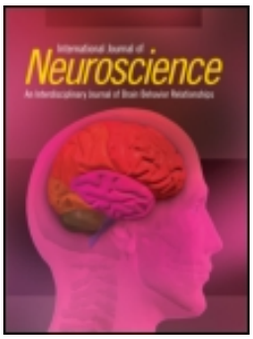

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NEUROPSYCHOLOGICAL TESTING IN ADULT ATTENTION DEFICIT HYPERACTIVITY DISORDER: A PILOT STUDY

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Diagnosing adult ADHD is frequently problematic because behavioral information from the patient's childhood, and multiple informants who can delineate the patient's current behavior, are often unavailable. This preliminary study was designed to explore whether objective neuropsychological testing may be a useful adjunct in the diagnosis of adult ADHD. Nineteen adults diagnosed with ADHD according to DSM-IV criteria, along with 10 controls, were assessed using a neuropsychological battery which comprised tests assessing linguistic, visual-spatial perceptual, academic, attentional and inhibitory control, mnestic and executive functions. Following preliminary analyses, designed to determine which variables best discriminated the groups, receiver operating characteristic (ROC) curves were constructed to determine the sensitivity and specificity of the best measures both alone and in combination. Only three measures significantly ($p < 0.01$) distinguished the groups; Digits Backwards from the WAIS-R and two reaction time measures from a computerized task modeled after Luria's Competing Motor Programs. ROC curve analyses indicated that in combination these measures had greater than 90% accuracy for classifying ADHD and non-ADHD patients. While further research is necessary these preliminary findings suggest that neuropsychological testing may be a useful adjunct in the differential diagnosis of adult ADHD.

Keywords: Adults; ADHD; neuropsychological testing; diagnosis

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It is generally accepted that the symptoms of Attention Deficit Hyperactivity Disorder (ADHD) persist into adulthood in a significant proportion of cases (Weiss and Hechtman, 1993; Klein and Mannuzza, 1991). Residual symptoms in adults frequently cause disruption of occupational and family life and general underachievement in lifestyle.

Diagnosing ADHD in adults is more complicated than in children. Verifiable behavioral information from the patient's childhood (which in children is provided by parents and teachers) is often unavailable for adult patients. Although DSM-IV provides criteria for ADHD that can presumably be applied to adults as well as children, in practice no consensus has been reached as to how to apply them to adults (Kane *et al.*, 1990).

Co-morbid learning disabilities and psychiatric syndromes, which can overlap with ADHD symptomatology, further complicate accurate diagnosis (Zametkin, 1996). These disorders, which often include developmental language disorders, depression or generalized anxiety, are frequently characterized by poor attention and concentration (Bond *et al.*, 1974; Sternberg and Jarvik, 1976).

The clinical problems encountered in diagnosing adult ADHD create a potentially useful role for neuropsychological testing to assist in the diagnosis of this disorder, since it relies on more objective, quantifiable measures, and does not depend on obtaining valid historical information. However, neuropsychological testing has not been found to be as helpful for clinical diagnosis in children as anticipated. The total classification power of continuous performance tests, and other tests believed to tap frontal lobe functions has been shown to be relatively poor in relation to normal controls, individuals with learning disabilities or non-psychotic psychiatric disorders (Barkley and Grodzinsky, 1994; Matier *et al.*, 1995). Thus, although a potential role exists for neuropsychological testing in assisting in the diagnosis of adult ADHD, it has yet to be demonstrated that such testing has adequate classification power in the clinical setting. To achieve such power, tests must be able to discriminate adults with ADHD from normal controls, as well as from individuals with other non-psychotic psychiatric disorders.

The purpose of the current pilot study was to determine whether specific neuropsychological testing can distinguish adults with ADHD from individuals with other disorders, in a group of patients who were referred to a specialty clinic at a tertiary care hospital.

