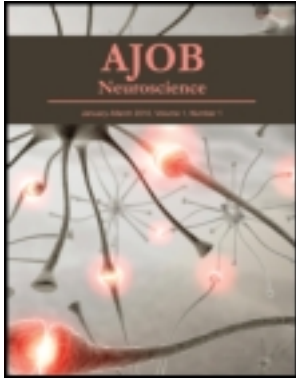


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### Lengthy and Expensive? Why the Future of Diagnostic Neuroimaging May Be Faster, Cheaper, and More Collaborative Than We Think

Michael Lifshitz<sup>a</sup>, Daniel S. Margulies<sup>b</sup> & Amir Raz<sup>c</sup>

<sup>a</sup> McGill University

<sup>b</sup> Max Planck Institute for Human Cognitive and Brain Sciences

<sup>c</sup> McGill University and Lady Davis Institute for Medical Research

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# Lengthy and Expensive? Why the Future of Diagnostic Neuroimaging May Be Faster, Cheaper, and More Collaborative Than We Think

Michael Lifshitz, McGill University

Daniel S. Margulies, Max Planck Institute for Human Cognitive and Brain Sciences

Amir Raz, McGill University and Lady Davis Institute for Medical Research

In their target article, Farah and Gillihan (2012) argue that identifying brain signatures of psychiatric disorders represents a daunting task on many levels, from the intellectual challenge of theoretical development to the logistical hurdles of time and money. In this commentary, we illustrate how the growing movement of “open neuroscience”—that is, data-sharing initiatives and online collaborative platforms—renders large-scale neuroimaging research more feasible and productive than previously imagined. Whether or not neural assays will ultimately prove useful as diagnostic or nosologic tools, the unrestricted sharing of data, methods, and ideas is our best bet for exploring how neuroimaging can elucidate the brain in health as well as in pathology.

Until recently, the progress of neuroscientific knowledge was restricted by the speed at which individual laboratories could collect, analyze, and publish their own data. This situation posed significant barriers to scientific progress. Researchers kept data concealed for many years until publication, if they released it at all. Labs were forced to cultivate broad skill sets rather than focus on their particular strengths. Neuroscientists remained isolated within a select community of researchers who had enough time, money, and expertise to collect their own brain data. Taking up the example of other scientific disciplines such as molecular genetics, however, members of a growing group of neuroscientists have begun to adopt a philosophy of open neuroscience. This novel paradigm encourages the unrestricted sharing of data, resources, and knowledge in pursuit of a more united, efficient, and data-driven brain science (Milham 2011). Although it may seem that embracing this

framework would necessitate a major cultural shift within neuroscience, wherein advancing communal knowledge takes precedence over promoting individual prestige, there are tangible benefits to be won for the individual researcher as well. Open neuroscience has already begun to accelerate the pace of discovery in brain science and holds important implications for the translation of neuroscientific knowledge to the domain of clinical practice.

In March 2011, a group of forward-thinking neuroscientists collaborating with the International Neuroimaging Data-Sharing Initiative (INDI) launched the ADHD-200 global competition to demonstrate the real-world feasibility and potential merits of large-scale collaborative brain science (<http://fcon.1000.projects.nitrc.org/indi/adhd200>). Their aim was to encourage researchers around the world to develop analytic tools for diagnosing attention-deficit hyperactivity disorder (ADHD) through the free and unrestricted public release of a large repository of functional and anatomical brain scans. The general tenor of this initiative was hardly new; researchers had proposed a public functional magnetic resonance imaging (fMRI) data repository as far back as 2002 (Van Horn and Gazzaniga 2002). Yet these earlier efforts never took off, in large part due to difficulties associated with standardizing task-based imaging paradigms across research groups.

