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Using Brain-Based Cognitive Measures to Support Clinical Decisions in ADHD

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Measures of cognition support diagnostic and treatment decisions in attention deficit hyperactivity disorder. We used an integrative neuroscience framework to assess cognition and associated brain-function correlates in large attention deficit hyperactivity disorder and healthy groups. Matched groups of 175 attention deficit hyperactivity disorder children/adolescents and 175 healthy control subjects were assessed clinically, with the touch screen-based cognitive assessment battery "IntegNeuro" (Brain Resource Ltd., Sydney, Australia) and the "LabNeuro" (Brain Resource Ltd., Sydney, Australia) platform for psychophysiologic recordings of brain function and body arousal. IntegNeuro continuous performance task measures of sustained attention classified 68% of attention deficit hyperactivity disorder patients with 76% specificity, consistent with previous reports. Our additional cognitive measures of impulsivity, intrusive errors, inhibition, and response variability improved sensitivity to 88%, and specificity to 91%. Positive predictive power was 96%, and negative predictive power, 88%. These metrics were stable across attention deficit hyperactivity disorder subtypes and age. Consistent with their brain-based validity, cognitive measures were correlated with corresponding brain-function and body-arousal measures. We propose a combination of candidate cognitive "markers" that define a signature for attention deficit hyperactivity disorder: "sustained attention," "impulsivity," "inhibition," "intrusions," and "response variability." These markers offer a frame of reference to support diagnostic and treatment decisions, and an objective benchmark for monitoring outcomes of interventions.

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Introduction

Attention deficit hyperactivity disorder is the most common psychiatric disorder in patients aged 6-17 years, with prevalence estimates ranging from 2-16%, or in other words, with at least one patient in every classroom. Its economic impact is substantial, affecting society and the individual's family [1]. A diagnosis of attention deficit hyperactivity disorder is currently based on a ''classic triad'' of signs: inattention and/or hyperactivity with impulsivity [2].

The addition of objective measures may enhance the reliability of clinical decisions, and provide concrete benchmarks for monitoring progress. These benchmarks offer the additional benefit of engaging both patient and family, and providing them with explicit feedback [3]. In the move toward a fifth edition of the Diagnostic and Statistical Manual for Mental Disorders, the importance of objective measures linked to underlying brain function has also been highlighted [4,5]. Assessments of cognition provide such measures. In this regard, cognition encompasses the aspects of thinking that allow for attention, memory, and planning

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(or executive function), and that are linked to the interaction of cortical with subcortical brain systems [6]. Objective measures of cognition and brain-function may provide further insights into the pathophysiologic processes underlying the overt signs of attention deficit hyperactivity disorder.

Although a consensus is emerging that the signs of attention deficit hyperactivity disorder reflect disturbances in cognition and underlying brain function [7], no similar theoretical consensus exists regarding their cause. We propose an ''integrative neuroscience'' model that draws on the theories that emphasize the involvement of multiple and dynamic brain pathways in the development of attention deficit hyperactivity disorder, and the corresponding maturational context [8-11]. In this model, attention deficit hyperactivity disorder is hypothesized to exhibit a core disturbance in sustained attention, a ''thinking'' process vital to maintaining focus and concentration over time [6]. Without the capacity to sustain attention, nonsignificant or irrelevant information may intrude on thinking. Moreover, the capacity to react effectively to significant stimuli, and withhold reactions to nonsignificant stimuli, may be diminished, producing impulsive responses. These three interrelated processes are proposed to underlie the triad of inattention, hyperactivity, and impulsivity signs. They draw on the evidence to date for cognitive disturbances in attention deficit hyperactivity disorder [12]. In addition, the combination of poor attention, intrusions, and impulsive responding is likely to produce inconsistent responses to tasks, as reflected in an excessive variability of response times. These thinking processes implicate the cortical brain systems and their interactions with the major subcortical systems, i.e., striatal (basal ganglia) and limbic [6]. These systems are modulated by monoamines such as dopamine and norepinephrine which are also linked to attention deficit hyperactivity disorder.