The specific neuropsychological battery was chosen according to the following considerations. Tests were included to objectify the existence of major co-morbid factors. Academic achievement tests and tests of basic

language processing evaluated the possibility of learning disabilities. Objective screening tests for depression and anxiety assessed the presence of psychiatric variables known to distort attention. The battery was also designed to assess attention from different aspects. In addition to standard measures of sustained attention (*i.e.*, continuous performance tasks) tests of set shifting and reversal, working memory, short term memory and incidental memory were included. These require efficient modulation of attention for normal performance. Inclusion of WAIS-R subtests, along with a demographically based formula for estimating WAIS-R IQ scores, provided reasonable estimates of general intellectual functioning.

METHOD

Subjects

The subjects studied were patients seen consecutively at an interdisciplinary clinic for the diagnosis and treatment of adult ADHD at North Shore University Hospital. Most were self-referred following exposure to reports in the media about ADHD. Sixteen of the nineteen ADHD subjects were self-referred, as were nine of the ten control subjects. Of the remaining subjects three were referred by psychiatrists (2 ADHD and 1 control) and one by an internist (ADHD).

Twenty nine Caucasian adults between ages 18 and 57 were evaluated. Nineteen of them received a diagnosis of ADHD; 10 were not diagnosed with ADHD and served as the control group. The diagnoses of the control group included mainly non-psychotic psychiatric disorders (2 subjects had depression, 3 had generalized anxiety, 1 had depression and anxiety combined, 1 had a narcissistic personality disorder, and 3 had pre-diagnosed learning disabilities).

The ADHD group contained 14 males and 5 females, while the control group was comprised of 8 males and 2 females. Due to the limited sample size no attempt was made to break out subtypes of ADHD in the formal analysis. Eleven of those subjects who received a primary diagnosis of ADHD had this disorder alone. Four had also received previous diagnoses of learning disabilities, and four had co-morbid symptoms of depression and/or anxiety. No subject had known medical or neurological illness that could account for ADHD symptoms. No subject was taking psychoactive medication at the time of testing.

Procedure

Each patient was evaluated independently by a psychiatrist, neurologist and neuropsychologist. Prior to clinical evaluation each patient completed a personal information form which included developmental, employment, social, medical and alcohol histories, and an ADHD symptom rating scale. Patients were urged to obtain their records from elementary and secondary schools, as well as from any previous psychiatric, neurological or psychological evaluations.

A comprehensive psychiatric interview and semi-structured interview were conducted to investigate other psychiatric comorbidities, using DSM-IV criteria (American Psychiatric Association, 1994). Using all historical, questionnaire, and interview data, clinicians reviewed the 18-item rating scale which consisted of the DSM-IV items for ADHD, and which had been completed by patients, and significant others, for childhood and current time periods.[1] This approach ensured a systematic basis for assessing the presence absence of each ADHD symptom, and helped generate a "best-estimate" diagnosis of ADHD according to DSM-IV criteria. Similar scales, based on DSM-IV items, completed by parents (DuPaul, 1991), teachers (Atkins *et al.*, 1985; DuPaul, 1991), and clinicians (Halperin *et al.*, 1993), have been used by several investigators and found to have acceptable reliability and validity.

The psychiatrist and neurologist arrived at a diagnosis independently while still blind to the neuropsychological test data. A team meeting was held following the clinical evaluations to formalize the diagnosis. The neuropsychologist did not make a formal diagnosis but provided information from his test battery (*e.g.*, on academic achievement, depression and anxiety) at the team meeting. No diagnoses were altered as a consequence of exposure of neuropsychological data to team members at the joint meetings.

Neuropsychological testing consisted of a two and one half hour screening battery. This was comprised of the following tests in six areas; (1) Language-Vocabulary Subtest of the WAIS-R (Wechsler, 1981) and the Boston Naming Test (Kaplan *et al.*, 1983), (2) Visual-spatial perception and reasoning-Block Design Subtest of the WAIS-R and the Benton Test of Facial Recognition (Benton *et al.*, 1975), (3) Academic skills-Wide Range Achievement Test Revised – WRAT-R, (Jastak and Wilkinson, 1984), and the speed and accuracy subtest of the Gates-MacGinitie Reading Test (Gates and MacGinitie, 1969), (4) Short term memory and working

[1] In 81 percent of cases the significant other was present during the consultation. In the remainder of cases, information was provided by direct telephone interview.

