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# Quantitative EEG in Childhood Attention Deficit Hyperactivity Disorder and Learning Disabilities

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**Abstract**

The clinical use of the quantitative EEG (QEEG) from the pioneering work of John has received a new impetus thanks to new neuroimaging techniques and the possibility of using a number of normative databases both of normal subjects and of subjects with definite pathologies. In this direction, the term *personalized medicine* is becoming more and more common, a medical procedure that separates patients into different groups based on their predicted response to the quantitative EEG. This has allowed the study of single subjects and to customize health care, with decisions and treatments tailored to each individual patient, as well as improvement of knowledge of the pathophysiological mechanisms of specific diseases. This review article will present the most recent evidence in the field of developmental neuropsychiatric disorders obtained from the application of quantitative EEG both in clinical group studies (attention deficit hyperactivity disorder, developmental dyslexia, oppositional defiant disorder) and in individual case studies not yet published.

**Keywords**

quantitative EEG, QEEG, developmental dyslexia, oppositional defiant disorder, reading delay, atomoxetine, methylphenidate, micrography.

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## Introduction

Historically, conventional EEG has added little to the understanding of childhood psychiatric disorders, other than to rule out epilepsy or space occupying lesions. However, the advent of computerized, quantitative methods, from the pioneering work of John,[1] together with new neuroimaging techniques as brain sources localization and the availability of normative databases both of normal subjects and of subjects with definite pathologies has greatly enhanced the clinical application in neurodevelopmental disorders. Furthermore, in these past years, it has become more and more apparent that groups of patients with neuropsychiatric disorders, who meet symptom based diagnostic criteria for specific disorders (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [*DSM-IV*] or International Classification of Diseases, 10th Revision [ICD-10]) have varied responses to treatment, despite their relatively homogeneous clinical presentation. Using clinical diagnosis, the "treatment of choice" leads to a positive response approximately 60% of the time.[2] This poor response rate suggests heterogeneity within these relatively homogeneous clinical populations. In this direction, the term *personalized medicine* is becoming more and more common, a medical procedure that separates patients into different groups based on their electrophysiological profiles and predicted response to the quantitative EEG. This has allowed the study of single subjects and to customize health care, with decisions and treatments tailored to each individual patient, as well as improvement of knowledge of the pathophysiological mechanisms of specific diseases.

## The Debate Around the Use of the Quantitative EEG in Clinical Practice

The use of quantitative EEG (QEEG) in clinical practice has always been hotly debated. The Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents of the American Academy of Pediatrics[3] states that to make a diagnosis of attention deficit hyperactivity disorder (ADHD), clinicians should conduct a clinical interview with parents, examine and observe the child, and obtain information from parents and teachers through *DSM*-based ADHD rating scales. One of the research questions developed by an ad hoc subcommittee was the following: "What is the comparative diagnostic accuracy of

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EEG, imaging, or executive function approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals aged 7 to their 18th birthday?" The only answer to this question is the following: "The use of neuropsychological testing has not been found to improve diagnostic accuracy in most cases, although it may have benefit in clarifying the child or adolescent's learning strengths and weaknesses."

The use of QEEG as a diagnostic tool has always been widely debated with numerous works in favor and others against. This uncertainty, in my opinion, stems from the fact that ADHD is not a disease but a syndrome. This primarily implies that the inclusion and exclusion criteria are not always homogeneous in the various studies, the diagnostic criteria are mainly based on clinical evaluations and scales that introduce further variability. This is to mention just a few factors without neglecting the more strictly technical ones related to the recording of the QEEG and to the physiological conditions of the subject examined, both normal and with ADHD. Quintana et al[4] in a recent study of comparison of a standard psychiatric evaluation to rating scales and EEG in the differential diagnosis of attention deficit hyperactivity disorder affirm that numerous studies have been conducted to establish the validity and reliability of ratings scales as an assessment tool for ADHD as covered in a recent 10-year review.[5] A broad review of the literature demonstrates that when taking statistical methods and experimental designs of these studies into consideration, the expected range of accuracy for rating scales is 55% to 79% in the identification of ADHD versus controls. In their study, Quintana et al[4] report that

> . . . rating scales were likely to classify attention, impulsivity, and/or hyperactivity symptoms as being due to ADHD, regardless of the actual underlying disorder, leading to a sensitivity of 81% and a specificity of 22% for the rating scales when applied to a clinical sample. The overall classification accuracy of the rating scales was 60%.

As far as the accuracy of the QEEG, Quintana et al[4] write that

> the age-matched EEG pattern for ADHD was observed to be present in 15 of 16 subjects diagnosed by the standard psychiatric evaluation as having ADHD (sensitivity = 94%). Regardless of the presence of ADHD-like symptoms, the EEG pattern for ADHD did not occur in any of these non-ADHD patients (specificity = 100%). The overall classification accuracy of the EEG test was 96%.

The authors conclude that QEEG may play a significant role in ADHD differential diagnosis. Similar classification accuracy results were obtained in other studies.[6-12]

On the contrary, recent review of meta-analysis failing to confirm the usefulness of theta-beta ratio in eyes open condition in the diagnosis of ADHD.[13] In addition, Ogrim et al[14] reported a significant elevated theta characteristic of a subgroup of ADHD patients that was correlated with inattention and executive problems with an accuracy of 62% at Cz.

