

The role of quantitative electroencephalography in child and adolescent psychiatric disorders

Robert J. Chabot, PhD^{a,*}, Flavia di Michele, MD^b,
Leslie Prichep, PhD^{a,c}

^a*Department of Psychiatry, Brain Research Laboratories, New York University School of Medicine, 462 First Avenue, OBV—Room 884, New York, NY 10016, USA*

^b*Department of Neuroscience, Tor Vergata University, IRCCS, 00133 Rome, St. Lucia, Italy*

^c*Nathan Kline Institute for Psychiatric Research, Orangeburg, NY 10962, USA*

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

* Corresponding author.

E-mail address: Robert.chabot@med.nyu.edu (R.J. Chabot).

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 (μV^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, Saletu 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 \geq 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 intra-hemisphere 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 latter 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

age. 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.

References

- [1] Duffy FH, Hughes JR, Miranda F, Bernard P, Cook P. Status of quantitative EEG (qEEG) in clinical 1994. *Clin Electroencephalogr* 1994;25:6–22.
- [2] Llinas R. The intrinsic properties of mammalian neurons: insights into central nervous system function. *Science* 1988;242:1654–64.
- [3] Lopes Da Silva FH. The generation of electric and magnetic signals the brain by local networks. In: Greger R, Windhorst U, editors. *Comparative human physiology*. Berlin: Springer-Verlag; 1996. p. 509–31.
- [4] McCormick DA. Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. *Prog Neurobiol* 1992;39:337–88.
- [5] Steriade M, Gloor P, Llinas RR, Lopes Da Silva F, Mesulam MM. Basic mechanisms of cerebral rhythmic activities. *Electroencephalogr Clin Neurophysiol* 1990;76:481–508.
- [6] van Beijsterveldt CEM, Boomsma DI. Genetics of the human electroencephalogram (EEG) and event-related brain potentials (ERPs): a review. *Hum Genet* 2000;94(4):319–30.

- [7] van Beijsterveldt CE, Molenaar MPC, de Geus EJ, Boomsma DI. Heritability of human brain functioning as assessed by electroencephalography. *Am J Hum Genet* 1996;58(3):562–73.
- [8] van Beijsterveldt CEM, Molenaar PC, de Geus EJ, Oomsma DI. Genetic and environmental influences on EEG coherence. *Behav Genet* 1998;28:6443–53.
- [9] Matousek M, Petersen I. Norms for the EEG. In: Kellaway P, Petersen I, editors. *Automation of clinical electroencephalography*. New York: Raven Press; 1973. p. 75–102.
- [10] John ER, Ahn H, Prichep LS, Trepetin M, Brown D, Kaye H. Developmental equations for the electroencephalogram. *Science* 1980;210:1255–8.
- [11] Ahn H, Prichep LS, John ER, Baird H, Trepetin M, Kaye H. Developmental equations reflect brain dysfunction. *Science* 1980;210:1259–62.
- [12] Gasser T, Bacher P, Mochs J. Transformation towards the normal distribution of broadband spectral parameters of the EEG. *Electroencephalogr Clin Neurophysiol* 1982;53:119–24.
- [13] Jonkman EJ, Poortvliet DCJ, Veering MM, DeWeerd AW, John ER. The use of neurometrics in the study of patients with cerebral ischemia. *Electroencephalogr Clin Neurophysiol* 1985;61:333–41.
- [14] Yingling CD, Galin D, Fein G, Peltzman D, Davenport L. Neurometrics does not detect pure dyslexics. *Electroencephalogr Clin Neurophysiol* 1986;63:426–30.
- [15] Harmony T, Alvarez A, Pascual-Marqui R, Ramos A, Marosi E, Diaz de Leon A, et al. EEG maturation of children with different economic and psychosocial characteristics. *Int J Neurosci* 1987;31:103–13.
- [16] Alvarez A, Pascual R, Valdes P. EEG development equations confirmed for Cuban school children. *Electroencephalogr Clin Neurophysiol* 1987;67(4):330–2.
- [17] Diaz de Leon AE, Harmony T, Marosi E, Becker J, Alvarez A. Effect of different factors on EEG spectral parameters. *Int J Neurosci* 1988;43:123–31.
- [18] Oken BS, Chiappa KH. Short-term variability in EEG frequency analysis. *Electroencephalogr Clin Neurophysiol* 1988;69:191–8.
- [19] Ritchlin CT, Chabot RJ, Alper K, Buyon J, Belmont HM, Roubey R, et al. Quantitative electroencephalography: a new approach to the diagnosis of cerebral dysfunction in systemic lupus erythematosus. *Arthritis Rheum* 1992;35(11):1330–42.
- [20] Valdes-Sosa P, Bosch J, Gray F, Hernandez J, Riera J, Pascual R, et al. Frequency domain models of the EEG. *Brain Topogr* 1992;4(4):309–19.
- [21] Veldhuizen RJ, Jonkman EJ, Poortvliet JDC. Sex differences in age regression parameters of healthy adults—normative data. *Electroencephalogr Clin Neurophysiol* 1993;86(6):377–84.
- [22] Duffy FH, Albert MS, McAnulty GB. The pattern of age-related differences in electrophysiological activity of healthy subjects. *Neurobiol Aging* 1993;14:73–4.
- [23] Duffy FH, Jones K, McAnulty GB, Albert M. Spectral coherence in normal adults: unrestricted principal components analysis. *Clin Electroencephalogr* 1995;26:30–46.
- [24] Matsuura M, Okubo Y, Toru M, Kojima T, He Y, Hou Y, et al. A cross-national study of children with emotional and behavioral problems: a WHO collaborative study in the Western Pacific region. *Biol Psychiatry* 1993;34:59–65.
- [25] John ER, Prichep LS, Ahn H, Easton P, Fridman J, Kaye H. Neurometric evaluation of cognitive dysfunctions and neurological disorders in children. *Prog Neurobiol* 1983;21:239–90.
- [26] John ER, Prichep LS, Friedman J, Easton P. Neurometrics: computer assisted differential diagnosis of brain dysfunctions. *Science* 1988;293:162–9.
- [27] John ER, Prichep LS. Principles of neurometrics and neurometric analysis of EEG and evoked potentials. In: Niedermeyer E, Lopes Da Silva F, editors. *EEG: basic principles, clinical applications and related fields*. Baltimore: Williams and Wilkins; 1993. p. 989–1003.
- [28] Fisch BJ, Pedley TA. The role of quantitative topographic mapping on “neurometrics” in the diagnosis of psychiatric and neurological disorders: the cons. *Electroencephalogr Clin Neurophysiol* 1989;73:5–9.
- [29] Nuwer M. Assessment of digital EEG, quantitative EEG and brain mapping: mapping: report of the American Academy of Neurology and the American American Clinical Neurophysiology Society. *Neurology* 1997;49:277–92.