The aims of this study were to identify core cognitive indicators of attention deficit hyperactivity disorder and its triad of signs, along with the brain correlates of these cognitive indicators. To date, the cognitive assessment of attention deficit hyperactivity disorder has focused in particular on single cognitive tasks, which have robust sensitivity but are not designed for specificity [13]. We used a cognitive battery encompassing multiple domains of cognition. Our first step involved identifying the cognitive measures that distinguished patients with attention deficit hyperactivity disorder from healthy control subjects. Secondly, we identified which measures formed core composites, taking intercorrelations between them into account. Third, using an integrative theoretical framework, the brain-function correlates of cognitive measures were assessed. It was predicted that core composites of cognition would provide a sensitive and specific differentiation of attention deficit hyperactivity disorder, and that these composites would relate to brain function.

Methods

Participants

One hundred and seventy-five children and adolescents with attention deficit hyperactivity disorder (12.29 ± 3.08 years S.D.; range, 6-18 years; 40 girls), and 175 age-matched and sex-matched healthy control subjects (12.24 ± 3.10 years S.D.; range, 6-18 years; 40 girls), were recruited from metropolitan regions as part of the standardized Brain Resource International Database [14,15]. Attention deficit hyperactivity disorder and control participants were also matched on grade at school (patients with attention deficit hyperactivity disorder, 6.8 ± 3.1 S.D.; control subjects, 7.0 ± 3.0 S.D.) and intelligence quotient, as estimated by the Spot the Word Test of premorbid intelligence [16]. All participants spoke English. In this sample, 63% were Caucasian, and the rest were Asian.

A primary diagnosis of attention deficit hyperactivity disorder was based on Diagnostic and Statistical Manual for Mental Disorders-IV criteria, and was determined via clinical interview by the referring pediatrician (authors S.D.C., M.R.K., or C.L.). The interrater reliability of diagnoses was high (κ, $r = 0.91$). In addition to clinical diagnosis, participants with attention deficit hyperactivity disorder exhibited a clinically meaningful severity of signs on the Conner's Parent Rating Scales: Revised-Long Version (t-scores ≥65 for Inattentive or Hyperactivity/Impulsivity subscales). Ratings for all scales are provided in Table 1.

One hundred and three patients with attention deficit hyperactivity disorder (24 girls) were of the combined subtype, 66 (15 girls) were of the inattentive subtype, and six (one girl) were of the hyperactive/impulsive subtype. Comorbid diagnoses (oppositional defiant disorder, learning disorder, conduct disorder, depression, and anxiety) were accepted, but were categorized into broad subgroups, wherein 11% exhibited internalizing comorbidities, 35% exhibited externalizing comorbidities, and 12% exhibited learning disorder comorbidities.

Brain Resource web-based screening was used to assess demographic details and exclusion criteria. These criteria for both groups included a personal or family history of an Axis I psychiatric disorder (other than those listed above for attention deficit hyperactivity disorder participants), a physical brain injury, a neurologic disorder, a genetic disorder or other serious medical condition, or a personal history of drug or alcohol addiction. Axis I disorders were also screened using the Somatic and Psychological Health Report [17], which identifies the signs of these major psychiatric disorders. All participants were included only if their estimated intelligence quotient was ≥80, as assessed by the Spot the Word Test estimate of premorbid intelligence [16].

One hundred and fifteen participants with attention deficit hyperactivity disorder were medication-naive, and 60 were withdrawn from stimulant medication at least 2 days before testing. Control participants were not medicated, and were free of a history of medication that might affect cognition. All participants were asked to refrain from drinking caffeinated beverages and smoking cigarettes for 2 hours before a study session. Each participant

Table 1. Means for Conner's Parent Rating Scale-Revised

Conner's Parent Rating Scale-Revised: L Measures	Mean Rating	
	Mean	S.D.
Global index	75.21	10.89
Diagnostic and Statistical Manual for Mental Disorders-IV: Inattentive	71.70	9.64
Diagnostic and Statistical Manual for Mental Disorders-IV: Hyperactive-Impulsive	74.17	12.64
Diagnostic and Statistical Manual for Mental Disorders-IV: Total	75.14	10.24
Oppositional	70.60	12.59
Cognitive Problems/Inattentive	71.58	9.41
Hyperactivity	74.21	13.65
Anxious-Shy	59.53	13.67
Perfectionism	53.05	10.26
Social Problems	62.57	14.47
Psychosomatic	63.08	15.73
Attention Deficit Hyperactivity Disorder Index	73.26	9.29
Restless-Impulsive	74.46	10.64
Emotional Lability	68.55	14.11