However, it is a well-known fact that EEG activity shows a high variability with age. To assess what is normal or what deviates from normality, the subject's age has to be considered. To facilitate deviation from normality, assessment in the QEEG normative database have been recorded and regression equation against the age have been calculated. In this way, *z* scores are obtained using the raw spectra parameters and the means and standard deviations calculated from the normative data for the same parameter. This transformation accounts for the age variability in the EEG data.[15] Although EEG differences between eyes open and eyes closed are important to assess some pathological activities in the brain, the majority of databases used in the QEEG contain only information about eyes closed condition.

In this article, we focus on the study of EEG activity during resting state, which is the purpose of QEEG analysis. However, it has to be understood that EEG analysis is not appropriate when analyzing task-related brain activities. For that case, we suggest the technique of event-related potentials.

In order to provide a further contribution to the clinical utility of the quantitative EEG, the most recent evidences in the field of developmental neuropsychiatric disorders are presented in this review article obtained from the application of quantitative EEG both in clinical group studies, developmental dyslexia, reading retardation, ADHD with and without oppositional defiant disorder and in 2 case studies, not yet published and selected from the database of the International Center for Learning, Attention and Hyperactivity Disorders (CIDAAI).

The appendix describes the method of acquisition and processing of EEG signal used in studies whose results will be described here below.

## Developmental Dyslexia and Reading Retardation

Boder and Jarrico[16] have developed a diagnostic screening procedure which identifies three main subtypes of dyslexia: dysphonetic dyslexia (DD), dyseidetic and mixed, besides a fourth group defined nonspecific reading delay (NSRD). These subgroups are identified by an algorithm that considers the reading quotient and the percentage of errors of the spelling test. The early identification of this NSRD subgroup, frequently overlooked or confounded with dysphonetic dyslexia, has evident clinical implications for diagnosis, therapy, and prognosis. While specific learning disabilities have been extensively studied with QEEG, reading retardation has not received the same attention instead. John[1] and Duffy et al[17] reported QEEG abnormalities in both hemispheres in dyslexic children at rest as well as during complex testing. John et al[18] found abnormal QEEGs present in 32.7% of the children with specific learning disorder (SLD) and 38.1% of the children with learning disorder (LD) groups, whereas only 5.5% of an independent sample of normal children had abnormal QEEGs. Children with learning disorders were shown to have different patterns of brain maturation than normal control subjects. Normal subjects, with increased age show an increase of posterior/vertex EEG

coherence and a decrease in coherence in frontal areas. Increased differentiation of frontal cortical regions, with age, leads to increased communication across basic sensory and association cortex. These systematic maturational changes are often not seen in children with learning disorders. Flynn and Deering[19] and Flynn et al,[20] using the Boder test classification,[21] investigated whether electrophysiological evidence among dyslexic subgroups, could be demonstrated by analysis of QEEG patterns during school-related tasks. The authors found increased left temporo-parietal theta activity in dyseidetic children assuming an overuse of the left-language system activation in patients with visuo-spatial problems recognition. Casarotto et al,[22] using reading-related potentials recorded during reading aloud self-paced single-letter, showed that children with DD had *abnormal activation* at short latencies in the left temporal polar area, at middle latencies in the temporal polar and inferior frontal regions bilaterally and at long latencies in fronto-temporal regions of the right hemisphere. This indicates an early involvement of frontal regions during reading and it may be related to a significantly higher activation of the right hemisphere. This would seem very likely to be related to compensatory mechanisms adopted by reading-impaired children to improve their performance. On the contrary, *impaired activation* of the dyslexic group was present in the left and medial parietal regions: at short and middle latencies, it was present in the angular and then in the supramarginal gyrus; at long latencies, it moved in the middle precuneus and occipital lobe. Therefore, behavioral signs of reading impairment can be related to reduced activation in the left dorsal parieto-occipital regions that have been shown to be specifically involved in reading processes and particularly in the storage and processing of the visual and auditory representations of alphabetic characters.[23] These results are consistent with previous findings of greater recruitment of cerebral regions in the right hemisphere in dyslexic children in comparison with controls.[24] Although all the cited studies identify the left temporo-parietal region as the region where the greatest differences between normal and dyslexic subjects are found, electrophysiological differences between subtypes of dyslexia according to Boder classification have not been further confirmed also due to different clinical classifications. Furthermore, we are not aware of studies that compare children with different subtypes of dyslexia with children with NSRD using electrophysiological methods. Recently, we have used QEEG to indicate which children with learning problems have a measurable underlying neurophysiological dysfunction and which do not.[25] The possibility of identifying early indicators of children with NSRD has obvious therapeutic and prognostic implications as well as clinical ones, above all to avoid that they are not identified, diagnosed, and treated belatedly, until the secondary school level or confounded with children with DD. In comparison with the children with reading delay, the children with DD showed significant excess in delta band in the middle line (Fz, Cz, and Pz), as well as Fp2 and the occipital leads bilaterally (O1 and O2). A significant excess in high theta (6-7.5 Hz) and low alpha (7.5-8.5 Hz) bands was also present in the Fz, Cz, and Fp2. Fz, Cz, and Pz also showed significant excess of activity in the DD group. However, a significant reduction of high alpha (11-12.5 Hz) activity was present in the DD group bilaterally in F3, C3, C4, and in P3. Additionally, significant reduction was also present in the left leads F7, F3, C3, P3, and T5. Figure 1 shows the significant differences of the *t* test at the source spectra of DD versus NSRD. The *t* tests at the sources showed a significant increase of activity of DD with regard to NSRD in delta, low (4.29 Hz) and high theta (7.5 Hz) bands, and a significant decrease of DD with regard to NSRD in beta band (18-19 Hz). In the delta band: bilaterally in the calcarine sulcus, cuneus, precuneus, lingual, occipital (superior, middle, and inferior lobes), fusiform and superior parietal gyrus; the right inferior parietal, the right angular gyrus and the right paracentral lobule. In the low theta band: the right superior parietal and the right inferior parietal gyrus. In the high theta band: bilaterally the frontal medial orbital and the right superior medial frontal gyri. In the beta band: bilaterally the calcarine sulcus, lingual and fusiform inferior gyri; the left occipital (superior, medial and inferior) gyrus, superior and inferior parietal gyrus, supramarginal gyrus, angular gyrus and middle and inferior temporal gyrus.

