Research Support for QEEG as a Diagnostic Aid for ADHD

The NeuroLex SM Indicator Report for ADHD is based on extensive research supporting the use of quantitative electroencephalography (QEEG) as an assessment aid for patients presenting with attention problems. In a recent Child and Adolescent Psychiatric Clinics of North America article, Chabot, di Michele, and Prichep (2005) reviewed the research support on the use of Quantitative EEG as an assessment aid for ADHD and concluded:

“these findings justify the clinical use of QEEG in the initial screening and treatment evaluation stages of children with ADD, ADHD, and LD.... A QEEG can aid in the detection of organicity as the cause of brain dysfunction in children who present with learning and attention problems...A QEEG can play a role in optimizing pharmacologic, remediation, or psychological intervention.”

This paper summarizes the research supporting this conclusion.

Background

Quantitative EEG (QEEG) is digital EEG and employs computerized acquisition of EEG data, refined signal processing, and mathematical transformations of EEG data so that EEG patterns associated with particular psychiatric disorders can be identified. The premise underlying this approach is that different neurocognitive disorders can be identified and characterized by distinctive patterns of brain electrical activity and that the identification of these patterns can provide a reliable biological marker of different disorders. The EEG pattern reliably present in individuals with ADHD involves reduced electrical activity in the prefrontal cortex. Specifically, individuals with ADHD typically show an abnormally high amount of slow frequency theta waves (3.5-7.5 HZ) relative to higher frequency beta waves (12.5-25 HZ).

When used as an assessment aid for ADHD, QEEG data for an individual patient is evaluated mathematically to determine various biological indicators that are compared to known values published in peer reviewed literature and derived from clinical data.

As you consider the QEEG research findings summarized below, be mindful of the studies’ basic method. Like all psychiatric disorders, ADHD is diagnosed using the criteria outlined in the DSM-IV. These include a number of specific behavioral symptoms, as well as the requirements that the symptoms create significant impairment, were evident relatively early in life, and are not better explained by another psychiatric condition. The studies examining the utility of QEEG as an assessment aid compared QEEG findings for meticulously diagnosed ADHD patients with findings obtained from normal controls. Repeatedly across studies, group differences for particular EEG variables were found providing direct evidence of the presence of a specific and unique EEG pattern in people meeting DSM-IV diagnostic criteria for ADHD. Thus, a biological marker for ADHD has been identified.

There are two related ways research results can be used to gauge whether QEEG procedures substantially enhance the accuracy of clinicians’ diagnostic decisions. One approach involves comparing the average difference in EEG variables between groups of individuals with and without ADHD. In research within this tradition, group differences are typically expressed using a statistic
called an “effect size”. Effect size is computed by considering the size of the difference between groups in relation to the amount of variability within groups. In behavioral research, an effect size above .80 is regarded as large and an effect size of 3 is typically interpreted to mean that the populations are distinctly different on the measure being considered; i.e., there is essentially no overlap between populations of interest.

The second approach for evaluating the clinical utility of QEEG findings is to examine how accurately individuals can be classified into ADHD vs. normal groups using QEEG results considered in isolation. If QEEG results provided a perfectly reliable indicator of ADHD, then 100% of individuals with ADHD would screen positive for the EEG marker and everyone without ADHD would screen negative. Such a measure would be said to have 100% sensitivity – everyone with ADHD shows the marker – as well as 100% specificity – no one without ADHD shows the marker. In medicine, assessment tools with 80% sensitivity and 80% specificity are considered useful for routine use within clinical practice. For example, mammograms have a reported sensitivity and specificity of 93% and 97% respectively (Eltahir, et al, 1999). As you shall see, the data supporting the use of QEEG to assist in the evaluation of ADHD is comparable to this mainstream medical procedure.

Research Findings – Dr. Steve Snyder, Lexicor’s Director of Research and Development, and Dr. James Hall, Professor, University of North Texas Health Sciences Center, recently completed a meta-analysis of studies examining QEEG as an assessment aid for ADHD. A meta-analysis involves a rigorous method for pooling and analyzing results from multiple studies so that the overall pattern of results in a particular research area can be obtained. The value of this approach is that by pooling information across studies, more reliable information can be obtained than that provided by a single investigation. Studies included in this meta-analysis were those in which EEG data of individuals diagnosed with ADHD via comprehensive DSM-IV evaluation procedures were compared to normal controls. Thirteen studies, completed by 5 different research groups with no affiliation to Lexicor, published since 1997 met the inclusion criteria. A total of 2642 subjects were included in these studies. A summary of the findings from these individual studies, along with complete references to the published articles, is provided at the end of this section.

Results of the meta-analysis indicated statistically significant and substantial differences in the size of the theta/beta ratio for individuals with ADHD vs. controls. Across the 13 studies, the pooled effect size was equal to 3.08. As explained above, an effect size of this magnitude indicates that the groups are essentially distinct in regards to this EEG marker of ADHD and there is very little overlap on this marker. To put the magnitude of this difference into context, the effect size typically found for medication treatment of ADHD is around 1.0. This means that, on average, treatment is associated with a decrease of about 1 standard deviation on a rating of ADHD symptoms. In contrast, the difference in the average QEEG theta/beta ratio between ADHD and control groups was just over 3 standard deviation units.

As noted above, another way to evaluate the clinical utility of QEEG findings is to examine the extent to which individuals with and without ADHD are correctly classified using QEEG data. There have been 2 studies published recently that provide data relevant to this approach (Monastra et al., 1999; Monastra, Lubar, & Linden, 2001.) The first study included 482 participants ages 6-30 who were classified as ADHD, Inattentive Type (n=176), ADHD, Combined Type (n=221), or normal controls (n=85) based on a comprehensive DSM-IV based evaluation. The researchers examined the accuracy of an elevated theta/beta ratio – the cut off they used was 1.5 standard
deviations above the normal population mean - for correctly identifying whether or not each participant met diagnostic criteria for ADHD. Results indicated that 86% of individuals with ADHD showed this elevated theta/beta ratio, i.e., the sensitivity was 86%. In contrast, the theta/beta ratio was below this level in 98% of normal controls, i.e., the specificity was 98%. In a second study published by this research group that included 469 participants between the ages of 6 and 20, the sensitivity and specificity figures obtained were 90% and 94% respectively.

Comparison of QEEG data to other tests used in the evaluation of ADHD – The QEEG findings summarized above are even more impressive when they are considered in relation to other procedures that are frequently used to assist in the evaluation of ADHD. A paper published recently in Neuropsychology (Frazier, Demaree, & Youngstrom, 2004) reports data on a wide range of neuropsychological tests that are often used for this purpose. The tests examined in this paper included IQ tests, computerized tests of attention (i.e., Continuous Performance Tests), and a number of neuropsychological measures of executive functioning (e.g., the Wisconsin Card Sorting Test, the Stop Signal Task, the Trail Making Test). Of note is that not a single measure was found to have an average effect size greater than 1.0. Thus, in comparison to the results discussed above for the QEEG, other widely used assessments are far less accurate in differentiating between individuals with and without ADHD.

What about the value of the standardized behavior rating scales that are frequently used by clinicians as part of their comprehensive ADHD evaluations? Because these scales are used to obtain ratings of specific ADHD symptoms, it is reasonable to expect that they would be highly accurate in distinguishing between individuals with ADHD and normal controls. However, the sensitivity and specificity data for such measures is not as robust as one might expect. In a recent paper reviewing the use of behavior rating scales used to assess ADHD (Collett, Ohan, & Myers, 2003) the sensitivity and specificity data reported for the most widely used rating scales ranged from 49-84%, substantially lower than what has been found for QEEG. The only rating scale with sensitivity and specificity data comparable to what has been found for QEEG were the Conners Rating Scales, although results reported for the Conners are likely to be inflated because of limitations in how the research was conducted (Snyder, Drozd, & Xenakis, 2004).

These data suggest that QEEG findings are more likely to accurately discriminate between individuals with and without ADHD than the most widely used behavior rating scales. These findings do not minimize the value of rating scales as part of a comprehensive ADHD evaluation, as such measures can play a very important role. It does point out, however, that incorporating QEEG results into a comprehensive diagnostic evaluation will provide an important source of independent information that can be extremely helpful in your diagnostic decisions. In addition, as discussed in the section on the clinical benefit of using NeuroLexSM, including this objective procedure to obtain a direct measure of a patient’s brain functioning is also substantial.

Summary – As discussed above, there is substantial research support for the use of QEEG as an assessment aid for ADHD. Although no single assessment aid, no matter how accurate, should ever be used in isolation to make diagnostic decisions about any individual, as part of a comprehensive evaluation, QEEG findings can play an important role. In fact, as this research overview indicates, the data supporting the use of QEEG as a diagnostic aid is actually stronger than for any of the other widely used tests and behavior rating scales. Professionals who begin using the NeuroLex ServiceSM can thus be confident that QEEG has extensive scientific support. According to Dr. Patricia Quinn, Director of the National Center for Gender Issues and ADHD, QEEG “is the only...
procedure that comes out of the laboratory setting and is practical enough for use in the clinician’s office. By providing an objective measure, it aids the clinician in dealing with several problem areas often encountered in the diagnostic process. QEEG solves problems in identification including: differences in parent vs teacher reports on rating scales; documentation of the inattentive type of the disorder which characteristically has been more difficult to diagnose; and the identification of females which DSM criteria and symptom checklists have characteristically overlooked. In addition, this technology and resulting pattern analysis allows for more accurate diagnosis when the symptoms of coexisting conditions cloud the diagnostic picture.”

Additional information on the use of QEEG in the assessment of psychiatric disorders can be found in the articles referenced below.

References


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The role of quantitative electroencephalography in child and adolescent psychiatric disorders

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This article focuses on computerized methods of quantifying electroencephalography (EEG) and the clinical use of comparing EEG features obtained from specific patients with psychiatric and neurologic disorders to values obtained from a population of normal individuals. The current status of quantitative EEG (qEEG) studies is reviewed with the goal of extracting information that would be useful to the practicing clinician. Although the major focus of this article is the use of qEEG in child and adolescent psychiatric disorders, preliminary sections of this article summarize qEEG findings from relevant adult psychiatric and neurologic disorders. The qEEG studies that involved children and adolescents have been, with a few exceptions, limited to individuals with attention or learning problems. Many qEEG studies of adult psychiatric populations have implications that can impact on our knowledge of childhood disorders and are summarized. Initial sections also present a discussion of the development of qEEG, controversial issues surrounding its clinical usage, and a summary of important methodologic issues.

The clinical uses of qEEG were described in a position paper of the American Medical Electroencephalographic Society [1]. These uses include the detection of an organic disorder as the underlying cause of brain dysfunction, roles in making

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differential diagnosis, and epileptic source localization. We add possible roles in determining appropriate medication selection, following treatment response, and delineating the underlying cause of specific psychiatric disorders. Sections of this article examine the current status of qEEG and how it can impact on these outstanding issues.

The greatest body of evidence regarding replicable neurophysiologic indices of psychiatric and developmental disorders has been provided by qEEG studies. Electrophysiologic assessment is also the most practical and economic neuroimaging method, because it uses relatively simple, inexpensive equipment that can be used in space readily available in clinics, hospitals or private offices. Special purpose qEEG analytic algorithms are widely available from commercial sources, training workshops with continuing medical education accreditation in collection, analysis, and interpretation of data are regularly presented by professional societies and equipment manufacturers, and certification examinations are administered by the American Medical EEG Association and the American Board of Clinical Neurophysiology.

