



Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience

The EEG Consistency Index as a Psycho-Physiological Marker of ADHD and Methylphenidate Response: Replication of Results

Jennifer Kim Penberthy PhD ^a, Daniel Cox PhD ^a, Raina Robeva PhD ^b, Boris Kovatchev PhD ^a & R. Lawrence Merkel MD and PhD ^a

^a Department of Psychiatric Medicine, Center for Behavioral Medicine Research, University of Virginia Health System, Charlottesville, Virginia

^b Department of Mathematical Sciences, Sweet Briar College, Sweet Briar, VA
Published online: 08 Sep 2008.

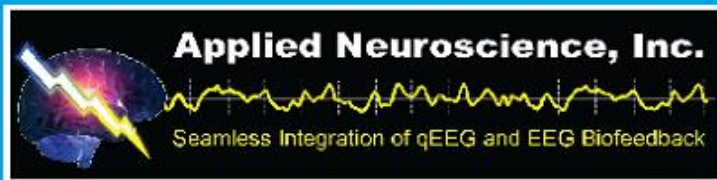
To cite this article: Jennifer Kim Penberthy PhD, Daniel Cox PhD, Raina Robeva PhD, Boris Kovatchev PhD & R. Lawrence Merkel MD and PhD (2006) The EEG Consistency Index as a Psycho-Physiological Marker of ADHD and Methylphenidate Response: Replication of Results, *Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience*, 10:1, 33-43

To link to this article: http://dx.doi.org/10.1300/J184v10n01_03

PLEASE SCROLL DOWN FOR ARTICLE

© International Society for Neurofeedback and Research (ISNR), all rights reserved. This article (the "Article") may be accessed online from ISNR at no charge. The Article may be viewed online, stored in electronic or physical form, or archived for research, teaching, and private study purposes. The Article may be archived in public libraries or university libraries at the direction of said public library or university library. Any other reproduction of the Article for redistribution, sale, resale, loan, sublicensing, systematic supply, or other distribution, including both physical and electronic reproduction for such purposes, is expressly forbidden. Preparing or reproducing derivative works of this article is expressly forbidden. ISNR makes no representation or warranty as to the accuracy or completeness of any content in the Article. From 1995 to 2013 the *Journal of Neurotherapy* was the official publication of ISNR (www.isnr.org); on April 27, 2016 ISNR acquired the journal from Taylor & Francis Group, LLC. In 2014, ISNR established its official open-access journal *NeuroRegulation* (ISSN: 2373-0587; www.neuroregulation.org).

THIS OPEN-ACCESS CONTENT MADE POSSIBLE BY THESE GENEROUS SPONSORS



The EEG Consistency Index as a Psycho-Physiological Marker of ADHD and Methylphenidate Response: Replication of Results

Jennifer Kim Penberthy, PhD
Daniel Cox, PhD
Raina Robeva, PhD
Boris Kovatchev, PhD
R. Lawrence Merkel, MD, PhD

ABSTRACT. The current study replicates the design and findings of earlier studies examining an EEG measure called the Consistency Index (CI) as a physiological measure of ADHD (Cox et al., 1998; Cox, Merkel, Kovatchev, & Seward, 2000; Kovatchev et al., 2001) and medication response (Merkel et al., 2000). Six males diagnosed with ADHD between the ages of 16 and 19 were examined in this study. The average CI for participants while off of medication was 26%, indicative of ADHD (CI < 40% strong likelihood of ADHD). These CI readings changed significantly when the participants were on therapeutic dosages of methylphenidate. Five of six participants demonstrated a CI > 50%, which is similar to the CI of an individual with no ADHD (Cox et al., 1998, 2000; Kovatchev et al., 2001). Overall, the average CI when on an effective dose of methylphenidate was 57% (CI > 50% strong likelihood of no ADHD). These changes in overall CI were statistically significant ($p < 0.05$) and demonstrate exciting possibilities for the utility of the CI as a physiological marker of ADHD. doi:10.1300/J184v10n01_03

KEYWORDS. ADHD assessment, EEG, consistency index, methylphenidate

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a common and debilitating condition that is associated with patterns of inatten-

tive, impulsive, and hyperactive behaviors (APA, 1994). Estimates of the prevalence of this disorder range from 5 to 15 percent of the school-age population (APA, 1994; Barkley, 1990). ADHD occurs more commonly in boys

Jennifer Kim Penberthy, Daniel Cox, Boris Kovatchev, and R. Lawrence Merkel are affiliated with the Center for Behavioral Medicine Research, Department of Psychiatric Medicine, University of Virginia Health System, Charlottesville, Virginia.

Raina Robeva is affiliated with the Department of Mathematical Sciences, Sweet Briar College, Sweet Briar, VA. Address correspondence to: Jennifer Kim Penberthy, Department of Psychiatric Medicine, P. O. Box 800137, UVA Health System, Charlottesville, VA 22908 (E-mail: jkp2n@virginia.edu).

This study was supported by a grant from McNeil Consumer & Specialty Pharmaceuticals, Inc.

than girls, with ratios ranging from 4:1 to 9:1 (Monastra et al., 1999) and the onset of the disorder typically occurs prior to age seven. ADHD can lead to significant academic, family, mental health, legal, and employment difficulties throughout development (Biederman et al., 1993; Mannuzza, Gittleman-Klein, Bessler, Malloy, & LaPadula, 1993; Mannuzza et al., 1991).