The observation of the differences of EEG source spectra between the 2 groups allows us to add further considerations. The first observation concerns the excess of delta and theta activity that is found in the dysphonetic subjects in a standard EEG recorded at rest, with eyes closed. This fact reinforces the hypothesis that dyslexia is not only a functional disorder, but the result of a structural disorder as reported by the studies of Galaburda,[26] which found in the brain of 5 severe dyslexics adults, the right temporal planum wider than the left in 100% of cases. In addition, a high frequency of microdysgenesis was also observed, particularly in the left frontal and temporal opercula. This report was subsequently confirmed by Shaywitz et al[27] who performed a series of language-based activation tasks with progressively increasing phonologic demands using functional magnetic resonance imaging (fMRI) in dyslexic adults. There was underactivation of the left posterior perysilvian and occipital regions (Wernicke's area, the angular gyrus, and striate cortex) and overactivation to even simple phonologic task in both left anterior (inferior frontal gyrus) and right posterior perisylvian regions. A certain dysregulation of the motor areas in dyslexic subjects has long been known.[28,29] Dyslexic patients have difficulty processing both rapid and visual stimuli as well as in generating rapid bimanual motor output. In 1982, Chiarenza et al[30] recorded the brain electrical activity, called "movement-related brain potentials," during a skilled motor task that to be performed adequately, required bimanual coordination, bimanual ballistic movements, adaptive programming and learning a proper timing. The dyslexic children presented a deficit of programming movements, a deficit of visual and kinesthetic sensory processes, and a reduced capacity to evaluate their performance and correct their errors. Chiarenza[31] advanced the hypothesis that dyslexia is not only a phonological or gestalt deficit but also a praxic disorder in which praxic abilities, such as motor programming, sequential and sensorial motor

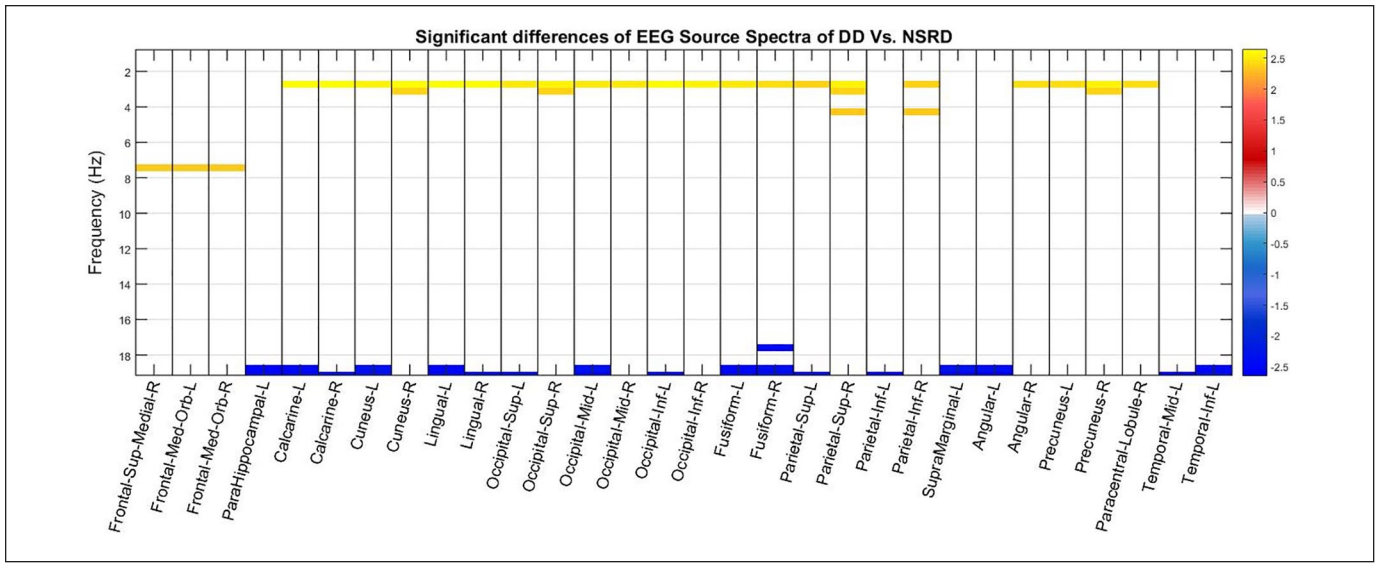


**Figure 1.** Significant differences of the *t* test at the source spectra of dysphonetic dyslexia (DD) versus nonspecific reading delay (NSRD). Red and yellow values indicate an excess of DD compared with NSRD; values in the blue scale indicate excess of NSRD compared with DD. Threshold corrected by multiple comparisons. Differences are concentrated in very narrow bands of frequencies. In general, DD have an excess of slow activity (delta and slightly theta) and a defect of fast activity (beta band). Age-dependent *z* score spectra of the EEG at the sources were used in this study. The *z* scores were calculated using the Cuban Normative Database and the QEEGT software developed by the Cuban Neuroscience Center.