Important technical terms are defined as follows:

- The four commonly used EEG frequency bands used include (1) delta (1.5–3.5 Hz), (2) theta (3.5–7.5 Hz), (3) alpha (7.5–12.5 Hz), and (4) beta (12.5–25 Hz). Total power represents the frequency range of 1.5 to 25 Hz.
- Absolute power: The average amount of power ($\mu\text{V}^2$) in each frequency band and in the total frequency spectrum of the EEG recorded from each electrode site.
- Relative power: The percentage of the total power contributed by each frequency band in the spectrum from each electrode site. These features define the frequency composition of the electrical signal independent of its total power. For example, relative alpha power is the ratio of total alpha power/total power at each electrode site.
- Power asymmetry: Interhemispheric: The ratio of absolute power between corresponding (homologous) regions of the two hemispheres in each frequency band and for the total power across all frequency bands. Intrahemispheric: The ratio of absolute power between regions within a hemisphere in each frequency band and for the total power. This addresses the question, “How similar is the observed activity between/or within hemispheres?”
- Coherence: Interhemispheric: The amount of synchronization of electrical events in corresponding brain regions, separately for each frequency band and for the entire frequency spectrum. Intrahemispheric: The amount of synchronization of electrical events between regions within a hemisphere in each frequency band and for the entire frequency spectrum. This addresses the question, “How synchronized is the observed activity?”
- Mean frequency: The frequency within each band, or for the entire spectrum, above and below which there is the same amount of power. This addresses the question, “Where in each frequency band—or in the entire frequency spectrum—is the concentration of power?”
Historical perspective: origins of the electroencephalogram

Research about the origins of the various EEG frequency bands makes it clear that anatomically complex regulatory systems are involved in the generation of the EEG power spectrum. Brain stem, thalamic, and cortical processes mediate this regulation using all the major neurotransmitters [2–5]. The EEG power spectrum can be argued to be characteristic for human beings, resulting from the coordination of brain processes normally produced in healthy individuals. These facts suggest that EEG frequency measures can be sensitive to brain dysfunctions believed to be abnormal in psychiatric disorders. Numerous twin and family studies have been conducted on normal variation in the human EEG. A recent review concluded that most EEG parameters are to a large extent genetically determined [6]. The effect size of genetic determination is between 76% and 89% for the four EEG frequency bands [7], and about 60% of the variance in theta, alpha, and beta coherence was explained by genetic factors. Environmental factors did not influence variation in coherence [8].

Initial qEEG studies showed systematic changes with maturation from birth to adulthood in the average power in the delta, theta, alpha, and beta frequency bands [9]. Replication studies not only confirmed these systematic changes with age but they also found no significant differences between the EEGs of normally functioning Swedish children and white or black US children [10]. Cultural independence and replication of qEEG findings has been extended to studies from Barbados, China, Cuba, Germany, Holland, Japan, Korea, Mexico, Netherlands, Sweden, United States, and Venezuela [11–24].

The independence from cultural and ethnic factors of normative qEEG descriptors makes possible objective assessment of brain integrity in persons of any age, origin, or background. The incidence of positive findings different from the normative database in healthy, normally functioning individuals repeatedly has been shown to be within the chance levels, with high test-retest reliability. Normative data have been extended to cover the age range from 1 to 95 years of age for each of the electrode positions in the standardized international 10/20 system and broadened to include measures of absolute power, relative power, mean frequency, coherence, and symmetry [25–27].

Controversial issues

The limited acceptance of qEEG in US psychiatry can be attributed largely to two major factors. First, most papers that report the results of qEEG studies of psychiatric patients have not appeared in journals widely read by psychiatrists but rather in specialized electrophysiologic or brain research publications. Reports of qEEG abnormalities in psychiatric patients have been regarded as nonspecific and are not included in the curriculum of medical students or psychiatric residents. Second, since 1989, skeptical statements about the use of qEEG in
psychiatry have appeared in professional journals [28] and in position statements by committees from some professional organizations, such as the American EEG Society, the American Academy of Neurology, and the American Psychiatric Association. These position statements indicated that published qEEG findings were promising but required further research before clinical use could be established. These negative conclusions were repeated in a report by subcommittees of the American Academy of Neurology, the American Clinical Neurophysiology Society, and a panel of experts [29].

Findings from a large number of excellent studies not reviewed by these committees and from numerous studies completed since the time of most of these reviews provide substantial additional support for the validity and clinical use of qEEG in several areas of child psychiatry, however. The American Medical EEG Association recently issued a positive position statement about the clinical value of qEEG in psychiatry [1], and the American Psychiatric Electrophysiological Association established a committee to assess the current use of qEEG examinations in the management of various psychiatric disorders. After a thorough review of more than 500 qEEG and conventional EEG studies of psychiatric patients published in the last 20 years, this positive report was adopted by the Steering Committee of the American Psychiatric Electrophysiological Association in May 1996.

The specificity of qEEG findings recently was questioned in a study that compared the EEGs of 100 normal controls with those obtained from an independent sample of 67 controls and 340 patients with 22 different psychiatric or neurological diagnosis [30]. The authors conclude that while decreases in delta and theta absolute and relative power are specific signs of brain dysfunction that correlate with cortical atrophy, no specific qEEG patterns could be found that were pathognomonic for any specific disorder. While this is an interesting study, there is a fatal flaw that invalidates their conclusion. The group sizes for any specific disorder were highly limited, with the largest group at 57 patients and with nine of the disorders having less than 10 patients. Clearly these numbers are too small to expect anything but non-specific findings. Interestingly, abnormal qEEG findings were reported in 11.9% of their normal controls, suggesting the inadequate number of individuals in their normal database. Furthermore, an editorial appeared in the same journal issue in support of their findings [31]. This editorial made general statements that reiterated potential problems with qEEG research. These included problems with EEG filter settings, artifact inclusion or exclusion, drowsiness, age effects, medication effects, and statistical problems due to the large number of qEEG variables often available for study compared to the size of the patient populations under study. It is interesting that this editorial praises the described study since it suffers from a major problem of small sample sizes. In the following methodological section of this article we address each of these criticisms. We also argue that the use of an appropriate normal database and method of collecting and analyzing qEEG can effectively make such criticism a non-issue. The present article reassess the current status of qEEG research findings in lieu of the criticisms described above.
It is the goal of this article to provide an up-to-date and comprehensive review of all of the relevant research published to date to allow for an informed consideration of the scientific knowledge base on the clinical value of qEEG in child and adolescent psychiatry.

Quantitative electroencephalographic methodologic issues

A brief description of the development, replication, validation, and sensitivity of the neurometric qEEG methodology follows. The neurometric qEEG normative database has been published, and findings using this technique have been replicated widely. Neurometrics is the only qEEG technology that has published normative data and been approved by the US Food and Drug Administration. Complete details have been published elsewhere [11,25,26,32]. The neurometric analytic method enables objective evaluation of brain function based on qEEG. Its initial development was supported by program grants from the Research Applied to National Needs Program of the National Science Foundation and the Bureau of Educational Handicapped of the US Office of Education. An understanding of the important methodologic issues that follow is necessary to offset the criticisms of qEEG that were described previously.

Normative database

The neurometric normative database contains the EEG records and features derived from 650 individuals, aged 6 to 90 years, with function confirmed as normal by multidisciplinary examinations [25]. The number of subjects required for reliability at each age was statistically determined and increased until consistent split half replications were obtained. This sample requirement was dynamic in that different ages required different Ns. For example, in the ages from 6 to 13, in which brain maturation changes are rapid, the Ns were greater, as were those in later adolescence, in which findings indicated that the frontal regions of the brain were maturing to adult levels [33].

Quantitative features were extracted from artifact-free data by spectral analysis of the EEG (qEEG), log transformed to obtain normal (Gaussian) distributions, age regressed, and evaluated statistically relative to the distributions of every feature in the qEEG database [27,34]. Great care was taken to include only artifact-free EEG and guard against changes in patient state, such as drowsiness. All features were transformed to Z scores and expressed in standard deviations from the normative values. This allows objective assessment of the statistical probability that the measurements obtained from an individual lie outside the normal limits for his or her age. The importance of selecting artifact-free EEG segments for analysis and the use of log transformation must be stressed, because the failure to follow these procedures validates the criticisms described previously. For example, qEEG normal control groups often rely on a reference sample of data obtained from individuals whose ages span one or several
decades. In neurometrics, the use of age-regression techniques yields an estimate of the range expected from persons exactly the same age as the subject. Computation of the Z score for the difference between the predicted normative value and the value obtained from the individual estimates the probability that such a value might be obtained by chance from a healthy peer. Using only significant Z values in feature selection for further statistical analyses acts as a preliminary step in data reduction. Test-retest reliability of neurometric qEEG has been confirmed by intensive short- and long-term follow-up studies in a large sample [35]. Although concern about normative databases can be valid, the widespread independent replications described previously provide confidence in the use of the neurometric normative database. Statistical evaluation of distributions of features by gender revealed small differences within the normal population compared with between-population variance (eg, normal versus abnormal). Neurometric qEEG contains combined gender norms, considered to be a more conservative approach.

Distinctive patterns of qEEG abnormalities have been described in diverse psychiatric disorders (eg, depression, schizophrenia, dementia, and attention deficit hyperactivity disorder [ADHD]). This allows differentiation of these disorders from normal and, where appropriate, from each other [36]. A large body of peer-reviewed published data from independent laboratories reports the sensitivity of neurometrics in varied clinical populations, including head injury [37], stroke and transient ischemic attack [13,38], schizophrenia [39], depression [40], marijuana abuse [41], and ADHD [42,43].

**Importance of reduction of quantitative electroencephalographic feature set**

Criticisms of qEEG studies often focus on the abundance of qEEG features available for study, which can lead to spurious findings if appropriate measures are not undertaken. Statistically guided data reduction is fundamental. Conventional methods of data reduction, such as feature selection from t-tests and analysis of variance (ANOVAs), used to identify variables significantly related to dependent variables of interest, should be used [44,45]. Variables should be selected that maximize adjusted multiple correlation coefficients between qEEG and dependent variables, minimizing the residual sum of squares with each feature set considered independently and appropriate corrections for multiple tests applied (eg, Bonferroni, Tukey, or Greenhouse-Geisser). In parallel, factor and discriminant analysis can be used to reduce the dimensionality of the variable set to better address specific hypotheses. Selected qEEG features can be pruned further by using stepwise procedures and split-half or jackknifed replications, always maintaining the conservative rule of 10:1 subject-to-variable ratios. These methods allow one to identify variables that independently account for the maximum variance in the model under study. In this way, the likelihood of spurious findings can be minimized and the sensitivity and specificity of qEEG findings increased.
Quantitative electroencephalographic source localization

Knowledge about the neuroanatomic generators of EEG frequency components has important implications for the generation of models of the neurophysiology of the EEG and the neuropathology of psychiatric disorders. For reviews of this literature, see Hughes and John [46] and Alper et al [47]. The major qEEG source localizations method currently available is variable resolution electromagnetic tomography (VARETA) [48]. Correlations of VARETA maps of broadband spectral parameters with radiologic studies in patients with space-occupying lesions have shown that EEG delta power is correlated with the volume of the lesion and EEG theta power is correlated with the volume of edema surrounding such lesions [49–52]. Recent research has further tested the accuracy of VARETA in a group of patients with various space-occupying lesions, evaluating the Z correspondence of VARETA solutions in the delta and theta frequency domains to the volume of brain edema and the centroid of the mass [53]. The authors concluded that VARETA achieved accurate location of brain lesions. Using LORETA analyses (a source localization algorithm mathematically akin to VARETA), Pascual-Marqui [54] reported further validation of such methods by demonstrating low error of sources and correct localization of primary sensory cortices of evoked potential data. In a recent study using LORETA, Salen et al [55] found different representative drugs to induce different changes in different brain regions, which they interpreted as supporting the use of such methods for studying the mode of action of psychotropic drugs. Differences between specific drug-free patient groups and normal individuals were found to be opposite to the observed changes induced by the respective drugs. In a subsequent section of this article we demonstrate how VARETA can be used in the development of a neuroanatomic model of attention deficit disorder (ADD) in children and adolescents.