Table 2. Individual cognitive tasks making up the IntegNeuro battery*

Task	Measures	Description
Continuous Performance Test	Accuracy (total, false-positive, and false-negative errors), RT, variability of RT	Sustained attention to series of letters (D, C, G, or T). Identify when same letter is repeated ('1-back'). Requires working memory updating.
Go-NoGo	Accuracy (total, false-positive, and false-negative errors), RT, variability of RT	Press response pad as quickly as possible to "Go" (green) trials, and withhold in "NoGo" (red) trials. Assessing impulsivity vs inhibition.
Switching of Attention	Accuracy (switching errors), completion time, connection time	Connect a sequence of alternating numbers and letters; assesses information-processing efficiency.
Executive Maze	Accuracy (total, overrun errors), completion time	Discover (by trial and error) a maze path; reflecting planning, monitoring feedback, and error correction.
Verbal Interference	Accuracy (errors), RT	Respond to name of color word (ignore color) and then color word (ignore name); assessing supression of automatic responses.
Verbal Memory Recall	Accuracy (recall and Intrusion errors), learning rate	Learn and then recall lists of 12 words; assesses learning, memory recall, and recognition.
Span of Visual Memory	Accuracy (total recall, and maximum recall span)	Repeat a sequence of visual blocks; assessing visual working memory.
Digit Span	Accuracy (total recall, and maximum recall span)	Repeat a series of digits in forward and backward order; assessing working memory.
Choice Reaction Time	RT	Respond to one of four circles as they light up; assesses decision-related reaction time. Assessing sensorimotor coordination and speed.
Word Generation	Accuracy (number of words, number of animal names)	Generate as many words (starting with F, A, and S) and animal names as possible in 60 s, assessing verbal and semantic fluency.
Motor Tapping	Number and variability of taps	Tapping index finger as fast as possible for 60 s; assessing sensorimotor response speed.
Emotion Identification	Accuracy, RT	Identify emotions revealed in facial expressions (anger, disgust, fear, sadness, or happiness).

* IntegNeuro also provides an estimate of premorbid IQ, using the Spot the Word task. Recent versions include Emotion Identification and Emotion Recognition tasks, that were not used in the present study, but have been in independent studies (26, 48).

Abbreviations:
CPT = Continuous performance test
RT = Reaction time
TOVA = Test of variables of attention

provided written, informed consent or assent to participate in the research. The institutional ethics review board at each institution provided approval.

Cognitive Assessment: IntegNeuro

All participants completed the standardized Brain Resource cognition assessment, "IntegNeuro," with demonstrated reliability, validity, and established norms for patients aged 6 to over 80 years [16,18,19]. Table 2 summarizes the individual tasks comprising the IntegNeuro battery. These tasks include a Continuous Performance Test, equivalent to the Test of Variables of Attention [20] and Conner's Continuous Performance Test [21] used commonly in assessments of attention deficit hyperactivity disorder.

IntegNeuro was used to assess multiple domains of cognition in the same individual subjects. Although the Continuous Performance Test was demonstrated to discriminate individuals with attention deficit hyperactivity disorder from healthy control subjects at moderate to high levels of sensitivity (60-80%), its specificity and predictive power have been more contentious [13]. There is evidence that when a Continuous Performance Test is used with additional measures, such as those assessing impulsivity, its specificity rises substantially [22]. A similar picture emerges for other individual cognitive tasks that assess selective attention, impulsivity, working memory, and executive functioning in attention deficit hyperactivity disorder [23-25].

Measures of accuracy and reaction time were extracted from the IntegNeuro cognitive tasks. Accuracy included false-positive and false-negative errors (Table 2).

Brain-Function Assessment: LabNeuro

Using the standardized Brain Resource methodology, LabNeuro, with a Neuroscan Compumedics Synamps system (Compumedics Ltd., Victoria, Australia), we undertook electroencephalogram recordings in the same subjects. These recordings were performed during resting baseline and during cognitive tasks, and were demonstrated in previous studies to differentiate attention deficit hyperactivity disorder from healthy subjects.

Resting A 2-minute recording was performed while the patient sat quietly with eyes closed, followed by a second 2-minute recording with the patient's eyes open [26]. These measures provided an index of brain activity. Brain activity was quantified by electroencephalogram power in δ, θ, α, and β bands, using previously established procedures for attention deficit hyperactivity disorder [27]. Simultaneous measures of heart rate were also used to assess related body (autonomic) arousal, quantified in terms of beats per minute.