- [30] Coutin-Churchman P, Anez Y, Uzctegui M, Alvarez L, Vergara F, Mendez L, et al. Quantitative spectral analysis of EEG in psychiatry revisited: drawing signs out of numbers in a clinical setting. *Clin Neurophysiol* 2003;114:2294–306.
- [31] Nuwer M. Clinical use of qEEG. *Clin Neurophysiol* 2003;114:2225.
- [32] John ER, Prichep LS, Easton P. Normative data banks and neurometrics: basic concepts, methods and results of norm construction. In: Gevins AS, Remond A, editors. *Handbook of electroencephalography and clinical neurophysiology*. Amsterdam: Elsevier; 1987. p. 449–95.
- [33] Hudspeth WJ, Pribram KH. Psychophysiological indices of cerebral maturation. *Int J Psychophysiol* 1992;12(1):19–29.
- [34] Halikas JA, Kuhn KL, Crosby R, Carlson G, Crea F. The measurements of craving in cocaine patients using the Minnesota Cocaine Craving Scale. *Compr Psychiatry* 1991;32:22–7.
- [35] Kondacs A, Szabo M. Long-term intra-individual variability of the background EEG in normals. *Clin Neurophysiol* 1999;110:1708–16.
- [36] Prichep LS, John ER. qEEG profiles of psychiatric disorders. *Brain Topogr* 1992;4(4):249–57.
- [37] Thatcher RW, Walker RA, Gerson I, Geisler FH. EEG discriminant analyses of mild head trauma. *Electroencephalogr Clin Neurophysiol* 1989;73:94–106.
- [38] de Weerd AW, Veldhuizen RJ, Eering MM, Poortvliet DC. Long-term reconstructive vascular surgery for cerebral ischemia. *Acta Neurol Scand* 1989;79:311–5.
- [39] Czobor P, Volavka J. Pretreatment EEG predicts short-term response to haloperidol treatment. *Biol Psychiatry* 1991;30:927–42.
- [40] Roemer RA, Shagass C, Dubin W, Jaffe R, Katz R. Relationship between pretreatment EEG coherence measures and subsequent response to ECT. *Neuropsychobiology* 1991;24:121–4.
- [41] Struve FA, Straumanis JJ, Patrick G. Persistent topographic quantitative EEG sequelae of chronic marijuana use: a replication study and initial discriminant function analysis. *Clin Electroencephalogr* 1994;25(2):63–75.
- [42] Chabot RJ, Merkin H, Wood LM, Davenport TL, Serfontein G. Sensitivity and specificity of qEEG in children with attention deficit or specific developmental learning disorders. *Clin Electroencephalogr* 1996;27(1):26–34.
- [43] Suffin SC, Emory WH. Neurometric subgroups in attentional and affective disorders their association with pharmacotherapeutic outcome. *Clin Electroencephalogr* 1995;26(2):76–83.
- [44] Weiner JM, Dunn OJ. Elimination of variates in discrimination problems. *Biometrics* 1966;22:268–75.
- [45] Oken BS, Chiappa KH. Statistical issues concerning computerized analysis of brainwave topography. *Ann Neurol* 1986;19:493–4.
- [46] Hughes JR, John ER. Conventional and quantitative electroencephalography in psychiatry. *J Neuropsychiatry Clin Neurosci* 1999;11(2):190–208.
- [47] Alper KR, Prichep LS, Kowalik SC, Rosenthal M. Neuroanatomical localization of qEEG abnormality related to treatment failure in cocaine dependence. In: Harris LS, editor. *Problems of drug dependence 1998*. In: *Proceedings of the 60th Annual Scientific Meeting*. NIDA Research Monograph No. 179. National Institute of Drug Abuse; 1998.
- [48] Valdes-Sosa P, Garcia F, Casanova R. Variable resolution electromagnetic tomography. In: Wood C, editor. *Proceedings of the 10th International Conference on Biomagnetism*. Santa Fe: Biomag; 1996.
- [49] Harmony T, Fernandez-Bouzas A, Marosi E. Correlation between computed tomography and voltage and current source density spectral EEG parameters in patients with brain lesions. *Electroencephalogr Clin Neurophysiol* 1993;87:196–205.
- [50] Harmony T, Fernandez-Bouzas A, Marosi E, Fernandez T, Valdes P, Bosch J, et al. Frequency source analysis in patients with brain lesions. *Brain Topogr* 1995;8(2):109–17.
- [51] Fernandez-Bouzas A, Harmony T, Bosch J, Aubert E, Fernandez T, Valdes P, et al. EEG source spectra in localized brain lesions. In press.
- [52] Fernandez-Bouzas A, Casanova R, Harmony T, Valdes-Sosa P, Aubert-Vazquez E, Silva-Pereyra J, et al. EEG frequency domain distributed inverse solutions in lesions. *Electroencephalogr Clin Neurophysiol* 1997;103(1):195.