Relevant quantitative electroencephalographic studies in adult psychiatric disorders

Dementias

Studies that use qEEG in dementia patients are in agreement with conventional EEG findings and report increased delta or theta power [56–70], decreased mean frequency [68,71–73], decreased beta power [74,75], and decreased occipital dominant frequency [60,65]. Many studies regard increased slow activity before reduction of alpha power as the earliest electrophysiologic indicator that appears in Alzheimer’s disease [57,65,69,70,76,77]. The amount of theta activity shows the best correlation with cognitive deterioration [70,78,79] and clinical outcome in longitudinal follow-up [66,69,70,76,80]. Increased delta seems to be a correlate of severe advanced dementia, subsequent to increased theta [67,70,80,81]. Multiple studies report accurate discrimination of patients
with Alzheimer’s disease from depressed patients and normal controls using qEEG measures of slow activity [26,56,71,82]. Several qEEG studies of dementia patients report high correlations between the severity of cognitive impairment and amount of EEG slowing. These features are absent in depression and are localized in multi-infarct dementia, which enables these disorders to be differentiated from Alzheimer’s dementia.

Alcohol and substance abuse

Several recent studies of substance abuse have used qEEG. Replicated reports have appeared of increased beta relative power in alcohol dependence [26,83–86]. Increased alpha power, especially in anterior regions, has been reported in withdrawal and after acute exposure to cannabis [41,87]. Increased alpha and decreased delta and theta have been reported in crack cocaine users in withdrawal [88–92]. Use of qEEG reveals marked abnormalities in alcohol and substance abuse. The effects vary depending on the drug. Either increased slow activity with lower alpha and beta or the converse has been reported, which reflects diversity of substances studied and the differences in anatomic regions or states focused on. There is a consensus regarding increased beta relative power in alcoholism and increased alpha in chronic cannabis or crack cocaine users.

In studies from our laboratory [93], a chronic crack cocaine—dependent population was divided by age of first use (age <20 or ≥20 years) (young onset, n = 52; adult onset, n = 48) to explore the consequences of use during adolescence. The qEEGs contained significantly more theta excess in individuals who started using as adolescents, which suggests enhanced vulnerability for such effects on brain function. Of note, theta excess characterized the group of cocaine abusers who relapsed most quickly [94]. A significantly larger (P<0.04) proportion of the group who began using as adolescents was found to have a history or current signs of ADHD. Clear differences were reported between crack cocaine—dependent subjects who began using as adolescents and subjects who began using as adults.

Schizophrenia

Numerous qEEG studies have been performed on carefully evaluated groups of patients with schizophrenia. A deficit in alpha power is consistently reported [26,95–100] with altered alpha mean frequency or diminished alpha responsiveness [101–103]. Numerous studies have reported increased beta activity in schizophrenia [98,104–107]. Neuroleptic medication typically increases alpha power [107–109] and reduces beta power [110,111], which suggests possible normalization of deviant features by medication. Increased delta or theta activity also has been reported in a large number of studies [95,98,99,106,112–119]. Increased slow activity apparently can result from long-term neuroleptic treatment [120,121], although there are reports of increased delta in patients off medication for several weeks [86,95,98] and reduction of delta or theta after
resumption of medication [108,118,122]. Patients with schizophrenia can be discriminated from controls by the presence of increased amounts of delta activity in the left anterior temporal area [123].

Heterogeneity within schizophrenia has been documented in a large sample of medicated, nonmedicated, and never-medicated persons with schizophrenia using cluster analysis based on qEEG variables. Five subtypes were described, with qEEG profiles characterized by (1) delta plus theta excess, (2) theta excess with decreased alpha and beta, (3) theta plus alpha excess with beta deficit, (4) alpha excess with decreases in delta, theta, and beta, and (5) beta excess [124]. Patients who were never medicated were classified into three of these subtypes. Individuals with schizophrenia with qEEG profiles that corresponded to some of the groups identified by this cluster analysis have been reported to display differential responses to treatment with haloperidol [39] or risperidone [125]. Heterogeneity in the schizophrenic population has been presented in other qEEG studies [126,127]. In the cluster analysis just cited, qEEG asymmetry was found in every frequency band for all five subtypes [124]. Increased coherence within cerebral hemispheres in anterior regions also has been consistently reported [115,124,128–130].

Mood disorders

Numerous qEEG studies have found increased alpha or theta power in depressed patients [26,71,131–137]. Asymmetry within cerebral hemispheres, especially in anterior regions, has been reported repeatedly [138–142], as has decreased coherence [26,115,143]. In bipolar illness, in contrast to unipolar depression, alpha activity is reduced [135,144] and beta activity increased [26,145]. This difference may serve to separate unipolar from bipolar patients who are evaluated while in a state of depression without prior history of mania [143,145].

Available qEEG studies suggest a high incidence of abnormalities in patients with anxiety, panic, and obsessive-compulsive disorder [146–150]. Diminished alpha activity has been found in anxiety disorder [151,152], and increased theta activity has been reported in obsessive-compulsive disorder [153,154]. Two subtypes of patients with obsessive-compulsive disorder have been described. One, with increased alpha relative power, responded positively (82%) to serotonergic antidepressants, whereas the second, with increased theta relative power, failed to improve (80%) [155]. Recent reports stated that a qEEG measure called cordance may play a role in predicting clinical response to different antidepressants [156–158]. A qEEG was obtained before treatment and 48 hours and 1 week after initiation of treatment with fluoxetine, venlafaxine, or placebo, with treatment response evaluated out to 8 weeks. No baseline qEEG differences were noted, whereas responders to placebo showed increased prefrontal cordance and medication responders showed decreased prefrontal cordance within 48 hours of treatment initiation. Nonresponders showed no change in cordance values. These results may indicate a role for the prefrontal cortex in mediating treatment
response, with changes in cordance values preceding favorable behavioral response. Currently, this research has not been replicated beyond this group of 51 patients.

Mild head injury or concussion syndrome

Patients with complaints of cognitive, memory, or attention deficit after mild head injury without loss of consciousness frequently present for psychiatric evaluation for worker’s compensation and disability benefits. Objective evidence of brain dysfunction in such cases is critical. Numerous qEEG studies of severe (Glasgow Coma Scale 4–8) and moderate head injury (Glasgow Coma Scale 9–12) have agreed that increased theta and decreased alpha power or decreased coherence and increased asymmetry are found in such patients. Changes in these measures provide the best predictors of long-term outcome [159–162]. The qEEG abnormalities that persist after mild or moderate head injury are similar in type to those found after severe head injury, namely increased power in the theta band, decreased alpha, low coherence, and increased asymmetry. It is noteworthy that similar EEG abnormalities have been reported in boxers [163] and professional soccer players who were “headers” [164]. There is a broad consensus that increased focal or diffuse theta, decreased alpha, decreased coherence, and increased asymmetry are common EEG indicators of postconcussion syndrome.

There are multiple reports of discriminant functions based on qEEG variables that successfully separated normal individuals from patients with a history of mild to moderate head injury years after apparent clinical recovery [37,165]. Thatcher et al [166] argued that qEEG findings meet all criteria for admissibility into the federal court system.

Quantitative electroencephalography in adult attention deficit hyperactivity disorder

A single qEEG study compared qEEG findings among normal controls, adults with ADD, and adults with attention problems that do not reach criteria for ADHD [167]. Results indicated that adults with ADHD show increased theta absolute and relative power in comparison to both control groups. This finding is consistent with that described later in children and adolescents with ADHD. Adults with attention problems but not ADHD showed reduced relative theta and increased relative beta power in comparisons to normal controls and adults with ADHD.

Quantitative electroencephalography: sensitivity to signs of cortical dysfunction

We have published several qEEG studies that attest to the sensitivity of qEEG in the documentation of signs of cortical dysfunction in various disorders. These studies attest to the use of qEEG to document brain dysfunction and evaluate the effectiveness of treatment of these abnormalities.
The use of qEEG was found to be a sensitive indicator of brain dysfunction in patients with systemic lupus erythematosus who present with or without neuropsychiatric manifestations of their illness [19]. In a sample of 52 such patients, qEEG was found to have a sensitivity of 87% and a specificity of 75% in documenting a neurophysiologic disorder. The qEEG profiles described varied with the severity and type of neuropsychiatric problem manifested. Patients with signs of memory and cognitive problems showed qEEG profiles similar to that described in dementia, whereas patients with clinical signs of depression showed qEEG findings similar to that seen in mood disorders. In 6 patients tested before and after treatment, qEEG changes mirrored changes in clinical state. The qEEG also was found to be useful in documenting the effects of Lyme disease on brain function [168]. Abnormal qEEG was seen in 75% of patients with active Lyme disease and was found to normalize after successful treatment. Use of qEEG also has been shown to be a sensitive indicator of cortical dysfunction caused by cerebral ischemia [169,170]. Signs of pre-existing cortical dysfunction were noted in 40% of 38 patients before undergoing cardiopulmonary bypass surgery, with the degree of abnormality predictive of the development of postoperative neuropsychological test performance deficits. A comparison of preoperative and 1-week postoperative qEEG showed a positive correlation with neuropsychological function 3 months after surgery. These results—in addition to the qEEG findings reported in mild head injury—are compatible with the notion that qEEG could provide useful information about brain function in situations in which unexplained changes in cognitive function occur in children and adolescents.

Quantitative electroencephalographic studies in childhood and adolescent disorders

Autism

Several studies have used varying types and degrees of EEG quantification to describe differences between autistic children and matched normal controls [171]. Studies that used different EEG recording conditions (normal waking, stage II sleep, and during cognitive activation) reported findings of hemispheric differences in normal controls and a lack of hemispheric differences in autism [172–174]. The largest such study examined qEEG in autistic children, normal controls, mental age-matched toddlers, and age-matched mentally handicapped individuals [175]. The autistic children showed increased frontal/temporal and left temporal total power and decreased power asymmetry when compared with normal or mentally handicapped controls. The autistic children and mental age-matched toddlers showed greater within-and-between cerebral hemispheric EEG coherence than the other two groups. The autistic children’s EEG findings indicated decreased cerebral hemispheric and topographic differentiation, which suggested a severe maturational lag [176]. No qEEG studies that compared large numbers of autistic children with children with other psychiatric disorders have
been published. The qEEG measurements of the degree of maturational lag and amount of EEG slowing in individual autistic children might prove useful in the development of educational intervention strategies [177].

Quantitative electroencephalography in children and adolescents with diabetes

Three qEEG studies of the effects of diabetes and hypoglycemia on brain function have been conducted. The first study examined qEEG in 44 persons with insulin-dependent diabetes and age-matched controls. A significant correlation was found between hemoglobin A1c concentrations and decreased alpha relative power. A positive history of ketoacidotic episodes was associated with increased delta-theta and decreased alpha relative power [178]. An examination of qEEG in 28 children with type 1 diabetes and 28 age- and sex-matched controls revealed a relationship between severe hypoglycemic episodes and increased theta in frontal/central regions and increased delta in occipital regions. Nonlocalized decreases in alpha power also were found [179]. A recent study examined the effects of a controlled reduction in plasma glucose concentration in 19 children with diabetes and 17 children without. Decreased glucose was associated with increased delta and theta activity in both groups but was more pronounced in the children with diabetes [180]. The authors concluded that improvement in glucose metabolism is an important factor in preventing the development of qEEG abnormality in children with diabetes.

Specific developmental disorders

The qEEG studies of eyes-closed resting EEG in dyslexia have resulted in inconsistent findings, including decreased and elevated alpha or beta power and increased theta power [181]. These inconsistencies most likely reflect small sample sizes, varying methods of defining dyslexia, and differences in qEEG recording and analysis techniques. For example, no differences were reported between normal controls and a highly screened sample of boys with pure dyslexia [14,182]. Several studies documented qEEG abnormalities in less selective samples of children with learning disorders (LDs). Children with severe spelling disorders showed decreased alpha and beta absolute and relative power in parietal and occipital regions and increased temporal-parietal/occipital power ratios—both signs of decreased topographic cortical differentiation [181]. Data that suggested that the nature of qEEG abnormalities in LDs may change with age also have been published [183]. Although 8- and 9-year-old children showed decreased alpha, the topographic distribution was different, and 10-year-old children showed focal theta excess. This age effect has not been replicated. The work of John et al [25] would suggest that when age-regression qEEG equations are used to compare normal children and children with LD, age effects disappear. The finding of increased theta and decreased alpha in children with LD has been replicated. Children with LDs without hyperactivity but with attention problems
showed increased theta and low alpha power [184]. Hyperactive children and children with learning disorders have been shown to have decreased alpha and beta power in comparison to normal controls [185]. The discrepant results of these studies most likely reflect differences in patient selection criteria and the location of recording electrodes. An examination of qEEG abnormalities across a wide topographic distribution of recording sites and a large sample of children with LDs reveal most of the qEEG abnormalities described previously are an indication of the heterogeneity of LDs [25].