integration and evaluation processes, are required and somehow defective in dyslexia. In addition, Chiarenza et al[30] have observed that dyslexic children showed a latency delay of movement-related potentials significantly different across the various cerebral areas during the same skilled motor task. Therefore, we have hypothesized that dyslexia could be the result of a timing defect that causes an integration defect and dysfunction of numerous processes hierarchically organized that occur at different levels and times. Also, Llinas[32] hypothesizes that at the base of the pathophysiology of dyslexia exists a more basic deficit of timing. This dynamic interplay of different frequencies in different brain areas confirms the idea of how the process of reading and writing occurs through a complex network in different brain areas and therefore it seems plausible that an alteration at one point in the network is inevitably reflected in other areas of the brain. A possible explanation of this temporal dysregulation could be a compensatory mechanism or, alternatively, the fact that in the dysphonetic subjects, the normal automatic interplay of gestalt and analytic-synthetic processes is interrupted. The DD subjects tend to persist in the gestalt approach preferring to guess at unfamiliar words rather than employ their word analysis skills. This apparently unusual reading mode of DD subjects is one of the reasons for early referral of teachers to child neuropsychiatrists. Subjects with NSRD, on the other hand, who made fewer misspellings both when reading and writing than DD subjects, but still present at the end of primary school, were referred late. Indeed, the comparison between the 2 groups of subjects revealed that the age of the Direct Test of Reading and Spelling (DTRS) testing was highly significant ($P = .0129$, $t = 12.51$). The children with NSRD were significantly older at the time of testing than those with DD and consequently had a significantly lower reading quotient than the subjects with DD.

## ADHD and Oppositional Defiant Disorder

Oppositional defiant disorder (ODD) and attention deficit hyperactivity disorder combined subtype (ADHD-C) are developmental disorders that are among the most commonly diagnosed mental health conditions in childhood.[33,34] ODD is a condition involving problems in self-control of emotions and behaviors. The essential features are frequent and persistent pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness.[35] The disturbance in behavior is associated with distress in the individual or others in his or her immediate social context or it affects negatively on social, educational, or other important areas of functioning. One of the most frequent comorbidities associated to ODD is ADHD. The frequency with which ODD is associated with ADHD is 39% while that of anxiety disorders is 34% and 14% that of conduct disorders.[36] The essential feature of ADHD is a persistent pattern of inattention and/or hyperactivity that interferes with functioning or development and causes impairment in multiple settings: home, school and work. Barkley[37-40] describes ADHD-C as a deficit in behavioral inhibition of 4 executive neuropsychological functions: working memory, self-regulation of affect–motivation–arousal, internalization of speech and reconstruction. Extensive neuroimaging studies (event-related potentials, positron emission tomography, fMRI) have

