BioBehavioral Diagnostics

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Hyperactivity Persists in Male and Female Adults with ADHD and Remains a Highly Discriminative Feature of the Disorder

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Abstract

Symptoms of hyperactivity are believed to fade with age leaving adults with attention-deficit/hyperactivity disorder (ADHD) mostly inattentive and impulsive. Our aim was to test this assertion using objective measure of hyperactivity, impulsivity and inattention in men and women with ADHD and healthy controls. Participants were 40 subjects with ADHD (23M/17F; 35±10 yrs) and 60 healthy controls (28M/32F; 29±9 yrs) blindly assesed using Wender Utah Interview, Structured Clinical Interviews for DSM-IV Disorders and DSM-IV criteria. A Quotient® ADHD System with modified motion collection for movement of the ankles was used to collect data on micromotion, attention and shift in attention state. The Adult Quotient attention task requires the subject to press the space bar when any of the three target stimuli appears (i.e., a 5-pointed, 8-pointed or 16-pointed star) and refrain from hitting the space bar when the non-target stimulus appears (i.e., 4-pointed star). Infrared motion capture systems tracked head and leg movements during performance of three different computerized attention tasks. Subjects also completed the Conners' CPT-II. ADHD and control subjects differed significantly in activity and attention. Effect sizes for activity measures (d'= 0.74 – 1.56) were, on average, two-fold larger than differences in attention or impulsivity, and were more discriminatory (**Quotient Results: ROC AUC=0.94 for combined activity and attention,** 0.87 for activity alone, 0.72 for attention alone; **ROC AUC=0.66 for Conner CPT-II**). Males and females with ADHD were equally active. However, male controls were more active than female controls, so ADHD/control differences were more marked in females than males. Objectively measured hyperactivity persists in adults with ADHD, and is a highly discriminative feature of the disorder. Women with ADHD, relative to female controls, appear to be even more hyperactive than men with ADHD.

Measures

The aim of this study was to compare head and lower extremity movement patterns of adults with ADHD to healthy controls during performance of a computerized attention task. If hyperactivity truly abates in adults with ADHD, then there should be little discernible difference between subjects with ADHD and healthy controls. If hyperactivity persists, then males with ADHD should be substantially more active than healthy male controls. Based on the literature, females with ADHD should be less hyperactive, on average, than males with ADHD as more girls than boys with ADHD are predominantly inattentive.

Design

This was a two-visit IRB-approved study. During the first visit, the study was explained and written informed consent obtained. Diagnostic assessment was made using the Wender Utah Interview and DSM-IV criteria. Comorbid Axis-I disorders were assessed using the Structured Clinical Interview for DSM-IV Disorders-I. Clinical investigators making the diagnosis were child and adult certified mental health professionals blind to the results of the motion/attention tests. Testing for capacity to sit-still and pay attention occurred during visits I and II (two tests per visit). Infrared motion capture systems (Qualysis ProReflex) were used to track head and lower extremity (shin and ankle) movements (0.04 mm resolution, 50 measures per second) during performance of three different 20-minute computerized attention tasks. Subjects also completed the Conners' CPT-II attention task (Ver 5) without concomitant motion measures. The four attention tasks (3 with motion capture plus Conners CPT-II) were administered in random order. Activity results were similar across all three motion capture/attention tasks, and results from only one of the tasks (the Quotient Adult test) will be presented here along with the Conners' CPT-II. Satistical analyses were conducted using R.

Subjects

Subjects were 100 adults in good physical health, between 18-40 years of age, recruited from the community by advertisements, with a primary diagnosis of ADHD, or were healthy unmedicated controls without psychiatric disorders. Exclusion criteria included any use of alcohol, drugs, herbal remedies, or non-ADHD medications (except contraceptives) for at least 2 weeks (or longer to ensure washout) prior to enrollment, assessed by self-report and by negative urine toxicology screening tests. Subjects receiving treatment for ADHD were excluded if treated with anything other than stimulants. Further, they needed to be willing to stop stimulants for at least 18 hours prior to each study visit. Additional exclusion criteria included a history of any major medical or neurological disorder that could affect motor activity or attention, current major depression, bipolar disorder or anxiety disorders as a primary diagnosis within the past 6 months, or any past or present history of alcohol or substance abuse. The ADHD group consisted of 40 subjects (23M/17F) with a mean age of 35 ± 10 years. Forty-one percent of the ADHD females and 39% of the males were diagnosed as predominantly inattentive subtype. Controls included 60 subjects (28M/32F) with a mean age of 29 ± 9 years.