Like most psychiatric disorders, the diagnosis of ADHD relies on subjective criteria. The difficulty in clinical diagnosis is reflected in the frequent shifts in the diagnostic criteria for ADHD. The DSM-III (APA, 1980), DSM-III-R (APA, 1987), and DSM-IV (APA, 1994) all present different conceptualizations of ADHD. The most current criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) distinguish three subtypes of ADHD: predominantly inattentive type also known as attention deficit disorder (ADD), predominantly hyperactive-impulsive type, and combined type. In addition to the core clinical symptoms of ADHD, high levels of co-morbidity have been found with learning, oppositional defiant, conduct, mood, and anxiety disorders (Biederman, Newcorn, & Sprich, 1991). DSM-IV diagnostic criteria for ADHD include "a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals in a comparable level of development. Evidence of six of nine inattentive behaviors and/or six of nine hyperactive-impulsive behaviors must have been present before age seven, and must clearly interfere with social, academic, and/or occupational functioning" (APA, 1994). Consequently, diagnosis of ADHD is typically based on retrospective reports from parents and teachers of a child's behavior, and is highly dependent upon subjective judgments about the degree of relative impairment. Due to the subjective nature of assessment, precision in diagnosis has been elusive. Determining a biological measure that could aid in the diagnosis of ADHD would help to refine diagnostic criteria and may provide more specific diagnostic tests for ADHD and other disorders of attention and self-regulation. Although research supports a neurological basis for ADHD (Hynd et al., 1991; Castellanos, 1997; Berquin et al., 1998; Mostofsky, Reiss, Lockhart, & Denckla, 1998;

Raskin, Shaywitz, Shaywitz, Anderson, & Cohen, 1984; Crawford & Barbasz, 1996; Heilman, Voeller, & Nadeau, 1991; Zametkin et al., 1990; Castellanos et al., 2001; Castellanos et al., 2002) there are few definitive large studies examining EEG as a quantifiable physiological marker of ADHD.

Most investigators accept that ADHD exists as a distinct clinical syndrome and suggest a multi-factorial etiology that includes neurobiology as an important factor. Zametkin and Rapoport (1987) identified eleven separate neuroanatomical hypotheses that have been proposed for the etiology of ADHD. A majority of studies have concluded that either delayed maturation (Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992; Matsuura et al., 1993; Clarke, Barry, McCarthy & Selikowitz, 1998; El-Sayed, Larsson, Persson, & Rydelius, 2002) or defects in cortical activation (Chabot & Serfontein, 1996; Heilman et al., 1991; Lou, Henriksen, & Bruhn, 1984) play large roles in the pathophysiology of ADHD. Unfortunately, while neuroanatomical findings via magnetic resonance imaging (MRI; Giedd et al., 1996), functional MRI (Garcia-Sanchez, Estevez-Gonzalez, Suarez-Romero, & Junque, 1997), positron emission tomography (PET; Zametkin et al., 1990), and single photon emission computed tomography (SPECT; Seig, Gaffney, Preston, & Hellings, 1995) support the notion that ADHD is a distinct clinical syndrome and add to our understanding of the etiology of ADHD, neuroimaging techniques are too expensive for general use, are restricted to a few centers, and generally lack clear specificity and sensitivity in the diagnosis of ADHD. One technique suggested by a National Institute of Mental Health committee as a possible method to identify functional measures of child and adolescent psychopathology is that of quantitative electroencephalography (QEEG; Jensen et al., 1993). Compared to methods of functional neuroimaging (such as PET or SPECT), QEEG is easier to perform, less expensive, does not involve radioactive tracers, and is noninvasive (Kuperman, Gaffney, Hamdan-Allen, Preston, & Venkatesh, 1990).

QEEG is based on analysis of brain activity that is originally recorded as frequent samples of brain waves. The frequency of sampling is usually about 256 Hz, which allows for a math-

emational reconstruction of brain wave frequencies to 64 Hz. The standard method employed for processing of the data is Fast Fourier Transformation (FFT), which produces power spectrums of brain activity every two to three seconds. These power spectrums are further analyzed for abnormalities associated with ADHD. Thus, the resolution of these analyses is on the order of seconds.

Using a combination of visual inspection and quantitative techniques, during the 1970s several laboratories reported differences between the EEGs of hyperactive and normal children (Wolraich & Baumgaertel, 1997). Among the differences discovered were: a higher percentage of abnormal EEG patterns (abnormal usually meaning excessive slow wave activity) in clinical subjects than in controls (APA, 1994); more power in the 0 to 8 Hz spectrum in hyperactive children compared to normal controls (Satterfield, Cantwell, Lesser, & Podosin, 1972); less power in the 10 Hz range for hyperactive children versus controls (Montague, 1975); and less beta and weaker stimulus-locked alpha attenuation in hyperactive children than in non-hyperactive children (Grunewald-Zuberbier, Grunewald, & Rasche, 1975). However, early research demonstrated no definitive patterns of EEG data to discriminate hyperactive, inattentive, or impulsive children from controls.

Numerous investigators have reported that only when subjects are engaged in behavioral paradigms (particularly those manipulating attention) do electrophysiological differences appear between normal and hyperactive or LD children (Dykman, Holcomb, Oglesby, & Ackerman., 1982). Partially in response to this deficit in the research literature, Dykman et al. (1982) investigated the EEGs of four groups of boys (10 hyperactive, 10 learning-disabled, 10 with both hyperactivity and LD) engaged in a complex visual search task. Spectral analysis of EEG data indicated that LD boys, hyperactive boys, and boys with a mixed diagnosis displayed less beta and less stimulus-locked alpha than normal boys.

Research in the mid 1980s to mid 1990s began to address issues of uniformity of diagnosis, methodology, and accuracy in EEG acquisition, both in terms of theoretical understanding and technical application. In an

attempt to clarify some of the EEG differences between hyperactive and normal subjects, Satterfield, Schell, Backs, and Hidaka (1984) examined the impact of age upon EEGs and determined that EEG power spectral intensities of normal male children decrease with increasing age. However, EEG power declines slower with increasing age in hyperactive subjects. Overall, they concluded “. . . electrophysiological differences between hyperactive and normal male children are complex and vary markedly with age” (Satterfield et al., 1984). More recent studies employing spectral analysis of EEG have also shown varying patterns of EEG activity in ADHD subjects. Mann et al. (1992) found increased theta (4-7.75 Hz) at both absolute and relative percent power calculations, and decreased beta (12.75-21 Hz) in temporal and frontal sites. Janzen, Graap, Stephanson, Marshall and Fitzsimmons (1995) demonstrated that their ADD group had higher theta amplitudes for all sites. However, unlike Mann et al. (1992), Janzen et al. (1995) found no differences between groups for beta at all amplitudes.