John [186] used the neurometric approach to qEEG to examine children with LDs. Samples of 155 children with generalized LD and 155 children with specific LD (SLD) had their qEEGs compared with the neurometric normal database. Abnormal qEEGs were found in 32.7% of the children with SLD and 38.1% of the children with LD, whereas only 5.5% of an independent sample of normal children had abnormal qEEGs. The percentage of children who showed various types of qEEG frequency abnormality also was presented and included increased delta or theta and decreased alpha relative power. A discriminant function that compared these groups of children to each other achieved sensitivity and specificity levels that were well above chance levels [25].

Using qEEG techniques similar to those just described, Harmony and associates [177,187] elucidated the nature of neurophysiologic abnormalities in children with documented LDs. Children with LDs were shown to have different patterns of brain maturation than normal controls. Within normal controls, there was an increase of posterior/vertex EEG coherence and a decrease in coherence among frontal recordings with increased age, which indicated increased differentiation of frontal cortical regions and increased communication across basic sensory and association cortex. These changes were not seen in children with LDs. Instead, these children showed no change in posterior/vertex coherence with age, and levels of frontal coherence remained high across all ages. Brain maturation as indexed by changes in EEG coherence indicated a developmental deviation in children with learning problems [177]. This finding was replicated using different but converging qEEG feature sets. Decreased spatial differentiation of the EEG was reported in children with spelling problems [181], and the structure of the parietal/temporal and occipital EEG could be explained by a single factor in children with specific reading disorders, whereas three factors were required in normal controls [188]. VARETA images of the qEEG of 46 children with LD and 25 control children showed increased theta in the frontal lobes of the children with LD and more alpha activity in the occipital lobes of the controls [189]. Coherence differences also were reported between children with dyslexia and a control population. Coherence between cerebral hemispheres was greater in the control children, which indicated a greater disconnection of cerebral hemispheres in the children with dyslexia [190].

The qEEG findings presented herein and our own research indicates that children with LDs represent a heterogeneous population. Harmony et al [187] showed that the nature of the qEEG abnormality present was directly related to academic performance in reading and writing. Increased power in delta or
decreased alpha power was associated with a poor educational evaluation, increased theta or decreased alpha was associated with mildly abnormal evaluations, and increased alpha and decreased theta were associated with good evaluations. Theta excess with alpha deficit was described as reflecting maturational lag, whereas delta excess indicated cerebral dysfunction. qEEG can be used to indicate which children with learning problems present with an underlying neurophysiologic dysfunction. This information may be useful for determining resource allocation and designing remediation programs.

The role that environmental and cultural factors may play in brain development recently was examined [191]. A comparison was made between the qEEGs of children at high and low risk of developing learning problems caused by residing in economically, socially, and culturally disadvantaged environments. These children were tested at 18 to 30 months, 4 years, and 5 to 6 years of age. High-risk children were found to have increased delta and theta in frontal regions and decreased alpha in posterior regions. Although these qEEG differences decreased with age, frontal theta excess and posterior alpha deficits persisted. This study indicates that sociocultural effects contribute to EEG maturation. Likewise, Ito et al [192] reported that severely abused children have EEGs characterized by increased interhemispheric coherence, which indicates delayed brain development.

**Quantitative electroencephalographic studies of attention deficit disorders**

The greatest amount of qEEG information available in children and adolescents involves those with ADD and ADHD. We examine this information in detail and conclude with a neurophysiologic model of these disorders. Many early studies conducted in children with attention deficit disorder had small samples of children with ADD or ADHD with recordings of eyes-open EEG from 2 to 3 leads within the central, parietal, or occipital regions. The results from these studies were relatively consistent despite these shortcomings. Hyperactive children were reported to show decreased alpha activity and increased intrahemisphere coherence [193], decreased alpha and beta activity [185], and decreased alpha and beta absolute power [194]. These studies suggested that central and parietal/occipital deficits of alpha and beta may characterize the eyes-open EEG of hyperactive children.

When the number of recording channels is increased or larger samples of children are tested, more consistent patterns of qEEG abnormality emerge. Samples of 21 Japanese, 41 Chinese, and 29 Korean children with ADHD were found to have eyes-closed resting EEGs characterized by increased delta and fast theta with decreased alpha activity over left central or occipital regions when compared with age-matched normal controls and children with conduct disorders [24]. Regional differences in ADHD/normal qEEG findings also have been reported [195]. Eyes-open resting EEG was recorded from 16 channels in 25 boys with ADD without hyperactivity or concomitant learning problems and 25 age-matched normal controls. The qEEG of these boys with ADD was characterized
by generalized theta excess and beta deficit, with the theta excess greater in frontal/temporal regions and the beta deficit greatest in temporal and posterior regions. The size of these differences increased when the EEG was recorded while reading or drawing. Similarly, El-Sayed reported that the amount of qEEG slowing in frontal regions and the degree of beta deficit increased in children with attention problems as the amount of attention load was increased while EEG was recorded during performance of a continuous performance task [233].

Several recently published studies examined qEEG in various subgroups of Australian children and adolescents with attention problems. A review of these and other relevant findings also was published [196]. Their initial study examined eyes-closed resting qEEG in 8- to 12-year-old children with ADHD and children with ADHD of predominantly inattentive type. Although both groups showed increased theta and decreased alpha and beta, the inattentive subgroup results were less severe [197]. The qEEG coherence differences were then examined between these subgroups of children with ADHD and normal controls. At shorter electrode distances, children with ADHD had increased intrahemispheric theta coherence and decreased lateral coherence differences. At longer distances, children with ADHD showed decreased alpha intrahemispheric coherence, whereas in frontal regions they showed increased theta and delta and decreased alpha interhemispheric coherence. Children of the inattentive subgroup with ADHD had less severe abnormality than those in the ADHD hyperactivity subgroup [196]. The authors concluded that these findings indicated reduced cortical differentiation and specialization in ADHD. Clarke et al [198] used cluster analysis of qEEG to document the existence of three ADHD subtypes in a sample of 184 boys with ADHD and 40 age- and gender-matched controls. Subtype 1 showed increased total power, increased relative theta, and decreased relative delta and beta waves; type 2 showed increased relative theta and decreased relative alpha and increased central/posterior relative delta. Subtype 3 showed increased relative beta and decreased relative alpha activity. Gender differences also were examined. They used cluster analysis to examine the qEEGs of 100 girls with ADHD and 40 age- and gender-matched controls [199]. Two clusters were identified. The largest subtype showed increased total power and increased relative theta and decreased relative delta and beta power in comparison to the control population. The second subtype showed increased high amplitude theta and decreases in delta, alpha, and beta. The relatively small number of normal controls may have influenced these results (see later discussions regarding our ADHD research).

The clinical use of qEEG as a possible diagnostic tool for ADHD has been examined using discriminant analyses techniques. A discriminant function was developed that correctly classified 80% of 25 children with ADHD and 74% of 27 normal controls [195]. These discriminant results were similar to those reported by Lubar et al [184,200] in children with ADD without hyperactivity but with reading disorders. The eyes-open resting EEG of this sample of children was characterized by an increased theta-beta power ratio, especially in frontal/temporal regions, with 79.2% correct identification of 69 children with ADD.
against 34 normal controls. More recently, Monastra et al [201,202] recorded eyes-open qEEG and used the theta-beta power ratio from the midline central region to distinguish 176 children, adolescents, and young adults with ADD and 221 children adolescents, and young adults with ADHD from 85 normal controls. They reported sensitivity rates from 86% to 90% and specificity rates between 94% and 98%.

Studies of medication effects in children with attention deficit hyperactivity disorder

Several studies have examined the relationships between pretreatment EEG and treatment response to methylphenidate or d-amphetamine. In an early study, it was reported that 6- to 9-year-old boys with minimal brain dysfunction were more likely to respond to methylphenidate if abnormal conventional EEG and neurologic soft signs were present versus if they were absent [203]. These findings have not been replicated. Halperin et al [204] reported that the presence or absence of conventional EEG abnormalities did not predict response to methylphenidate. The qEEG differences have been reported between ADHD responders and nonresponders to stimulants. Responders to d- or l-amphetamine showed predrug qEEGs characterized by increased predominant peak beta frequency and nonsignificant increases in theta and alpha power when compared with nonresponders. Increased visual evoked potential values of N220 more than 250 msec and increased average beta frequency more than 13 Hz correctly identified 100% of responders and 70% of nonresponders [205]. Age-regressed qEEG features extracted from eyes-closed resting EEG collected before medication with methylphenidate were used to develop a discriminant function to distinguish 16 responding from 12 nonresponding boys with ADHD. Responders were correctly identified 81% of the time and nonresponders were identified 83% of the time. Responders’ qEEGs were characterized by significant developmental deviation (qEEG findings abnormal at any age), whereas nonresponders were characterized by significant maturational lag (qEEG findings normal at a younger age) [206]. These findings increase the accuracy of the discriminant results over those found by Steinhausen et al [207], who correctly predicted methylphenidate response in 73.3% using qEEG features that had not been age regressed. Children with ADHD who responded to methylphenidate (n = 10) were reported to have less frontal theta and alpha and more frontal beta activity than nonresponders [208].

Three reports suggest that methylphenidate or d-amphetamine leads to a normalization of the qEEG of boys with ADHD who respond to treatment [199,209,210]. In a second study, however, Clarke et al [211] found that stimulant medication did not lead to a normalization of the qEEGs of boys with ADHD whose qEEG was characterized by beta excess. In each of these studies, the sample sizes involved were small (n< 25), which makes these conclusions premature. Suffin and Emory [43] examined qEEG in 100 patients diagnosed with either attention or affective disorders. They reported that 13 of 15 patients
with attention disorder and 9 of 10 patients with affective disorder with a frontal alpha excess responded to antidepressants; 7 of 7 patients with attention disorder with a frontal theta excess responded to stimulants; 17 of 20 patients with affective disorder and 5 of 5 patients with attention disorder with frontal alpha excess plus frontal hypercoherence responded to an anticonvulsant plus lithium, and 2 of 2 patients with affective disorder and 2 of 3 patients with attention disorder with a frontal theta excess plus hypercoherence responded to an anticonvulsant. Although interesting, these results are based on small samples, diagnostic criteria are not presented, and the results have yet to be replicated and are not in agreement with our studies (described later), which show that theta and alpha excess subtypes may respond to stimulant medication.

Neurometric quantitative electroencephalography in learning and attention disorders

Most studies cited previously indicated that qEEG can play a significant role in the diagnosis and evaluation of children with learning and attention problems. Despite this evidence, the clinical use of qEEG has been questioned for want of knowledge of the sensitivity and specificity of qEEG measures in mixed clinical populations [212,213]. It is the purpose of this section to provide this information using the child psychiatric qEEG database developed at the Brain Research Laboratories over the past 25 years. Within this section we review the study of John et al [25], who used qEEG to evaluate brain function in children with LDs, review our recent studies of qEEG in children with ADD and ADHD [214–216], and present a comparison of the normal children and children with LD and ADD/ADHD from these two studies [42]. We also present evidence that qEEG can be useful for optimizing medication selection during pharmacologic intervention in ADD and ADHD. We propose that this information and the cited research are sufficient to justify the routine clinical use of qEEG in the diagnosis and treatment of learning and attention disorders.