Continuous Performance Task A task equivalent to that used in the IntegNeuro cognitive assessment was used to elicit stimulus-locked changes in an electroencephalogram (or event-related potentials) [28]. The primary event-related potential component was P450, elicited within 350-600 ms after a stimulus. The name P450 refers to a positive deflection in the event-related potential occuring around 450 ms after stimulus.

Go-Nogo "Impulsivity" Task We used a Go-NoGo task equivalent to that used in the IntegNeuro cognitive battery. This task assesses the capacity to generate automatic reactions to relevant stimuli, and to withdraw responses to irrelevant stimuli in the environment. The resulting event-related potentials were associated with impulsivity [29]. In this task, we focused on the previously established N200 event-related potential [30]. The name N200 refers to a negative deflection in the event-related potential occuring around 200 ms after stimulus.

Data Reduction

We first took into account those variations in measures attributable to age and sex. A "peer regression modeling" technique was used, based

Tasks Assessing Equivalent Construct	References for Further Details
Conner's CPT, TOVA	16,18,19,42-47 (for use in other clinical groups)
	48,49 (for use in other clinical groups)
Trails A and B (paper and pencil)	16,18,19,42-47 (for use in other clinical groups)
Austin Maze	16,18,19,42-47 (for use in other clinical groups)
Stroop	16,18,19,42-47 (for use in other clinical groups)
Rey Auditory Verbal Learning Test, California Verbal Learning Test	16,18,19,42-47 (for use in other clinical groups)
Corsi blocks	16,18,19,42-47 (for use in other clinical groups) 16,18,19,42-47 (for use in other clinical groups)
	16,18,19,42-47 (for use in other clinical groups)
Controlled Oral Word Test	16,18,19,42-47 (for use in other clinical groups)
	16,18,19,42-47 (for use in other clinical groups)
Penn Emotion Test	49,50 (for further psychometric details), 29 (for previous use in attention deficit hyperactivity disorder)

on well-established psychometric principles. Age was modeled using both linear and logarithmic terms, and sex was modeled using a linear term. The expected score for each measure on each task was subtracted from the participant's actual score, and the resulting difference was divided by the standard error of the estimate of the regression equation. The resulting standardized score may be interpreted in a similar way to traditional *z*-scores. In line with traditional interpretations, a score of 1.0 or below was considered sufficiently impaired to be flagged for clinical attention, and a score of 2.0 or below was considered clinically significant. These standardized scores were used in statistical analyses.

Data Analyses

Attention Deficit Hyperactivity Disorder Vs Healthy Control Differences Analysis of variance was used to determine which IntegNeuro cognitive measures revealed significant differences between the patients with attention deficit hyperactivity disorder and the healthy control group. Given the number of measures, we addressed the issue of multiple comparisons by using an extremely stringent threshold of $P < 0.001$. With the sample size used in this study, the statistical power to identify group differences of 0.5 S.D. or greater at this significance level was 98%.

To identify the core composites of cognition that distinguished patients with attention deficit hyperactivity disorder from control subjects, we identified which of these measures represented highly correlated clusters.

Sensitivity, Specificity, and Predictive Power for Attention Deficit Hyperactivity Disorder For those core composites that differentiated patients with attention deficit hyperactivity disorder from the healthy control group, we determined the degree of severity of difficulty in each patient with attention deficit hyperactivity disorder. Based on previous research [24], impairment was defined as ≤1.0 S.D. below the mean. We computed sensitivity (percent with attention deficit hyperactivity disorder correctly classified) and specificity (percent of control subjects correctly classified) for each marker. We also computed the positive predictive power (the probability of those who were impaired on measures and who were diagnosed with attention deficit hyperactivity disorder) and negative predictive power (the probability of those who tested normal on measures and who were confirmed as controls).

Sensitivity, specificity, and predictive power were progressively recomputed for the cumulative combination of composites. To confirm the optimal combination of measures to classify attention deficit hyperactivity disorder, a discriminant function analysis was undertaken.

We then recomputed these metrics using a more stringent severity threshold for determining impairment on each measure, at ≤2.0 S.D. below the mean.