A few studies employed a coherence analysis, which involves a cross-correlation that measures the relationship of activity in one site of the brain to another. Chabot and Serfontein (1996) tested 407 children with attention deficits with and without hyperactivity, with and without learning problems, children with attention problems who failed to reach DSM-III criteria for the disorder, and 310 controls (ages 6-17). They employed coherence analysis and observed patterns of excess theta in frontal regions and increased alpha (relative power) in the posterior regions for the clinical groups versus controls. They also reported that one-third of their subjects showed signs of interhemispheric dysregulation characterized by this pattern of excessive theta/alpha power in the right temporal and premotor (frontal) areas. Bresnahan, Anderson, and Barry (1999) investigated patterns of activity with QEEG and observed increased theta activity and decreased beta activity across all age groups of children. The decline in beta activity reduced with age. Bresnahan et al. (1999) concluded that because the hyperactivity component in ADHD tends to decrease with age while the impulsivity tends to persist, their data suggests reduced beta activity

may be related to hyperactivity and that increased theta activity may be related to impulsivity. These patterns replicate findings of the study done by Mann et al. (1992).

Monastra et al. (1999) report similar results from their study on 482 subjects (ages 6-30). EEG data were used to test the hypothesis that prefrontal cortical slowing (excess theta) can differentiate ADHD subtypes from controls. Analysis of variance demonstrated cortical slowing that differentiated ADHD subjects, regardless of sex or age. Specifically, statistical analysis revealed that the ADHD groups (inattentive and combined type) displayed significantly higher levels of slow-wave (theta) relative to fast-wave (beta) EEG activity. Consequently, Monastra et al. (1999) derived an individual Attentional Index (AI) equal to the theta-beta power ratio of a subject. This index, which is the numerical inverse of a previously published ratio used by NASA (Engagement Index) to track attentional changes in pilots (Pope & Bogart, 1991; Pope, Comstock, Bartolome, Bogart, & Burdette, 1994) was significantly larger for the ADHD groups than for the control group. However, in research performed by Kuperman et al. (1990) ADHD subjects had the contrary findings of increased beta band relative to percent power (RPP) while ADD subjects had less delta band RPP and more beta band RPP. Only the ADD group demonstrated significant asymmetry between hemispheres. Clarke et al. (1998) also found contradictory results in the form of a decrease in alpha activity. In contrast to Mann et al. (1992), Clarke et al. (1998) report less posterior absolute beta power in posterior regions.

A few studies have found excessive slow and low alpha activity associated with ADHD in children and young adults, and some researchers have proposed that these findings may support a maturational lag theory of ADHD EEG abnormalities of the brain (Matsuura, et al., 1993; Crawford, Corby, & Kopell, 1996; Clarke et al., 1998; Chabot & Serfontein, 1996). Activities of the waking EEG in alpha frequencies have special significance in that they form the "alpha rhythm," a posteriorly dominant activity that attenuates (or "blocks") with eye opening. This rhythm first emerges at age three to four months and gradually increases in frequency until adult levels are attained in late childhood.

Since the alpha rhythm is slowed or absent during heightened anxiety or extremely low arousal such as drowsiness, attaining alpha enhancement (increasing power of alpha) is more difficult for both over-aroused subjects (such as ADHD subjects) and for under-aroused subjects (again, such as ADHD subjects or other persons suffering from inattention). Therefore, alpha blockade would be predicted between cognitive tasks for persons with ADHD.

Overall, numerous studies have contrasted ADHD versus non-ADHD children using various EEG acquisition and analysis techniques and have found differences (e.g., increased alpha and beta band frequency), but the specific differences have been inconsistent. However, one important trend in the literature is the finding of patterns of higher levels of theta relative to beta (Mann et al., 1992; Bresnahan et al., 1999; Lazzaro et al., 1998). The presence of theta and the absence of beta may be the neural substrate of the inability to shift between tasks in order to focus on the task at hand. This is affirmed in a recent research that hypothesizes that an ADHD individual has difficulty in responding to the target task, not difficulty with ignoring peripheral stimuli (McDonald, Bennett, Chambers, & Castiello, 1999).

Although several studies have examined the EEGs of children while performing various tasks (e.g., reading and arithmetic), only one research group has examined the children specifically while they transition from one cognitive task to another cognitive task (Cox, Kovatchev et al., 1998; Cox, Merkel et al., 2000; Merkel et al., 2000; Kovatchev et al., 2001; Robeva, Penberthy, Loboschewski, Cox, & Kovatchev, 2004; Penberthy et al., 2005). Because both clinical experience and research (Schachar, Tannock, Marriott, & Logan, 1993) support the notion that children with ADHD have difficulty cognitively transitioning from one task to another, Cox and his colleagues (Cox et al., 1998) measured differences between a small sample of boys with ADHD ($n = 4$) and non-ADHD boys ($n = 4$) as they cognitively shifted from watching a video to reading a book. They found a marker based on EEG data, labeled the Consistency Index (CI) that clearly differentiated the two groups ($p < .001$). It was discovered that the EEG power patterns of boys with and without ADHD differed substantially when the

boys transitioned between two contiguous cognitive tasks. It became apparent that the EEG power shift from one task to another, calculated spatially and temporally, was more “consistent” in non-ADHD boys than in boys diagnosed with ADHD. Specifically, the EEG power shifts found in non-ADHD boys was mathematically more uniform and predictable than the power shifts found in the EEGs of the children diagnosed with ADHD. Thus, a measure that quantified the EEG power consistency during participants’ transition from one cognitive task to another was developed via a mathematical model of EEG transition consistency and called the Consistency Index (CI).