Over the past decade two major paradigm shifts in cognitive neuroscience have rendered large-scale data-sharing initiatives considerably more feasible than before. First, cognitive neuroscientists have begun to appreciate the value of investigating spontaneous neural activity during the ‘resting state’, that is, in the absence of external, variable

Address correspondence to Prof. Amir Raz, 4333 Cote Ste. Catherine, Montreal, QC, H3T 1E4, Canada. E-mail: [amir.raz@mcgill.ca](mailto:amir.raz@mcgill.ca)

task-demands (Raichle 2010). Second, advances in anatomical imaging techniques, including methods of quantifying structural connectivity among distributed brain regions (e.g., diffusion tensor imaging), have provided new avenues for elucidating the relationship between individual brain anatomy (i.e., the connectome) and mental traits (Sporns 2011). Since the inception of these resting-state fMRI (rsfMRI) and connectomics approaches less than a decade ago, hundreds of studies have investigated intrinsic brain function and anatomical variability to elucidate the neural underpinnings of mental disorders (for reviews, see Fornito and Bullmore 2010; Thomason and Thompson 2011).

Although many cognitive neuroscientists and psychiatrists have jumped aboard the resting-state train, some experts have highlighted important methodological caveats that the research community will need to address before we can fully appreciate the strengths and weaknesses of these new methodologies (Kelly et al. 2012). Furthermore, the sheer complexity of intrinsic brain dynamics calls for vast computational and analytic resources, as well as nontraditional investigative approaches that supplement a priori hypothesis testing with data-driven, or discovery-based, science (Biswal et al. 2010). Open neuroscience is an ideal vehicle for exploring the promises and pitfalls of such new neuroimaging paradigms because it provides a platform for accumulating the immense data and analytical creativity necessary for effective discovery-based research (Poline et al. 2012). Moreover, sharing data and analytic resources further opens neuroscience to the purview of complementary disciplines (e.g., mathematics, computer science, biostatistics) that will likely prove instrumental to unraveling the intricacies of brain function. On the flip side, rsfMRI and anatomical assays provide excellent mediums for open neuroscience because they obviate the difficulties associated with standardizing task-based paradigms and thus render multisite data aggregation realistic.

The ADHD-200 global competition leveraged the versatility and standardizability of task-free neuroimaging to gather 776 rsfMRI and anatomical data sets from 8 independent imaging sites spread across the globe. Of these data sets, 285 presented brain scans from children and adolescents diagnosed with ADHD, while the rest comprised scans from children of comparable ages with healthy developmental profiles. The competition organizers distributed these brain scans online freely and without restriction. To make these weighty data sets more manageable and encourage interdisciplinary participation beyond the narrow community of neuroscience specialists, the Neuro Bureau—a grass-roots initiative supporting open neuroscientific collaboration—freely offered preprocessed versions of the data for online download (<http://neurobureau.projects.nitrc.org/ADHD200/Introduction.html>). Thus, researchers lacking familiarity with the nuances of fMRI data preprocessing could still contribute their analytic expertise.

Four months after distributing the original data sets, the competition organizers put the participating teams to the test by releasing 197 additional unlabeled scans includ-

ing both ADHD and healthy children (<http://fcon.1000.projects.nitrc.org/indi/adhd200/results.html>). All but one of the 21 international teams succeeded in successfully labeling the data sets above chance. The winning team, a group of statisticians from John Hopkins University, employed the preprocessed data offered by the Neuro Bureau to develop an analytic model capable of identifying typically developing children with an impressive specificity of 94%. Although their model's sensitivity to ADHD was comparably weak at just over 20%, it was able to differentiate between diagnostic subtypes with more than 89% accuracy. Other teams, although scoring lower overall, demonstrated significantly higher sensitivity in correctly labeling ADHD data sets. These results paint a promising picture of the potential of perhaps one day using neuroimaging for psychiatric diagnosis. Despite these encouraging results, however, another outcome of the competition should sober our enthusiasm. The group that demonstrated the highest classification accuracy, hailing from the University of Alberta, eschewed neuroimaging entirely from its predictive model and was therefore disqualified from the competition. This group outperformed the winning team using only the available phenotypic data consisting of age, sex, handedness, and IQ.

