A PRACTICAL APPROACH TO OBJECTIVE ADHD DIAGNOSIS AND MANAGEMENT

ADHD is one of the most prevalent of all the cognitive disorders. The prevalence rate in North American schoolchildren is at least 5% (1-3). In the majority of cases, the symptoms of ADHD persist into adult life. ADHD can be as troublesome to adults at work or at home as it is to kids at school.

The diagnosis of ADHD, in the vast majority of cases, is based entirely on subjective reports of perceived symptoms. Medication follow-up is also largely based on subjective reports. Neuropsychological testing and direct classroom observations are objective measures that can strengthen the diagnosis process, but they are expensive, time-consuming, and simply unavailable to the large majority of ADHD patients.

Many, if not most, psychiatrists and psychologists who specialize in ADHD utilize cognitive tests for patient evaluation and treatment monitoring. The most commonly used tests are variants of the CPT (4), like the Conners CPT-II (Conners) and the TOVA (5). The CPT is problematic, because of problems with reliability, and because it measures sustained or vigilance attention and nothing more. Modern theories of ADHD posit an underlying deficit in executive control functions, for example, in the efficient allocation of attentional resources and behavioral self-regulation in response to changing environmental demands (6).

Expert panels have tended to diminish the importance of cognitive testing as a diagnostic instrument in ADHD (7). Studies of the CPT have, not surprisingly, demonstrated little correlation between test performance and clinical diagnosis or clinical outcome (8-11). This may simply reflect the dubious utility of the CPT itself. On the other hand, it may simply reflect the erroneous reliance on testing as a diagnostic measure. ADHD is a clinical diagnosis, made by a physician who is appropriately trained in and experienced with the condition. Proper diagnosis of ADHD, like virtually all other medical conditions, requires the synthesis of data from many different sources. One of those sources is cognitive testing. In our opinion it is inappropriate to diagnose or to treat a cognitive disorder like ADHD without taking an objective measure of the patient's clinical state.

In the next few pages, we shall describe a method for evaluating and treating patients with ADHD, using computerized neurocognitive testing, in the context of a modern neuropsychiatric clinic. The purpose is to elevate the process to a level that reflects the importance of the clinical problem and the aspirations of our field to the most rigorous standards of practice.

The system that we shall describe is in current use at the North Carolina Neuropsychiatry Clinics in Chapel Hill and Charlotte. It is made up five steps:

1. Web-based data collection prior to the patient's first visit.
2. The clinical examination
3. Interpretation of neurocognitive testing
4. A "test dose" of a short-acting stimulant

5. Objective comparison of treatment efficacy

1. WEB-BASED DATA COLLECTION.

The clinical history, family history and rating scales are essential for clinical diagnosis. These are the most time-consuming elements of the diagnostic process. A proper history and analysis of rating scale results will take at least an hour, and sometimes longer.

Much of this data, however, can be obtained before the patient ever arrives at the physician's office. Medical history forms and rating scales can be attached to the practice website and downloaded by prospective patients. Forms can be downloaded, completed and brought to the clinic on the occasion of the first visit.

Web-based versions of neurocognitive tests can also be downloaded from the website, completed by the patient, and uploaded to the practice database. Data from rating scales and cognitive tests can be analyzed, and a report generated, before the patient arrives for his or her first visit.

Since ADHD usually runs in families, prospective patients can be invited to test other family members as well. These data can also be reviewed at the first visit. Thus, an ADHD evaluation includes not only a systematic evaluation of the prospective patient, but also a screening battery for other family members.

An example of how this works can be seen by visiting our website at www.ncneuropsych.com. Go to **Patient** on the menu, and download the forms you are interested in seeing. To take a web-based screening test, go to **Neurocognitive Screener**, and register using this password: **Psychiatry2005**.

2. THE CLINICAL EVALUATION.

The neuropsychiatric office should employ a medical office assistant who can take vital signs, measure height and weight, perform urine drug screening and venipunctures. The offices should include an examining table, and several comfortable chairs for prolonged interviews and counseling. A couple of very small offices, big enough for a computer and two small chairs, should be devoted to neurocognitive testing.

The initial evaluation should include the following steps:

1. A medical/developmental history
2. Physical, neurological and mental state examination
3. Height, weight, pulse, blood pressure
4. Rating scales for ADHD and other likely disorders
5. Urine drug screening for adolescents and selected adults.
6. Differential diagnosis, and exclusion of alternative pathology (e.g., substance abuse, bipolar disorder, OCD).
7. Review data from web-based cognitive testing.

3. INTERPRETING THE RESULTS OF NEUROCOGNITIVE TESTING

A number of different computerized neurocognitive tests are appropriate for ADHD testing (See Table 1). As a rule, computerized test batteries are composed of a number of different tests that address different cognitive domains, like memory, information processing speed, complex, divided and sustained attention, working memory and executive control. Measures of attention, processing speed and executive control are especially pertinent to the evaluation of ADHD patients.

Table 1. Computerized Neurocognitive Tests Appropriate for ADHD

ANAM	www.dtic.mil/matris/ddsm/srch/ddsm0082.htm
CNS Vital Signs	www.cnsvs.com
CogScreen	www.cogscreen.com
CogState	www.cogstate.com
CogTest	www.cogtest.com
HeadMinder	www.headminder.com
Microcog	Psychological Corporation
NES3	12
Neurotrax	www.mindstreamshealth.com

The following data is taken from our research with CNS Vital Signs, a battery we developed ourselves, and that is available (like the other tests listed in Table 1) for the reader's evaluation at the website listed. Tests in the CNS Vital Signs battery that are especially relevant to ADHD evaluation are: the Stroop Test, the Shifting Attention Test and the Continuous Performance Test.