Attention Deficit Hyperactivity Disorder Subtypes and Comorbidity We examined whether the combination of composite measures resulting from the above analyses varied according to diagnostic subtype of attention deficit hyperactivity disorder, i.e., inattentive, hyperactive/impulsive, or combined. We also examined whether these composites would vary with allied (or comorbid) conditions.

Brain-Function Correlates Analysis of variance was used to determine which LabNeuro measures of brain and body function revealed significant differences between patients with attention deficit hyperactivity disorder and healthy control groups at the stringent threshold of $P < 0.001$.

Pearson correlation analyses were then used to determine which cognitive composites that distinguished patients with attention deficit

hyperactivity disorder from control subjects also produced correlates with brain-body measures.

Results

Differences in Patients with Attention Deficit Hyperactivity Disorder and Healthy Control Subjects

Table 3 lists the individual IntegNeuro cognitive measures that distinguished patients with attention deficit hyperactivity disorder from the healthy control group at $P < 0.001$. Based on an intercorrelation threshold of >0.80, the results indicate that these individual cognitive measures can be grouped into four composites, representing candidate cognitive ''markers'' as follows:

(1) Sustained Attention: Errors and reaction time on the Continuous Performance Test (visual).
(2) Impulsivity: False-positive errors on the Continuous Performance Test and Go-NoGo tasks.
(3) Inhibition: Errors for part 1, and the difference in errors and reaction time for verbal interference part 1 (naming words) vs part 2 (naming colors).
(4) Intrusions: Errors of perseveration on the Switching of Attention task, Executive Maze overrun errors, and errors of intrusion on the Verbal Memory Recall task.
(5) Response Variability: Variability of reaction time on the Continuous Performance Test and Go-NoGo tasks.

These composites were identified as candidate markers for confirmatory investigation.

Sensitivity, Specificity, and Predictive Power for Attention Deficit Hyperactivity Disorder

Calculation of the sensitivity, specificity, and predictive power for these candidate cognitive markers was undertaken for Sustained Attention first, as the equivalent of previous assessments of attention deficit hyperactivity disorder using a Continuous Performance Test (Table 4). These metrics were then calculated for the addition of the Impulsivity, Intrusions, Inhibition, and Response Variability markers, over and above sustained attention, to determine if they added to the specificity and predictive power (Table 4).

Sustained Attention was the most sensitive and predictive marker, and individually classified 68% of participants with attention deficit hyperactivity disorder (Table 4). Each metric of sensitivity, specificity, and predictive power increased substantially with the addition of three cognitive markers, i.e., Impulsivity, Intrusions, and Response Variability (Table 4). Inhibition did not contribute over and above these three markers, but was impaired in attention deficit hyperactivity disorder, in addition to Impulsivity, Intrusions, or Response Variability, thereby providing further confidence in the presence of cognitive alterations. The increase in specificity and negative predictive power (91% and 88%, respectively) was consistent with the hypothesis that multiple testing would enhance the correct classification of healthy control subjects as well as patients with attention deficit hyperactivity disorder. These increases indicate that the inclusion of these markers provides additional information important in differentiating parts of the spectrum of attention deficit hyperactivity disorder.

There was only a small reduction in sensitivity, with an increase in specificity, when a highly stringent threshold of ≤ 2 S.D. was used for each candidate marker. At this threshold, the sensitivity was 84%, the specificity was 94%, the positive predictive power was 88%, and the negative predictive power was 95%. A confirmatory discriminant function analysis supported this separation, confirming the sensitivity and specificity for this combination of candidate markers.

Brain-Function Correlates

The task-related brain-function markers also provided convergent support for the candidate cognitive markers. Firstly, the measures of brain function distinguished patients with attention deficit hyperactivity disorder from the healthy control group at $P < 0.0001$, consistent with the view that these markers are brain correlates of cognitive measures (Table 5).

The brain-function measures revealed the following composites:

Electroencephalogram θ (brain arousal): A global increase in θ power in attention deficit hyperactivity disorder, relative to a significant decrease in β power (Table 5). This increase was particularly pronounced over medial frontocentral sites, which were averaged to form the composite for electroencephalogram θ, relative to β power.