The development of the CI was based upon a quantitative representation of the idea that ADHD is reflected by chaotic changes in the EEG power spectrum when participants shift from one cognitive task to another. The CI contains a rigid mathematical frame that incorporates this idea. This frame is based on the EEG data stream as represented by a three-dimensional numeric array: at any given moment one dimension is frequency of brain waves, another is spatial (the location of the electrode on a subject’s head) and the third is time. ADHD can cause irregularity or inconsistency either in the frequency or the spatial dimension, or in both, when shifting across cognitive tasks (Kovatchev et al., 2001). The algorithm for computing the CI is described in detail in the methods section.

In previous research, the CI clearly separated ADHD from control participants (Cox et al., 1998; Kovatchev et al., 2001; Merkel et al., 2000) and these findings were highly reliable when test-retest reliability was evaluated (Cox et al., 1998). The CI was highly stable over three months and correlated .85 ($p < .001$) with a checklist of ADHD symptoms based on the DSM-IV criteria for diagnosing the disorder (Cox et al., 1998; Kovatchev et al., 2001). Cox et al. (1998) concluded “more research is needed to determine whether measures of cognitive transition such as the CI are reliable and generalize, as they might allow for more effective assessment and diagnosis of ADHD as well as a greater understanding of its etiology and course.”

Merkel et al. (2000) acquired EEGs from male subjects (ages 19 to 25) while they performed two easy and two hard tasks, both audi-

tory and visual, of the Gordon Diagnostic System. The study was a double blind, placebo versus methylphenidate controlled crossover design. Six ADHD participants were found to have a significantly lower CI than six non-ADHD males while transitioning from two simple tasks during placebo condition, while only the ADHD participants demonstrated a significant improvement in their CI while on methylphenidate. Similar but non-significant trends were observed while transitioning across hard tasks.

In addition, Loo, Teale, and Reite (1999) and Loo, Hopfer, Teale, and Reite (2004) found that ADHD children exhibiting a positive medication response to methylphenidate, had reductions of theta and alpha activity as well as increased beta activity in the frontal regions, while non-responders showed the opposite pattern ($p < .05$). They also found that increased frontal beta activity was significantly correlated with medication-related improvement in performance on the Conners’ Continuous Performance Test (CPT) and parent behavior ratings in attention and hyperactivity. Loo et al. (1999, 2004) conclude that stimulant medication increases frontal region beta activity in children with ADHD.

Thus, preliminary research appears to support that electrophysiologic differences are found between children with ADHD and those without ADHD. Specifically, beta activity and the EEG CI have been used as physiological correlates of ADHD, and have been found in preliminary research to normalize in ADHD children who are responsive to a therapeutic dose of methylphenidate.

The purpose of the current study is to replicate portions of the Cox et al. (1998 and 2000), Kovatchev et al. (2001) and Merkel et al. (2000) preliminary studies with a sample of older males who have been diagnosed with ADHD, and to examine the changes in the EEG CI when such individuals are adequately medicated with methylphenidate. Since it is estimated that there are fewer adolescent males diagnosed with ADHD, primarily hyperactive-impulsive type, than are diagnosed with either combined type or primarily inattentive type (DSM-IV), and the fact that we did not recruit any adolescent males who met criteria for ADHD, primarily hyperactive-impulsive type, we did not in-

clude this subtype in our study. Our hypotheses were as follows: (a) lower EEG consistency during transitions from one cognitive task to another (Consistency Index of $\leq 40\%$) will be a significant physiological marker associated with individuals with ADHD-Combined (ADHD-Com) type or ADHD-Inattentive type (ADHD-In), and (b) the EEG CI will increase or normalize ($CI \geq 50\%$) in individuals with ADHD-com or ADHD-In who are treated with adequate doses of methylphenidate.

METHODS

Participants

This study was approved by the local Institutional Review Board, and potential participants were recruited through local high school nurses and newspaper advertisement. Eleven adolescent males responded to advertising or recruitment efforts, and were screened over the phone. Four of these were excluded based on their reported inability to dedicate the time required to complete the study. Seven adolescent males, with a mean age of 17.2 ± 1.2 years met the initial criteria on the phone screen and were invited to participate in this repeated measures study. One of the participants (subject No. 2) dropped out of the study after being accepted, due to the unexpected death of a close friend. Therefore, six participants completed the entire study protocol. Please see Table 1 for details regarding subject data, including age and diagnosis. Four of the participants met criteria for Attention Deficit Hyperactivity Disorder—Primarily Inattentive Type (ADHD-In) and two of the participants met criteria for Attention Deficit Hyperactivity Disorder—Combined Type (ADHD-Com).

The inclusion criteria for the study included diagnosis of current ADHD as determined by self-report questionnaire and structured diagnostic clinical interview and positive history of methylphenidate responsiveness as reported by subject and parents. Persons were excluded from the study if they reported a history of tics or other adverse reactions to methylphenidate; had a history of substance abuse as reported by subject or parents; or currently met diagnostic

TABLE 1. Subject Characteristics and Medication Dosage

Subject	Age	Diagnosis	Weight (lbs)	MPH/t.i.d. dosage	Co-Morbid Disorders
1	17	ADHD-In	128	10 mg	None
3	16	ADHD-Com	135	10 mg	None
4	18	ADHD-In	197	20 mg	None
5	17	ADHD-Com	208	20 mg	None
6	16	ADHD-In	171	20 mg	Social Phobia
7	19	ADHD-In	309	40 mg	ODD

criteria for a psychiatric disorders of severe depression, anxiety, or psychosis. Three participants (numbers 1, 6, 7) reported that they had been diagnosed with learning disorders such as dyslexia. Two participants met diagnostic criteria for co-morbid psychiatric disorders based upon the Diagnostic Interview Schedule for Children-Parent version (DISC-P IV; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) which was administered to the participants' parent(s) or guardian(s). Specifically, subject number 6 met criteria for social phobia and subject number 7 met current diagnostic criteria for oppositional defiant disorder. These were not exclusionary diagnoses, and therefore these three participants were enrolled in the study.