INSERT BOXES AROUND HERE: THE STROOP TEST, THE SHIFTING ATTENTION TEST, THE CONTINUOUS PERFORMANCE TEST

The ADHD patient is capable of doing poorly on any or all of the tests in CNS Vital Signs. ADHD patients are notorious for ignoring the instructions for a particular test, terse as they are; they hasten to take the test with no idea at all what they are supposed to be doing. Even though the test results are invalid, the patient's performance in taking the test is telling.

Tests in the CNS Vital Signs battery can be taken by children with a fourth grade reading level, without assistance. Some ADHD children are simply too inattentive to take the test at all, unless one of their parents is there to make sure they understand the instructions and take the tests in an appropriate manner. Even with their parents' help, though, ADHD patients usually make a lot of mistakes.

HOW ADHD PATIENTS PERFORM

The following data were generated from a clinical series of 175 ADHD patients age 10-29 evaluated at the Neuropsychiatry Clinics, compared to 175 normal controls matched for age, race and gender. The ADHD patients were tested during their initial work-up. They were all drug-free, and had no significant psychiatric, neurological or medical comorbidity. Data from normal subjects were taken from the CNS Vital Signs normative database.

THE CPT

Tests of sustained attention, like the CPT, have been traditionally used for the diagnosis of ADHD. ADHD patients make fewer correct responses and more errors on the CPT, and their CPT reaction time is usually longer than normals'.

Figure 1. CPT Correct Responses in ADHD Patients & Matched Controls, t=4.5, P<0.0001

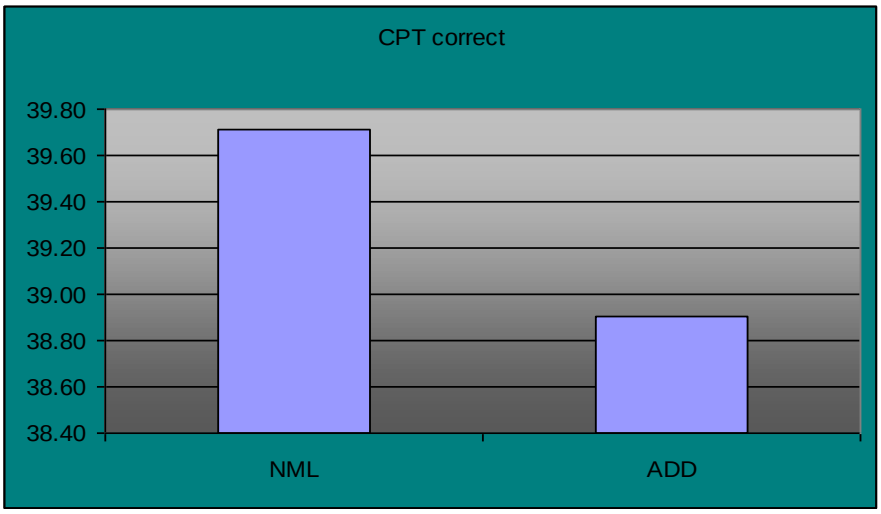


Figure 2. CPT Errors in ADHD Patients & Matched Controls, t=2.5, P<0.01

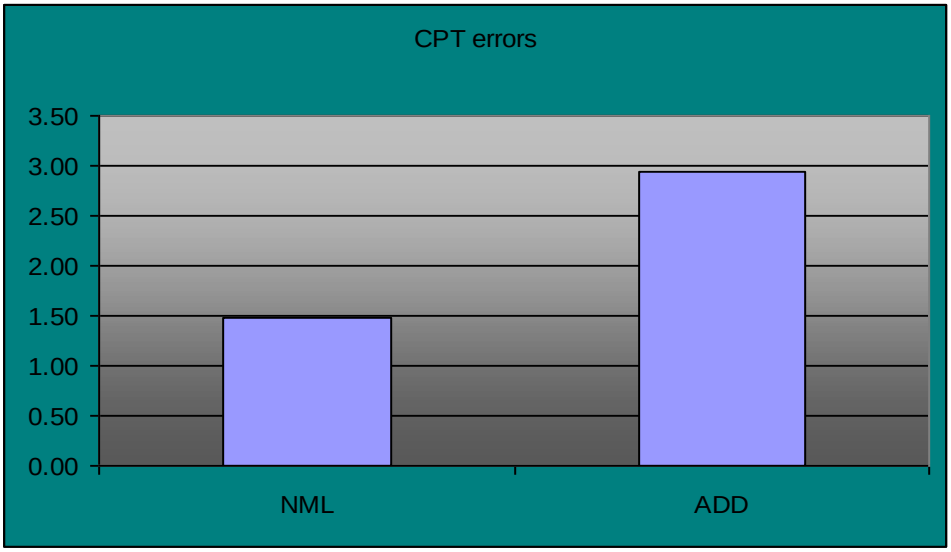
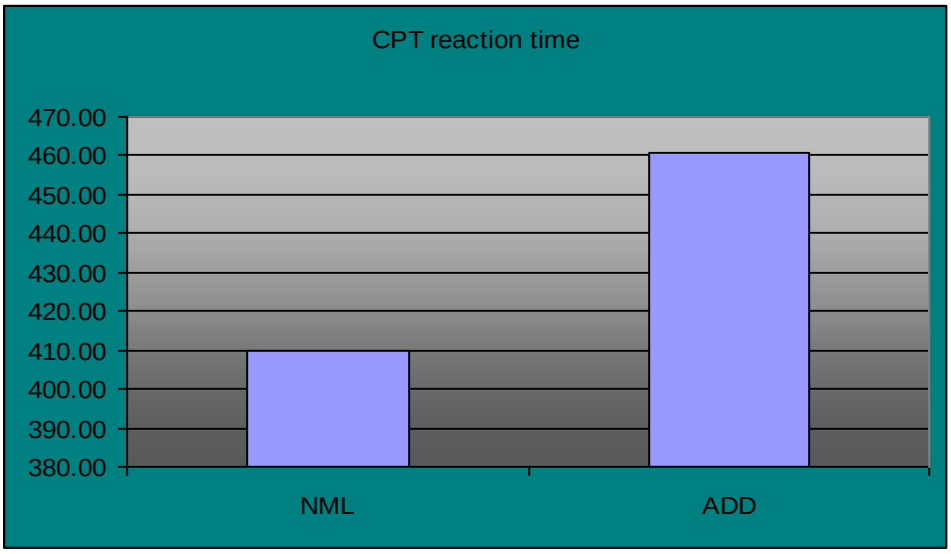