Heart rate (body arousal): A corresponding reduction in mean heart rate, which was most pronounced in the

Table 3. IntegNeuro cognitive measures that significantly distinguished patients with attention deficit hyperactivity disorder from healthy control subjects at $P < 0.001$, and effect size of differences (η^2)

Composite and Contributing Tasks	F Value	Effect Size
Sustained Attention		
CPT total errors	53.18	0.15
CPT reaction time	17.89	0.06
Impulsivity		
CPT: false-positive errors	36.21	0.11
Go-NoGo: false-positive errors*	13.26	0.04
Intrusions		
Switching of Attention perseveration errors	23.57	0.07
Executive maze overrun errors	40.71	0.12
Verbal memory recall, errors of intrusion	19.39	0.06
Inhibition		
Verbal interference part 1 errors	7.32	0.02
Verbal interference part 2 − part 1 errors	7.25	0.02
Verbal interference part 2 − part 1 RT	10.63	0.03
Response Variability		
CPT: variability in reaction time	32.00	0.10
Go-NoGo variability in reaction time	39.49	0.11

* Falsely responding to a ''NoGo'' stimulus.

Abbreviation:
CPT = Continuous performance test
RT = Reaction time

Table 4. Summary of sensitivity, specificity, and predictive power for candidate cognitive markers of attention deficit hyperactivity disorder

Candidate Markers	Sensitivity	Specificity	Positive Predictive Power	Negative Predictive Power
Sustained Attention (composite of CPT errors and reaction time)	0.68	0.76	0.75	0.71
Impulsivity (composite of CPT and Go-NoGo false-positive errors)	0.88	0.91	0.96	0.88
Intrusions (composite of Switching of Attention connection time, maze overrun errors, and Verbal Recall errors of intrusion)				
Inhibition (composite of errors for verbal interference part 1 and difference in reaction time between parts 1 and 2)				
Response Variability (composite of variability of reaction time in CPT and Go-NoGo)				

Abbreviation:
CPT = Continuous performance test

executive maze task (contributing to the Intrusions marker from IntegNeuro).

Continuous Performance Test P450 event-related potential: A reduction in P450 elicited by updating the working memory in the visual Continuous Performance Test, which was particularly pronounced over parietal-occipital sites (Pz, P4, Oz, and O2). The event-related potentials data for these sites were averaged to form the Continuous Performance Test P450 event-related potential composite.

No-Go N200 event-related potential: A global enhancement in N200 to ''No-Go'' stimuli, consistent with impulsivity. This enhancement was especially pronounced across the medial frontal to parietal sites used to form the composite.

These brain-function measures were confirmed as significant correlates of the candidate cognitive markers (Table 6). Correlations were moderate, consistent with their ecological validity, i.e., with large numbers of subjects, it is expected that meaningful and highly significant correlations would be on the order of 0.2-0.3, reflecting the genuine magnitude of the relationship, rather than a somewhat inflated correlation because of the variance in smaller sample sizes.

Attention Deficit Hyperactivity Disorder Subtypes and Comorbidity

The values of sensitivity, specificity, and negative and positive predictive power did not differ by more than 3% when attention deficit hyperactivity disorder subtypes were examined. However, specific profiles of correlations between candidate markers and severity were evident, according to subtype:

Inattentive: The most significant correlations were between severity (indexed by Conner's Parent Rating Scale total score) and Response Variability ($r = -0.33$).

Hyperactivity/Impulsivity: The most significant associations were between severity (indexed by Conner's Parent Rating Scale total score) and both Impulsivity ($r = -0.21$) and Intrusions ($r = -0.25$).

For the combined markers, there was only a slight variation of ±2% in sensitivity according to age, with 88% sensitivity for older (aged 13-18 years) and 92% for younger (aged 8-12 years) patients with attention deficit hyperactivity disorder. There was equivalent sensitivity across markers for males (89%) and females (90%) with attention deficit hyperactivity disorder.

There were also no significant effects of comorbidity in analyses of covariance conducted for each candidate marker. Rather, comorbid conditions were distinguished by the several indicators, over and above the attention deficit hyperactivity disorder markers.

Learning Disorder In the 12% of participants with an allied learning disorder, this allied disorder was indicated by a relatively lower performance (of >1 S.D.) on verbal vs nonverbal tasks, consistent with the profile across Weschler tasks [31]. This differential was computed from a global average of verbal vs nonverbal tasks from the cognitive battery.