All children with ADD and ADHD were referred to the Developmental Pediatrics and Learning Disorders Clinic in Sydney, Australia. A sample of 407 children was evaluated between June 1991 and December 1992. All children were examined by a pediatric neurologist and had neuropsychological and qEEG evaluations. None of the children received medication at the time of testing. Children with histories of epilepsy, drug abuse, head injury, or psychotic disorders were excluded. Diagnostic and Statistical Manual-III criteria were used for clinical classification [214]. This sample included children from the ages of 6 to 17 years (mean age, 10.8 years), with 78% having normal IQ scores. Within this sample, 43.9% had ADHD, 40.5% had ADD, and 15.6% did not reach criteria for ADD. This later group rated high in attention problems but showed no impulsivity or hyperactivity and is called the attention subgroup-ATT. A reading disorder was present in 58% of the entire sample.

Treatment response data were available on 152 of these children, with 42.8% showing a positive response to dexamphetamine, 53.3% to methylphenidate, and
3.9% to thioridazine. The choice of medication was based on the clinical presentation of the child and a challenge paired-associate learning task given before medication at the time of initial evaluation and repeated after a trial dose of dexamphetamine or methylphenidate. An adverse reaction (decreased memory performance) resulted in new testing and placement on the other medication in 13 children initially tested on methylphenidate and 18 initially tested on dexamphetamine. All 6 children who responded to thioridazine had either adverse reaction or no change in paired-associate performance to dexamphetamine and methylphenidate. Treatment response was evaluated 6 months after treatment initiation. This evaluation included parent and teacher ratings of changes in learning or in behavior and parent/teacher ratings on the Connors and Diagnostic and Statistical Manual-III rating scales.

The populations with LD included 127 children with SLD (mean age, 11.4 years) whose LD occurred in only one academic area and who had normal full-scale IQ scores and 115 children with LD (mean age, 11.8 years) whose LD spanned two or more academic areas and who had full-scale IQ scores between 65 and 84 [25]. Although these children with LD and SLD were not specifically screened for ADD or ADHD, children with hyperactivity were excluded, and all had been selected by their respective school systems because of learning problems. No known neurologic disorder was noted in these children.

The normal controls included 310 children between the ages of 6 and 17 years. Details concerning the collection and validation of this normal sample have been published [10]. Statements about the reliability and validity of these normal databases were described in initial sections of this article.

The following section represents a summary of our previously published research involving children with attention and learning problems [42,214–216]. Most children with ADHD and ADD in the normal and low IQ groups showed qEEG abnormalities when compared with the normal database. The qEEG frequency abnormality occurred in more than 80% of the 407 children in this population, with theta and alpha excess the most prevalent abnormal finding. Frontal and central regions were the most likely to be involved, and when the abnormality was generalized, its magnitude was usually greatest in these regions. Inter- and intrahemispheric abnormality was present in approximately 35% and included (1) increased coherence of theta or alpha activity between left and right frontal recordings and between frontal and temporal recordings within each hemisphere, (2) decreased coherence between left and right posterior temporal and parietal regions, (3) frontal/posterior power asymmetry within each hemisphere reflecting increased frontal power, and (4) left/right hemisphere power asymmetry in posterior temporal and parietal regions, with the right hemisphere most likely to show a power excess. Two major subtypes of qEEG abnormality were identified that involved theta or alpha excess accompanied by either normal or decreased alpha mean frequency. Beta excess was present in approximately 10% of these children.

Stepwise multivariate discriminant procedures were used to examine the sensitivity and specificity of several two-way comparisons. Normal controls were
distinguished from children with ADHD/ADD with a sensitivity of 93.7% and a specificity of 88.0%. The qEEG differences between the normal children and children with low IQ and ADHD or ADD and between the children with ADHD and ADD were present but minimal in comparison to the differences between the normal population and population with ADD or ADHD. The presence or absence of a secondary LD did not contribute to any of the qEEG differences observed. When the population with ADHD or ADD was compared with the population of children with LDs not secondary to an attention problem, qEEG differences were observed. Children with ADHD or ADD could be distinguished from children with LDs with a sensitivity of 97% and a specificity of 84.2%.

A qEEG also proved useful in the management of treatment response to stimulant medication. The qEEG differences were found between individuals who showed a short-term (initial response to one dose) positive response to treatment with dextroamphetamine or methylphenidate and individuals who did not benefit. Although the sensitivity and specificity levels of this discriminant function were modest (68.7% and 67.5%, respectively), the function was accurate (84.8%) in classifying children who had initially shown a negative response to either dextroamphetamine or methylphenidate. Pretreatment qEEG and behavioral measures showed a sensitivity of 83.1% and a specificity of 88.2% in predicting long-term treatment response to either dextroamphetamine or methylphenidate. Within the population with ADHD, 93.7% of the alpha excess \((n = 16)\), 83.3% of the beta excess \((n = 6)\), and 75% of the theta excess \((n = 40)\) children showed a positive long-term response to stimulants. None of the children with ADHD with an alpha or beta excess showed a negative response to either stimulant, whereas 17.5% of the children with a theta excess showed a negative response to treatment with dextroamphetamine. Within the population of children with ADD, 66.7% of the beta excess \((n = 6)\), 54.5% of the alpha excess \((n = 11)\), and 33.3% of the theta excess \((n = 27)\) children showed a positive response to stimulant therapy. None of the children with ADD with beta excess showed a negative response to either stimulant. One of eight children with an alpha excess treated with methylphenidate showed a negative long-term response. In contrast, the likelihood of a negative response to either dextroamphetamine or methylphenidate reached 30% for the children with theta excess.

Attention deficit hyperactivity disorder and attention deficit disorder: maturational lag or developmental deviation?

The neurometric qEEG features of maturational lag (qEEG normal at a younger age) and developmental deviation (qEEG abnormal at any age) indicated that a developmental deviation was present in 35% of our sample localized mainly to frontal and central regions, with signs of maturational lag mainly in posterior regions present in 7%. To seek further evidence of maturational lag as the underlying neurophysiologic mechanism involved in ADHD and ADD, the qEEGs of our population with ADHD or ADD were assessed as a function of
Multiple ANOVAs were used to compare relative power, absolute power, mean frequency, power asymmetry, and coherence values across four age ranges (5–7, 8–10, 11–13, and 14–17 years). The degree of qEEG abnormality remained stable, with no significant systematic decreases in the degree of abnormality occurring across this age span. When qEEG values are age regressed, the pattern of normal ADHD and ADD differences remains constant from the early school years into late adolescence. The elevated frontal theta activity seen in children with ADHD also has been reported in adults with ADHD, although the beta deficit has been found to decrease with age [167,217].

Neurophysiologic subtypes in attention deficit hyperactivity disorder and attention deficit disorder and learning disability

Cluster analyses procedures were used to identify the major neurophysiologic subtypes within samples of 344 children with ADHD or ADD and 245 children with LD or SLD. To comply with the statistical assumptions underlying cluster analyses, we preselected qEEG features and limited the number entered into the analyses in a systematic fashion. The qEEG variables chosen were those for which the highest ANOVA values were obtained when comparing the children with ADHD and ADD to normals, the children with LD and SLD to normals, and the children with ADHD or ADD to the children with LD or SLD. We selected variables that showed the greatest variance across the entire population of children. Cluster analyses were performed using 35 qEEG variables that met these criteria. An iterative approach was taken as we examined cluster solutions starting at three clusters and progressing until the next new cluster solution failed to further subdivide the population into clusters with more than ten members. The five-cluster solution showed the most clearly defined cluster structure. The cluster analyses were performed on split-half replications of our database and the entire database. The split-half results were optimal for five clusters and replicated each other.

Cluster one was characterized by generalized excess of alpha and deficit of delta absolute and relative power, increased frontal theta coherence and alpha coherence, and parietal and posterior temporal power asymmetry. Cluster two was characterized by generalized excess of theta absolute and relative power, decreased alpha mean frequency, and increased frontal theta coherence. Cluster three was characterized by a generalized deficit of theta, alpha, and beta absolute power, a generalized excess of delta and deficit of alpha relative power, and decreased frontal alpha coherence. Cluster four was characterized by excess frontal/central delta and theta, a generalized deficit of alpha absolute power, generalized delta and theta excess and alpha deficit of relative power, decreased theta and alpha mean frequency, decreased frontal and central alpha coherence, and frontal, central, and temporal power asymmetry. Cluster five was characterized by essentially normal qEEG findings. In this five-cluster solution, more than 98% of the children with ADHD or ADD were placed into clusters one or two. The children with LDs were evenly distributed among the five clusters.
Long-term stimulant treatment response data were available on 49 children with ADD or ADHD from cluster one and 59 children with ADD or ADHD from cluster two. Within cluster one, 75.5% showed a positive response to stimulants, 18.4% showed no measurable change, and 6.1% showed a negative response. Within cluster two, 50.8% showed a positive response to stimulants, 33.9% showed no change, and 15.2% showed a negative response.

VARETA images were calculated for the five patients with ADHD or ADD closest to the centroid of clusters 1 and 2. Currently, technical problems prevent us from examining the VARETA results for the children with LD or SLD. The VARETA images associated with cluster one (alpha excess) at 11 Hz show primarily cortical abnormalities that are maximal and seem to originate in right parietal cortical regions. VARETA images of cluster two (theta excess at 5.4 Hz) show primarily temporal cortical and hippocampal abnormalities. VARETA images at the 5.4-Hz band for cluster one and at the 11-Hz band for cluster two were within normal limits.

Proposed neurophysiologic model of attention deficit hyperactivity disorder/attention deficit disorder

The results of the cluster analyses described previously indicate that the major qEEG frequency abnormalities seen in ADHD and ADD involve excess of theta or alpha absolute or relative power [218–220]. Evidence exists that two different but interconnected neural systems are involved in the generation of EEG within the theta and alpha frequency bands [3,5]. Theta seems to be generated within the septal-hippocampal pathway, whereas the alpha frequency involves thalamocortical and cortical-cortical circuitry. Within the theta-generating septal-hippocampal pathway, the septal nucleus and the nucleus accumbens receive inhibitory modulation through dopaminergic innervation from the ventral tegmental area via D2 receptors [221,222]. Cholinergic efferents modulate hippocampal and cingulate cortex, with these hippocampal pathways acting to regulate the septal nucleus. Theta excess can occur with overactivation of the septal-hippocampal pathway or secondary via disinhibition from negative dopaminergic regulation [223].

Several different alterations in the thalamocortical alpha-generating pathway can result in alpha excess. The thalamic pathway receives positive modulation from the midbrain reticular formation via acetylcholine and negative regulation through nucleus reticularis of the thalamus via gamma-aminobutyric-acid with further modulation via the dopaminergic striatal/nigral system. Alterations in the regulation of this system can lead to alpha excess by overactivation of the thalamus that may be caused by decreased modulation via the dopaminergic nigral system or underactivation of the prefrontal cortex and a resulting disinhibition from nucleus reticularis. A theta or alpha excess might result from low dopamine levels, and our qEEG findings are in agreement with the dopaminergic theory of ADHD expressed by Levy [224], which conceptualizes ADHD as a
disorder of the polysynaptic dopaminergic circuits between prefrontal and striatal centers of activity. These findings are also compatible with the neurophysiologic model of ADHD proposed by Niedermeyer and Naidu [225], which also emphasizes prefrontal, frontal and striatal, and thalamic interconnections. The previously mentioned model also is supported by MRI and positron emission tomographic imaging studies and by behavioral, pharmacologic, and neuro-anatomic studies on the nature of cortical and subcortical disturbances in function that characterizes children with attention and learning problems [226–232].

In our opinion, ADD cannot be conceptualized as a single disease entity with a narrow phenotype and a distinct cause. Rather, ADD represents a spectrum of disorders that may be represented by different neurophysiologic subtypes present within the population of children with attention and learning problems. qEEG may prove to be the most clinically relevant imaging technique for use in children with attention and learning problems. Of all neuroimaging techniques, qEEG is less expensive, less invasive, and easier to perform and has the largest patient database, which indicates the presence of different subtypes of attention and LDs that may be differentially amenable to various treatment approaches. The emergence of EEG biofeedback treatment techniques offers a direct application of qEEG for determining qEEG biofeedback treatment parameters and may offer effective treatment that is not medication oriented.