Figure 3. CPT Reaction Time in ADHD Patients & Matched Controls, t=7.82, P<0.00001



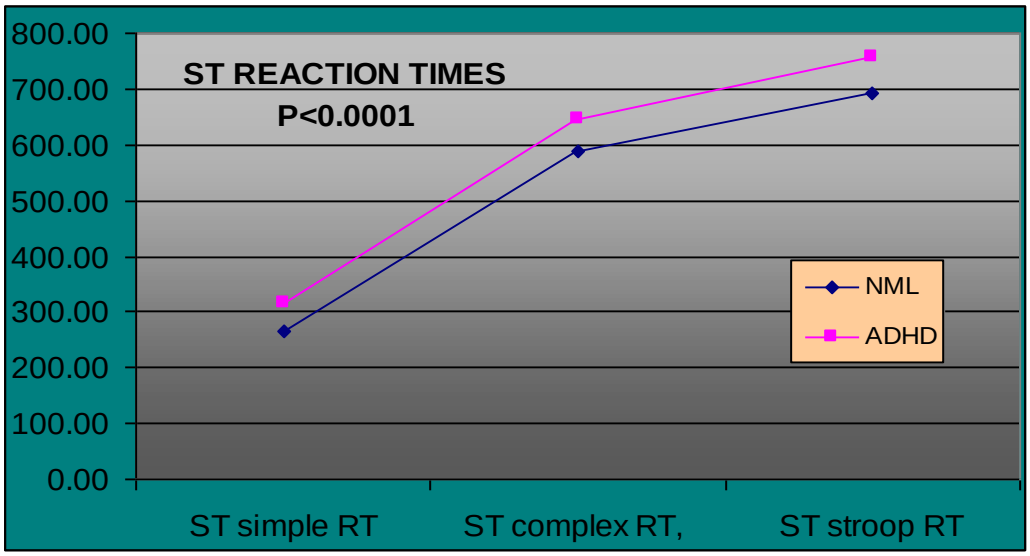
Normal people over the age of 10 seldom make more than 2 errors on the CPT and rarely, if ever, make more 4 errors. In some cases, for example, intelligent and motivated adolescents with ADHD who are not particularly hyperactive or impulsive, performance on the CPT may be normal. Or, the results may only be suggestive: scores in the 50th percentile, for example, in a patient whose IQ is clearly superior.

It may be surprising to learn that ADHD patients have reaction times on the CPT that are *slower* than normals. It is, however, in keeping with modern theories of ADHD that refer to a primary deficit in executive control systems, and a relative inefficiency in processing information in effortful tasks.

THE STROOP TEST

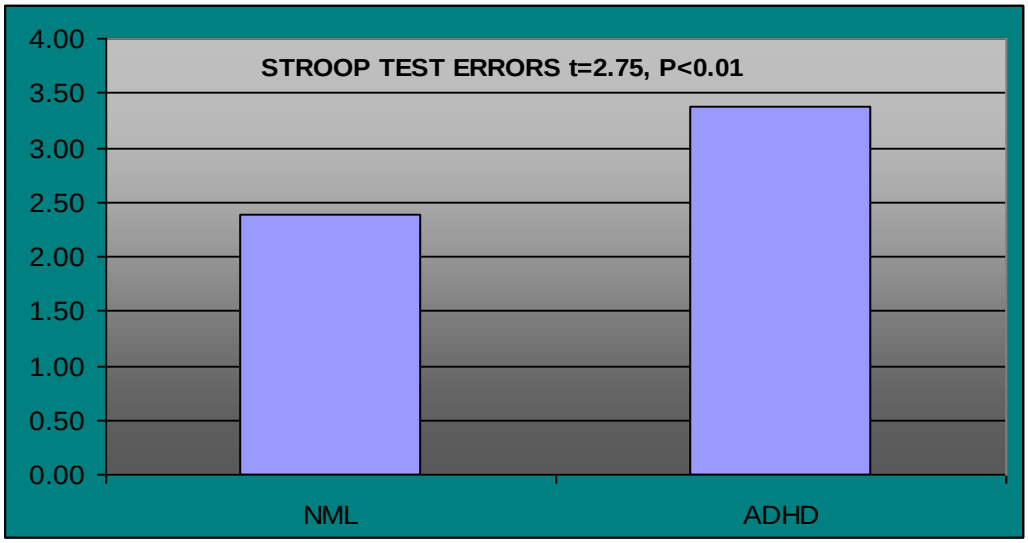
The ST is a measure of executive control, specifically, inhibition/disinhibition. ADHD patients also have slower reaction time scores on the Stroop test – for simple RT, complex RT and the Stroop RT. On the average, they are about 58 msecs slower. This indicates their relative inefficiency in this complex task.

Figure 4. ST Reaction Times in ADHD Patients and Normal Controls



They also make more mistakes on Part 3 of the ST. So: not only do they take longer, but they make more mistakes. As ADHD patients grow older, they learn to make fewer mistakes on tasks like the ST, but their RT's remain comparatively slower.