Quotient® ADHD system

Objective Technology for ADHD Assessment

FDA-cleared for the objective measurement of hyperactivity, inattention and impulsivity to aid in the assessment of ADHD

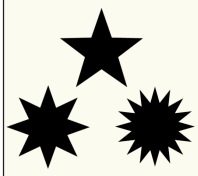
Child Test: 15 min.
1 target, 1 non-target

Press SPACE BAR

Don't press any key

Adolescent/Adult Test: 20 min.
3 targets, 1 non-target

Press SPACE BAR when the star is:



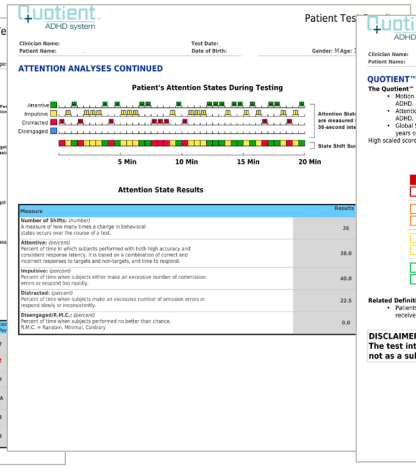
Don't press any key when the star is:

The Quotient® Report

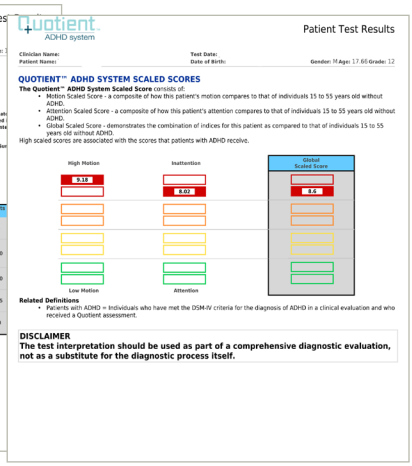
Motion Analysis

Attention Analysis

Attention State Analysis



Scaled Scores & Global Score



Definitions of Motion and Attention Parameters

Motion	Immobility Duration	Average time not moving greater than 1 mm.
	# Movements	Average number of position changes >1 mm.
	Total Displacement	Total distance traveled by the reflector.
	Area	Two-dimensional space in which the reflector moved.
	Spatial Complexity	Complexity of the movement path. Patients with ADHD tend to have low values, indicating simple motion.
	Temporal Scaling	Infrequent movements yield values close to 0. Incessant movement produces values close to 1.
Attention	Accuracy	Percentage of correct responses to both the targets and the non-targets.
	Omission errors	% of task that the patient failed to respond to the target. Measures distraction and/or inattention.
	Commission errors	% of hits to the non-targets. Measures impulsivity or inability to inhibit a response.
	Latency	Mean reaction time (milliseconds) to respond to a target.
	Variability	Variation in response times to the correct target. High levels indicate inconsistent task performance.
	COV	Variability that is adjusted to take into account difference in response latency.
Attention Shifts	# Shifts	Number of attention state shifts during the test.
	Attentive/On-Task	Patient hits many targets and few non-targets.
	Impulsive	Patient hits many targets and some non-targets.
	Distracted	Misses some targets and hits some non-targets, with accuracy better than chance.
	DISENGAGED	Accuracy no better than chance.

Results

Table 2. Differences in Selected Attention and Activity Measures between ADHD Subjects and Normal (NL) Controls.

	NL-MALE	NL-FEMALE	ADHD-MALE	ADHD-FEMALE	F value	Prob	Effect Size (d')
Attention Measures							
Accuracy (%)	97.50 (2.22)	97.52 (1.37)	95.62 (3.00)	95.80 (2.50)	16.73	0.0001	0.804
Time Attentive/On-Task (%)	60% (20%)	59% (21%)	38% (24%)	47% (18%)	18.81	0.00004	0.843
Latency (ms)	499 (65)	473 (56)	488 (72)	472 (66)	0.11	0.74	0.065
Latency Coef of Variation (COV)	20.99 (5.57)	19.94 (4.86)	24.91 (5.87)	23.36 (4.92)	13.42	0.0004	0.718
Activity Measures (head)							
Movements (number)	1842 (835)	1291 (825)	2467 (1093)	2395 (1086)	22.98	$< 10^{-5}$	0.921
Movement area (cm^2)	91.7 (68.4)	58.6 (85.1)	154.3 (72.3)	146.7 (112.0)	22.13	$< 10^{-5}$	0.916
Displacement (meters)	2.92 (1.71)	1.84 (1.75)	4.10 (1.92)	3.96 (2.27)	20.90	0.00002	0.882
Spatial Complexity	1.269 (0.181)	1.379 (0.265)	1.106 (0.161)	1.119 (0.051)	32.42	$< 10^{-6}$	1.095
Temporal Scaling	0.480 (0.250)	0.297 (0.257)	0.588 (0.227)	0.601 (0.256)	18.48	0.00004	0.820
Activity Measures (legs)							
Movements (number)	464 (407)	188 (185)	941 (994)	1316 (1434)	24.68	$< 10^{-5}$	0.980
Movement area (cm^2)	19.1 (20.0)	6.6 (7.2)	44.0 (43.6)	41.0 (21.5)	35.53	$< 10^{-7}$	1.175
Displacement (meters)	0.76 (0.79)	0.24 (0.28)	1.71 (2.12)	2.30 (2.49)	24.13	$< 10^{-5}$	0.974
Spatial Complexity	2.013 (0.757)	2.550 (0.708)	1.458 (0.225)	1.341 (0.192)	56.72	$< 10^{-10}$	1.419
Temporal Scaling	0.160 (0.290)	0.049 (0.217)	0.422 (0.180)	0.507 (0.292)	69.68	$< 10^{-12}$	1.567

