Neurobiological measures to classify ADHD: a critical appraisal

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Published online: 26 April 2014
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“We need to get rid of the uncertainty of psychiatric diagnoses. We should instead use a biological test, based on—for instance—brain activation or blood levels. Using such tests, we will be able to objectively determine whether someone suffers from attention-deficit/hyperactivity disorder (ADHD) or from psychosis. That way, the problem of over- and under-diagnosing in psychiatry will be solved. In addition, we will know for certain whether treatment—medication, therapies, or a diet—will be effective” (translation of the first paragraph of the article ‘The ADHD brain can not be known’ [Het ADHD brein laat zich niet kennen] written by S. Voormolen and published in a leading Dutch newspaper NRC [Nieuwe Rotterdamse Courant], 30 November 2014). The article discusses the clinical implications of the recent study by Mazaheri et al. [13], who examined oscillatory changes in theta, alpha, and beta EEG bands in 57 adolescents (34 with ADHD) performing a cued flanker task. Adolescents with ADHD showed, on average, weaker functional connectivity between frontal theta and posterior alpha, suggesting a top-down impairment of control. In addition, there were some specific differences in underlying neuronal activation

patterns between children with ADHD-predominantly inattentive (ADHD-PI) and children with ADHD-combined (ADHD-C) subtypes, with the ADHD-PI children showing less post-cue alpha suppression at the electrode contralateral to the cued response hand (suggesting diminished processing of the cue in the visual cortex) and the ADHD-C children showing less beta suppression at the electrode contralateral to the cued response hand (suggesting poor motor planning). Mazaheri and colleagues concluded that “task-induced changes in EEG oscillations provide an objective measure, which in conjunction with other sources of information might help distinguish between ADHD subtypes and therefore aid in diagnoses and evaluation of treatment.” At first glance, these results, although interesting, are not particularly novel. There have been earlier reports of differences in neuropsychological or brain imaging findings between ADHD and control subjects, or between subjects with different ADHD subtypes (for example, [14, 18, 19]). Why then, did this specific article prompt the publication of a provocative article in a leading national newspaper? Perhaps it was the first sentence of the abstract that spurred popular interest—“a neurobiological-based classification of ADHD subtypes has thus far remained elusive.” Mazaheri and colleagues apparently think that it would be better to classify ADHD on the basis of neurobiological markers instead of the current methods based on informant report and clinical evaluation of behavior. Indeed, many investigators have expressed the hope that biological markers will be included as diagnostic criteria in the DSM [11, 15].

Mazaheri and colleagues are not alone in searching for a more objective method for diagnosing mental illnesses, as illustrated by the numerous studies that have attempted to dissociate cases from controls using classification algorithms based on neuropsychological measures [7, 12, 17],

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brain morphology measures (for example [2, 3, 9, 17]), brain activation measures (for example, [2, 10, 21]), and/or molecular genetic markers. In a few studies, sensitivity and specificity were modest to good, with about 80 % of subjects being correctly classified. However, methodological constraints strongly limit any generalization of findings beyond such specialized studies [2]. The study by Ecker et al. [9] is often cited as supporting the view that a high level of accuracy in classification can be achieved by using structural brain imaging measures and advanced machine learning algorithms (Support Vector Machines). In age- and sex-matched patients with autism spectrum disorders (ASD) and controls, the best discrimination achieved for each pair was with a sensitivity of 88 % and specificity of 86 %. However, as the authors stated, the results of the classification algorithm varied substantially between pairs. That is, no overall classification algorithm could be derived that could differentiate all ASD patients from controls with acceptable sensitivity and specificity. In other words, the brain phenotype of children with ASD is highly variable, and this is possibly also true of typically developing children.

While these results are undoubtedly exciting scientifically, it is unlikely that neurobiological measures will be soon used in clinical practice. Moreover, they raise a number of questions. In view of the large heterogeneity within and between mental disorders at both the clinical/phenotypic and neurobiological level, what is the gain in diagnostically classifying a behaviorally defined syndrome on the basis of neurobiological measures? An often-heard criticism of current psychiatric practice is that it relies too much on subjective information/perception, which makes it difficult to establish a clear diagnosis when informant rating or information is contradictory, which could lead to over- or under-diagnosis. The availability of objective measures in addition to or, as a more extreme view, a substitute for, current clinical procedures would undoubtedly be helpful in these instances. Moreover, it could also aid in the more complex problem of establishing a differential diagnosis—not so much if the individual suffers from a mental disorder, but from which mental disorder. Yes, a clinician's life would be much easier if we could simply obtain a brain scan of patients and receive a clear-cut answer as to which disorder(s) the patient suffers from. As unlikely as this may sound, we should not forget that over the last 20 years the research community expected and hoped to be able to define mental disorders reliably on the basis of genetic, neurobiological, and neuropsychological information [15]. However, the substantial behavioral and neuropsychological comorbidity between disorders has considerably tempered this expectation.