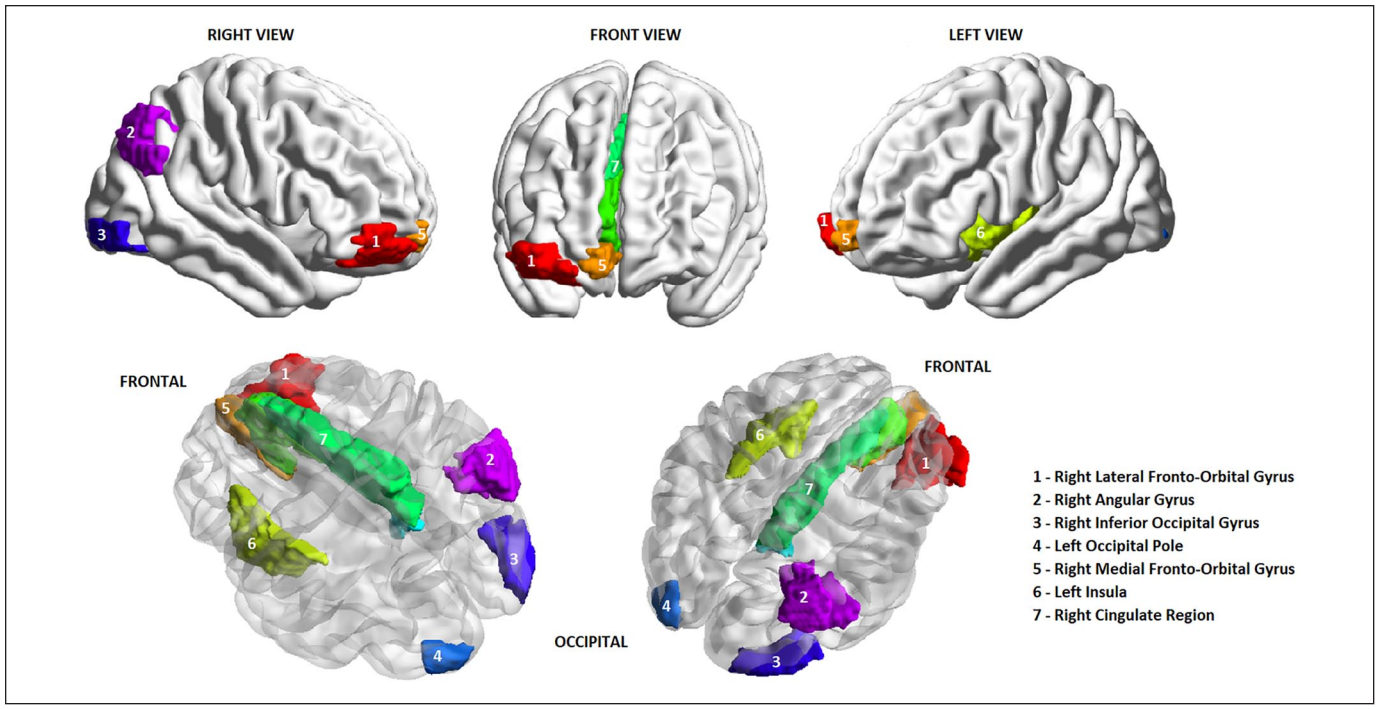


**Figure 2.** Brain regions selected by the classification procedure as biomarkers at the sources: left insula, right lateral orbito-frontal gyrus, right cingular region, right angular gyrus, right inferior occipital gyrus, left occipital pole, right medial orbito-frontal gyrus. The classification algorithm was applied to the age-dependent z score spectra of the EEG at the sources. The z scores were calculated using the Cuban Normative Database and the QEEGT software developed by the Cuban Neuroscience Center.

demonstrated that during the execution of cognitive tasks, children with ADHD show a pattern of hypoactivation of the prefrontal lobes and of the striatal regions.[41-48] Neurophysiological studies have shown that different EEG patterns exist in ADHD children. The most frequent EEG patterns consist of elevated high amplitude theta with deficit or excess of beta activity and reduced alpha activity. This profile has been found primarily in children with the combined type of ADHD.[6,49,50] Several studies have been conducted to associate these neurophysiological patterns with the diverse and multiform comorbidities present in ADHD subjects.[6,51,52,53] Although ADHD-C and ODD seem to share some similarities at neurofunctional level, Barry and Clarke[54] found little EEG difference between groups of children with ADHD, with and without ODD.

Chiarenza et al[55] compared the QEEG at the scalp and at the sources of subjects with ADHD-C with those of subjects with ADHD-C and ODD in order to identify possible electrophysiological biomarkers able to differentiate the 2 groups.

Significant differences between the groups were found in the absolute power spectra *z*-score in the right hemisphere: F4 at 1.7 Hz and at 5.4 Hz and F8 at 17.5 Hz. The group of children with ADHD-C had significant higher values in the delta, theta, and beta bands than the group of children with ADHD-C + ODD. It has been frequently reported that children with ADHD have EEG patterns consisting of elevated delta and theta absolute power with deficit or excess of beta activity. This profile has been found primarily in children with the combined type of ADHD.[56] F4 and F8 cover part of the prefrontal cortex and middle frontal gyrus and in particular the dorso-lateral prefrontal cortex. These areas play a fundamental role in several executive functions, executive control of behavior,[57] inferential reasoning,[58] decision making.[59] These functions are impaired in children with ADHD_C.[37,38] These 2 groups of children that have ADHD-C in common, seem to lack in the executive control of behavior. It is also known that these areas of the right hemisphere are involved in modulating emotions, reacting properly to stressful situations, understanding other intentions for deciding appropriate behavior.

Figure 2 shows the brain regions selected as biomarkers by the classification procedure.[60] In theta band, the left insula and the right lateral fronto-orbital gyrus were selected. In alpha band, the most significant regions were the right lateral fronto-orbital gyrus, the right angular gyrus, and the right cingular region. In beta band, the most significant sources were the right lateral fronto-orbital gyrus, the right medial fronto-orbital gyrus, the right inferior occipital gyrus, and the left occipital pole. The orbito-frontal cortex (OFC), therefore, is the area most present in all frequency bands except delta band where no regions of interest were significantly present. Many researches support that the main disorders associated with dysregulated OFC connectivity/circuitry are related with decision making, emotion regulation, and reward expectation.[61-63] More specifically, a large meta-analysis of the existing neuroimaging studies demonstrated that activity in medial parts of the OFC is related to the monitoring, learning, and memory of the reward value of reinforcers, whereas activity in lateral OFC is related

to the evaluation of punishers, which may lead to a change in ongoing behavior.[64-66] OFC seems to be important in signaling the expected rewards/punishments of an action given the details of a situation. In doing this, the brain can compare the expected reward/punishment with the actual delivery of reward/punishment, thus making the OFC critical for adaptive learning.[67] Children with ADHD-C + ODD appear more dysregulated in modulating social behavior and in the control of mood and motivational drive, function(s) that are important components of the personality of an individual.