Externalizing Disorders: Conduct and Oppositional Defiance In males with conduct disorder in addition to attention deficit hyperactivity disorder, the NoGo Impulsivity event-related potential was particularly

Table 5. LabNeuro brain-function measures that significantly distinguished patients with attention deficit hyperactivity disorder from healthy control subjects at $P < 0.001$, and effect size of differences (η^2)

Brain-Function Measure	Contributing Regions	F Value	Effect Size
Continuous performance test			
450 event-related potential	Pz	11.56	0.04
	P4	13.88	0.05
	Oz	11.57	0.04
	O2	12.07	0.04
Go-NoGo			
NoGo N200 event-related potential	Fz	9.48	0.03
	Cz	9.24	0.03
	Pz	13.00	0.04
Brain arousal			
Electroencephalogram θ*	Fz	6.89	0.02
	Fcz	7.01	0.03
Body arousal			
Heart rate		23.05	0.07

* Electroencephalogram θ power relative to β power.

Table 6. Candidate cognitive markers and their correlates and effect size (Cohen's D estimate) in brain-function composites for attention deficit hyperactivity disorder*

Candidate Markers	Brain Function correlate	Correlation, *P* value	*P* Value	Effect Size
Sustained Attention	CPT P450 event-related potential	0.33	<0.0001	0.70
	Heart rate	0.28	0.001	0.60
Impulsivity	NoGo N200 event-related potential	0.25	0.002	0.50
	Electroencephalogram θ	0.21	0.008	0.45
Intrusions	CPT P450 event-related potential	0.23	0.006	0.48
	Heart Rate	0.20	0.016	0.40
Inhibition	Electroencephalogram θ	0.30	<0.0001	0.65
Response Variability	CPT P450 event-related potential	0.24	0.005	0.50
	NoGo N200 event-related potential	0.20	0.014	0.40
	Heart rate	0.36	<0.0001	0.80

* For consistency of interpretation, correlations are presented in a consistent direction such that positive associations reflect poorer performance on cognitive markers with poorer brain function and lower body arousal.

Abbreviation:
CPT = Continuous performance test

pronounced (and demonstrated an impairment of at least 1 S.D. in 90% of cases).

Internalizing Disorders: Anxiety and Depression The markers that distinguished anxiety and depression as allied conditions were beyond the scope of this study, and were reported elsewhere [29]. Anxiety in attention deficit hyperactivity disorder was associated with impairments in the early P120 event-related potential component, elicited around 120 ms poststimulus by negative facial emotion stimuli over occipitotemporal brain regions, consistent with a neural negativity bias.

Discussion

In this study, we used an integrative approach to identify candidate cognitive markers for attention deficit hyperactivity disorder that have a basis in brain-function correlates. These markers reflected difficulties in ''Sustained Attention'' (defined by Continuous Performance Test measures), ''Impulsivity'' (defined by false-positive errors), ''Intrusions'' (characterized by errors of intrusion from irrelevant information), ''Inhibition'' (lack of suppression of interfering information), and ''Response Variability'' (variability of reaction times across tests). This combination of cognitive measures from the IntegNeuro battery provided a highly robust classification of attention deficit hyperactivity disorder, with a sensitivity of 88%, a specificity of 91%, a positive predictive power of 96%, and a negative predictive power of 88%. Although these metrics were adequate for the Continuous Performance Test considered on its own, the inclusion of other measures provided maximal sensitivity, specificity, and predictive power.

These candidate cognitive markers were correlated with corresponding measures of brain function, providing initial support for their basis in biological processes. These findings indicate that brain-based cognitive markers may provide valuable support for clinical decisions in the diagnosis and treatment of attention deficit hyperactivity disorder and allied conditions. A simple touch-screen platform for assessing cognition may be readily implemented in the clinical setting.

Our findings that multiple measures provided maximal specificity as well as sensitivity for distinguishing attention deficit hyperactivity disorder are consistent with previous studies [13,32]. These findings reinforce the need to consider composite cognitive measures and integrative theoretical models [10,11,22].

The ''Sustained Attention'' marker provided the best single measure for the differentiation of attention deficit hyperactivity disorder versus healthy subjects. This domain reflects a general dysfunction in sustained attention or vigilance, consistent with previous evidence using the Continuous Performance Test [32,33]. The Impulsivity marker aligns with the notion that deficits in suppressing prepotent responses may be fundamental to attention deficit hyperactivity disorder [34], whereas the Intrusions marker reflects concomitant impairments in the control of attention and in incorporating important new information into memory [34]. Furthermore, the Inhibition marker aligns with the notion that deficits in inhibitory control may be fundamental to attention deficit hyperactivity disorder [34]. The Response Variability marker accords with evidence that abnormally high variability is characteristic of attention deficit hyperactivity disorder [33,35].