- [53] Fernandez-Bouzas A, Harmony T, Bosch JAE, Fernandez T, Valdes P, Silva J, et al. Sources of abnormal EEG activity in the presence of brain lesions. *Clin Electroencephalogr* 1999;30(2): 1–7.
- [54] Pascual-Marqui RD. Low resolution brain electromagnetic tomography (LORETA): methodological considerations [abstract]. *Int J Neuropsychopharmacol* 2000;3(1):S84.
- [55] Saletu B, Anderer G, Saletu-Zyhlarz RD, Pascual-Marqui R. Identifying target regions of psychotropic drugs in mental disorders by means of LORETA [abstract]. *Int J Neuropsychopharmacol* 2000;3(1):S85.
- [56] Duffy FH, Albert MS, McNulty G. Brain electrical activity in patients with presenile and senile dementia of the Alzheimer type. *Ann Neurol* 1984;16:439–48.
- [57] Coburn KA, Danziger WL, Storandt M. A longitudinal EEG study of mild senile of Alzheimer type: changes at 1 year and at 2.5. *Electroencephalogr Clin Neurophysiol* 1985;61:101–12.
- [58] Leuchter AF, Spar JE, Walter DO, Weiner H. Electroencephalographic spectra and coherence in the diagnosis of Alzheimer's-type and multi-infarct dementia. *Arch Gen Psychiatry* 1987; 44:993–8.
- [59] Breslau J, Starr A, Sicotte N, Higa JBMS. Topographic EEG changes with normal aging and SDAT. *Electroencephalogr Clin Neurophysiol* 1989;72:281–9.
- [60] Prinz PN, Vitiello MV. Dominant occipital (alpha) rhythm frequency in early stage Alzheimer's disease and depression. *Electroencephalogr Clin Neurophysiol* 1989;73:427–32.
- [61] Soininen H, Partanen J, Laulumaa V. Longitudinal EEG spectral analysis in early stage of Alzheimer's disease. *Electroencephalogr Clin Neurophysiol* 1989;72:290–7.
- [62] Coburn KA, Danziger WL, Berg L. Replication of a study of frequency of resting awake EEG in mild probable Alzheimer's disease. *Electroencephalogr Clin Neurophysiol* 1990;75: 148–54.
- [63] Rice DM, Buchsbaum MS, Starr A, Auslander L. Abnormal EEG slow activity in left temporal areas in senile dementia of the Alzheimer's type. *J Gerontol* 1990;45:145–51.
- [64] Streletz LJ, Reyes PF, Zolewska M. Computer analysis of EEG activity in dementia of the Alzheimer type and Huntington's disease. *Neurobiol Aging* 1990;11:15–20.
- [65] Williamson PC, Merskey H, Morrison S, Rabheru H, Fox H, Wands K, et al. Quantitative electrophysiologic correlates of cognitive decline in normal elderly subjects. *Arch Neurol* 1990; 47:1185–8.
- [66] Heikala EL, Laulumaa V, Soikkeli R, Partanen J, Soininen H, Riekkinen PJ. Slow wave activity in the spectral analysis the electroencephalogram is associated with cortical dysfunction in patients Alzheimer's disease. *Behav Neurosci* 1991;105:409–15.
- [67] Hier DB, Mangone CA, Ganellen R, Warach RV, VanEgeren SJ, Perlik SJ, et al. Quantitative measurement of delta activity in Alzheimer's disease. *Clin Electroencephalogr* 1991;22:178–82.
- [68] Saletu B, Anderer P, Paulus E, Grunberger J, Wicke L, Neuhold A, et al. EEG brain mapping in diagnostic and therapeutic assessment of dementia. *Alzheimer Dis Assoc Disord* 1991; 5(1):S57–75.
- [69] Soininen H, Partanen J, Laulumaa V, Paakkonen A, Helkala EL, Riekkinen PJ. Serial EEG in Alzheimer's disease: 3 year follow-up and clinical outcome. *Electroencephalogr Clin Neurophysiol* 1992;79:342–8.
- [70] Prichep LS, John ER, Ferris HS, Reisberg B, Alper KR, Cancro R. Quantitative EEG correlates of cognitive deterioration in the elderly. *Neurobiol Aging* 1994;15(1):85–90.
- [71] Brenner RP, Ulrich RF, Spiker DG, Scabassi RJ, Reynolds CF, Marin RS, et al. Computerized EEG spectral analysis in elderly normal, demented and depressed subjects. *Electroencephalogr Clin Neurophysiol* 1986;64:483–92.
- [72] Visser SL, Van Tilburg V, Hooijer C, Jonker C, de Rijke W. Visual evoked potentials (VEPs) in senile dementia (Alzheimer type) and in non-organic behavioural disorders in the elderly: comparison with EEG parameters. *Electroencephalogr Clin Neurophysiol* 1985;60:115–21.
- [73] Giannitrapani D, Collins J, Vassiliadis D. The EEG spectra of Alzheimer's disease. *Int J Psychophysiol* 1991;10:259–69.
- [74] Soininen H, Partanen VJ, Helkala EL, Riekkinen PJ. EEG findings in senile dementia and normal aging. *Acta Neurol Scand* 1981;65:59–70.