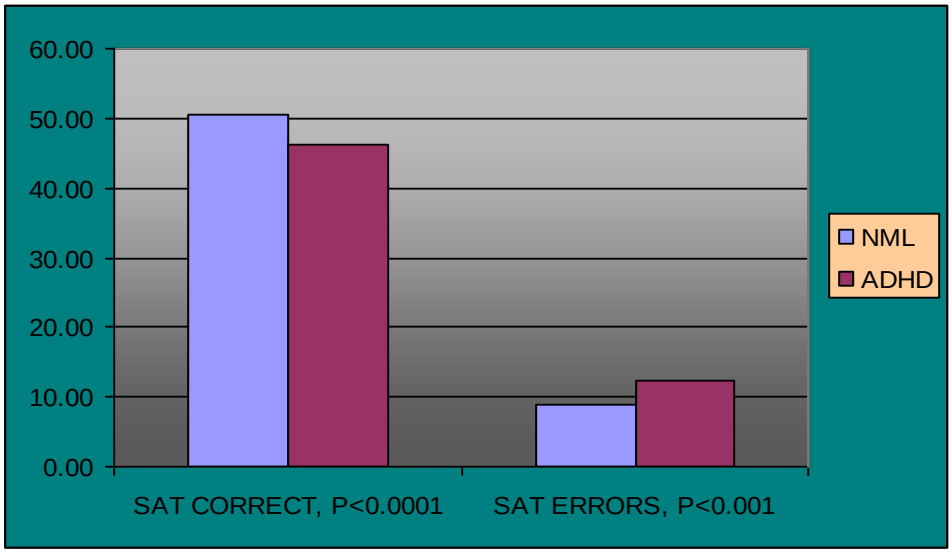
Figure 5. ST Errors in ADHD Patients and Normal Controls



THE SHIFTING ATTENTION TEST

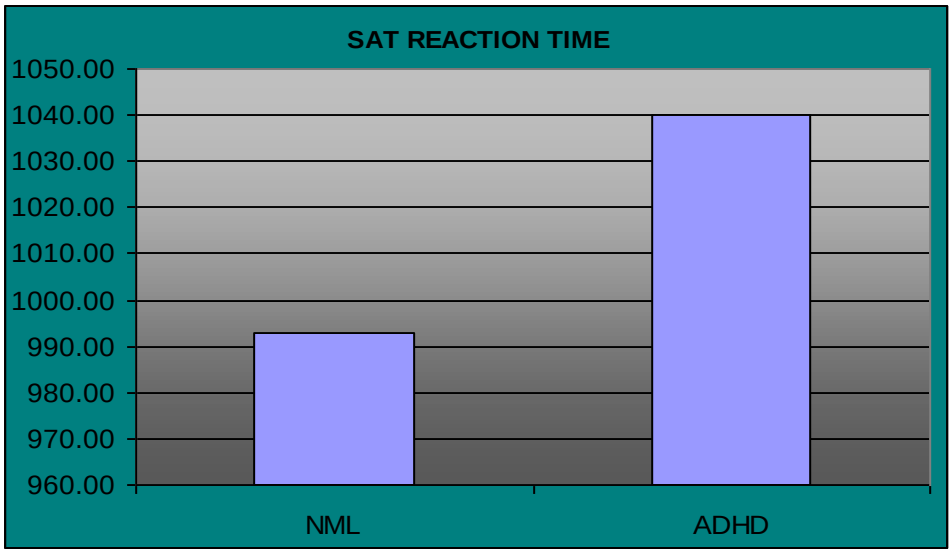
The SAT is another test of executive control, specifically, a test of cognitive flexibility. ADHD patients tend to do poorly on this test. Of all the tests in CNS Vital Signs, it is probably the most sensitive. In the figure below, ADHD patients make fewer correct responses than normals, and more errors.

Figure 6. The SAT in ADHD Patients and Normals



ADHD patients, as a group, have longer reaction times on the SAT.

Figure 7. SAT Reaction Time in ADHD Patients and Normals, P<0.02



The SAT, however, is also what is called a "speed-accuracy tradeoff test." That means the subject can choose to go faster on the test, with more correct responses and a shorter reaction time. That strategy, though, will generate more errors. An alternative strategy is to minimize errors by going more slowly; in this case, the subject will get fewer correct responses and will have a longer reaction time. As a group, ADHD patients are slower and less accurate than normals. However, some ADHD patients are much faster than normals on this test, but much less accurate.

The key to interpreting the SAT is the number of errors made. A high number of errors with a short reaction time indicates an impulsive response style. A high number of errors with a slow reaction time indicates cognitive inefficiency.

SENSITIVITY AND SPECIFICITY

The seven tests in the Vital Signs battery generate six domain scores: the "Cognitive Flexibility" domain is calculated from the ST and the SAT; the "Complex Attention" domain score is calculated from the ST, the SAT and the CPT; the "Attention/Vigilance" is generated from the CPT alone. Patients with ADHD will usually do poorly in cognitive flexibility and the two attention domains.

This is a typical pattern for the domain scores in an ADHD patient:

Table 2. Neurocognitive Profile of a Patient with ADHD

	Above	Average	Below	Well Below
NEUROCOGNITION INDEX (NCI)				
MEMORY				
PSYCHOMOTOR SPEED				
REACTION TIME*				
COMPLEX ATTENTION*				
COGNITIVE FLEXIBILITY				
ATTENTION/VIGILANCE				

Factor Analysis indicates that performance on tests of cognitive flexibility and complex attention (ST, SAT, CPT) are the most important components of the ADHD diagnosis.

Another way to examine CNS Vital Signs in the diagnosis of ADHD is sensitivity and specificity analysis. Taking the data from 175 ADHD patients and 175 normal controls, we can draw what is called a Receiver Operating Characteristic Curve (ROC). The area under the ROC curve is a measure of the sensitivity and specificity of the different tests in CNS Vital Signs.