memory–Warrington Recognition Memory Test–WRMT (Warrington, 1984), incidental recognition memory for the temporal order of words (Kovner *et al.*, 1988), and the Gold Letter-Number-Span Test (Gold *et al.*, 1997), (5) Attention-Digit Span Subtest of the WAIS-R, Connors Continuous Performance Test (Connors, 1992), a repeated stimuli Continuous Performance Test (Hinton *et al.*, 1995), and a Shifting Sets Test (McKay *et al.*, 1994) modeled after Luria's Competing Motor Programs, (6) Personality-Beck Depression Inventory and Spielberger State and Trait Anxiety Scales (Beck, 1978; Spielberger *et al.*, 1968). Tests were presented to subjects in differing semi-random orders, with the restriction that the three tests of attention were separated from each other by at least thirty minutes of other testing.

The three tests of sustained attention had differing response requirements. Although the continuous performance tasks both necessitated go/no-go responses the Connors test had a ratio of 90% targets to 10% distracters, while the repeated stimuli CPT had the converse ratio. Both took about fourteen minutes to complete. The Connors task presented single letters of the alphabet in the center of the computer screen for 250 milliseconds, with intertrial intervals ranging between 1 and 4 seconds. Subjects were required to press the space bar for any letter except an *x*. Eighteen blocks of 20 trials were presented.

The repeated stimuli CPT involved the presentation of 4-digit numbers in the center of the computer screen for 200 milliseconds, with an interstimulus interval of 1.5 seconds. Subjects were required to monitor the numbers and press the space bar whenever one 4-digit number was immediately followed by the same 4-digit number. The test presented 400 stimuli. Successful completion of a shorter practice trial was necessary to demonstrate comprehension of the task before testing.

During the Shifting Sets Test subjects were seated in front of the computer monitor with a standard keyboard on which labels with a number 1 or 2 were placed over the two central keys of the bottom row of letters (*i.e.*, the B and N keys). The numbers 1 and 2 were presented singly in the center of the screen for a total of 60 trials distributed across two conditions. In a noncompeting condition, subjects were instructed to press the key labeled 1 when a 1 appeared on the screen, and to press the key labeled 2 when a 2 appeared on the screen. In the competing condition, subjects were asked to press the key labeled 2 when a 1 appeared on the screen, and to press the key labeled 1 when a 2 appeared. Numbers remained on the screen until the subject responded. Numbers were presented in a random order within each block of trials. Subjects began the test with the noncompeting condition for

30 trials (set 1), followed by two consecutive sets of 30 trials each of the competing condition (sets 2 and 3). Finally, 30 trials of the noncompeting condition were repeated (set 4).

Data Analysis

Mann-Whitney Tests were used to compare the two groups of patients (19 ADHD subjects and 10 controls) on 43 parameters. Five consisted of demographic variables (age, education and estimated Full Scale, Verabl and Performance IQ; Barona *et al.*, 1984). Thirty eight reflected neuropsychological test scores (raw scores).

Due to the large number of variables being studied, a more conservative level of alpha was chosen ($p < 0.01$) to determine a significant difference between groups.[2] Limited sample size precluded the use of a formal classification analysis. Instead an exploratory approach was adopted. Standardized differences were calculated for those variables found to be significant (*i.e.*, mean difference between the two groups/pooled standard deviation). The three variables with the highest absolute standardized differences were included in a multiple stepwise regression anlaysis to determine which independently discriminated between the ADHD group and controls. The choice of three variables was made because, for the sample size in this study a logistic regression analysis will only support approximately three variables as predictors.

Receiver operating Characteristic (ROC) Curves were constructed for the three variables (separately and in pairswise combinations) to investigate the sensitivity and specificity as a function of varying cutoff points. Another ROC curve using all three together was also constructed to examine if this significantly improved discrimination between groups.