## ADHD and Pharmacotherapy

Recent evidence indicates that quantitative EEG is a powerful tool in pharmaco-EEG applications. The identification of treatment responsive QEEG subtypes has been described in depression,[68,69] obsessive-compulsive disorder,[70] and schizophrenia,[71] suggesting that understanding of the underlying neurophysiology of the patient can contribute significantly to treatment optimization. QEEG has been shown to distinguish between ADHD responders (R) and nonresponders (NR) to stimulant medication with sensitivity levels that fell between 68.7% and 81% with response to stimulants related to ADHD subtypes based on QEEG profile differences.[42,72] Another class of drugs used in ADHD is a selective inhibitor of norepinephrine transporters (SNRI), atomoxetine (ATX). Barry et al[54,73] investigated the effects of a single dose of ATX, on the EEG and performance of children with ADHD. After 1 hour, ATX produced significant global increases in absolute and relative beta, with several topographic changes in other bands. This was accompanied by a significant reduction in omission errors on a continuous performance task. The authors concluded that SNRIs can produce substantial normalization of the ADHD profile, together with behavioral performance improvements. Recently, Chiarenza et al[74] have reported the quantitative EEG characteristics of responders and nonresponders to long-term treatment with ATX in children with ADHDs. The subjects were classified as responders (R) and nonresponders (NR) based on an increase/decrease of SNAP (Swanson, Nolan, and Pelham–IV Questionnaire) *z* scores values between baseline and each of the time points (treatment). Subjects with a 30% increase or greater in SNAP scores were classified as responders. Subjects with a decrease of 30% or more in SNAP scores were called nonresponders. Figure 3 presents color coded head maps of *Z*-absolute power (compared with database of normal children) separately for the R and NR groups at baseline, 6 months, and 12 months following treatment. The effects of therapy are clearly visible at 6 months when R are compared with NR. Differences between R and NR were seen at baseline: The R show greater activity in the right prefrontal and frontal regions compared with the NR in the delta band. Theta activity is greater in the NR in the left temporal and parietal areas. The NR had greater alpha absolute power in central and left temporo-parietal and occipital regions bilaterally. Absolute power in the beta band especially in the posterior regions is higher in

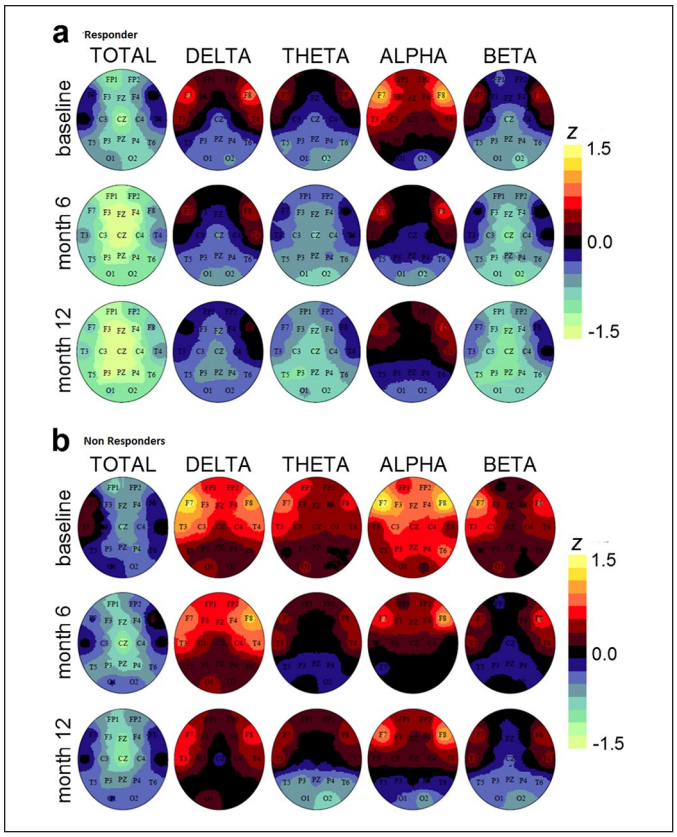


**Figure 3.** Average *Z*-score maps of absolute power for the delta, theta, alpha, and beta frequency bands of the responders (a) and nonresponders (b) at baseline, 6 months, and 12 months. *Z*-scores are relative to the normal population with statistical significance at the $P = .01$ level equal to a *Z*-score of $1.96/\sqrt{N}$. Age-dependent *z* score spectra of the EEG at the sources were used in this study. The *z* scores were calculated using the Nxlink data and software.

the NR. At 12 months of therapy, the R show a normalization of absolute power in all frequency bands while the NR maintain the excess of activity in all frequency bands except the alpha band. The differences between R and NR at 12 months were highly significant especially in the delta band posteriorly, the theta band centrally and the beta band anteriorly. Source localization proved also useful by indicating the cortical structures which show abnormal function in children with ADHD. ATX responders showed increased activation in right middle, superior, and inferior temporal gyrus, right insula, pre- and postcentral gyrus, supramarginal gyrus, middle frontal gyrus, posterior cingulate region, angular gyrus, medial frontal gyrus, and superior parietal lobe. This increased activation decreased after 6 and 12 months of ATX. Nonresponders to ATX showed increased activation in right medial, inferior, and superior temporal gyrus, pre- and postcentral gyrus, left inferior frontal gyrus, supramarginal gyrus, left medial frontal gyrus, the angular gyrus. This increased activation remained constant despite 12 months of treatment with ATX. The reduced activation remained the same in the occipito-temporal gyrus and the cerebellum. Similar findings have been reported with different

techniques supporting the evidence that these cerebral areas are involved in the pathophysiology of ADHD.[40] The analysis of sources localization shows that at baseline the brain regions that show an excess of beta activity are the same in R and in NR. This might suggest that subjects with ADHD-C both R and NR share the same structural organization. What distinguishes the R from NR is the functional organization as it appears by absolute power spectra. The NR continued to have an excess of beta activity and an excess of delta and theta activity.