Table 3. ROC Curve Data for the NCI and Six CNS Vital Signs Domains

	AUC	P<
NCI	0.670	0.0000
MEMORY	0.519	0.5376
PSYCHOMOTOR	0.601	0.0011
REACTION TIME	0.641	0.0000
COGN FLEX	0.651	0.0000
COMPL ATT	0.664	0.0000
VIGILANCE	0.512	0.7076
Null hypothesis: true area = 0.5		

Domain scores generated by the Stroop test and the shifting attention test (reaction time, cognitive flexibility and complex attention) yielded the highest levels of sensitivity/specificity. The Neurocognition index, a general summary score, was even better, indicating that ADHD affects cognitive performance in general. The CPT (Vigilance) did not yield impressive results. Neither did the Memory domain.

4. THE "TEST-DOSE PARADIGM"

The next step in ADHD evaluation is the "test-dose" parading. If the diagnosis of ADHD is supported by the evaluation thus far, it is appropriate to administer a "test dose" of methylphenidate (0.30 mg/kg/dose) or amphetamine (0.15 mg/kg/dose). The patient can be sent away to have some lunch, and then return after an hour. Then the test battery is repeated, the patients pulse and blood pressure are measured, and inquiries are made about subjective response, parents' observations and side effects. The comparative test scores are reviewed with the patient and his or her parents. (This is also an opportunity to teach patients how the tests work, so they can use the web-based screener for follow-up testing on their own.)

The following data is taken from a study of 127 ADHD patients, age 7-55, who were given the "test dose" procedure as part of their initial evaluation. Seventy three patients were administered a single dose methylphenidate (0.40 mg/kg, maximum 30 mg), and 54, amphetamine salts (0.15 mg/kg, maximum 20 mg). Domain scores are reported as standard scores (mean of 100, standard deviation of 15). In addition, a "Neurocognition Index" is also presented, an average score generated from the various domain scores. The differences are highly significant (two tailed t test) except for the memory domain score.

Table 4. Domain Scores Before and After a Test Dose of Stimulant

DOMAIN SCORES	METHYLPHENIDATE			AMPHETAMINE		
	PRE	POST	P<	PRE	POST	P<
NCI	84.8	95.9	0.0007	87.5	98.0	0.0000
MEMORY	89.8	88.5	0.7555	91.8	90.9	0.7774
PSYCHOMOTOR SPEED	87.3	100.0	0.0006	89.2	98.0	0.0150
PROCESSING SPEED	86.3	98.7	0.0051	90.0	99.7	0.0032
COGNITIVE FLEXIBILITY	83.1	99.7	0.0000	85.5	100.3	0.0000
COMPLEX ATTENTION	78.8	97.5	0.0000	82.0	98.0	0.0000
VIGILANCE ATTENTION	79.6	98.7	0.0000	83.5	100.2	0.0000

Figure 8a. Test Dose Data with Methylphenidate

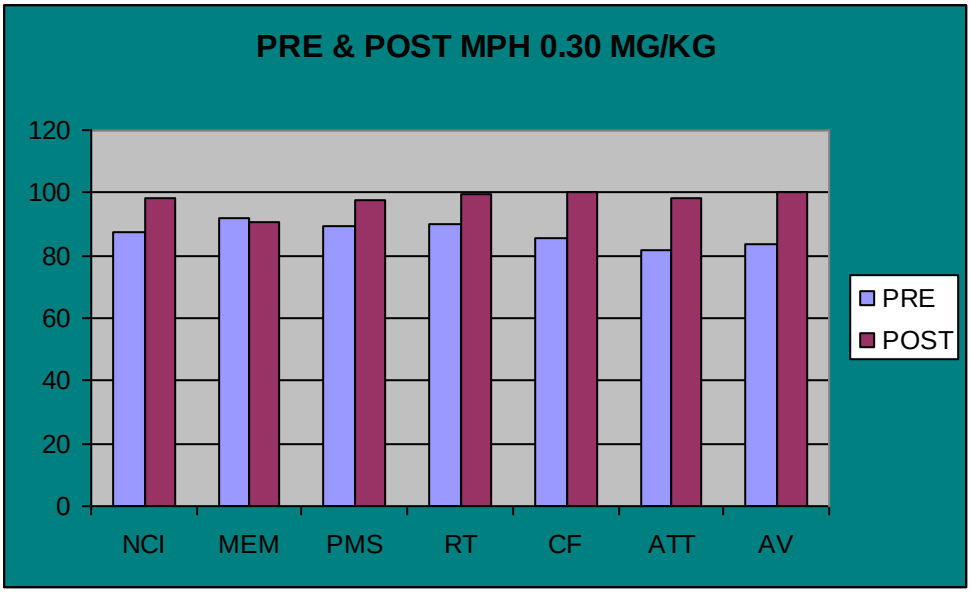
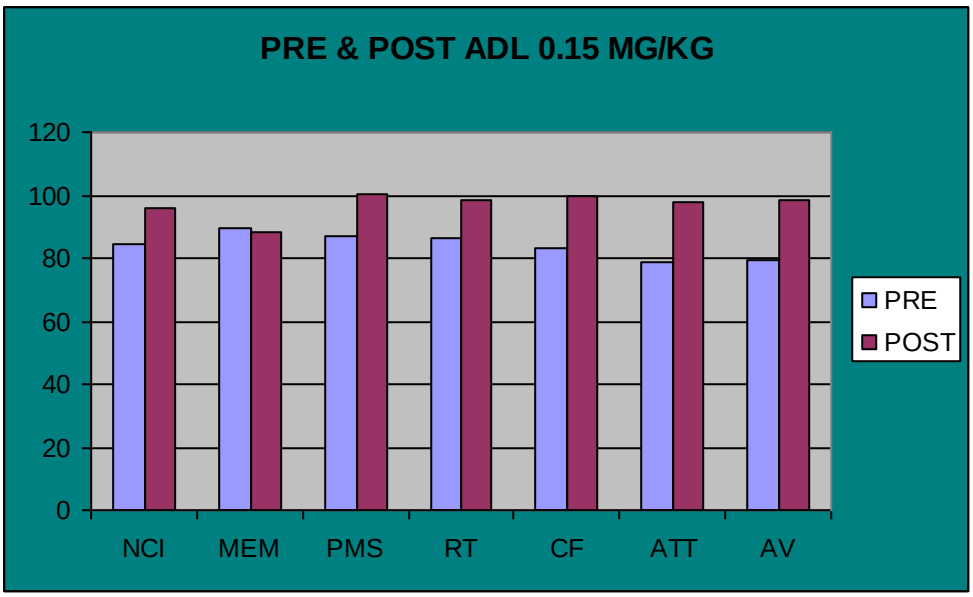