We believe that these findings justify the clinical use of qEEG in the initial screening and treatment evaluation stages of children with ADD, ADHD, and LD. A qEEG can act as an adjunct to clinical evaluation and behavioral testing and play several of the roles set forth in the introduction to this article. A qEEG can aid in the detection of organicity as the cause of brain dysfunction in children who present with learning and attention problems. It also can aid in the differential diagnosis of ADD or ADHD and LD. A qEEG can play a role in optimizing pharmacologic, remediation, or psychological intervention. Finally, qEEG-based models may help explain the pathophysiology of these disorders.

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Outline of an AD/HD – QEEG Meta-analysis

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NOTE: This document includes an outline of an AD/HD - QEEG meta-analysis manuscript, as well as additional figures for illustrative purposes. Please be aware that as the full manuscript has been submitted to a peer-reviewed journal, that we must adhere to standard journal policies limiting distribution prior to publication. As such, we would appreciate it if you limited your distribution of this outline to your own internal review.
Introduction

Reviews of pre-1997 research concluded the results of electroencephalographic (EEG) studies with Attention Deficit/Hyperactivity Disorder (AD/HD) are inconsistent, and therefore EEG is not clinically useful for AD/HD assessments. However, the improved experimental designs of more recent research studies have elucidated a consistent quantitative EEG (QEEG) pattern for AD/HD.

This paper details the findings of a meta-analysis of QEEG studies conducted since 1997. Results show a consistent and clinically useful QEEG pattern associated with AD/HD.
Background

What is EEG?
- Electroencephalography (EEG) refers to the recording of electrical signals from the brain using smooth electrodes which rest on the surface of the scalp. The electrical signals are generated by brain structures (neurons) near the surface of the scalp.

How is EEG Used to Detect a Disorder?
- When a psychological disorder results in a change in the electrical signals of neurons near the brain’s surface, then such changes can be detected using EEG. If the individuals with a disorder show similar electrical changes, then the EEG recording can be used to create a marker for the disorder.

What is QEEG?
- Quantitative EEG (QEEG) refers to the set of techniques used to distill useful information out of EEG recordings. Developments in QEEG technology have greatly facilitated the use of EEG recordings in clinical and research settings.
- By utilizing QEEG techniques including computerized acquisition, refined signal processing, mathematical transformations, advanced data analysis, and large database comparisons, EEG patterns for some populations can be precisely determined.

What is a Meta-analysis?
- A meta-analysis is a rigorous method of collecting and analyzing results from existing studies to determine whether two populations score differently for a particular measure. The present meta-analysis was used to show that AD/HD and normal subjects are distinctly different for certain QEEG measures.
- A meta-analysis includes a comprehensive search of the literature for studies which examined the measure and the populations in question. Well-defined exclusion/inclusion criteria are formulated to ensure that the selected studies have produced quality data meeting the highest clinical standards.
- The ultimate result of a meta-analysis is a statistic called the ‘effect size’. The effect size quantitatively summarizes the results of multiple studies, examining the difference between two populations for a measure. The larger the effect size, the greater the difference between the two populations. An effect size of three is typically interpreted as showing that the two populations are distinctly different for the measure.
Effect Size Results of the QEEG Pattern

The present meta-analysis identified 13 studies (N = 2642) since 1997 which met inclusion criteria (Appendix A) requiring well-designed studies using comprehensive AD/HD assessment batteries per guidelines of the American Academy of Pediatrics. Details of the 13 studies are listed in Appendix B, including the effect size results of the meta-analysis.

Effect size results of the 13 studies consistently show an increase in theta power and decrease in beta power for AD/HD. This pattern, expressed in the form of a theta/beta ratio, shows an effect size of 3.08. An effect size of this magnitude demonstrates that the QEEG pattern of AD/HD is distinct from that of the general population, and is therefore clinically useful in the identification of AD/HD.

Clinical Utility

The clinical utility of the QEEG pattern has been established with demonstration of 86-90% sensitivity and 94-98% specificity. The results show that there is supportive evidence for the QEEG characterization of AD/HD and that this characterization exceeds that of widely-used AD/HD assessment tests in sensitivity and specificity (Table 1). For comparison, these results can be summarized as diagnostic efficiencies (QEEG 89-91% vs. other tests 55-79%).

<table>
<thead>
<tr>
<th>Category</th>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>QEEG</td>
<td>Theta/Beta Ratio&lt;sup&gt;1&lt;/sup&gt;</td>
<td>90%</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>Theta/Beta Ratio&lt;sup&gt;2&lt;/sup&gt;</td>
<td>86%</td>
<td>98%</td>
</tr>
<tr>
<td>Behavior Rating Scale</td>
<td>Child Behavior Checklist (CBCL), combined, (T≥65)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>76%</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td>CBCL, inattentive, (T≥65)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>81%</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td>CBCL, tested by discriminant analysis&lt;sup&gt;4&lt;/sup&gt;</td>
<td>65%</td>
<td>49%</td>
</tr>
<tr>
<td></td>
<td>CBCL, Parent, inattentive&lt;sup&gt;6&lt;/sup&gt;</td>
<td>56%</td>
<td>63%</td>
</tr>
<tr>
<td></td>
<td>CBCL, Parent, combined&lt;sup&gt;6&lt;/sup&gt;</td>
<td>78%</td>
<td>63%</td>
</tr>
<tr>
<td></td>
<td>CBCL, Teacher, inattentive&lt;sup&gt;6&lt;/sup&gt;</td>
<td>56%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>CBCL, Teacher, combined&lt;sup&gt;6&lt;/sup&gt;</td>
<td>53%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>Behavior Assessment System for Children (BASC), Parent, inattentive&lt;sup&gt;6&lt;/sup&gt;</td>
<td>81%</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td>BASC, Parent, combined&lt;sup&gt;7&lt;/sup&gt;</td>
<td>82%</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td>BASC, Teacher, inattentive&lt;sup&gt;6&lt;/sup&gt;</td>
<td>73%</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>BASC, Teacher, combined&lt;sup&gt;6&lt;/sup&gt;</td>
<td>60%</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>BASC, Parent, tested by discriminant analysis&lt;sup&gt;4&lt;/sup&gt;</td>
<td>74%</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>Devereaux Scales of Mental Disorders (DSMD), combined, (T≥65)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>80%</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td>DMSD, inattentive, (T≥65)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>78%</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td>Early Childhood Inventory-4 (ECI-4), Parent&lt;sup&gt;6&lt;/sup&gt;</td>
<td>66%</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>ECI-4, Teacher&lt;sup&gt;6&lt;/sup&gt;</td>
<td>68%</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td>ADHD – IV, Teacher, inattentive, (T≥90)&lt;sup&gt;7&lt;/sup&gt;</td>
<td>67%</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>ADHD – IV, Teacher, combined, (T≥90)</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>ADHD – IV, Parent, inattentive, (T≥93)&lt;sup&gt;7&lt;/sup&gt;</td>
<td>83%</td>
<td>49%</td>
</tr>
<tr>
<td></td>
<td>ADHD – IV, Parent, combined, (T≥93)&lt;sup&gt;7&lt;/sup&gt;</td>
<td>84%</td>
<td>49%</td>
</tr>
</tbody>
</table>
AD/HD vs. Other Disorders

Reviews have also reported differences in QEEG patterns between AD/HD and other psychiatric disorders.\textsuperscript{10, 11} Research has compared the theta/beta ratios of subjects with AD/HD to a pool of subjects with oppositional defiant disorder, mood disorder, or anxiety disorder but not AD/HD (N=209). Seventy-eight percent of AD/HD subjects were correctly identified using the theta/beta ratio, while 97% of subjects with the other disorders fell within the normal range for the theta/beta ratio.\textsuperscript{12}

Relative Risk of AD/HD

Compared to known genetic and environmental risk factors, the presence of this brain electrical activity pattern is a major risk factor for AD/HD (Table 2). The relative risk outcome means that a child with the QEEG pattern is 76.6 times more likely to have AD/HD than a child without the pattern.

Table 2. Risk Factors for AD/HD

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional Stress During Pregnancy*</td>
<td>2.3</td>
</tr>
<tr>
<td>Maternal Smoking*</td>
<td>2.9</td>
</tr>
<tr>
<td>D4 Gene Polymorphism*</td>
<td>3.3</td>
</tr>
<tr>
<td>Low Birth Weight (&lt; 1500 g)*</td>
<td>3.5</td>
</tr>
<tr>
<td>Early Injurious Accident*</td>
<td>5.6</td>
</tr>
<tr>
<td>Surgery First Month of Life*</td>
<td>19.9</td>
</tr>
<tr>
<td>QEEG: Increased Theta/Beta Ratio†</td>
<td>76.6</td>
</tr>
</tbody>
</table>

Estimated from reported values (\textsuperscript{* or †}), using AD/HD prevalence = 5%.
Discrepancies with Pre-1997 Reviews

Meta-analytic procedures on studies conducted after 1997 show a distinct and consistent QEEG pattern associated with AD/HD. In contrast, reviews of pre-1997 research concluded that EEG-AD/HD results were too inconsistent for clinical applications. However, not one of the included studies of the pre-1997 reviews would have passed the inclusion criteria necessary for a rigorous review of the QEEG assessment of AD/HD. Specifically:

1. **AAN & ACNS.** (American Academy of Neurology & American Clinical Neurophysiology Society). Of the 22 attention-related studies reviewed by the AAN and ACNS, only 3 actually examined AD/HD vs. controls using QEEG power variables, and not one of the 3 used a comprehensive AD/HD assessment battery. Those 3 studies relied exclusively on behavioral rating scales as the sole grouping variable. Considering the poor - moderate sensitivity and specificity of these measures, the validity of the AD/HD groups is suspect.

2. **AHCPR.** (Agency for Health Care Policy and Research of the U.S. Department of Health and Human Services). Of the 8 studies reviewed by the AHCPR, not one examined AD/HD vs. controls using QEEG power variables and comprehensive assessment protocols. Most of these studies covered a range of ‘EEG’ techniques, from evoked response potentials to brainstem auditory evoked potentials (BAEP), which do not provide direct insight into QEEG power variable results. The one study that did measure QEEG variables did not report the actual differences between AD/HD and controls.

3. **AAP.** (American Academy of Pediatrics). The AAP reviews relied exclusively on the aforementioned AHCPR review. One of the AAP reviews cited only 3 of the 8 AHCPR reviewed studies, of which 2 relied on a checklist for AD/HD assessment, and the third examined BAEP.

In other words, not one of the studies included in the previous expert reviews actually examined the ability of QEEG power variables to distinguish controls vs. AD/HD with AD/HD clearly diagnosed using accepted clinical standards.

The question remained as to whether there were other studies prior to 1997 which reported results that are consistent with the current meta-analysis. A search of MEDLINE (1966-2002) was conducted using expanded search criteria including: 1) use of traditional EEG with descriptions of activity changes in theta and beta bands, and 2) legacy terminology for AD/HD. The search uncovered 13 studies published prior to 1997. Although these studies did not use comprehensive assessment batteries, and therefore were excluded from the meta-analysis, all results support the finding of a distinct QEEG pattern associated with AD/HD. Combining these studies with those included in the meta-analysis yields a total of 26 studies from over the last 30 years which support the QEEG pattern for AD/HD.
AD/HD Behavior and QEEG: Similar Age Patterns of Decline

Studies show that behavioral and cognitive symptoms of patients with AD/HD diminish with age. A mathematical model has been precisely fit to the diagnostic results of 8 clinical studies (N=595), demonstrating the age decline of full AD/HD diagnosis. An additional clinical study has repeated these results (N=128). The age decline results were compared with QEEG data for AD/HD at different age ranges (N=611).

![Graph showing age decline in Theta/Beta Ratio and AD/HD diagnoses](Note to figure: Diagnoses are according to criteria of the DSM-III and DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders, Third Edition and Third Edition-Revised*).

The QEEG data follows an age decline similar to the mathematical model of 8 diagnostic studies (Pearson correlation coefficient, 0.996, p=0.004, 4 data points), and similar to the additional study (Pearson correlation coefficient, 0.993, p=0.078, 3 data points).