While the results of the ADHD-200 Global Competition suggest that neuroimaging may not yet be ready to contribute directly to psychiatric practice, the very fact of the competition confirms that the research community is ready to join forces in pursuit of that goal. The success of the competition shows that remarkable achievements in clinical neuroimaging require neither powerful top-down organization nor debilitating financial or temporal investment. The ADHD-200 initiative demonstrates how a competitive spirit can incentivize productivity and prompt researchers to contribute their data, skill, and time toward the collaborative advancement of a scientific aim. Beyond the intrinsic rewards of innovation, the competition encouraged global visibility and spurred several participating groups to publish their methods and results in peer-reviewed journals (e.g., Cheng et al. 2012). The open neuroscience movement heralds a profound shift in the values of neuroscientific culture. Sharing of data and resources fundamentally changes the currency of a research field—from the possession of raw materials to the valuation of analytic and conceptual insights. It is still too early to say whether neuroimaging will one day change how psychiatrists do their job. But the movements underway in neuroscience may bring an answer sooner than we'd thought.

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# Neuroimaging and Validity in Psychiatric Diagnosis

Carl E. Fisher, Columbia University and New York State Psychiatric Institute

In the fight which we have to wage incessantly against ignorance and quackery among the masses and follies of all sorts among the classes, diagnosis, not drugging, is our chief weapon of offense. Lack of systematic personal training in the methods of recognition of disease leads to the misapplication of remedies, to long courses of treatment when treatment is useless, and so directly to that lack of confidence in our methods which is apt to place us in the eyes of the public on a level with empirics and quacks. (William Osler, in Huth and Murray 2000, 93)

In the early 1900s, when Sir William Osler was teaching internal medicine, his field was in a descriptive stage, with physicians still working to define the boundaries of the disease entities they were attempting to treat. He cautioned practitioners to exercise care in reaching diagnostic conclusions and to consider carefully the pragmatic relationships between diagnosis, prognosis, and treatment. Approximately 100 years later, psychiatry is in a similar position, as researchers struggle to demarcate disorder from health and disorders from one another. I suggest that a closer consideration of the provisional nature of psychiatric diagnosis and the uncertain way it maps onto notions of validity may help to understand the challenges involved with neuroimaging and psychiatric diagnosis.

## DIAGNOSTIC CATEGORIES AND THE CONTINUUM PROBLEM

The authors of this target article (Farah and Gillihan 2012) suggest that “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” (32). They go on to note that there are limitations to neuroimaging related to the current psychiatric diagnostic categories themselves and briefly acknowledge that the existence of categories per se has been questioned. These ideas warrant further attention; in particular, there are assumptions underlying the identification of “patients with that diagnosis” in the first place that deserve exploration.

Diagnostic categories are concepts, used to organize clinical experience and make inferences about prognosis and predictions about treatment (Kendell and Jablensky 2003). From the time of Robins and Guze in the 1970s, many researchers in this field have assumed that psychiatric disorders are distinct entities: distinct in the sense of both “normal” being distinct from “disorder,” and “disease A” being distinct from “disease B.” As some aspects of the DSM-5 development process implicitly recognize, however, psychiatric disorders may lack naturally clear boundaries and instead exist on a continuum, complicating any attempt to find something like a “brain signature” specific to a particular diagnosis.

Psychiatric researchers have recognized this continuum problem for years, independent of neuroimaging research, simply on the basis of clinical observation and measurement. For example: “major depression—as articulated by DSM-IV—may be a diagnostic convention imposed on a continuum of depressive symptoms of varying severity and duration” (Kendler and Gardner 1998, 172), as demonstrated by studies of depressive symptoms in a population

Address correspondence to Carl E. Fisher, MD, Columbia University, The New York State Psychiatric Institute, Unit 90, 1051 Riverside Drive, New York, NY 10032, USA. E-mail: carl.e.fisher@gmail.com