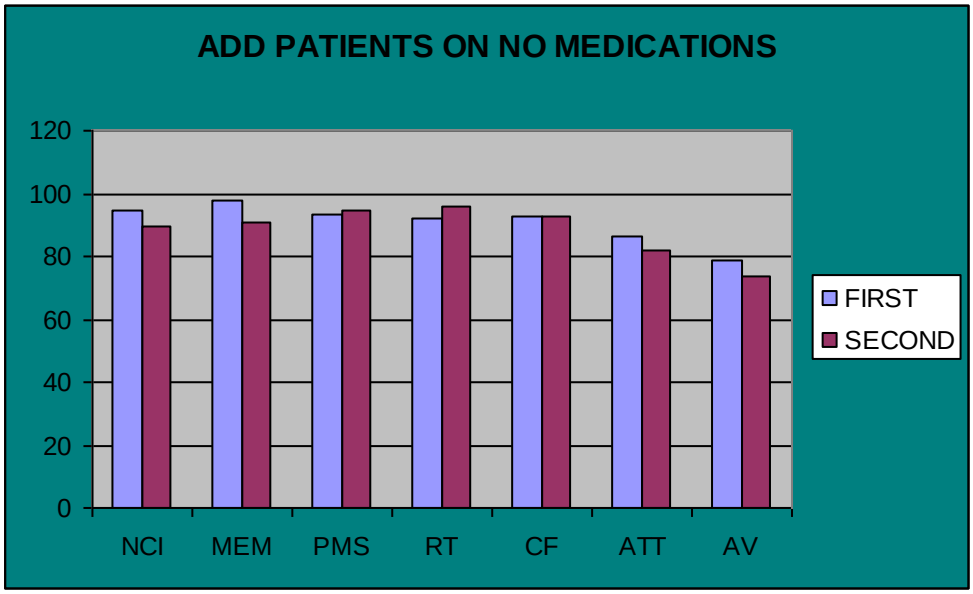
Table 8b. Test Dose Data with Amphetamine



The changes after a test dose, either with methylphenidate or amphetamine are clearly apparent. Multivariate analysis indicates equal effects for both drugs, and no effect relative to age or gender.

Nor can the changes be attributed simply to taking the test twice – a "learning effect." For illustrative purposes, here is data from 24 ADHD patients, age 7-55, who took the Vital Signs battery on two occasions, off-drug both times. None of the differences are significant (two-tailed t test):

Figure 9. CNS Vital Signs Scores in ADHD Patients Tested Twice on No Medications



5. OBJECTIVE TREATMENT EVALUATION

The "test dose" paradigm" yields a great deal of data about the patient and his or her response to a psychostimulant drug. It is also a good way to educate patients about how drugs work, and how psychiatrists monitor drug treatment. It does not, however, indicate how well a patient will do clinically on a particular drug, or even which drug, or dose, is ideal for that patient.

It has been our custom to write two prescriptions for patients who do, in fact, have ADHD, and who seem to do well after a test dose. One is for a two-week trial of long acting methylphenidate, and the second is for a two-week trial of long-acting amphetamine. We give the patient a likely dose range to try, and make arrangements to adjust doses and deal with problems by phone. We arrange for follow-up in one month, to determine which drug was preferable, and, if necessary, consider trials of alternative medications.

During these clinical trials, the patient is invited to use the tests on the Internet Screener, under different drug and dose conditions, and to take advantage of the rating scales on the website as well. These data can be printed out by the patient, or downloaded as a report from the database, for the next follow-up visit.

Improvement in performance on Vital Signs or the Web Screener is not the only criterion one should use to determine whether an ADHD drug is indicated, or effective. But it certainly does address several of the cardinal problems of ADHD: inattention, impulsive responding,

deficits in complex attention, and executive dysfunction. It is not sufficient for diagnosing and managing ADHD, but it is certainly a necessary component.

This is an extremely informative and cost-effective approach to the management of ADHD. It combines clinical evaluation with computerized tests and systematic evaluation of drug response. It takes advantage of the rapid onset of action of the psychostimulant drugs, and the drug-sensitivity of CNS Vital Signs. It establishes continuity between evaluation and treatment.

SUMMARY

Poor performance on a neurocognitive battery does not prove that a patient has ADHD, or that a stimulant drug is warranted. ADHD is a clinical diagnosis, and physicians have to synthesize data from numerous sources to generate a proper diagnosis. But it is appropriate to integrate neurocognitive data into the evaluation of any cognitive disorder, and also into the complicated process of treatment monitoring.

A positive response to a stimulant in the test dose paradigm does not prove that the patient really has ADHD, or that the test dose drug is the one the patient ought to take long-term. But it does give you confidence in trying a couple of drug alternatives, and it teaches the patient (or parents) a little about how to evaluate drug effects. (For the same reason, we recommend that one or both parents take CNS Vital Signs sometime during the kid's evaluation. It teaches them how the tests work; the kids like to see their parents suffer through the same test they had to take, twice; and, sometimes, you pick up a parent with ADHD.)