Therefore the apparent link between ADHD and brain electrical activity is supported by the observation that AD/HD behavior (full diagnosis) and AD/HD physiology (QEEG) conform to a mathematically similar age-dependent attenuation.
Medication Response

Studies of the brain electrical activity of methylphenidate responders have been performed as far back as the early 1970’s. For instance, Satterfield et al. demonstrated that methylphenidate responders have the pattern of an increase in theta activity.

More recently, AD/HD subjects were separated into groups characterized by good or poor response to methylphenidate, and compared against normal controls as well. With an estimated effect size of 3.5, the theta/beta ratio distinctly separates the good from the poor responders. Correspondingly, the effect size for AD/HD good responders vs. normal controls was 4.9.

(Note to figure: Relative power has been standardized against normal controls in the form of Z scores.)

This research shows that methylphenidate responsivity can be predicted using the same QEEG pattern (an increase in theta power and a decrease in beta power) that can be used to identify an AD/HD patient.
Electrophysiological Subtypes

Some studies provided more elaborate statistical analyses of QEEG, resulting in the further partitioning of AD/HD subjects into electrophysiological subtypes within the DSM-IV subtypes.

Such research has demonstrated that there are five electrophysiological subtypes for AD/HD.⁷⁷,⁷⁸ Four of the subtypes have the pattern of an increase in the theta power and a decrease in beta power, which represents approximately 90% of all AD/HD subjects. These general changes in theta and beta power are in agreement with the findings outlined in this meta-analysis (Appendix B).

(Note to figure: Relative power has been standardized against normal controls in the form of Z scores and separated by regions: F=frontal; C = central; P = posterior.)
The fifth electrophysiological subtype did not demonstrate an increase in the theta/beta ratio, but rather was marked by a distinct increase in frontal beta power. This subtype represents 10-13% of all AD/HD subjects, or 15-20% of the AD/HD combined subtype\textsuperscript{13, 38-41}.

The effect size for this variable is 4.1, at a level supporting that there is a distinct departure from normal in brain electrical activity for this electrophysiological subtype.

(Note to figure: Relative power has been standardized against normal controls in the form of Z scores and separated by regions: F=frontal; C = central; P = posterior.)

The sensitivity provided with the theta/beta ratio (86-90\%),\textsuperscript{8, 9} may stand to improve by simply accounting for electrophysiological subtypes. An increased theta/beta ratio may account for as much as 90% of the AD/HD population, and the frontal beta power subtype would account for the remaining 10-13% of the AD/HD population.
Conclusions

The supportive evidence for the QEEG characterization of AD/HD clearly exceeds that of existing AD/HD assessment tests. In consideration of the evidence outlined in this meta-analysis, a case can be made that QEEG offers a unique and objective view of AD/HD, in position to complement the multiple assessment protocols used in the clinician’s comprehensive evaluation of this disorder. Supportive evidence includes:

1. Combining studies of a qualitative review (pre-1997) with those included in the quantitative meta-analysis (post-1997) yields a total of 26 studies from over the last 30 years which support the QEEG pattern for AD/HD.

2. The meta-analysis identified 13 eligible studies since 1997 which met guidelines of the American Academy of Pediatrics and criteria of the DSM-IV.
   a. Using these studies (N=2642), the meta-analysis demonstrated a QEEG pattern of an increase in theta power and a decrease in beta power, summarized as the theta/beta ratio with a pooled effect size of 3.08 (95% CI, 2.90, 3.26) for AD/HD vs. controls.
   b. This effect size is at a level which supports that the two populations are relatively distinct in terms of the theta/beta ratio.

3. The QEEG pattern has been used to identify AD/HD with 86-90% sensitivity and 94-98% specificity.

4. In addition, 97% of subjects with oppositional defiant disorder, mood disorder, or anxiety disorder fell within the normal range for the theta/beta ratio.

5. In terms of relative risk, a patient with the QEEG pattern is 76.6 times more likely to have AD/HD than a patient without the pattern.

6. It has also been shown that strength of response to an AD/HD treatment, methylphenidate, is strongly associated with this brain electrical activity pattern (effect size = 4.9).

7. There is an agreement of AD/HD behavior (DSM diagnosis) and AD/HD physiology (QEEG) in the age pattern of decline (Pearson correlation coefficient, 0.996, p=0.004).

8. The performance of the QEEG test exceeds that of the widely-used AD/HD assessment tests:
   a. Diagnostic Efficiency: QEEG 89-91% other tests 55-79%
Appendix A: Methods and Inclusion Criteria of the Meta-analysis

**METHODS and INCLUSION CRITERIA**

The literature searches were conducted on MEDLINE (1966-July 2002) for articles examining QEEG power differences between AD/HD subjects and normal controls. The bibliographies of relevant articles and expert reviews\(^1\)\(^4\) were examined as well. Eligible studies had been published in peer-reviewed journals by researchers independent of the authors of this meta-analysis.

The meta-analysis was limited from 1997 to present, mainly because previous expert reviews had already reported that pre-1997 studies had not produced consistent results. However, after completion of the meta-analysis, a further qualitative review of pre-1997 studies was conducted to seek EEG results for comparison with the current meta-analysis, using search criteria with a sharper focus on EEG and AD/HD than that of the previous reviews.

To concentrate the meta-analysis on studies which definitely examined AD/HD, only studies were included which used the current ‘gold standard’ diagnostic protocol for AD/HD. The general consensus of healthcare professionals addressing the diagnosis of attention deficit/hyperactivity disorder (AD/HD) currently supports the utilization of multiple assessment protocols\(^5\)\(^-\)\(^47\) A widely accepted set of guidelines provided by the American Academy of Pediatrics recommends a clinician’s evaluation using criteria of the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV)\(^48\) with support from an array of tests and evidence.\(^3\) In the meta-analysis, studies were excluded if the AD/HD assessment was not sufficiently documented in the article, or if the assessment was not comprehensive, such as relying solely on behavior rating scales.

Eligible studies compared AD/HD subjects vs. normal (asymptomatic) controls for differences in QEEG power variables with baseline readings in the eyes opened and/or eyes closed states. Studies were excluded if they only provided brain electrical activity data in the form of evoked response potential (ERP), brain auditory stem potential (BAEP), seizure activity analysis, or traditional EEG.

In the meta-analysis, standardized mean effect sizes were calculated for QEEG power variables for AD/HD vs. controls. QEEG variables of relative power were used when available; absolute power was substituted when necessary. When the published data was sufficient or when the data was supplied by the original authors, Glass’ delta was directly calculated.\(^7\) Otherwise, F-statistics or p-values were converted using standard methods.\(^7\) Effect sizes of relevant variables were reported and pooled for all included studies using sample-weighted mean combinations of effect sizes.
### Appendix B: Summary of Meta-analysis Results

#### Table 3. A Meta-analysis for the General QEEG Power Pattern of AD/HD

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Clinical Assessment/Referral</th>
<th>Clinical Site</th>
<th>Evaluative Tests and Evidence</th>
<th>Comparison</th>
<th>Study Details</th>
<th>Effect Sizes (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>Clarke et al.⁶⁶</td>
<td>Agreement of Pediatrician and Psychologist</td>
<td>Private Pediatric Practice</td>
<td>DSM-IV, medical history, physical examination, behavioral observations, neurological assessment, school reports, reports from other professionals, structured interview with parent, WISC-III, Neale-Reading, WRAT-Spelling</td>
<td>AD/HD (combined) vs. Normal Controls</td>
<td>MF 8-12 120</td>
<td>1.95 -0.51 2.60</td>
</tr>
<tr>
<td>2002</td>
<td>Clarke et al.⁶⁶</td>
<td>Agreement of Pediatrician and Psychologist</td>
<td>Private Pediatric Practice</td>
<td>same as Clarke et al.⁶⁶ (above)</td>
<td>AD/HD (inattentive) vs. Normal Controls</td>
<td>M 8-13 140</td>
<td>1.53 -0.2 2.73</td>
</tr>
<tr>
<td>2002</td>
<td>El-Sayed et al.⁶⁹</td>
<td>Neuropsychiatric Assessment, Pediatric Neurologist, Hospital Teacher</td>
<td>Children’s Hospital, Psychiatric</td>
<td>DSM-IV, ICD-10, neuropsychiatric &amp; neurological assessment, YCI, WISC-III, speech and language evaluation, GDS</td>
<td>AD/HD vs. Normal Controls</td>
<td>MF 6-16 99</td>
<td>0.56 -0.36 0.73</td>
</tr>
<tr>
<td>2001</td>
<td>Monastero et al.⁵</td>
<td>Physician, Mental Health Professionals, School</td>
<td>Private Outpatient Psychological Clinic</td>
<td>DSM-IV, physician’s evaluation, ADDES, Barkley’s ADHD Clinical Parent Interview, TOVA</td>
<td>AD/HD vs. Normal Controls</td>
<td>MF 6-20 469</td>
<td>* * 4.33</td>
</tr>
<tr>
<td>2001</td>
<td>Clarke et al.⁶⁹</td>
<td>Agreement of Pediatrician and Psychologist</td>
<td>Private Pediatric Practice</td>
<td>same as Clarke et al.⁶⁶ (above), and CPRS-48</td>
<td>AD/HD vs. Normal Controls</td>
<td>MF 8-12 378</td>
<td>1.87 -0.71</td>
</tr>
<tr>
<td>2001</td>
<td>Clarke et al.⁶⁹</td>
<td>Agreement of Pediatrician and Psychologist</td>
<td>Private Pediatric Practice</td>
<td>same as Clarke et al.⁶⁶ (above), and CPRS-48</td>
<td>AD/HD (combined) vs. Normal Controls</td>
<td>MF 8-12 224</td>
<td>1.91 -0.58 2.43</td>
</tr>
<tr>
<td>2001</td>
<td>Clarke et al.⁶⁹</td>
<td>Agreement of Pediatrician and Psychologist</td>
<td>Private Pediatric Practice</td>
<td>same as Clarke et al.⁶⁶ (above), and CPRS-48</td>
<td>AD/HD vs. Normal Controls</td>
<td>MF 8-12 120</td>
<td>1.60 -0.43</td>
</tr>
<tr>
<td>1999</td>
<td>Bresnahan et al.⁷⁷</td>
<td>Pediatrician and Psychologist, Confirmed by an independent Psychiatrist</td>
<td>Private Pediatric Practice</td>
<td>DSM-IV, CBCL, CPRS, CTRS, Barkley’s Semi Structured Interview for Adult AD/HD, WURS, childhood history</td>
<td>AD/HD vs. Normal Controls</td>
<td>MF 6-42 150</td>
<td>0.99 -0.38 0.87</td>
</tr>
<tr>
<td>1999</td>
<td>Lazzaro et al.⁷⁴</td>
<td>Physician, Psychiatrist, Clinical Psychologist</td>
<td>Hospital, Cognitive Neuroscience</td>
<td>DSM-IV, semi-structured interview, history, clinical records, CBCL, CPRS, CTRs, K-BIT, WIAT</td>
<td>AD/HD vs. Normal Controls</td>
<td>M 11-17 108</td>
<td>0.55 -0.70</td>
</tr>
<tr>
<td>1999</td>
<td>Monastero et al.⁷⁵</td>
<td>Physician, Mental Health Professionals, School</td>
<td>Private Outpatient Psychological Clinic</td>
<td>DSM-IV, ADDES, ADD-II: Comprehensive Teacher’s Rating Scale, Barkley’s ADHD Clinical Parent Interview, Conners’ CPT, TOVA, GDS</td>
<td>AD/HD vs. Normal Controls</td>
<td>MF 6-30 482</td>
<td>* * 3.84</td>
</tr>
<tr>
<td>1998</td>
<td>Clarke et al.⁷⁶</td>
<td>Agreement of Pediatrician and Psychologist, Referral from Family Doctor</td>
<td>Private Pediatric Practice</td>
<td>same as Clarke et al.⁶⁶ (above), and CPRS-48</td>
<td>AD/HD vs. Normal Controls</td>
<td>MF 8-12 60</td>
<td>1.45 -0.43</td>
</tr>
<tr>
<td>1998</td>
<td>Lazzaro et al.⁷⁷</td>
<td>Physician, Cognitive Neuroscience</td>
<td>DSM-IV, neurological examination, structured interview, history, clinical records, CPRS, CTRs, K-BIT, WIAT</td>
<td>AD/HD vs. Normal Controls</td>
<td>M 11-17 52</td>
<td>0.60 -0.36</td>
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</tbody>
</table>

**POOLED RESULTS:**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Theta</th>
<th>Beta</th>
<th>Theta/Beta</th>
</tr>
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<tr>
<td></td>
<td>2642</td>
<td>1.57</td>
<td>-0.055</td>
<td>3.08</td>
</tr>
</tbody>
</table>

*Variable not examined in original study. †Original data not available for meta-analysis; effect size estimated using p value conversion; tendency for underestimation of effect size. ‡Original data not available for meta-analysis; effect size estimated using F value conversion; tendency for underestimation of effect size. §Reported absolute instead of relative power.