- [75] Albert MS, Duffy FH, McAnulty GB. Electrophysiologic comparisons between two groups of patients with Alzheimer's disease. *Arch Neurol* 1990;47:857–63.
- [76] Soininen H, Partanen J, Paakkonen A, Koivisto E, Riekkinen P. Changes in absolute power values of EEG spectra in the follow-up of Alzheimer's disease. *Acta Neurol Scand* 1991; 83:133–6.
- [77] Brenner RP, Reynolds CF, Ulrich RF. EEG findings in depressive pseudodementia and dementia with secondary depression. *Electroencephalogr Clin Neurophysiol* 1989;72:298–304.
- [78] Dierks T, Perisic I, Frolich L, Ihl R, Maurer K. Topography of the quantitative electroencephalogram in dementia the Alzheimer type: relation to severity of dementia. *Psychiatr Res* 1991;40:181–94.
- [79] Richards M, Folstein M, Albert M, Miller L, Bylsma F, Lafleche G, et al. Multicenter study of predictors of disease course Alzheimer disease (the predictors study). II. Neurological, psychiatric and demographic influences on baseline measures of disease. *Alzheimer Dis Assoc Disord* 1993;7:22–32.
- [80] Rae-Grant A, Blume W, Lau C, Hachinski VC, Fisman M, Merskey H. The electroencephalogram in Alzheimer-type dementia: a sequential study correlating the electroencephalogram with psychometric and quantitative pathologic data. *Arch Neurol* 1987;44:50–4.
- [81] Hughes JR, Shanmugham S, Wetzel LC. The relationship between EEG changes and cognitive functions in dementia: a study in a VA population. *Clin Electroencephalogr* 1989;20:77–85.
- [82] O'Connor KP, Shaw JC, Ongley CO. The EEG and differential diagnosis in psychogeriatrics. *Br J Psychiatry* 1979;135:156–62.
- [83] Cogger RW, Dymond AM, Serafetinides EA. EEG signs of brain impairment in alcoholism. *Biol Psychiatry* 1978;13:729–39.
- [84] Bauer LO, Hesselbrock VM. EEG autonomic and subjective correlates for alcoholism. *J Stud Alcohol* 1993;54:577–89.
- [85] Gabrielli WF, Mednick SA, Volavka J. EEGs in children of alcoholic fathers. *Psychophysiology* 1982;19:404–7.
- [86] Cogger RW, Dymond AM, Serafetinides EA. Electroencephalographic similarities between chronic alcoholics and chronic non-paranoid schizophrenics. *Arch Gen Psychiatry* 1979; 36:91–4.
- [87] Struve FA, Straumanis JJ, Patrick G, Price L. Topographic mapping of quantitative EEG variables in chronic heavy marijuana users: empirical findings with psychiatric patients. *Clin Electroencephalogr* 1989;20(1):6–23.
- [88] Alper KR, Chabot RJ, Kim AH, Pritchep LS, John ER. Quantitative EEG correlates of crack cocaine dependence. *Psychiatr Res* 1990;35:95–106.
- [89] Alper KR, Chabot R, Pritchep LS, John ER. Crack cocaine dependence: discrimination from major depression using qEEG variables. In: Mauer K, editor. *Imaging of the brain in psychiatric and related fields*. Berlin: Springer-Verlag; 1993. p. 289–93.
- [90] Cornwell A, Roemer RA, Jackson P, Dew D. Paroxysmal-like EEG abnormalities associated with chronic polydrug abuse. *Biol Psychiatry* 1994;35:692–3.
- [91] Pritchep LS, Alper K, Kowalik SC, John ER, Merkin HA, Tom M, et al. Quantitative electroencephalographic characteristics of crack cocaine dependence. *Biol Psychiatry* 1996; 40(10):986–93.
- [92] Roemer RA, Cornwell A, Jackson P, Dewart D. Quantitative EEG measures: correlations with lifetime exposure to cocaine, alcohol, and marijuana in chronic polydrug. *Biol Psychiatry* 1994;35:624–5.
- [93] Pritchep LS, Howard B, Merkin H, Rausch L, Alper K. Adolescent substance abuse intensifies brain dysfunction. *Ann N Y Acad Sci* 2003.
- [94] Pritchep LS, Alper KR, Sverdlow L, Kowalik SC, John ER, Merkin HTM, et al. Outcome related electrophysiological subtypes of cocaine dependence. *Clin Electroencephalogr* 2002; 33(1):8–20.
- [95] Fenton GW, Fenwick PBC, Dollimore J, Dunn TL, Hirsh SR. EEG spectral analysis in schizophrenia. *Br J Psychiatry* 1980;136:445–55.

- [96] Koukkou M. EEG states of the brain, information processing, and schizophrenic primary symptoms. *Psychiatry Res* 1982;6:235–44.
- [97] Stevens JR, Livermore A. Telemetered EEG in schizophrenia: spectral analysis during abnormal behavior episodes. *J Neurol Neurosurg Psychiatry* 1982;45:385–95.
- [98] Morihisa JM, Duffy FH, Wyatt RJ. Brain electrical activity mapping (BEAM) in schizophrenic patients. *Arch Gen Psychiatry* 1983;40:719–28.
- [99] Dierks T, Maurer K, Ihl R, Schmidtke A. Evaluation and interpretation of topographic EEG data in schizophrenic patients. In: Maurer K, editor. *Topographic brain mapping and evoked potentials*. Berlin: Springer-Verlag; 1989. p. 507–17.
- [100] Merrin EL, Floyd TC. Negative symptoms and EEG alpha activity in schizophrenic patients. *Schizophr Res* 1992;8:11–20.
- [101] Small JG, Milstein V, Sharpley PH, Lapper M, All IF. Electroencephalographic findings in relation to diagnostic constructs in psychiatry. *Biol Psychiatry* 1984;19:471–87.
- [102] Itil TM, Freyhan FA, Ban JH, editors. *Psychotropic drugs and the human EEG*. New York: Karger, S. Inc.; 1974.
- [103] Columbo C, Gambini O, Macciardi F. Alpha reactivity in schizophrenia and in schizophrenic spectrum disorders: demographic, clinical and hemispheric assessment. *Int J Psychophysiol* 1989;7:47–54.
- [104] Laurian S, Bryois C, Gaillard JM. Some aspects of brain electrical activity in schizophrenia. *Recent Adv Biol Psychiatry* 1984;15:60–8.
- [105] Kemali D, Maj M, Galderisi S. Clinical, biological and neuropsychological features associated with lateral ventricular enlargement in DSM III schizophrenic disorder. *Psychiatry Res* 1986; 21:137–49.
- [106] Karson CN, Coppola R, Morihisa JM, Weinberger DR. Computerized electroencephalographic activity mapping in schizophrenia. *Arch Gen Psychiatry* 1987;44:514–7.
- [107] Galderisi S, Maj M, Mucci A, Buccì P, Kemali D. qEEG alpha 1 changes after a single dose of high-potency neuroleptics as a predictor of short-term response to treatment in schizophrenic patients. *Biol Psychiatry* 1994;35:367–74.
- [108] Saletu B, Kufferle B, Grunberger J, Foldes P, Topitz A, Anderer P. Clinical, EEG mapping and psychometric studies in negative schizophrenia: comparative and psychometric trials with amisulpride and fluphenazine. *Neuropsychobiology* 1994;29:125–35.
- [109] Schellenberg R, Milch W, Schwarz A, Schober F, Dimpfel W. Quantitative EEG and BPRS data following haldol-decanoate administration in schizophrenics. *Int Clin Psychopharmacol* 1994;9:17–24.
- [110] Niedermeyer E. EEG and clinical neurophysiology. In: Niedermeyer E, Lopes Da Silva F, editors. *Electroencephalography: basic principles, clinical applications and related fields*. Baltimore: Urban & Schwarzenberg; 1987. p. 97–117.
- [111] Herrmann WM, Schaerer E. Pharmac-EEG: computer EEG analysis to describe the projection of drug effects on a functional cerebral level in humans. In: Lopes Da Silva FH, Storm van Leeuwen W, Remond A, editors. *Handbook of electroencephalography and clinical neurophysiology*. New York: Elsevier Science; 1986. p. 385–445.
- [112] Kemali D, Vacca L, Marciano T, Celani T, Nolfè G, Iorio G. Computerized EEG in schizophrenics. *Neuropsychobiology* 1980;6:260–7.
- [113] Etevenon P, Peron-Magnan P, Rioux P, Pidoux B, Bissierbe JC, Verdeau G, et al. Schizophrenia assessed by computerized EEG. *Recent Adv Biol Psychiatry* 1981;6:29–34.
- [114] Gunther W, Breitline D. Predominant sensorimotor area left hemisphere dysfunction in schizophrenia measured by brain electrical activity mapping. *Biol Psychiatry* 1985;20:515–32.
- [115] Ford MR, Goethe JW, Dekker DK. EEG coherence and power in the discrimination of psychiatric disorders and medication effects. *Biol Psychiatry* 1986;21:1175–88.
- [116] Muller HF, Achim A, Aur A, Burchbinder A. Topography and possible physiological significance of EEG amplitude variability in psychosis. *Acta Psychiatr Scand* 1986;73:665–7.
- [117] Williamson P, Mamelak M. Frontal spectral EEG findings in acutely ill schizophrenics. *Biol Psychiatry* 1987;22:1021–4.