### Case Studies

QEEG is also a useful tool to validate medication efficacy on a case by case basis using prescriptive databases that enable to "predict" the likelihood of yielding a therapeutic effect (either positive or negative). A 9.6-year-old girl was diagnosed with a severe ADHD-C with moderate mental retardation of genetic nature. Her full IQ was 44 measured with WPPSI-III (Wechsler Preschool and Primary Scale of Intelligence–III) when she was 7 years old. Before therapy, the *DSM-IV* Conners teacher rating scale,[75] for inattention and for hyperactivity and impulsivity were above 90. The z scores absolute power maps showed an excess of delta and theta activity, reduced alfa in the posterior regions, significant asymmetry (left > right) on the central and temporal areas in the delta, theta and alpha bands and a significant hypercoherence in the prefrontal and occipital regions. The discriminant scores were suggestive of ADHD ($P < .0025$). One of the EEG characteristics commonly present in ADHD include increased theta, particularly in frontal regions, and decreased or increased beta, particularly in posterior regions of the brain.[76-79] The majority of the literature suggests that acute administration of stimulants in patients with ADHD produce global EEG shifts toward normalization of EEG patterns characterized by increased beta and decreased slow waves.[80,81] Lubar et al[82] have also reported other acute positive effects following stimulant medication on other EEG measures, such as phase, coherence, and symmetry, suggesting improvement in cortical communication. Those who respond positively to stimulants treatment have also corresponding improvements in cognition.[83] Stimulants have been shown to reduce certain risk-prone behaviors,[84] enhance working memory in children[85] and adults,[86] and improve inhibitory control, performance accuracy and intellectual function.[87,88] Another important clinical sign of this subject was her mental retardation. EEG abnormalities in subjects with intellectual disability with a frequency ranging from 23% to 50% depending on the degree of severity of mental retardation is found quite frequently. These abnormalities have been found mainly in the frontal and left temporal cortex.[89] In subjects with fragile X syndrome (FXS), Van der Molen and Van der Molen[90] have reported significantly higher mean relative theta power and mean upper alpha power significantly lower in FXS than in controls. Therefore, based on the evidences reported in the literature,[91] despite the understandable initial resistance of parents and of the attending physician to accept and initiate drug therapy, the objective evidence reported by the QEEG and the Conners rating scales recommended the use of methylphenidate as a first-choice drug. After 3 months of treatment with methylphenidate hydrochloride (20 mg/d), the absolute power in the delta band was normalized and the excess of theta was restricted only to frontal areas. The asymmetry in the delta, theta, and alpha bands was not anymore present as well as the hypercoherence in the delta and theta band in the posterior regions (Figure 4). The patient's discriminant scores of the QEEG were not anymore indicative of ADHD but suggested the presence of abnormal features. The features making the largest contribution to this classification were: bipolar relative power for F7-T3 at combined frequencies and bipolar coherence for C3-Cz and C4-Cz at theta frequency. These features, as reported above, could be related to her mental retardation. After treatment, the Conners teacher rating scale showed that the oppositional behavior and perfectionism were within normal limits, her cognitive and attentional problems and hyperactivity were of borderline values (Table 1).

The 3-month follow-up of the QEEG and of the Conners rating scales confirmed the correctness of the pharmacological indication with stimulants and its continuation.

## QEEG and Diagnostic Confirmation

The new techniques of EEG sources localization (sLORETA,[92] VARETA[15]) has given a new impulse to neuropsychological studies as it allows to associate clinical symptoms with possible dysregulation of brain rhythms. FL is a 14-year-old boy sent by teachers for a suspect of specific learning disabilities. All the clinical and neuropsychological tests were in the normal range except for the presence of micrography, which was orthographically correct but making the text almost illegible. The current source density analysis showed an hypoactivation at 3.5 Hz. The 3D sources localization (sLORETA) showed that the most probable sources with minimum value ($z$ score = −3.9) were located at temporal lobe, fusiform gyrus, Brodmann area 37 bilaterally. In addition, an hyperactivation at 11.7 Hz was observed: the most probable sources with maximum value ($z$ score = 4.8) were located at frontal lobe, paracentral lobule, Brodmann area 5 (Figure 5).