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Lexicor Medical Technology

PAGE BREAK
Summary of Current Research on the QEEG Assessment of ADHD

Steven M. Snyder, Ph.D.
Director of Research and Development
Lexicor Medical Technology, Inc.

SUMMARY OF CURRENT RESEARCH:

Recent reviews (Barry et al., 2003; Chabot et al., 2005) have reported a considerable body of evidence which supports that quantitative electroencephalographic (QEEG) results have been significantly associated with the presence of Attention Deficit Hyperactivity Disorder (ADHD). Of particular note are those studies which examined the direct application of QEEG in the identification of ADHD.

The results of eight studies (Table 1) support that QEEG can be used to identify ADHD with reasonable accuracy (77 to 96%) when utilized vs. asymptomatic controls and learning disorders.

SUMMARY OF CRITICISMS:

Criticisms of research covering the use of QEEG in the assessment of ADHD are summarized in the following from the American Academy of Neurology and the American Clinical Neurophysiology Society (AAN/ACNS) (Nuwer, 1997):

1. “No blinded comparisons have been made with a clinical standard.”
2. “Many studies do not use an appropriate spectrum of patients for whom the diagnostic tests would be applied in clinical practice.”

The author agrees that the AAN/ACNS offer valid criticisms and the appropriate research must be performed to support clinical applications.

It is worthy of note that the AAN/ACNS criticisms also apply to ADHD rating scales research, as demonstrated by a recent 10 year review of rating scales (Collett et al., 2003) in which studies were limited to comparisons of ADHD vs. controls with no blinding in the protocols.

CURRENT DIRECTIONS:

There are two clinical studies in progress (Quintana et al. 2005; Snyder et al., 2005) which address the AAN/ACNS criticisms for both QEEG and rating scales in the assessment of ADHD. Important features of the experimental designs include:

1. Previously validated variables and cutoffs of QEEG and rating scales have been selected for replication.
2. The samples include all subjects who present to participating clinics with suspected ADHD-like symptoms, however only a portion have ADHD.
3. Subjects with comorbid conditions are included.
4. The first study includes a single child psychiatric site with sample size of 26.
5. The follow-up study includes 3 psychiatric sites and 1 pediatric site with a sample size of 159.
6. Blinded comparisons are performed for both the QEEG results and the rating scales vs. a clinical standard.
7. The clinical standard was designed by a child psychiatrist (H. Quintana, M.D.) who has participated in over 10 previous ADHD clinical trials and is director of a child psychiatric clinic at Louisiana State University Health Sciences Center.
8. The clinical standard follows DSM-IV criteria and includes a semi-structured interview (K-SADS-PL and supplements) as well as an unstructured clinical interview coupled with measures of functioning and impairment.

As such, the two studies promise to clarify the accuracy of QEEG and ratings scales when applied in clinical practice.

CONCLUSIONS:

• The results of eight studies (from 1992 to present) support that QEEG can be used to identify ADHD with reasonable accuracy (77 to 96%) vs. controls and learning disorders.

• After review of literature up to 1997, the AAN and ACNS called for blinded validation studies investigating assessment tools according to the applications in clinical practice.

• There are two studies in progress which address the concerns of the AAN/ACNS for both rating scales and QEEG, and therefore stand to clarify the accuracy of these assessment tools in clinical practice.

REFERENCES:


Snyder, S. M., Quintana, H., et al. (2005). Comparison of a standard psychiatric diagnostic evaluation to a qEEG assessment in the diagnosis of children and adolescents suspected of having ADHD. *In progress.*
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>DSM</th>
<th>Comparison</th>
<th>Setting</th>
<th>Standard</th>
<th>Analysis</th>
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<th>N</th>
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<th>Specificity</th>
<th>Overall Accuracy</th>
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<tbody>
<tr>
<td>1. Mann et al.</td>
<td>1992</td>
<td>III</td>
<td>ADHD vs. Controls</td>
<td>Clinical Research Center</td>
<td>Rating Scales</td>
<td>Discriminant Analysis</td>
<td>no</td>
<td>52</td>
<td>80%</td>
<td>74%</td>
<td>77%</td>
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<tr>
<td>2. Chabot &amp; Serfonstein</td>
<td>1996</td>
<td>III</td>
<td>ADHD vs. Controls</td>
<td>Pediatrics Clinic</td>
<td>Rating Scales</td>
<td>Discriminant Analysis (split half cross validation)</td>
<td>no</td>
<td>717</td>
<td>94%</td>
<td>88%</td>
<td>91%</td>
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<td>3. Chabot et al.</td>
<td>1996</td>
<td>III</td>
<td>ADHD vs. Learning Disorders</td>
<td>Pediatrics Clinic</td>
<td>Rating Scales</td>
<td>Discriminant Analysis (split half cross validation)</td>
<td>no</td>
<td>649</td>
<td>97%</td>
<td>86%</td>
<td>93%</td>
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<td>4. Monastra et al.</td>
<td>1999</td>
<td>IV</td>
<td>ADHD vs. Controls</td>
<td>8 Clinical Research Centers</td>
<td>Battery of tests</td>
<td>Cutoff</td>
<td>no</td>
<td>482</td>
<td>86%</td>
<td>98%</td>
<td>89%</td>
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<td>5. Kovatchev et al.</td>
<td>2001</td>
<td>IV</td>
<td>ADHD vs. Controls</td>
<td>Research Center</td>
<td>Rating Scales</td>
<td>Using a derived ‘Consistency Index’</td>
<td>no</td>
<td>36</td>
<td>82%</td>
<td>77%</td>
<td>80%</td>
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<td>6. Monastra et al.</td>
<td>2001</td>
<td>IV</td>
<td>ADHD vs. Controls</td>
<td>Psychological Clinic</td>
<td>Battery of tests</td>
<td>Cross-validated cutoff</td>
<td>no</td>
<td>129</td>
<td>90%</td>
<td>94%</td>
<td>91%</td>
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<tr>
<td>7. Clarke et al.</td>
<td>2002</td>
<td>IV</td>
<td>ADHD vs. Controls</td>
<td>Pediatrics and Psychological Clinic</td>
<td>Clinicians’ Diagnosis</td>
<td>Discriminant and Cluster Analysis</td>
<td>no</td>
<td>140</td>
<td>n/a</td>
<td>n/a</td>
<td>96%</td>
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<td>8. Magee et al.</td>
<td>2005</td>
<td>IV</td>
<td>ADHD vs. Controls</td>
<td>Pediatric and Psychological Clinic</td>
<td>Clinicians’ Diagnosis</td>
<td>Logistic Regression</td>
<td>no</td>
<td>320</td>
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Lexicor Medical Technology

PAGE BREAK
Title: Comparison of a Standard Psychiatric Evaluation to Rating Scales and EEG in the Differential Diagnosis of ADHD

Authors: Humberto Quintana, M.D., Steven M. Snyder, Ph.D., William Purnell, M.D., Carolina Aponte, M.D., and Janis Sita, B.S., R.N.

Affiliations: Drs. Quintana, Purnell, and Aponte, and Ms. Sita are with the Department of Psychiatry, Louisiana State University Health Sciences Center; Dr. Snyder is with the Department of Psychology, University of North Texas Health Science Center at Fort Worth.

Financial Disclosure: Dr. Quintana is primary investigator and/or consultant to Eli Lilly, Pfizer, Otsuka, and Abbott. Drs. Purnell and Aponte are research fellows under the mentorship and supervision of Dr. Quintana at LSUHSC. Dr. Snyder holds a salaried position at Lexicor.

OBJECTIVE: To determine the prevalence of Attention Deficit Hyperactivity Disorder (ADHD) in a diverse clinical sample, and to investigate the effectiveness of rating scales and electroencephalography (EEG) in detecting the presence of ADHD.

METHOD: A standard psychiatric evaluation was used to assess 26 children/adolescents who presented to a clinic because a parent and/or school official suspected the presence of ADHD. Rating scales and EEG data were collected as well.

RESULTS: Although the subjects presented with ADHD-like symptoms, only 62% actually had ADHD, while the remaining 38% had other disorders or no diagnosis. Rating scales readily classified inattentive, impulsive, and/or hyperactive symptoms as being due to ADHD, regardless of the actual underlying disorder, leading to a sensitivity of 81% and a specificity of 22%. Previous studies have supported that there is an EEG marker specific to ADHD, and this marker was present in 15 out of 16 of the ADHD subjects (sensitivity, 94%) and in none of the subjects with ADHD-like symptoms due to other disorders (specificity, 100%).

CONCLUSIONS: In the detection of ADHD in a diverse clinical sample, rating scales and EEG were both sensitive markers, whereas only EEG was specific. These results may have important implications to ADHD differential diagnosis.
Study: Comparison of a Standard Psychiatric Diagnostic Evaluation to a qEEG Assessment in the Diagnosis of Children and Adolescents Suspected of Having ADHD.

Co-Principal Investigators: Humberto Quintana, M.D. and Steven M. Snyder, Ph.D.

Study Coordinator: Donald A. Reynolds, M.D.

Affiliations: Dr. Quintana is with the Department of Psychiatry, Louisiana State University Health Sciences Center; Dr. Snyder is with the Division of Clinical Neuroscience, Department of Psychology, University of North Texas Health Science Center at Fort Worth. Dr. Reynolds is the sponsor’s chief medical expert.

Financial Disclosure: Dr. Quintana is primary investigator and/or consultant to Eli Lilly, Pfizer, Otsuka, and Abbott. Drs. Snyder and Reynolds hold salaried positions at Lexicor.

OBJECTIVE: A double-blinded, cross-validation study investigated the effectiveness of qEEG analysis results as provided by Lexicor’s NeuroLexSM service in determining the presence of ADHD in children and adolescents within a diverse, clinical sample.

METHOD: A standard psychiatric diagnostic evaluation (SPDE) was used as the gold standard. A clinical sample of 159 patients (ages 6-18) was examined at 4 sites (2 university child psychiatric sites, 1 private pediatric site, and 1 private child psychiatric site). Subjects were included when presenting to the clinic because a parent and/or school official suspected the child/adolescent might have ADHD.

RESULTS: Of those patients with ADHD verified by the SPDE, a significant majority were found to have tested positive in the qEEG assessment for ADHD. Of those determined to have other disorders not ADHD verified by the SPDE, a significant majority were found to have tested negative in the qEEG assessment for ADHD.

The generalizability of qEEG results to clinical ADHD applications was supported by: 1) the consistency of results between multiple centers in current and previous studies, 2) the consistency of results between groups based on race, gender, and age, 3) the examination of patients all with ADHD-like behavioral symptoms but only a portion with ADHD diagnosis, and 4) the presence of other disorders and comorbidities throughout the entire sample requiring differential diagnosis.

CONCLUSIONS: The study supports that quantitative EEG, as standardized and processed within the NeuroLexSM system, is consistent with a structured clinical diagnosis by a psychiatric professional in the ability to identify ADHD.

The above contents are provided for information only and represent results from a recently completed study with a manuscript under preparation for submission for publication. The information is intended for limited distribution only and is the property of Lexicor Medical Technology, Inc.