- [118] Galderisi S, Mucci A, Mignone ML, Maj M, Kemali D. qEEG mapping in drug-free schizophrenics: differences from healthy subjects and changes induced by haloperidol treatment. *Schizophr Res* 1992;6:15–24.
- [119] Primavera A, Fonti A, Novello P, Roccatagliata G, Cocito L. Epileptic seizures in patients with catatonic syndrome. *J Neurol Neurosurg Psychiatry* 1994;57(11):1419–22.
- [120] Westphal KP, Grozinger B, Diekmann V, Reess W, Leibing U, Kornhuber HH. Slower theta activity over the midfrontal cortex in schizophrenic patients. *Acta Psychiatr Scand* 1990; 81:132–8.
- [121] Matsuura M, Yoshino M, Ohta K, Onda H, Nakajima K, Kojima T. Clinical significance of diffuse delta EEG activity chronic schizophrenia. *Clin Electroencephalogr* 1994;25(3):115–21.
- [122] Lifshitz K, Lee KL, Susswein S. Long-term replicability of EEG spectra and auditory potentials in schizophrenic and normal subjects. *Neuropsychobiology* 1988;18:205–11.
- [123] Gattaz WF, Mayer S, Ziegler P, Platz M, Gasser T. Hypofrontality on topographic EEG in schizophrenia: correlations with neuropsychological and psychopathological parameters. *Eur Arch Psychiatry Clin Neurosci* 1992;241:328–32.
- [124] John ER, Prichep LS, Alper KR, Mas F, Cancro R, Easton P, et al. Quantitative electrophysiological characteristics and subtyping of schizophrenia. *Biol Psychiatry* 1994;36: 801–26.
- [125] Czobor P, Volavka J. Quantitative EEG effect of risperidone in schizophrenic patients. *J Clin Psychopharmacol* 1993;13(5):332–42.
- [126] Gunther W, Steinberg R, Petsch RSP, Kugler J. EEG mapping in psychiatry: studies of type I/II schizophrenia using motor activation. In: Maurer K, editor. *Topographic brain mapping and evoked potentials*. Berlin: Springer-Verlag; 1989. p. 438–50.
- [127] Shagass C, Roemer RA. Evoked potential topography in unmedicated and medicated schizophrenics. *Int J Psychophysiol* 1991;10:213–24.
- [128] Merrin EL, Floyd TC, Fein G. EEG coherence in unmedicated schizophrenic patients. *Biol Psychiatry* 1989;25:60–6.
- [129] Pockberger H, Thau K, Lovrek A, Petsche H, Pappelsberger P. Coherence mapping reveals differences in the of EEG psychiatric patients and healthy persons. In: Maurer K, editor. *Topographic brain mapping of EEG and evoked potentials*. Berlin: Springer-Verlag; 1989. p. 451–7.
- [130] Nagase Y, Okubo Y, Matsuura M, Kojima T, Toru M. EEG coherence in unmedicated schizophrenic patients: topographical study. *Biol Psychiatry* 1992;32:1028–34.
- [131] Alper K. Quantitative EEG and evoked potentials in adult psychiatry. In: Pankseep J, editor. *Advances in biological psychiatry*. Greenwich (CT): JAI Press; 1995. p. 65–112.
- [132] Monakhov K, Perris C. Neurophysiological correlates of depressive symptomatology. *Neuropsychobiology* 1980;6:268–79.
- [133] Itil TM. The discovery of antidepressant drugs by computer-analyzed human cerebral bio-electrical potentials (CEEG). *Prog Neurobiol* 1983;20:185–249.
- [134] Nystrom C, Matousek M, Hallstrom T. Relationships between EEG and clinical characteristics in major depressive disorder. *Acta Psychiatr Scand* 1986;73:390–4.
- [135] Knott VJ, Lapiere YD. Computerized EEG correlates of depression and antidepressant treatment. *Prog Neuropsychopharmacol Biol Psychiatry* 1987;11:213–21.
- [136] Pollock VE, Schneider LS. Topographic quantitative EEG in elderly subjects with depression. *Psychophysiology* 1990;27(4):438–44.
- [137] Nieber D, Schlegel S. Relationships between psychomotor retardation and EEG power spectrum in major depression. *Biol Psychiatry* 1992;25:20–3.
- [138] Schaffer CE, Davidson RH, Saron C. Frontal and parietal electroencephalogram asymmetry in depressed and nondepressed subjects. *Biol Psychiatry* 1982;18:753–62.
- [139] Kemali D, Vacca L, Marciano F, Nolfi G, Galderi S, Salvati A. CEEG findings in schizophrenics, depressives, obsessives, heroin addicts and normals. *Recent Adv Biol Psychiatry* 1981;6:17–28.
- [140] Henriques JB, Davidson RJ. Regional brain electrical asymmetries discriminate between previously depressed and healthy control subjects. *J Abnorm Psychol* 1990;99(1):22–31.