Similarly, a negative response to the test dose does not mean that the patient does not have ADHD or that drug treatment is unwarranted. It does give pause, though; you may take the opportunity to reconsider your differential diagnosis before proceeding. The test dose paradigm is not an infallible procedure. But it does give the physician objective data upon which to base his or her clinical decisions.

Psychiatry has not had good luck as a procedure-based discipline, with unfortunate consequences for the economic stature of psychiatrists. As a rule, procedure-based specialties are much more remunerative than their non-procedure-oriented counterparts; compare invasive cardiology to non-invasive cardiology. That economic reality reflects what patients want from a specialist: not simply the ability to fill out a DSM checklist, but rather, the generation of specialized information in the service of proper diagnosis and appropriate, individualized treatment. The availability of efficient computerized neurocognitive screening measures provides psychiatrists with procedures that are precise, reliable, and sensitive. They are good for psychiatrists, and good, too, for the patients.

THE STROOP TEST

In 1935, the psychologist JR Stroop demonstrated that naming is slowed when subjects are asked to name the ink color of an incongruous color word; for example, the word "blue" printed in red ink (13). The incongruity of word color and word meaning generates an "interference" effect.

The Stroop test is still used as part of standard neuropsychological batteries and several computerized versions of the test have been developed. It is a favorite test in studies of the neurocognitive effects of CNS drugs, especially anti-epileptic drugs.

There have been several versions of the Stroop test over the years. The modification adopted for CNS Vital Signs uses only four colors/color words (red, green, yellow, blue), and only one key is in play, the space bar. The test has three parts. In the first, the words RED, YELLOW, BLUE and GREEN (printed in black) appear at random on the screen, and the subject presses the space bar as soon as he or she sees the word. This generates a simple reaction time score.

In the second part, the words RED, YELLOW, BLUE and GREEN appear on the screen, printed in color. The subject is asked to press the space bar when the color of the word matches what the word says. This generates a complex reaction time score.

In the third part, the words RED, YELLOW, BLUE and GREEN appear on the screen, printed in color. The subject is asked to press the space bar when the color of the word does not match what the word says. This part also generates a complex reaction time score, called the "Stroop reaction time." The Stroop reaction time is, on average 120 msecs longer than the complex reaction time generated in part two of the test (range, 78-188 msecs). Part three also generates an error score.

A domain score for "reaction time," or, to be more precise, information processing speed, is generated by averaging the two complex reaction time scores from the Stroop test.

THE SHIFTING ATTENTION TEST

The Shifting Attention Test (SAT) measures the subject's ability to shift from one instruction set to another quickly and accurately. In the SAT test, subjects are instructed to match geometric objects either by shape or by color. Three figures appear on the screen, one on top and two on the bottom. The top figure is either a square or a circle. The bottom figures are a square and a circle. The figures are either red or blue; the colors are mixed randomly. The subject is asked to match one of the bottom figures to the top figure. The rules change at random. For one presentation, the rule is to match the figures by shape, for another, by color. This goes on for 90 seconds. The goal is to make as many correct matches as one can in the time allotted. The scores generated by the SAT are: correct matches, errors, and response time in milliseconds.

There is not a precise parallel to the SAT in the compendium of conventional neuropsychological tests, although Trails B and the Wisconsin Cart Sort are considered to be tests of shifting attention. Computerized tests, however, like the NES2, CogState and CANTAB have shifting attention tests that are not dissimilar to the SAT, and color-shape tests like the SAT have been used in cognitive imaging studies (14,15).

A domain score for cognitive flexibility is generated by taking the number of correct responses on the SAT and subtracting the number of errors on the SAT and the Stroop test.

THE CONTINUOUS PERFORMANCE TEST

The CPT is a measure of **vigilance** or **sustained attention** or attention over time (16). It has been a popular test because of its robust relationship to psychiatric disorders. Poor performance on the CPT has been reported in ADHD (17,18), learning disabilities (11,19,20), patients with epilepsy (21) and schizophrenics (22,23). It is sensitive to CNS dysfunction in general, and is not specific to any particular condition (24).

The CPT is also sensitive, for better or worse, to the effects of various drugs. In ADHD children, performance on the CPT is reliably improved by stimulant medications (25,26). Alcohol consumption (27) adversely affects performance on the CPT, but nicotine tends to improve performance on the test (28). Certain anticonvulsant medications impair performance on the CPT (29).

The CPT in Vital Signs is a conventional version of the test, although it is shorter than some other versions. In the Vital Signs CPT, the subject is asked to respond to target stimulus "B" but not to any other letter. In five minutes, the test presents 200 letters. Forty of the stimuli are targets (the letter "B"), 160 are non-targets (other letters). The stimuli are presented at random, although the target stimulus is "blocked" so it appears eight times during each minute of the test.

Scoring is correct responses, commission errors (impulsive responding), and omission errors (inattention). The CPT also reports subjects' choice reaction time for each variable. A domain score for "complex attention" is generated by adding the number of errors committed in the CPT, the SAT and the Stroop.

REFERENCES

1. Wender P. *Attention-Deficit Hyperactivity Disorder in Adults*. New York: Oxford University Press, 1995.

2. Rowland AS, Lesesne CA, Abramowitz AJ. The epidemiology of attention-deficit/hyperactivity disorder (ADHD): a public health view. *Mental Retardation & Developmental Disabilities Research Reviews* 2002; 8: 162-170.

3. Barbaresi WJ, Katusic SK, Colligan RC, Pankratz VS, Weaver AL, Weber KJ, Mrazek DA, Jacobsen SJ. How common is attention-deficit/hyperactivity disorder? Incidence in a population-based birth cohort in Rochester, Minn. *Archives of Pediatrics and Adolescent Medicine* 2002; 156: 217-224.

