Predictive Neurofunctional Markers of Attention-Deficit/Hyperactivity Disorder Based on Pattern Classification of Temporal Processing

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Objective: Attention-deficit/hyperactivity disorder (ADHD) is currently diagnosed on the basis of subjective measures, despite evidence for multi-systemic structural and neurofunctional deficits. A consistently observed neurofunctional deficit is in fine-temporal discrimination (TD). The aim of this proof-of-concept study was to examine the feasibility of distinguishing patients with ADHD from controls using multivariate pattern recognition analyses of functional magnetic resonance imaging (fMRI) data of TD. **Method:** A total of 20 medication-naive adolescent male patients with ADHD and 20 age-matched healthy controls underwent fMRI while performing a TD task. The fMRI data were analyzed with Gaussian process classifiers to predict individual ADHD diagnosis based on brain activation patterns. **Results:** The pattern of brain activation correctly classified up to 80% of patients and 70% of controls, achieving an overall classification accuracy of 75%. The distributed activation networks with the highest delineation between patients and controls corresponded to a distributed network of brain regions involved in TD and typically compromised in ADHD, including inferior and dorsolateral prefrontal, insula, and parietal cortices, and the basal ganglia, anterior cingulate, and cerebellum. These regions overlapped with areas of reduced activation in patients with ADHD relative to controls in a univariate analysis, suggesting that these are dysfunctional regions. **Conclusions:** We show evidence that pattern recognition analyses combined with fMRI using a disorder-sensitive task such as timing have potential in providing objective diagnostic neuroimaging biomarkers of ADHD. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(5):569–578. **Key Words:** ADHD, fMRI, Gaussian process classifier, time discrimination

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common child psychiatric disorders, defined by age-inappropriate problems with inattention, impulsivity, and hyperactivity.[1] Children with ADHD are impaired in executive functions (EF) and in their underlying fronto-striato-parietal and fronto-cerebellar networks.[2-5] More recent evidence shows that ADHD is also consistently associated with temporal processing deficits,[6-9] most prominently in fine-temporal discrimination (TD), that is, the discrimination of intervals that differ by milliseconds,[6,7,9,10] shown to be the most discriminative measure for persons with ADHD relative to controls among disorder-relevant tasks.[7] Furthermore, functional magnetic resonance imaging (fMRI) studies show reduced activation in key inferior frontal, striatal, parietal and cerebellar time perception areas relative to controls during TD performance.[6,8,11]

Despite consistent evidence for brain structure and function deficits, currently ADHD is diagnosed solely on the basis of subjective clinical and rating measures, which can lead to diagnostic variability among clinicians, cultures, and countries.[12] Sensitivity of classification of children with ADHD with clinical measures based on the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition*


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(*DSM-IV*) criteria has been shown to be 70% to 90%[13]; thus misdiagnoses are approximately 10% to 30%. It is therefore highly desirable to develop additional diagnostic methods that rely on objectively measurable neuroimaging data. Attempts to find individual objective neuroimaging biomarkers for ADHD, however, have been limited by the use of univariate group statistics,[2,8] which have shown small to moderate effect sizes,[4] and which usually show extensive group overlap even for the regions/voxels exhibiting the most pronounced differences. Therefore such methods are unlikely to satisfactorily discriminate patients from controls at the individual subject level.

Recently, multivariate pattern analyses have been applied to neuroimaging data with 2 main advantages. First, they are sensitive to spatially distributed, subtle interactions in the brain. Second, and most important, they are able to make individual classifications, thereby yielding results with a potentially high level of clinical translation. Such multivariate methods have been shown to provide accurate sensitive and specific diagnostic indicators for individual patients with other pathologic conditions, such as autism, depression, and Alzheimer's disease.[14] Gaussian process classifiers (GPCs) are kernel classifiers used in machine learning, similar to support vector machines (SVMs), which have excellent performance for fMRI.[15] The main advantage of GPCs over alternative methods such as SVMs is that they provide probabilistic class predictions, thereby accurately quantifying the predictive confidence assigned to each data point, which is useful to adjust predictions to accommodate unbalanced diagnostic settings or variations in disease prevalence, which is crucial for clinical studies as disorders are typically less prevalent than healthy control populations.[16]

To date, however, few imaging studies have used multivariate analyses to classify patients with ADHD. A recent competition to apply multivariate methods on a multicenter resting state functional imaging dataset of 285 children with ADHD and 491 controls, together with anatomical and phenotype data, elicited a range of classification approaches (ADHD-200 Consortium; available at http://fcon_1000.projects.nitrc.org/indi/adhd200/).[17,18] Accuracies derived by internal cross-validation ranged from 55% to 78%, with lower external validation accuracies (61% for the winning team[17]) because of lack of standardization between sites, resulting in multiple confounds including missing data and site-specific differences in behavioral measurements, imaging acquisition, processing, protocols, and scanner quality. Furthermore, the competition dataset was highly unbalanced, with more controls than patients with ADHD (63% and 37%, respectively), biasing findings toward specificity. Balanced accuracy, calculated as the mean of sensitivity and specificity,[19] for the winning team was only 57.5%. In addition, the competition scoring rewarded specificity more than sensitivity, so that all teams reported high specificity but poor sensitivity (21% for the winning team).

The aims of the present study were therefore as follows: to provide proof of concept regarding the potential of the application of GPCs to fMRI data during TD as a tool for identifying distributed neurofunctional patterns that could provide individual diagnostic classification of ADHD; to replicate our previous findings of reduced activation in medication-naive patients with ADHD in inferior and medial frontal and striatal regions during TD[6,11] in another medication-naive ADHD sample; and to assess to what extent multivariate and traditional univariate methods overlap. The functional neuroanatomy of time discrimination was selected for the following reasons: TD is consistently impaired in patients with ADHD[6,9]; patients with ADHD show consistent neurofunctional abnormalities in key regions of TD, including the inferior frontal (IFC) and dorsolateral prefrontal cortices (DLPFC), supplementary motor area (SMA), anterior cingulate cortex (ACC), basal ganglia, and cerebellum[6,8,9,11,20]; and the reduced brain activation in patients with ADHD during TD performance is no longer observed after a single dose of methylphenidate,[6] suggesting that these reductions in activation are core ADHD mechanisms that are targeted with psychostimulant treatment.

For these purposes, and given the evidence for long-term effects on stimulant medication on brain structure and function,[3,5,8] a total of 20 medication-naive boys with ADHD and 20 healthy control boys underwent scanning during an fMRI TD task, and both univariate and GPC analyses were applied to the data.

METHOD

Participants

Twenty-eight medication-naive, right-handed boys between 10 and 17 years of age, with a clinical diagnosis of inattentive/hyperactive-impulsive combined ADHD as assessed using the standardized Maudsley diagnostic