- The most robust differences in **attention** were on the following parameters:
  - Percent of time spent fully on-task ($F1,97 = 18.81$, $p < 0.00004$, $d' = 0.72$)
  - Accuracy ($F1,97 = 16.73$, $p < 0.0001$, $d' = 0.80$)
  - Coefficient of variation in response latency ($F1,97 = 13.42$, $p < 0.0004$, $d' = 0.72$).
- Differences between ADHD and controls were even more robust on **motor** measures. The most notable parameters were:
  - temporal scaling exponent ($F1,95 = 69.68$, $p < 10\text{-}12$,, $d' = 1.56$)
  - spatialcomplexity exponent ($F1,95= 56.72$, $p < 10\text{-}10$, $d' = 1.42$)
  - coefficient of variation ($F1,95 = 65.38$, $P < 10\text{-}11$, $d' =1.55$) in mean right and left shin movements.
- On average, subjects with ADHD moved their **heads 2-fold** as often and their **legs 5.4-fold** more often than controls.
- There were no differences between males and females with ADHD in movement measures. However, male controls were more active than female controls, so that differences between ADHD and controls were more marked in females than males. For example, males and females with ADHD moved their leg markers through an average area of 42.1 and 42.0 cm^2, respectively ($p >0.9$). However, this represented a 9-fold ADHD vs. control differential in females ($d' = 1.71$, $p < 10^{-10}$), but only a 3-fold differential in males ($d' = 0.73$, $p<0.004$).

Explanation of the Statistical Analysis

Statistical differences between groups were computed using analysis of covariance (ANCOVA). This results in two numbers:

- F value is a ratio that indicates the result of the statistical comparison (and the associated degrees of freedom)
- p value indicates the significance of derived F value (how likely would an F value of this size occur by chance)

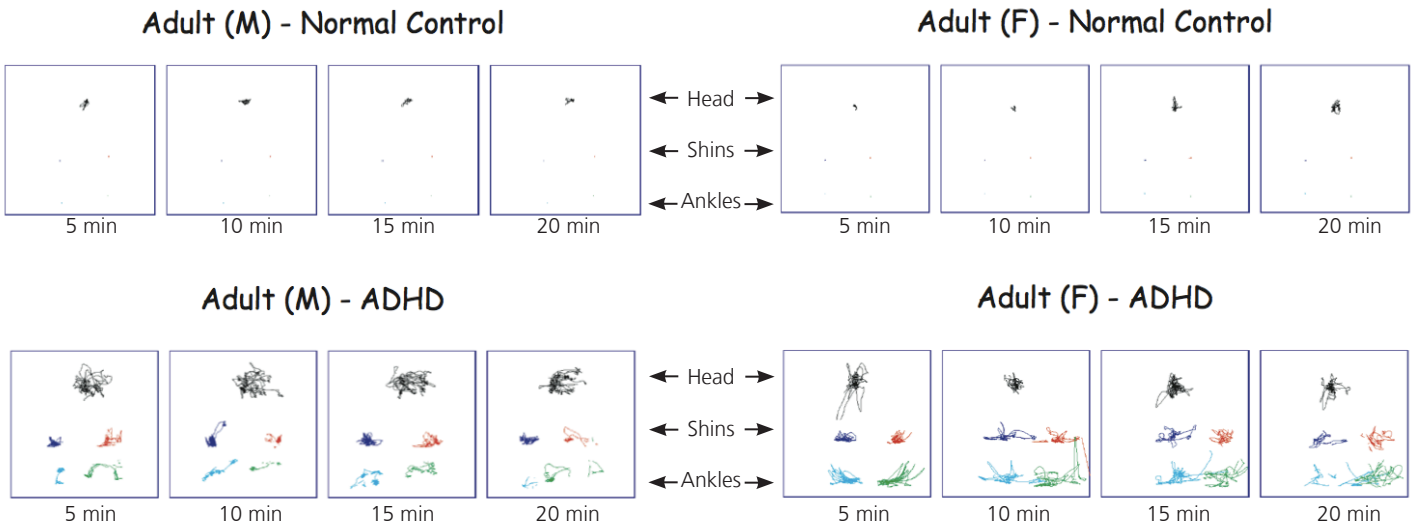
Generally, the larger the F value, the more significant the result (i.e., the lower the p value). However, the statistical significance of a test does not tell the whole story. A small difference across a very large population can appear highly significant, but it may not be relevant biologically or clinically. Hence, there are other measures that provide information about the magnitude of the difference, taking into account the variability of the measures. The most common 'effect size' measure is Cohen's d' (d' is the difference between the mean of two groups divided by their pooled standard deviation.)