- [141] Henriques JB, Davidson RJ. Left frontal hypoactivation in depression. *J Abnorm Psychol* 1991;100(4):535–45.
- [142] Allen JJ, Iacono WG, Depue RA, Arbisi P. Regional electroencephalographic asymmetries in bipolar seasonal affective disorder before and after exposure to light. *Biol Psychiatry* 1993; 33:642–6.
- [143] Prichep LS, John ER, Essig-Pepard T, Alper KR. Neurometric subtyping of depressive disorders. In: Cazzullo CL, Invernizzi G, editors. *Plasticity and morphology of the CNS*. London: MTP Press; 1990.
- [144] Clementz BA, Sponheim SR, Iacono W. Resting EEG in first-episode schizophrenia patients, bipolar psychotic patients, and their first-degree relatives. *Psychophysiology* 1994;31:486–94.
- [145] Prichep LS, John ER, Alper K, Gomez-Mont F, Essig-Pepard T, Flitter M. Quantitative EEG in depressive disorders. In: Shagass C, Josiassen RC, Roemer RA, editors. *Brain electrical potentials and psychopathology*. Amsterdam: Elsevier; 1986. p. 223–44.
- [146] Small JG. Psychiatric disorders and EEG. In: Niedermeyer E, Lopes Da Silva F, editors. *Electroencephalography: basic principles, clinical applications, and related fields*. Baltimore: Williams & Wilkins; 1993. p. 581–96.
- [147] Jenike MA, Brotman AW. The EEG in obsessive-compulsive disorder. *J Clin Psychiatry* 1984; 45:122–4.
- [148] Abraham HD. Stimulants, panic, and BEAM EEG abnormalities. *Am J Psychiatry* 1989; 146(7):947–8.
- [149] Louie AK, Lannon RA, Ketter TA. Treatment of cocaine-induced panic disorder. *Am J Psychiatry* 1989;146:40–4.
- [150] Abraham HD, Duffy F. Computed EEG abnormalities in panic disorder with and without drug abuse. *Biol Psychiatry* 1991;29:687–90.
- [151] Buchsbaum MS, Hazlett E, Sicotte N, Stein J, Wu J, Zetin M. Topographic EEG changes with benzodiazepine administration in generalized anxiety disorder. *Biol Psychiatry* 1985;20: 832–42.
- [152] Siciliani O, Schiavon M, Tansella M. Anxiety and EEG alpha activity in neurotic patients. *Acta Psychiatr Scand* 1975;52:116–31.
- [153] Perros P, Young ES, Ritson JJ, Price GW, Mann P. Power spectral EEG analysis and EEG variability in obsessive-compulsive disorder. *Brain Topogr* 1992;4:187–92.
- [154] Silverman JS, Loychik SG. Brain-mapping abnormalities in a family with three obsessive-compulsive children. *J Neuropsychiatry Clin Neurosci* 1990;2:319–22.
- [155] Prichep LS, Mas F, Hollander E, Liebowitz M, John ER, Almas M, et al. Quantitative electroencephalographic (qEEG) subtyping of obsessive compulsive disorder. *Psychiatry Res* 1993;50(1):25–32.
- [156] Cook IA, Leuchter AF. Prefrontal changes and treatment response prediction in depression. *Semin Clin Neuropsychiatry* 2001;6(2):113–20.
- [157] Cook IA, Leuchter AF, Morgan M, Witte E, Stubbeman WF, Abrams MT, et al. Early changes in prefrontal activity characterize clinical responders to antidepressants. *Neuropsychopharmacology* 2002;27(1):120–31.
- [158] Leuchter AF, Cook IA, White EA, Morgan M, Abrams M. Changes in brain function of depressed subjects during treatment with placebo. *Am J Psychiatry* 2002;159:133–9.
- [159] Bricolo A, Turazzi S, Faccioli F, Odorizzi F, Sciarretta G, Erculiani P. Clinical application of compressed spectral array in EEG monitoring of comatose patients. *Electroencephalogr Clin Neurophysiol* 1978;45:211–25.
- [160] Steudel WI, Krüger J. Using the spectral analysis of the EEG prognosis of severe brain injuries in the first post-traumatic week. *Acta Neurochir* 1979;28(Suppl):40–2.
- [161] Rimel RW, Giordani B, Barth JT, Jane JA. Moderate head injury: completing the clinical spectrum of trauma. *Neurosurgery* 1982;11:344–51.
- [162] Thatcher RW, Cantor DS, McAlaster R. Comprehensive predictions of outcome in closed head-injured patients. *Ann N Y Acad Sci* 1983;82:82–101.
- [163] Ross RJ, Cole M, Thompson JS, Kim KH. Boxers: computer tomography, EEG, and neurological. *JAMA* 1983;249:211–3.