In fact, diagnostic classifiers based on imaging or neuropsychological measures are a clear example of circular

The circular reasoning of 'diagnostic' MRI

Fig. 1 The circular reasoning of 'diagnostic' MRI

reasoning by trying to predict a DSM category based on group differences, which are based on DSM categories to begin with (Fig. 1). Even if a classification algorithm is based on clear-cut cases and controls (where the clinician is, for instance, 99 % certain of the diagnosis, or its absence), it is highly unlikely that it can resolve the diagnostic ambiguity of less clear-cut cases. Even if it could, would it be meaningful? If we merely re-define behavioral diagnostic criteria in biological terms, is this more reliable or "real" than a behavioral classification? In fact, any deviation from 100 % correctly classified cases means that classification based on behavior alone is in fact more reliable. In essence, the brain does not function categorically: distinguishing between impaired and unimpaired, patient or non-patient, disorder X or Y on the basis of MRI/EEG measures will be just as difficult as it is on the basis of questionnaire ratings. For this reason, we think that it will prove fruitless to ascribe MRI/EEG measures a diagnostic function in the *DSM syndrome classification*. This approach ignores the large neurobiological heterogeneity within disorders and the behavioral and neurobiological overlap between disorders.

An interesting question is whether brain imaging (structural or functional) and neuropsychological testing without imaging measures are of the same clinical/diagnostic value. Neuropsychological testing is in some ways decades ahead of task-based functional MRI: more studies have been performed, which have shown that (1) ADHD is robustly—albeit usually not strongly—associated with impairments in a wide range of higher-order and more basic functions [5], (2) there are large differences in the neuropsychological impairments of ADHD patients, with the presence of neuropsychological problems not necessarily meaning that the child will develop ADHD [20], and (3) none of these dysfunctions are unique to ADHD and are also found in other disorders [1, 6, 16]. In other words, to date no study has succeeded in distinguishing patients with

ADHD from healthy controls on the basis of neuropsychological parameters, let alone in distinguishing ADHD patients from psychiatric controls. Why then are expectations so high for imaging measures? Is it the belief that by directly ‘tapping into’ the brain, we come to the essence of the disorder? Brain imaging cannot diagnose impairment; it cannot indicate to what extent a child will experience problems at school or at home; it does not reflect the complexity of environmental risk and protective factors that may exacerbate or ameliorate the individual child’s ADHD symptoms. Psychiatric diagnostic practice is—and will always be—inherently complex, because it reflects the multiple pathways that interact to give rise to a disorder.

Is there then no future for brain imaging in clinical practice? There probably is, but then the emphasis needs to change from using such investigations to classify psychiatric disorders to using them to explain why these disorders occur. Neurobiological measures, such as brain imaging, can be used to examine possible neurobiological factors that may (have) contribute(d) to the development of the disorder in a given individual (for an elaborate discussion, see [4, 11]). This information might provide treatment targets and be used to monitor the effect of treatment, just as neuropsychological assessments are used in ADHD diagnostic practice. Many children are now routinely screened for overall intellectual ability and for weaknesses in specific cognitive abilities, such as response inhibition, working memory, sustained attention, etc. This information can be used by parents and teachers to modify the child’s environment so as to minimize the burden of the disorder to the child and its environment and to maximize the child’s ability to learn. Indeed, specific treatments to ameliorate specific neuropsychological weaknesses are continually being developed. In a similar manner, brain imaging can be used to detect a reduced activation and/or structural integrity of certain brain networks known to be associated with ADHD in certain patients, so that targeted treatments can be developed. To do so, however, the target of neuroimaging research needs to focus not on testing the “neuroimaging correlates” of behavioral categories (the uneasy leitmotiv in imaging research reports) but on addressing “behavioral correlates” or patterns associated with dysfunctions in particular brain networks [8]. Imaging, and neurobiological research in general, can be used for more than merely reiterating behavioral categories. However, the ability of neuroscience to contribute to our understanding of mental disorders has paradoxically been reduced by the continued division of syndromes into ever more categories, as occurs with each new edition of the DSM [10].

In conclusion, we do not believe that neuropsychology or neuroimaging can be used to achieve a neurobiological-based classification of attention-deficit/hyperactivity

disorder (ADHD) that obviates the need for behavioral assessment. The lack of sensitivity and specificity of these measures when comparing ADHD patients and (psychiatric) controls prevents their use for diagnostic purposes. In addition, these measures do not reflect the complexity of interacting individual and environmental factors that give rise to a disorder, nor do they circumvent the often-difficult diagnostic process when conflicting information and data are available. Why do investigators want to use these measures to replicate DSM-based, behavioral categories? As long as the DSM (or any other equivalent classification system) remains the gold standard in clinical practice, using a neurobiologically based classification is pointless and uninformative. Instead, neurobiological investigations can help us gain a better understanding of the biological vulnerabilities that may underlie ADHD in a specific patient or that may moderate the response to treatment thereby contributing to better and more effective treatment.

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