The number c (coefficient of concordance), which lies between 0 and 1, was computed from the logistic regression analysis, and is one of several measures used to assess the discriminatory ability of the fitted model. c approximates the probability of correctly distinguishing an ADHD subject

[2] This was an exploratory analysis, the objective of which was to find candidate items that might help discriminate adult ADHD subjects from subjects receiving other diagnoses. Since there were 43 measures, a strict Bonferroni adjustment would have declared a variable significant only if its p-value was less than $0.05/43 = 0.0012$. It is well known that a Bonferroni adjustment to this extent is too conservative. Therefore, a less conservative (albeit arbitrary) approach was to use $p < 0.01$ as a cutoff point for statistical significance. The effect of this *liberalization* of the adjustment was to compensate for Bonferroni's conservatism.

from a non-ADHD subject. c also approximates the area under the ROC curve, when the response variables in a logistic regression are binary (Hanley and McNeil, 1982). As an example, $c = 0.80$ can be interpreted to mean that, if a randomly selected ADHD subject and a randomly selected non-ADHD subject were evaluated using the fitted logistic model, then 80% of the time the model would correctly discriminate between the two subjects.

RESULTS

The two groups did not differ on major demographic variables (see Tab. I). The groups also did not differ on variables associated with learning disabilities (*e.g.*, single word reading $p = 0.09$, spelling $p = 0.06$, paper and pencil arithmetic $p = 0.12$, speeded reading comprehension $p = 0.43$, and object naming $p = 0.32$). They also did not differ in the presence of psychiatric factors (depression $p = 0.95$, and state and trait anxiety $p = 0.96$, and $p = 0.31$).

A set of only three of the neuropsychological variables were found to be significantly different ($p < 0.01$) between groups (see Tab. II). Standardized differences were calculated for each of them. The three variables ranked by decreasing absolute value are as follows; Digits backwards–(DGBR) from the Digit Span Subtest of the WAIS-R (−1.187), mean reaction time-(HSST4MNR) from the fourth set of the Shifting Sets Test (1.107), and reaction time variability-(HSST4SDR) from the same set on the same task (0.879). A negative (positive) standardized difference indicates that the mean of the ADHD group was lower (higher) than the Control group.

Areas under each ROC Curve were used to rank the efficiency of each of the three variables in discriminating ADHD subjects from controls. A Stepwise Logistic Regression analysis showed that using DGBR and

TABLE I Characteristics of ADHD and control groups

	ADHD ($N = 19$)		*Control* ($N = 10$)		*Mann-Whitney statistic*	p
	x	*S. D.*	x	*S. D.*		
Age	33.1	11.3	29.3	10.7	−0.87	0.38
Years of Education	13.7	2.2	14.6	1.9	1.04	0.30
*Full Scale IQ	109	7.1	111	7.2	0.92	0.36
*Verbal IQ	108	7.4	110	7.3	0.76	0.45
*Performance IQ	108	5.4	109	5.5	0.97	0.33

*Estimated from formula of Barona *et al.*

TABLE II Comparison of ADHD and control groups on the three discriminating neuropsychological measures

	ADHD ($N = 19$)		*Control* ($N = 10$)		*Mann-Whitney*	
	$\bar{x}$	*S. D.*	$\bar{x}$	*S. D.*	*statistic*	*p*
DGBR*	4.79	1.40	6.30	0.98	2.66	.008
HSST4MNR†	575.44	76.82	443.95	174.68	−2.66	.008
HSST4SDR‡	222.01	129.74	122.65	68.50	−2.64	.008

* Digit Backwards From the WAIS-R.
† Mean Reaction Time on the 4th Set of the Shifting Sets Test.
‡ Reaction Time variability on the 4th Set of the Shifting Sets Test.

HSST4MNR jointly ($c = 0.905$) was sufficient to discriminate ADHD subjects from controls. Adding HSST4SDR resulted in a nonsignificant improvement in discriminating power ($c = 0.953$). The ROC cutoff points for all three variables used jointly are presented in Figure 1. The results of the analyses indicate that given a randomly selected pair of subjects (one with ADHD and one control), the probability of classifying both correctly is between 90.5 and 95.3%.