Convention in the social sciences defines an effect size d' as follows:

- 0.2 - 0.3 is "small",
- 0.4 - 0.5 is "medium"
- 0.8 or greater is "large"

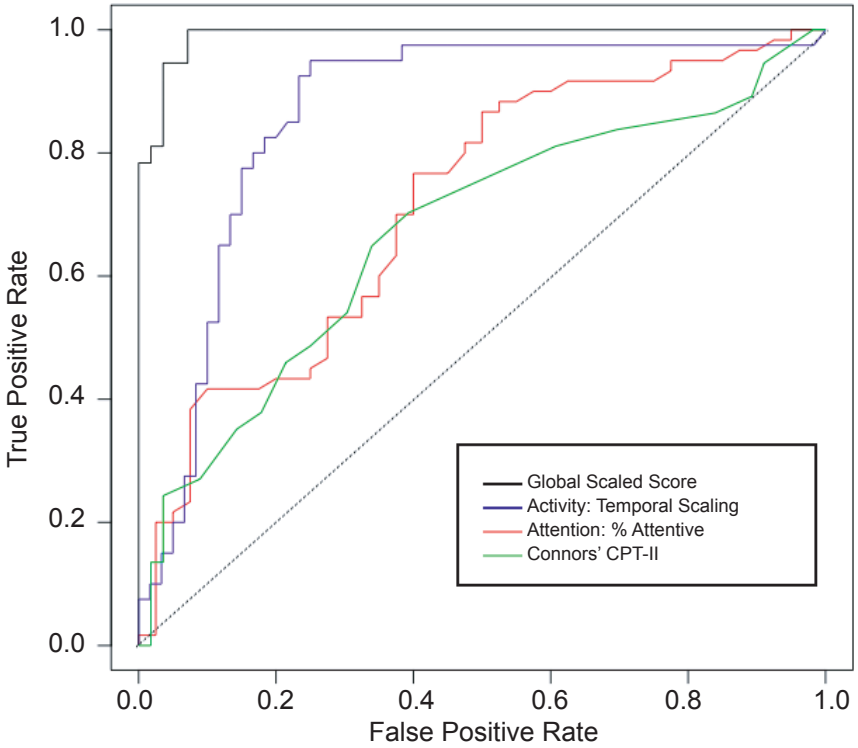
Ideally, a diagnostic test should have effect sizes substantially greater than 1.

Motion Results by Gender



- There were no differences in performance between males and females.
- There were no significant gender x diagnosis interactions.

ROC Analysis of Motion and Attention Composites



The area under the Receiver Operating Characteristic curve (ROC AUC) was used to assess the discriminative capacity of theses variables, as it provides the best overall index of performance of a diagnostic measure. An ROC AUC of 1.0 indicates perfect discrimination, whereas an ROC AUC of 0.5 indicates performance no better than chance.

- The most discriminative parameter on the Conners' CPT-II (**green line**) had an ROC AUC of only 0.66 (p= 0.014). This is consistent with other reports.
- The most discriminative attention measure for the Quotient ADHD Test was percent time spent in the Attentive state (**red line**, ROC AUC = 0.72).
- All but 2 of the motor activity measures had a greater ROC AUC. The best single motion metric was the mean temporal scaling exponent (**blue line**, ROC AUC = 0.87).
- A combination of activity and the Quotient Adult Attention Test measures yielded an ROC AUC=0.94 (**black line**). This is reported as the Global Scaled Score on the Quotient report.

Conclusions

- Contrary to conventional wisdom, adults with ADHD were substantially more active than healthy controls
- Objective measures of hyperactivity were more effective in discriminating between ADHD and control subjects than computer-based measures of attention or impulsivity.
- These results are strikingly similar to findings we have reported in children with ADHD (Ohashi et al., 2010; Teicher et al., 1996; Teicher et al., 2006). Hence, it may be incorrect to assume that hyperactivity abates to a greater degree than other symptoms of the disorder, or that females with ADHD are predominantly inattentive.
- Objective measures may differ from clinical impressions as subjective ratings of hyperactivity are markedly skewed by the valance of the behavior, such that aggressive individuals tend to be rated as hyperactive regardless of their actual activity levels (Abikoff et al., 1993).

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