Procedure

Once screened over the phone, the participants and their parents were invited for an initial meeting and interview. At this first meeting, all participants met with a licensed clinical psychologist who described the study and obtained written informed consent and assent from parents and participants. Parents/guardians then completed the DuPaul ADHD Rating Scale-IV (DuPaul, Power, Anastopoulos, & Reid, 1998) and were administered the DISC-P IV (Shaffer et al., 2000). They were reminded to answer questions about their son's typical behavior when not taking medications for ADHD. Participants and their parents/guardians then met with a psychiatrist who administered a physical exam and confirmed the ADHD diagnosis by the Standardized Interview for Adult ADHD (Barkley, 1998) administered to the subject.

The psychiatrist also gathered information about the participants' pre-study methylphenidate dose and used this to determine the starting drug dose for the treatment condition portion of the study.

The current study was part of a larger, repeated-measure, three-condition study with a two-medication crossover study arm, which examined participants' performance on multiple measures at each condition. The portion of the overall study which we present involved only the first two conditions, specifically examining EEG data acquired when participants performed a procedure involving transitioning between cognitive tasks. The EEG assessments were acquired during the following times: (a) while participants were off medication, and (b) while participants were taking an optimal dose of methylphenidate and had remained on that stable optimal dose for a period of at least seven days. Optimal dosage included achieving a balance of maximizing effectiveness for symptom relief while minimizing negative side effects. For the first EEG acquisition, all short-acting stimulant medications were discontinued for at least 24 hours prior to the assessment, which is considered to be an adequate amount of time for the stimulant to be out of the participants' systems, and therefore not impact the EEG data (Wang et al., 2003). No participants were currently taking long-acting stimulant medications.

EEG Data Acquisition

Participants were seated comfortably in front of a television, and an appropriately sized EEG cap was placed over their heads. Electrode placement was in accordance with the International 10-20 System. Six electrode sites were prepared: a ground in front of Cz, a right earlobe reference electrode, and Cz, Pz, P3, P4. These sites were chosen in accordance with current EEG data research indicating positive findings with these sites (Robeva et al., 2004; Penberthy et al., 2005). EEG signals were amplified and processed by the Lexicor Neurosearch-24 system. Automated artifact rejection software associated with the Lexicor Neurosearch-24 system was implemented during the conversion of raw EEG data into frequency bands. The EEG data collection used standard settings of a clinical

EEG acquisition that include 5 K Ohms impedance criterion measured by a Prep-Check electrode impedance meter. The total frequency range was 0.5 to 32 Hz. Fast Fourier Transform (FFT) was used to compute within each 2.56-second data series the relative power of the following frequency bands: theta (4-7.5 Hz), low alpha (7.5-10 Hz), high alpha (10-13 Hz), and beta (13-22 Hz). Residual power was carried by frequencies below 4 Hz or above 22 Hz. The band powers were converted into percent power for each band and percent residual power. This procedure results in 16 EEG parameters (4 bands \times 4 channels) recorded into a data file every 2.56 seconds. The data was recorded and converted into EEG parameters while the participants completed the following sequence: watched an age-appropriate movie for twenty minutes, rested quietly with eyes open for five minutes, and then read age-appropriate materials silently for ten minutes. Participants were observed and prompted to not fall asleep, as this causes low or absent alpha rhythm and the presence of delta waves in brain activity, clinical signs of sleep, which could confound a CI calculation as it would be measuring a subject's transition from sleeping to waking and not cognitive transition between tasks. One subject (number 4) reported that he was sleepy and repeatedly fell asleep during the EEG acquisition. His initial data were therefore considered invalid, and his EEG while off medications was repeated at another time when he was well rested and able to stay awake throughout the acquisition.

Computing the CI

The algorithm for computing the CI works as follows:

- a. Discrete spectra, including residual power, are calculated for all EEG channels through a standard FFT algorithm. The relative power of the theta, low alpha, high alpha, and beta frequency bands was computed.
- b. Power change distances (PCD) between two contiguous tasks separated by a break are computed for each EEG band and channel, utilizing data from the entire EEG series during two tasks compared to each other. Each PCD is normalized us-

ing the formula below, where $M1$ and $M2$ are the mean powers at two contiguous tasks, $SD1$ and $SD2$ are their standard deviation, and $N1$ and $N2$ are the epoch counts at these tasks. Thus, PCD are specific differences in EEG patterns observed during contiguous tasks.

$$PCD = \frac{M1 - M2}{\sqrt{\frac{SD1^2}{N1} + \frac{SD2^2}{N2}}}$$

- c. PCD undergo filtering to eliminate changes below a “noise threshold” of 1.0: The PCD values that are larger by an absolute value than the threshold will be marked with 1 or -1 depending on their direction, while all PCD below threshold will be marked by zero. This procedure transforms the PCD sequence into a sequence of 1, 0, -1 that indicates, for each EEG band and channel, whether a significant power change was observed while the person shifted from the first task to the next. The CI is defined as the count of non-zero components of this sequence. The maximum CI equals the number of EEG channels multiplied by the number of EEG bands used during spectrum discretization. For our study, with 8-channel EEG equipment and 4 bands, the CI ranges from 0 to 32. In order to make the results comparable across different experiments, the CI is expressed in terms of percentage from its maximum value. As already stated, a CI lower than 40% is indicative of the presence of ADHD and a CI of 50% or more is associated with normal or consistent cognitive transition, and is considered to be indicative of the absence of ADHD.