- [164] Tysvaer AT, Stroll OV, Bachen I. Soccer injuries to the brain: a neurologic electroencephalographic study of former players. *Acta Neurol Scand* 1989;80:151–6.
- [165] Randolph C, Miller MH. EEG and cognitive performance following closed head injury. *Neuropsychobiology* 1988;20:43–50.
- [166] Thatcher RW, Biver CJ, North DM. Quantitative EEG and the Frye and Daubert standards of admissibility. *Clin Electroencephalogr* 2003;34(2):39–53.
- [167] Bresnahan SM, Barry RJ. Specificity of quantitative EEG analysis in adults with attention deficit hyperactivity disorder. *Psychiatry Res* 2002;112(2):133–44.
- [168] Chabot RJ, Sigal LH. qEEG and evoked potentials in central nervous system Lyme disease. *Clin Electroencephalogr* 1995;26(3):137–45.
- [169] Gugino LD, Chabot RJ, Aglio LS, Maddi R, Gosnell J, Aranki S. qEEG and neuropsychological profiles of patients prior undergoing cardiopulmonary bypass surgical procedures. *Clin Electroencephalogr* 1997;28(2):87–97.
- [170] Chabot RJ, Gugino LD, Aglio LS, Maddi R, Cote W. qEEG and neuropsychological profiles of patients after cardiopulmonary bypass surgical procedures. *Clin Electroencephalogr* 1997;28:98–105.
- [171] Tsai LY. Neuropsychologic studies of infantile autism. *Adv Dev Behav Pediatr* 1987;235–60.
- [172] Small JH, Small IF, Milstein V, et al. Familial associations with EEG variants in manic-depressive disease. *Arch Gen Psychiatry* 1975;32:43–8.
- [173] Dawson G, Warrenburg S, Fuller P. Cerebral lateralization in individuals diagnosed as autistic early childhood. *Brain Lang* 1982;15:353–68.
- [174] Ogawa T, Sugiyama A, Ishiwa S, Sizuki M, Ishihara T, Sato K. Ontogenic development of EEG-asymmetry in early infantile. *Brain Dev* 1982;4:439–49.
- [175] Cantor DS, Thatcher RW, Hrybyk M. Computerized EEG analyses of autistic children. *J Autism Dev Disord* 1986;16:169–87.
- [176] Kinsbourne M. Hemispheric specialization and the growth of human. *Am Psychol* 1982;37:411–20.
- [177] Marosi E, Harmony T, Sanchez L, Becker J, Bernal J, Reyes A, et al. Maturation of the coherence of EEG activity normal and learning-disabled children. *Electroencephalogr Clin Neurophysiol* 1992;83:350–7.
- [178] Hauser E, Strohmayer C, Seidl R, Birnbacher R, Lischka A, Schober E. Quantitative EEG in young diabetics. *J Child Neurol* 1995;10(4):330–4.
- [179] Bjorgaas M, Sand T, Gimse R. Quantitative EEG in type 1 diabetic children with and without episodes of severe hypoglycemia: a controlled, blind study. *Acta Neurol Scand* 1996;93(6):398–402.
- [180] Bjorgaas M, Sand T, Vik T, Jorde R. Quantitative EEG during controlled hypoglycemia in diabetic and non-diabetic children. *Diabet Med* 1998;15(1):30–7.
- [181] Byring RF, Salmi T, Sainio K, Orn H. EEG in children with spelling disabilities. *Electroencephalogr Clin Neurophysiol* 1991;79:247–55.
- [182] Galin D, Herron J, Johnstone J, Fein G, Yingling C. EEG alpha asymmetry in dyslexics during speaking block design tasks. *Brain Lang* 1988;35:241–53.
- [183] Colon EJ, Notermas SLH, de Weerd JPC. The discriminating role of EEG power spectra in dyslexic children. *J Neurol* 1979;221:257–62.
- [184] Lubar JF, Bianchini KJ, Calhoun WH. Spectral analysis of EEG differences between children with and without learning disabilities. *J Learn Disabil* 1985;18:403–8.
- [185] Dykman RA, Holcomb PJ, Oglesby DM. Electroocortical frequencies in hyperactive, learning-disabled, mixed and normal children. *Biol Psychiatry* 1982;17:675–85.
- [186] John ER. Neurometric evaluation of brain function related to learning disorders. *Acta Neurol Scand* 1981;64(Suppl 89):87–100.
- [187] Harmony T, Hinojosa G, Marosi E, Becker J, Rodriguez M, Reyes A, et al. Correlation between EEG spectral parameters and an evaluation. *Int J Neurosci* 1990;54:147–55.
- [188] Mechelse K, Gemund JJ, Nije J, Burg L, Laurs J. Visual and quantitative analysis of EEGs of school children, children, and school children with specific reading disability. *Electroencephalogr Clin Neurophysiol* 1975;39:106–8.

- [189] Fernandez T, Harmony T, Fernandez-Bouzas A, Silva J, Herrera W, Santiago-Rodriguez E, et al. Sources of EEG activity in learning disabled children. *Clin Electroencephalogr* 2002; 33(4):160–4.
- [190] Leisman G. Coherence of hemispheric function in developmental dyslexia. *Brain Cogn* 2002; 48(2–3):425–31.
- [191] Otero GA, Pliego-Rivero FB, Fernandez T, Ricardo J. EEG development in children with sociocultural disadvantages: a follow-up study. *Clin Neurophysiol* 2003;114(10):1918–25.
- [192] Ito Y, Teicher MH, Glod CA, Ackerman E. Preliminary evidence for aberrant cortical development in abused children: a quantitative EEG study. *J Neuropsychiatry Clin Neurosci* 1998;10:298–307.
- [193] Montagu JD. The hyperkinetic child: a behavioural, electrodermal and EEG investigation. *Dev Med Child Neurol* 1975;17:299–305.
- [194] Callaway E, Halliday R, Naylor H. Hyperactive children's event related potentials fail to support underarousal and maturational-lag theories. *Arch Gen Psychiatry* 1983;40:1243–8.
- [195] Mann CA, Lubar J, Zimmerman A, Miller C, Muenchen R. Quantitative analysis of EEG in boys with deficit hyperactivity disorder: controlled study with clinical implications. *Pediatr Neurol* 1992;8:30–6.
- [196] Barry RJ, Clarke AR, Johnstone SJ. A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clin Neurophysiol* 2003;114(2):171–83.
- [197] Clarke AR, Barry RJ, McCarthy R, Selikowitz M. EEG analysis in attention-deficit/hyperactivity disorder: a comparative study of two subtypes. *Psychiatry Res* 1998;81(1):19–29.
- [198] Clarke AR, Barry RJ, McCarthy R, Selikowitz M. EEG-defined subtypes of children with attention-deficit/hyperactivity disorder. *Clin Neurophysiol* 2001;112:2098–105.
- [199] Clarke AR, Barry RJ, McCarthy R, Selikowitz M, Brown CR, Croft RJ. Effects of stimulant medications on the EEG of children with attention-deficit/hyperactivity disorder predominantly inattentive type. *Int J Psychophysiol* 2003;47(2):129–37.
- [200] Lubar JF. Discourse on the development of EEG diagnostics biofeedback for attention-deficit/hyperactivity disorders. *Biofeedback Self Regul* 1991;16:201–24.
- [201] Monastra VJ, Lubar JF, Linden M, VanDeusen P, Green G, Wing W, et al. Assessing attention deficit-hyperactivity disorder via quantitative electroencephalography: an initial validation study. *Neuropsychology* 1999;13(3):424–33.
- [202] Monastra VJ, Lubar JF, Linden M. The development of a quantitative electroencephalographic scanning process for attention deficit-hyperactivity disorder: reliability and validity studies. *Neuropsychology* 2001;15(1):136–44.
- [203] Satterfield J. EEG issues in children with minimal brain. *Semin Psychiatry* 1973;5:35–46.
- [204] Halperin JM, Gittleman R, Katz S. Relationship between stimulant effect, electroencephalogram, and clinical neurological findings in hyperactive children. *J Am Acad Child Psychiatry* 1986;25:820–5.
- [205] McIntyre H, Firemark M, Cho A. Computer analyzed EEG in amphetamine responsive hyperactives. *Psychiatry Res* 1981;4:189–97.
- [206] Prichep LS, John ER. Neurometric studies of methylphenidate responders and non-responders. In: Pavlidis GT, editor. *Perspectives on dyslexia*. New York: John Wiley & Sons; 1990. p. 133–9.
- [207] Steinhausen H, Romahn G, Gobel D. Computer analyzed EEG methylphenidate responsive hyperactive children. *Neuropediatrics* 1984;15:28–32.
- [208] Loo SK, Teale PD, Reite ML. EEG correlates of methylphenidate response among children with ADHD: a preliminary report. *Biol Psychiatry* 1999;45(12):1657–60.
- [209] Craggs MD, Wright JJ, Werry JS. A pilot study of the effects of methylphenidate on the vigilance-related EEG in hyperactivity. *Electroencephalogr Clin Neurophysiol* 1980;48: 34–42.
- [210] Surwillo WW. Changes in the electroencephalogram accompanying the use stimulant drugs (methylphenidate and dextroamphetamine) in hyperactive children. *Biol Psychiatry* 1977;12:787–99.