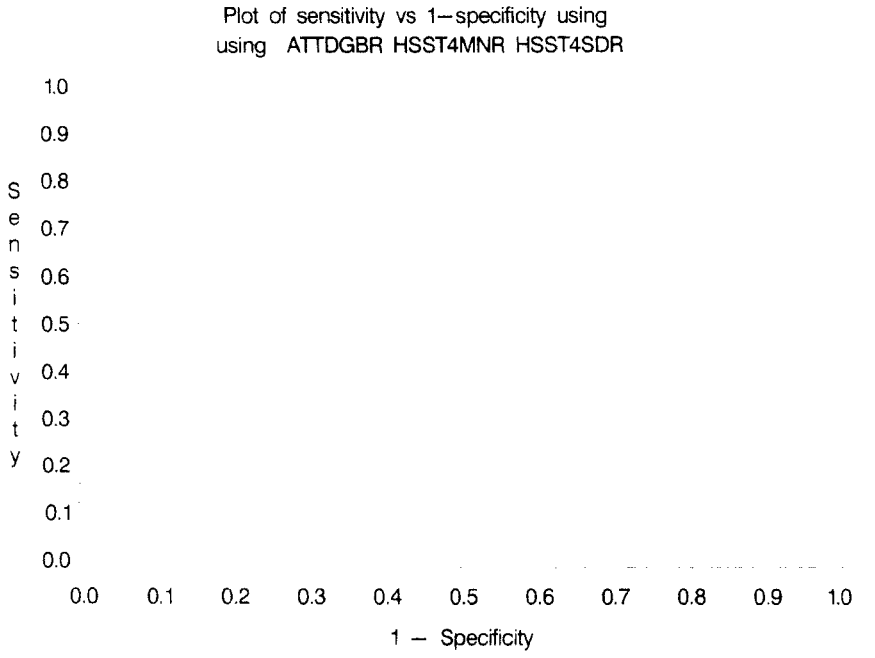

FIGURE 1 Receiver operating characteristic (ROC) curves estimating sensitivity and specificity as a function of varying cutoff points. All 3 significant variables are used jointly. (See results section for variable abbreviations).

DISCUSSION

The results of this pilot study suggest that adult ADHD patients may have circumscribed deficits in reversing, inhibiting and re-engaging specific cognitive and motor sets. This raises the possibility that these defects might be used to help discriminate them from patients without ADHD in a clinical setting. The measures of set reversal found to have effective discriminating power are relatively simple (*i.e.*, they are not confounded by higher-order cognitive variables such as conceptualization or short term memory).

The groups did not differ on other cognitive measures that involve attention (*e.g.*, short term memory and working memory), or on other direct measures of sustained attention (continuous performance tests). When these observations are combined with the apparent circumscribed nature of the ADHD deficits, some assurance is provided that the significant findings are not chance events. Despite this, caution should be used in attempting to generalize the results. Larger sample sizes might alter the significant findings. Additionally, a relatively limited sample size may have prevented other important predictor variables from being judged statistically significant.

The significant findings can not be explained by major co-morbid factors (*i.e.*, learning disabilities, depression, anxiety) and their cognitive sequellae, since the groups did not differ on these variables.

The findings that adult ADHD patients experience a particular problem with the reversal of cognitive and motor set, and with the re-engagement of such set once inhibited, appear to be consistent with current theories of the psychophysiology of the disorder. Recent neuroimaging findings demonstrate significant reductions in right caudate volume in ADHD subjects (Castellanos *et al.*, 1994). Lesions in fronto-striatal circuits have been found to impair set shifting behavior (Gotham *et al.*, 1988).

ADHD is increasingly conceptualized as involving deficiencies in inhibitory control and impaired executive functioning relating to self regulation. Recent research (Schachar *et al.*, 1995) indicates that children with ADHD have difficulties with inhibitory control, as well as with the capacity to re-engage specific response patterns after inhibition. These concepts might explain why, in the current study, the ADHD subjects' response latencies, and response latency variability, worsened significantly with reference to the control group only following inhibition and re-engagement of specific response patterns, during the fourth block of the Shifting Sets Test. This is the only trial block that meets the joint criterion of response re-engagement following inhibition. The joint significant finding on

Digits Backwards indicates that reversal of a set is also involved as a distinct factor. Some support for this hypothesis may be found in the observation that the slower reaction times of ADHD patients following the first shift in the Shifting Sets Test, constituting a reversal, just missed significance.

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