RESULTS

A significant increase ($t = -2.82$, 2-tail $p = 0.037$) from 26.04% (no medication) to 57.29% (on medication) was observed in the average CI when the participants were on therapeutic doses of methylphenidate. In the ADHD-In group, as summarized in Table 2, four of six participants had a Consistency Index (CI) of

40% or lower when taking no medication, while all but one subject achieved a CI of 50% or more when on methylphenidate.

The results from a classification based on a cutoff of $<40\%$ for ADHD-Com and ADHD-In and $\geq 50\%$ and higher for absence of ADHD-Com and ADHD-In were compared off and on medication. Three out of six participants showed improvement comparable to normal zone ($\geq 50\%$) on methylphenidate. The pre/post classifications of the participants were compared using Wilcoxon matched-pairs signed-rank test resulting in a significant pre/post change from ADHD-Com or ADHD-In to non-ADHD status, $z = -2.02$, 2-tailed $p = 0.043$. In other words, overall, the CIs of participants significantly changed between the conditions of being off medication and being on a therapeutic dose of methylphenidate.

DISCUSSION

In this study we evaluated six males with ADHD-Com or ADHD-In, both on and off methylphenidate. Participants were males between the ages of 16 to 19, and reported a previous positive response to methylphenidate. Four of six ADHD participants had Consistency Indices of 40% or lower when taking no medication, but all participants displayed an increase in their CI when tested on methylphenidate. All but one subject achieved a CI of 50% or more when on methylphenidate and a CI of 50% or more is associated with normal or consistent cognitive transition, and is considered to be in-

TABLE 2. Consistency Index (%) off and on Methylphenidate Medication

Subject	Age	Diagnosis	*CI No Medication	*CI On Medication	Significance
1	17	ADHD-In	18.75	50.00	
2	16	ADHD-Com	68.75	93.75	
4	18	ADHD-In	50.00	50.00	
5	17	ADHD-Com	00.00	68.75	
6	16	ADHD-In	00.00	56.25	
7	19	ADHD-In	18.75	25.00	
Average	17.2		26.04	57.29	$P < 0.05$

*CI ≤ 40 = ADHD-Com or ADHD-In;
 CI ≥ 50 = “normal control” or no ADHD-Com or ADHD-In

dicative of the absence of ADHD-Com or ADHD-In.

This study confirmed the hypotheses that lower EEG consistency during transitions from one cognitive task to another (Consistency Index of $\leq 40\%$) could be a significant physiological marker associated with individuals with ADHD-Com or ADHD-In if further researched. The study also confirmed the hypothesis that the EEG CI will increase or normalize (CI $\geq 50\%$) in individuals with ADHD-Com or ADHD-In who are treated with appropriate doses of methylphenidate.

The results of this study specifically support our earlier work, which demonstrated that the CI during transition between cognitive tasks is associated with diagnosis of ADHD (Cox et al., 1998; Cox et al., 2000; Kovatchev et al., 2001) and that the CI is responsive to methylphenidate (Merkel, 2000). Results of this study also generally support findings by others regarding changes in the EEGs of ADHD children who are responders to methylphenidate (Loo et al., 1999; 2004).

The current results, when combined with previous research data from this lab, lend considerable support to the utility of the EEG Consistency Index as not only a physiological marker of ADHD, but also as a tool capable of detecting treatment effectiveness. Our results indicate that the measures assessed are reactive to methylphenidate, and confirm the ability of the CI to accurately detect treatment efficacy.

Limitations of the present study include small sample size, no female participants, small age range, and lack of non-ADHD control group. Further research is needed, including not only ADHD and non-ADHD controls, but also another diagnostic control group, such as bipolar disorder. Such research would help discern the sensitivity and specificity of the CI to diagnose ADHD versus non-ADHD, both on and off medication, and also begin to determine if the CI findings are specific to ADHD. Development of a reliable method to evaluate a physiological marker of ADHD would increase accurate diagnosis of this potentially destructive disorder and thereby facilitate and ensure that appropriate treatment is administered.

REFERENCES

- American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington, DC: Author.
- American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., rev.). Washington, DC: Author.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.
- Barkley, R.A. (1990). A critique of current diagnostic criteria for attention deficit hyperactivity disorder: Clinical and research implications. *Journal of Developmental & Behavioral Pediatrics*, *11*, 343-352.
- Barkley, R. A. (1998). *Attention deficit hyperactivity disorder: A handbook for diagnosis and treatment* (2nd ed.). New York: Guilford Press.
- Berquin, P. C., Giedd, J. N., Jacobsen, L. K., Hamburger, S. D., Krain, A. L., Rapoport, J. L., et al. (1998). Cerebellum in attention-deficit hyperactivity disorder: A morphometric MRI study. *Neurology*, *50*, 1087-1093.
- Biederman, J., Faroane, S. V., Spencer, T., Wilens, T., Norman, D., Lapey, K. A., et al. (1993). Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention-deficit hyperactivity disorder. *American Journal of Psychiatry*, *150*, 1792-1798.
- Biederman, J., Newcorn, J., & Sprich, S. (1991). Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. *American Journal of Psychiatry*, *148*, 564-577.
- Bresnahan, S. M., Anderson, J. W., & Barry, R. J. (1999). Age-related changes in quantitative EEG in attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *46*, 1690-1697.
- Castellanos, F. X. (1997). Toward a pathophysiology of attention-deficit/hyperactivity disorder. *Clinical Pediatrics (Philadelphia)*, *36*, 381-393.
- Castellanos, F. X., Giedd, J. N., Berquin, P. C., Walter, J. M., Sharp, W., Tran, T., et al. (2001). Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, *58* (3), 289-295.
- Castellanos, F. X., Lee, P. P., Sharp, W., Jeffries, N. O., Greenstein, D. K., Clasen, L. S., et al. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Medical Association*, *288* (14), 1740-1748.
- Chabot, R. J., & Serfontein, G. (1996). Quantitative electroencephalographic profiles of children with attention deficit disorder. *Biological Psychiatry*, *40*, 951-963.
- Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (1998). EEG analysis in attention deficit/hyperactivity disorder: A comparative study of two subtypes. *Psychiatry Research*, *81*, 19-29.