4. Rosvold HE, Mirsky AF. The closed-field intelligence test for rats adapted for water-escape motivation. *Canadian Journal of Psychology* 1954; 8: 10-16.

5. Greenberg LM, Waldman ID. Developmental normative data on the test of variables of attention (T.O.V.A.). *Journal of Child Psychology and Psychiatry* 1993; 34: 1019-1030.

6. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin* 1997; 121: 65-94.

7. Dulcan M. Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. American Academy of Child and Adolescent Psychiatry. *Journal of the American Academy of Child & Adolescent Psychiatry* 1997; 36: 85S-121S.

8. Forbes GB. Clinical utility of the Test of Variables of Attention (TOVA) in the diagnosis of attention-deficit/hyperactivity disorder. *Journal of Clinical Psychology* 1998; 54: 461-476.

9. Raggio DJ, Rhodes RL, Whitten JD. Factor analysis of the continuous performance test and parent-teacher reports of attention deficit disorder. *Psychology Reports* 1999; 85: 935-941.

10. Rielly NE, Cunningham CE, Richards JE, Elbard HJ, Mahoney WJ. Detecting Attention Deficit Hyperactivity Disorder in a communications clinic: diagnostic utility of the Gordon Diagnostic System. *Journal of Clinical and Experimental Neuropsychology* 1999; 21: 685-700.

11. McGee RA, Clark SE, Symons DK. Does the Conners' Continuous Performance Test aid in ADHD diagnosis? *Journal of Abnormal Child Psychology* 2000; 28: 415-424.

12. Letz R, DiIorio CK, Shafer PO, Yeager KA, Schomer DL, Henry TR. Further standardization of some NES3 tests. *Neurotoxicology* 2003; 24: 491-501.

13. Mead LA, Mayer AR, Bobholz JA, Woodley SJ, Cunningham JM, Hammeke TA, Rao SM. Neural basis of the Stroop interference task: response competition or selective attention? *Journal of International Neuropsychological Society* 2002; 8: 735-42.

14. Le TH, Pardo JV, Hu X. 4 T-fMRI study of nonspatial shifting of selective attention: cerebellar and parietal contributions. *Journal of Neurophysiology* 1998; 79: 1535-1548.

15. Nagahama Y, Sadato N, Yamauchi H, Katsumi Y, Hayashi T, Fukuyama H, Kimura J, Shibasaki H, Yonekura Y. Neural activity during attention shifts between object features. *Neuroreport* 1998; 9: 2633-2638.

16. Rosvold HE, Delgado JM. The effect on delayed-alternation test performance of stimulating or destroying electrically structures within the frontal lobes of the monkey's brain. *Journal of Comparative & Physiological Psychology* 1956; 49: 365-72.

17. Sykes DH, Douglas VI, Weiss G, Minde KK. Attention in hyperactive children and the effect of methylphenidate (ritalin). *Journal of Child Psychology and Psychiatry* 1971; 12: 129-139.

18. Epstein JN, Johnson DE, Varia IM, Conners CK. Neuropsychological assessment of response inhibition in adults with ADHD. *Journal of Clinical & Experimental Neuropsychology* 2001; 23: 362-371.

19. Noland JS, Singer LT, Short EJ, Minnes S, Arendt RE, Lester KH, Bearer C. Prenatal drug exposure and selective attention in preschoolers. *Neurotoxicology and Teratology* 2005; 27: 429-438.

20. Lindsay RL, Tomazic T, Levine MD, Accardo PJ. Attentional function as measured by a Continuous Performance Task in children with dyscalculia. *Journal of Developmental & Behavioral Pediatrics* 2001; 22: 287-292.

21. Mirksy AF, van Buren JM. On the nature of the "absence" in centrencephalic epilepsy: a study of some behavioral, electroencephalographic and autonomic factors. *Electroencephalography and Clinical Neurophysiology* 1965; 18: 348.

22. Wohlberg GW, Kornetsky C. Sustained attention in remitted schizophrenics. *Archives in General Psychiatry* 1973; 28: 533-537.

23. Vadhan NP, Serper MR, Harvey PD, Chou JC, Cancro R. Convergent validity and neuropsychological correlates of the schedule for the assessment of negative symptoms (SANS) attention subscale. *Journal of Nervous and Mental Disease* 2001; 189: 637-641.

24. Riccio CA, Reynolds CR. Continuous performance tests are sensitive to ADHD in adults but lack specificity. A review and critique for differential diagnosis. *Annals of the New York Academy of Science* 2001; 931: 113-139.

25. Barkley RA. A review of stimulant drug research with hyperactive children. *Journal of Child Psychology and Psychiatry* 1977; 18: 137-165.

26. Riccio CA, Waldrop JJ, Reynolds CR, Lowe P. Effects of stimulants on the continuous performance test (CPT): implications for CPT use and interpretation. *Journal of Neuropsychiatry and Clinical Neuroscience* 2001; 13: 326-335.

27. Dougherty DM, Marsh DM, Moeller FG, Chokshi RV, Rosen VC. Effects of moderate and high doses of alcohol on attention, impulsivity, discriminability, and response bias in immediate and delayed memory task performance. *Alcohol and Clinical Experimental Research* 2000; 24: 1702-1711.

28. Levin ED, Conners CK, Silva D, Canu W, March J. Effects of chronic nicotine and methylphenidate in adults with attention deficit/hyperactivity disorder. *Experimental and Clinical Psychopharmacology* 2001; 9: 83-90.

29. Hutt SJ, Jackson PM, Belsham A, Higgins G. Perceptual-motor behaviour in relation to blood phenobarbitone level: a preliminary report. *Developmental Medicine and Child Neurology* 1968; 10: 626-632.