- [211] Clarke AR, Barry RJ, McCarthy R, Selikowitz M, Clarke DC, Croft RJ. Effects of stimulant medications on children with attention-deficit/hyperactivity disorder and excessive beta activity in their EEG. *Clin Neurophysiol* 2003;114(9):1729–37.
- [212] Levy F. Neurometrics: review and comments. *ADHD Report* 1994;2:35798.
- [213] Levy F, Ward P. Neurometrics, dynamic brain imaging and attention deficit. *J Paediatr Child Health* 1995;31:279–83.
- [214] Chabot RJ, Serfontein G. Quantitative EEG profiles of children with attention deficit disorder. *Biol Psychiatry* 1996;40:951–63.
- [215] Chabot RJ, Orgill AA, Crawford G, Harris MJ, Serfontein G. Behavioral and electrophysiological predictors of treatment response stimulants in children with attention disorders. *J Child Neurol* 1999;14(6):343–51.
- [216] Chabot RJ, diMichele F, Pritchep L, John ER. The clinical role of computerized EEG in the evaluation and treatment of learning and attention disorders in children and adolescents. *J Neuropsychiatry Clin Neurosci* 2001;13:171–86.
- [217] Bresnahan SM, Anderson JW, Barry RJ. Age-related changes in quantitative EEG in attention-deficit/hyperactivity disorder. *Biol Psychiatry* 1999;46(12):1690–7.
- [218] Riddle MA, Scahill L, King RA, Hardin MT, Anderson GM, Ort SI, et al. Double-blind, crossover trial of fluoxetine and placebo in children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry* 1992;31(6):1062–9.
- [219] Noble EP, Blum K, Khalsa ME, Ritchie T, Montgomery A, Wood RC. Allelic association of the D2 dopamine receptor gene with cocaine dependence. *Drug Alcohol Depend* 1993;33:271–85.
- [220] Ebstein RP, Gritsenko I, Nemanov L, Frish A, Osher Y, Belmaker RH. No association between the serotonin transporter gene regulatory polymorphism and the tridimensional personality questionnaire (TPQ) temperament of harm avoidance. *Mol Psychiatry* 1997;2:224–6.
- [221] DeBoer P, Abercrombie E. Physiological release of striatal acetylcholine in vivo: modulation of d1 and d2 dopamine receptor subtypes. *J Pharmacol Exp Ther* 1996;277:775–83.
- [222] Icarashi Y, Takahashi H, Aral T, Maruyama Y. Suppression of cholinergic activity via the dopamine d2 receptor in the rat striatum. *Neurochem Int* 1997;30:191–7.
- [223] Russel V, de Villiers A, Sagvolden T, et al. Altered dopaminergic function in the prefrontal cortex, nucleus accumbens and caudate-putamen of an animal model of attention deficit hyperactivity disorder. *Brain Res* 1995;676:343–51.
- [224] Levy F. The dopamine theory of attention deficit hyperactivity disorder. *Aust N Z J Psychiatry* 1991;25:277–83.
- [225] Niedermeyer E, Naidu SB. Attention deficit disorder and frontal motor cortex disconnection. *Clin Electroencephalogr* 1998;28:130–6.
- [226] Barkley RA, Grodzinsky G, DuPaul GJ. Frontal lobe functions in attention deficit disorder and without hyperactivity: a review and research report. *J Abnorm Child Psychol* 1992;20(2):163–88.
- [227] Hynd G, Semrud-Clikeman M, Lorys A, Novey E, Eliopoulos D, Lyytinen H. Corpus callosum morphology in attention deficit disorder: morphometric analysis of MRI. *J Learning Disord* 1991;24:141–6.
- [228] Kim BN, Lee JS, Cho SC, Lee DS. Methylphenidate increased regional cerebral flow in subjects with attention deficit/hyperactivity disorder. *Yonsei Med J* 2001;42(1):19–29.
- [229] Lou H, Henriksen L, Bruhn P, Borner H, Nielsen J. Striatal dysfunction in attention deficit and hyperkinetic. *Arch Neurol* 1989;46:48–52.
- [230] Robbins TW, Roberts AC, Owen AM, Sahakian BJ, Everitt BJ, Wilkinson L, et al. Monoaminergic-dependent cognitive functions in the prefrontal cortex monkey and man. *Motor and Cognitive Functions of the Prefrontal Cortex*. 1994. p. 94–111.
- [231] Shue KL, Douglas VI. Attention deficit hyperactivity disorder and the frontal syndrome. *Brain Cogn* 1992;20:104–24.
- [232] Zametkin AJ, Liebenauer LL, Fitzgerald GA, King AC, Minkunas DV, Herscovitch P, et al.

- Brain metabolism in teenagers with attention-deficit hyperactivity disorder. *Arch Gen Psychiatry* 1993;50:333–40.
- [233] El-Sayed E, Larsson JO, Persson HE, Rydelius PA. Altered cortical activity in children with attention-deficit/hyperactivity disorder during attentional load task. *J Am Acad Child Adolesc Psychiatry* 2002;41:811–9.