- Cox, D. J., Kovatchev, B. P., Morris, J. B., Phillips, C., Hill, R., & Merkel, L. (1998). Electroencephalographic and psychometric differences between boys with and without Attention-Deficit/Hyperactivity Disorder (ADHD): A pilot study. *Applied Psychophysiology and Biofeedback, 23*, 179-188.
- Cox, D. J., Merkel, R. L., Kovatchev, B., & Seward, R. (2000). Effect of stimulant medication on driving performance of young adults with attention-deficit hyperactivity disorder: A preliminary double-blind placebo controlled trial. *Journal of Nervous and Mental Disorders, 188*, 230-234.
- Crawford, H., & Barabasz, M. (1996). Quantitative EEG magnitudes in children with and without attention deficit disorder during neurological screening and cognitive tasks. *Child Study Journal, 26*, 71-86.
- Crawford, H. J., Corby, J. C., & Kopell, B. S. (1996). Auditory event-related potentials while ignoring tone stimuli: Attentional differences reflected in stimulus intensity and latency responses in low and highly hypnotizable persons. *International Journal of Neuroscience, 85*, 57-69.
- DuPaul, G., Power, T., Anastopoulos, A., & Reid, R. (1998). *ADHD rating scale-IV*. New York: Guilford Press.
- Dykman, R. A., Holcomb, P. J., Oglesby, D. M., & Ackerman, P. T. (1982). Electro cortical frequencies in hyperactive, learning-disabled, mixed, and normal children. *Biological Psychiatry, 1*, 7675-685.
- El-Sayed, E., Larsson, J. O., Persson, H., & Rydelius, P. A. (2002). Altered cortical activity in children with Attention-Deficit/Hyperactivity Disorder during attentional load task. *Journal of the American Academy of Child and Adolescent Psychiatry, 41* (7), 811-819.
- Garcia-Sanchez, C., Estevez-Gonzalez, A., Suarez-Romero, E., & Junque, C. (1997). Right hemisphere dysfunction in subjects with attention deficit disorder with and without hyperactivity. *Journal of Child Neurology, 12*, 107-115.
- Giedd, J. N., Snell, J. W., Lange, N., Rajapakse, J. C., Casey, B. J., Kozuch, P. L., et al. (1996). Quantitative magnetic resonance imaging of human brain development: Ages 4-18. *Cerebral Cortex, 6* (4), 551-560.
- Grunewald-Zuberbier, E., Grunewald, G., & Rasche, A. (1975). Hyperactive behavior and EEG arousal reactions in children. *Electroencephalographic Clinical Neurophysiology, 38*, 149-159.
- Heilman, K. M., Voeller, K. K., & Nedeau, S. E. (1991). A possible pathophysiological substrate of attention deficit hyperactivity disorder. *Journal of Child Neurology, 6*, Suppl, S76-S81.
- Hynd, G. W., Semrud-Clikeman, M., Lorys, A. R., Novey, E. S., Eliopoulos, D., & Lyytinen, H. (1991). Corpus callosum morphology in attention deficit-hyperactivity disorder: Morphometric analysis of MRI. *Journal of Learning Disabilities, 24*, 141-146.
- Janzen, T., Graap, K., Stephanson, S., Marshall, W., & Fitzsimmons, G. (1995). Differences in baseline EEG measures for ADD and normally achieving preadolescent males. *Biofeedback Self Regulation, 20*, 65-82.
- Jensen, P. S., Koretz, D., Locke, B. Z., Schneider, S., Radke-Yarrow, M., & Richters, J. E. (1993). Child and adolescent psychopathology research: Problems and prospects for the 1990s. *Journal of Abnormal Child Psychology, 21*, 551-581.
- Kovatchev, B. P., Cox, D. J., Hill, R., Reeve, R., Robeva, R. S., & Loboschewski, T. (2001). A psychophysiological marker of Attention Deficit/Hyperactivity Disorder: Defining the EEG consistency index. *Applied Psychophysiology and Biofeedback, 26*, 127-139.
- Kuperman, S., Gaffney, G. R., Hamdan-Allen, G., Preston, D. F., & Venkatesh, L. (1990). Neuroimaging in child and adolescent psychiatry. *Journal of the American Academy of Child and Adolescent Psychiatry, 29*, 159-172.
- Lazzaro, I., Gordon, E., Whitmont, S., Plahn, M., Li, W., Clarke, S., et al. (1998). Quantified EEG activity in adolescent attention deficit hyperactivity disorder. *Clinical Electroencephalography, 29*, 37-42.
- Loo, S. K., Teale, P. D., & Reite, M. L. (1999). EEG correlates of methylphenidate response among children with ADHD: A preliminary report. *Biological Psychiatry, 45*, 1657-1660.
- Loo, S. K., Hopfer, C., Teale, P. D., & Reite, M. L. (2004). EEG correlates of methylphenidate response in ADHD: Association with cognitive and behavioral measures. *Journal of Clinical Neurophysiology, 21* (6), 457-464.
- Lou, H. C., Henriksen, L., & Bruhn, P. (1984). Focal cerebral hypoperfusion in children with dysphasia and/or attention deficit disorder. *Archives of Neurology, 41*, 825-829.
- Mann, C. A., Lubar, J. F., Zimmerman, A. W., Miller, C. A., & Muenchen, R. A. (1992). Quantitative analysis of EEG in boys with attention-deficit-hyperactivity disorder: Controlled study with clinical implications. *Pediatric Neurology, 8*, 30-36.
- Mannuzza, S., Gittleman-Klein, R. G., Bessler, A., Malloy, P., & LaPadula, M. (1993). Adult outcome of hyperactive boys: Education achievement, occupational rank, and psychiatric status. *Archives of General Psychiatry, 50*, 565, 576.
- Manuzza, S., Klein, R. G., Bonagura, N., Malloy, P., Giampino, T. L., & Inalli, K. A. (1991). Hyperactive boys almost grown up. Replication of psychiatric status. *Archives of General Psychiatry, 48*, 77-83.
- Matsuura, M., Okubo, Y., Michio, T., Kojima, T., He, Y., Hou, Y., et al. (1993). A cross sectional EEG study of children with emotional and behavioral problems. *Biological Psychiatry, 34*, 59-65.
- McDonald, S., Bennett, K. M., Chambers, H., & Castiello, U. (1999). Covert orienting and focusing of attention in children with attention deficit hyperactivity disorder. *Neuropsychologia, 37*, 345-356.
- Merkel, R. L., Cox, D. J., Kovatchev, B. P., Morris, J., Seward, R., Hill, R., et al. (2000). The EEG consistency index as a measure of Attention Deficit/Hyper-

