a potential logical error committed when interpreting neuroimaging findings without recognizing that other states may produce the same findings (45). For example, volume reduction in the anterior cingulate cortex has independently been suggested as a potential biomarker for schizophrenia, depression, posttraumatic stress disorder, and OCD (46–49). The same finding has also been reported in the absence of any neuropsychiatric pathology (50,51). Avoiding this problem requires attention to the prevalence of disease-related findings in real-world populations, which is challenging because the literature with regard to psychiatric disease is still inconclusive (52).

Improvements in diagnostic accuracy are continually being sought and may help to reduce overdiagnosis (53). One promising avenue is multivoxel pattern analysis (54,55). This comprises a group of machine-learning algorithms that determine the specific radiologic patterns capable of optimizing diagnostic classification. The patterns recognized by these algorithms are often difficult to detect by the unaided eye because they do not always conform to known anatomic regions and can be distributed throughout the brain. Classifiers based on structural T1-weighted imaging have achieved sensitivity ranging from 67% to 93% for schizophrenia, with specificity ranging from 68% to 95% (56–59). A similar approach has achieved 94% sensitivity and 90% specificity for attention deficit hyperactivity disorder (ADHD) (59), and sensitivity and specificity of 80% each for borderline personality disorder (60). Classifiers using functional connectivity have achieved sensitivity ranging from 75% to 87% and specificity ranging from 70% to 74% for ADHD (61–63). A similar approach achieved sensitivity ranging from 62% to 97% and specificity ranging from 58% to 95% for autism (64–68). Classifiers based on diffusion tensor imaging have achieved 94% sensitivity and 90% specificity for autism (69), as well as 86% sensitivity and 96% specificity for major depressive disorder (70). In these examples, the reference standard was either the DSM-IV or (for autism studies) a widely accepted substitute. Despite the power of these techniques, image-based classifiers still underperform classifiers based on clinical