These findings provide support for an ''integrative neuroscience'' model that brings together theories of attention deficit hyperactivity disorder that focus on particular domains of function [8,9,12]. The Sustained Attention marker reflects disruptions to a ''thinking'' process that maintains focus and concentration on significant events in the environment [6]. Without the capacity to sustain attention, nonsignificant or irrelevant information may intrude on thinking, as reflected in the Intrusions marker. Moreover, the capacity to react effectively to significant stimuli, and to withhold reactions to nonsignificant stimuli, may be

diminished, producing impulsive responses, as captured by the Impulsivity marker. The poorer capacity to suppress irrelevant information (rather than focusing on relevant information) that defined the Inhibition marker complements the alterations captured by the Instrusions and Impulsivity markers. Individuals with attention deficit hyperactivity disorder tended to exhibit Inhibition impairments coupled with either Intrusions or Impulsivity, or both. These interrelated processes are proposed to underlie the triad of inattention, hyperactivity, and impulsivity signs, respectively. The combination of poor attention, intrusions, and impulsive responding is likely to account for the excessive variability of response captured by the Response Variability marker.

Correlations between these cognitive markers and related brain-function measures support the view that these thinking processes involve cortical brain systems and their interactions with the major subcortical systems, i.e., striatal (basal ganglia) and limbic [6]. The profile of attention deficit hyperactivity disorder disturbances in each of the brain-function measures was also consistent with previous reports. We observed excessive slow-wave electroencephalogram activity in attention deficit hyperactivity disorder, pronounced within the θ band. Excessive slow-wave neural activity was demonstrated previously to be sensitive in distinguishing patients with attention deficit hyperactivity disorder from healthy control subjects, and was associated with theories of altered brain maturation in this condition [36-39]. Similarly, the reduced P450 event-related potential for the Continuous Performance Test was consistent with studies focusing in detail on this measure [28]. The reduction in event-related potentials for NoGo stimuli was also evident in children with attention deficit hyperactivity disorder in previous research [40]. These disruptions to brain function also implicate monoamines such as dopamine and norepinephrine, which modulate the cortical-subcortical brain systems involved, and which were also linked to attention deficit hyperactivity disorder.

Research indicated that cognitive performance may vary with duration of previous stimulant use in attention deficit hyperactivity disorder [41]. This information was not collected for the unmedicated participants in this study. However, the lack of difference in cognitive function according to age may be considered an indirect indication that previous exposure to stimulants did not significantly affect performance, insofar as previous exposure may be longer for older vs younger children.

This study did not reveal variations in the signature of candidate markers across clinical subtypes, which may be attributable to the nature of the sample. Our sample primarily comprised inattentive and combined subtypes, which are the two most prevalent and most studied subtypes. Future studies would benefit from assessing more patients of the hyperactive-impulsive subtype.

Future research should examine the specificity of markers by including not only attention deficit hyperactivity disorder with comorbid conditions such as anxiety, conduct, and learning disorders, but also individuals with these disorders in the absence of attention deficit hyperactivity disorder. Research is also needed to provide convergent support for the comorbid conditions assessed in the present study, such as diagnosis by psychoeducational assessment to provide support for indicators of learning problems. In such studies, linkages between thinking and emotional alterations in attention deficit hyperactivity disorder, and their biological correlates might be examined, in light of evidence for emotional brain markers and theories of attention deficit hyperactivity disorder that highlight the integration of these alterations [10,29].

In future studies, it would also be meaningful to assess the integrative relationships between cognitive markers and other biological measures relevant to attention deficit hyperactivity disorder, including genetics and structural/functional imaging [4].

In conclusion, this study supports the utility of a standardized approach to computerized cognitive assessment of attention deficit hyperactivity disorder, to aid in clinical decision-making. An assessment that covers multiple domains of cognition enhances the specificity and sensitivity for differentiating patients with attention deficit hyperactivity disorder from healthy control subjects. Computerized assessment provides an efficient platform to assess these domains.

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