- activity Disorder and responsiveness to medication: A double blind placebo controlled pilot study. *Applied Psychophysiology and Biofeedback*, 25, 133-142.
- Monastra, V. J., Lubar, J. F., Linden, M., VanDeusen, P., Green, G., Wing, W., et al. (1999). Assessing attention deficit hyperactivity disorder via quantitative electroencephalography: An initial validation study. *Neuropsychology*, 13, 424-433.
- Montague, J. D. (1975). The hyperkinetic child: A behavioural, electrodermal and EEG investigation. *Developmental Medical Child Neurology*, 17, 299-305.
- Mostofsky, S. H., Reiss, A. L., Lockhart, P., & Denckla, M. B. (1998). Evaluation of cerebellar size in attention-deficit hyperactivity disorder. *Journal of Child Neurology*, 13, 434-439.
- Penberthy, J. K., Cox, D. J., Breton, M., Robeva, R., Loboschefski, T., & Kovatchev, B. P. (2005). Calibrated bio-behavioral assessment of ADHD: A prospective study of a meta-analysis method. *Applied Psychophysiology and Biofeedback*, 30 (1), 31-51.
- Pope, A. T., & Bogart, E. H. (1991). Extended attention span training. *Proceedings of Technology 2001 Conference*, 1, 368-404.
- Pope, A. T., Comstock, J. R., Bartolome, D. S., Bogart, E. H., & Burdette, D. W. (1994). Biocybernetic system validates index of operator engagement in automated tasks. In M. Mouloua & R. Parasuraman (Eds.), *Human performance in automated systems: Current research and trends* (pp. 300-306). Hillsdale, NJ: Lawrence Erlbaum Associates.
- Raskin, L. A., Shaywitz, S. E., Shaywitz, B. A., Anderson, G. M., & Cohen, D. J. (1984). Eurochemical correlates of attention deficit disorder. *Pediatric Clinics of North America*, 31, 387-396.
- Robeva, R., Penberthy, J. K., Loboschefski, T., Cox, D., & Kovatchev, B. (2004). Combined psychophysiological assessment of ADHD: A pilot study of Bayesian probability approach illustrated by appraisal of ADHD in female college students. *Applied Psychophysiology and Biofeedback*, 29 (1), 1-18.
- Satterfield, J. H., Cantwell, D. P., Lesser, L. I., & Podosin, R. L. (1972). Physiological studies of the hyperkinetic child. I. *American Journal of Psychiatry*, 128, 1418-1424.
- Satterfield, J. H., Schell, A. M., Backs, R. W., & Hidaka, K. C. (1984). A cross-sectional and longitudinal study of age effects of electrophysiological measures in hyperactive and normal children. *Biological Psychiatry*, 19, 973-990.
- Schachar, R., Tannock, R., Marriott, M., & Logan, G. (1993). Deficient inhibitory control in Attention-Deficit Hyperactivity Disorder. *Journal of Abnormal Child Psychology*, 23, 411-437.
- Seig, K. G., Gaffiney, G. R., Preston, D. F., & Hellings, J. A. (1995). SPECT brain imaging anomalies in attention deficit disorder. *Clinical Nuclear Medicine*, 20, 55-60.
- Shaffer, D., Fisher, P., Lucas, C. P., Dulcan, M. K., & Schwab-Stone, M. E. (2000). NIMH diagnostic interview schedule for children version IV (NIMH DICS-IV): Description, differences from previous versions, and reliability of some common diagnoses. *Journal of American Academy of Child & Adolescent Psychiatry*, 39, 28-38.
- Wang, Y., Lee, L., Somma, R., Thompson, G., Bakhtiar, R., Lee, J., et al. (2003). *In vitro* dissolution and *in vivo* oral absorption of methylphenidate from a bimodal release formulation in healthy volunteers. *Biopharmaceutics and Drug Disposition*, 25 (2), 91-98.
- Wolraich, M. L., & Baumgaertel, A. (1997). The practical aspects of diagnosing and managing children with attention deficit hyperactivity disorder. *Clinical Pediatrics (Philadelphia)*, 36, 497-504.
- Zametkin, A. J., & Rapoport, J. L. (1987). Neurobiology of attention deficit disorder with hyperactivity: Where have we come in 50 years? *Journal of the American Academy of Child and Adolescent Psychiatry*, 26, 676-686.
- Zametkin A. J., Nordahl, T. E., Gross, M., King, A. C., Semple, W. E., Rumsey, J., et al. (1990). Cerebral glucose metabolism in adults with hyperactivity of childhood onset. *New England Journal of Medicine*, 323, 1361-1366.

RECEIVED: 03/07/05
 REVISED: 08/09/05
 ACCEPTED: 10/14/05