It is well known that BA37 is involved in associations of words with visual percepts. It is involved in some aspects of reading (eg, single letter processing and orthography-phonology link), because of visual-language associations. Disturbances in drawing (constructional apraxia or simply visuo-constructive disorder) are observed in cases of right hemisphere pathology, and according to fMRI studies, drawing activates right Brodmann area 37. The Brodmann area 5, the superior parietal lobe, is part of the sensory-motor associative cortex and is clearly involved in the visuo-spatial processing and spatial images. It could therefore be proposed that the dysregulation of these two areas could play a role for the micrography. Currently, the EEG source localization technique is being used not only as diagnostic tool but also as therapeutic one Recently the z score

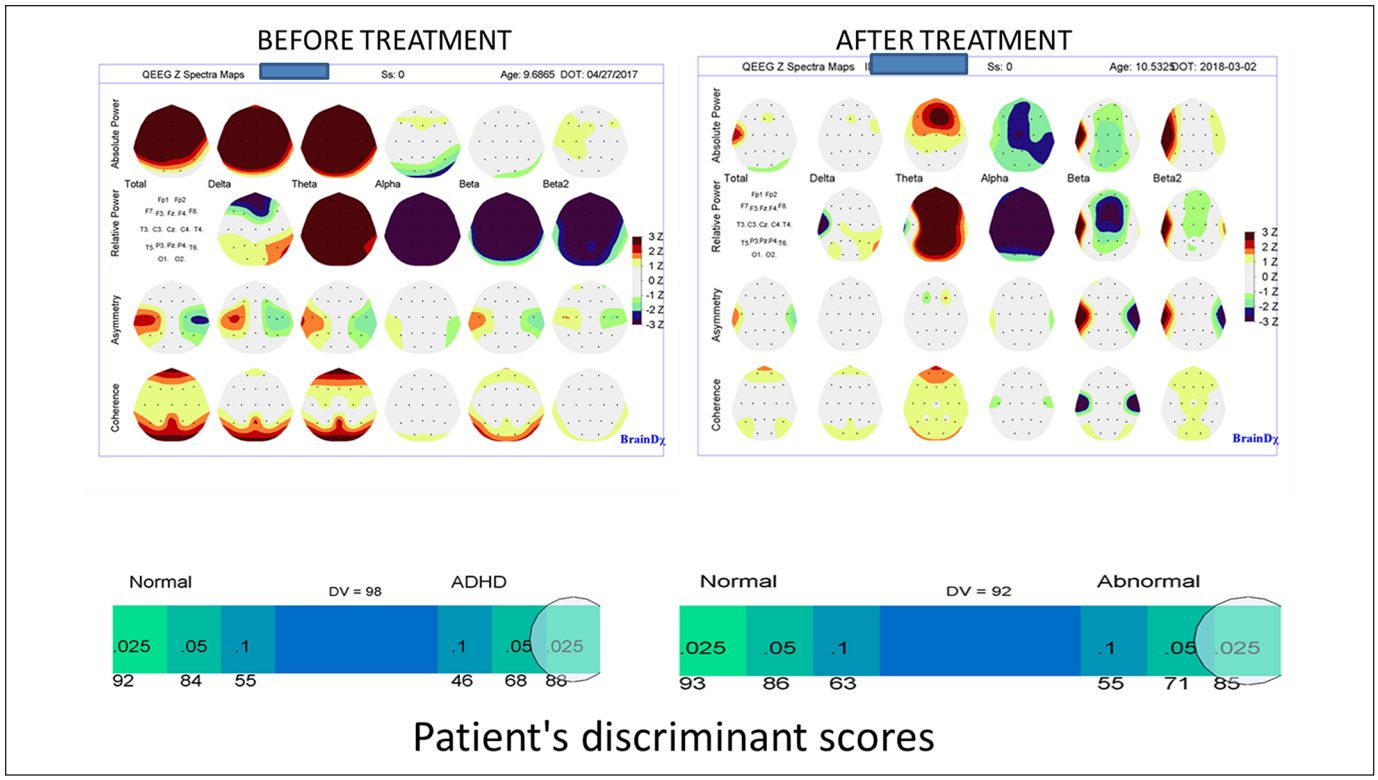


**Figure 4.** *Z*-score maps of absolute power, relative power, asymmetry and coherence for the delta, theta, alpha, and beta frequency bands and the discriminant score before and after treatment to methylphenidate hydrochloride 20 mg. Age-dependent z-score spectra of the EEG at the sources were used in this study. The z scores were calculated using the Nxlink data and software.

**Table 1.** Results of the Conners teachers' rating scale before and after treatment to methylphenidate hydrochloride 20 mg.

| Conners teachers' scale scores | Before treatment (*T* values)[a] | After treatment (*T* values)[a] |
|---|---|---|
| Oppositional | 74 | 46 |
| Cognitive/attention problems | 75 | 56 |
| Hyperactivity | 90 | 66 |
| Anxious/shy | 82 | 86 |
| Perfectionism | 58 | 43 |
| Social problems | 88 | 59 |
| ADHD Conners Index | 90 | 80 |
| DSM-IV: Attention | 90 | 77 |
| DSM-IV: Hyperactivity/impulsivity | 90 | 60 |
| DSM-IV: Total | 90 | 74 |

Abbreviations: ADHD, attention deficit hyperactivity disorder; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.
[a]*T* values: <55, not significant; 55-64, borderline; 65-69, significant; >70, highly significant.

sLORETA has been used to target the brain regions for neurofeedback training in depressed patients.[93]

In conclusion, using QEEG features, including age regression, clear abnormalities can be seen in all of the developmental disorders studied. Distinctive patterns of abnormalities can be seen in different diagnostic groups. The possibility to discriminate between different groups and normal with high sensitivity and specificity could help solve the problem of various comorbidities in a complex syndrome such as ADHD. The possibility to improve the neurophysiological typing of ADHD and the response to drugs could facilitate the identification of safer drugs and to monitor their therapeutic effects in the long term. Last but not least, QEEG may improve scientific knowledge of neurodevelopmental disorders.

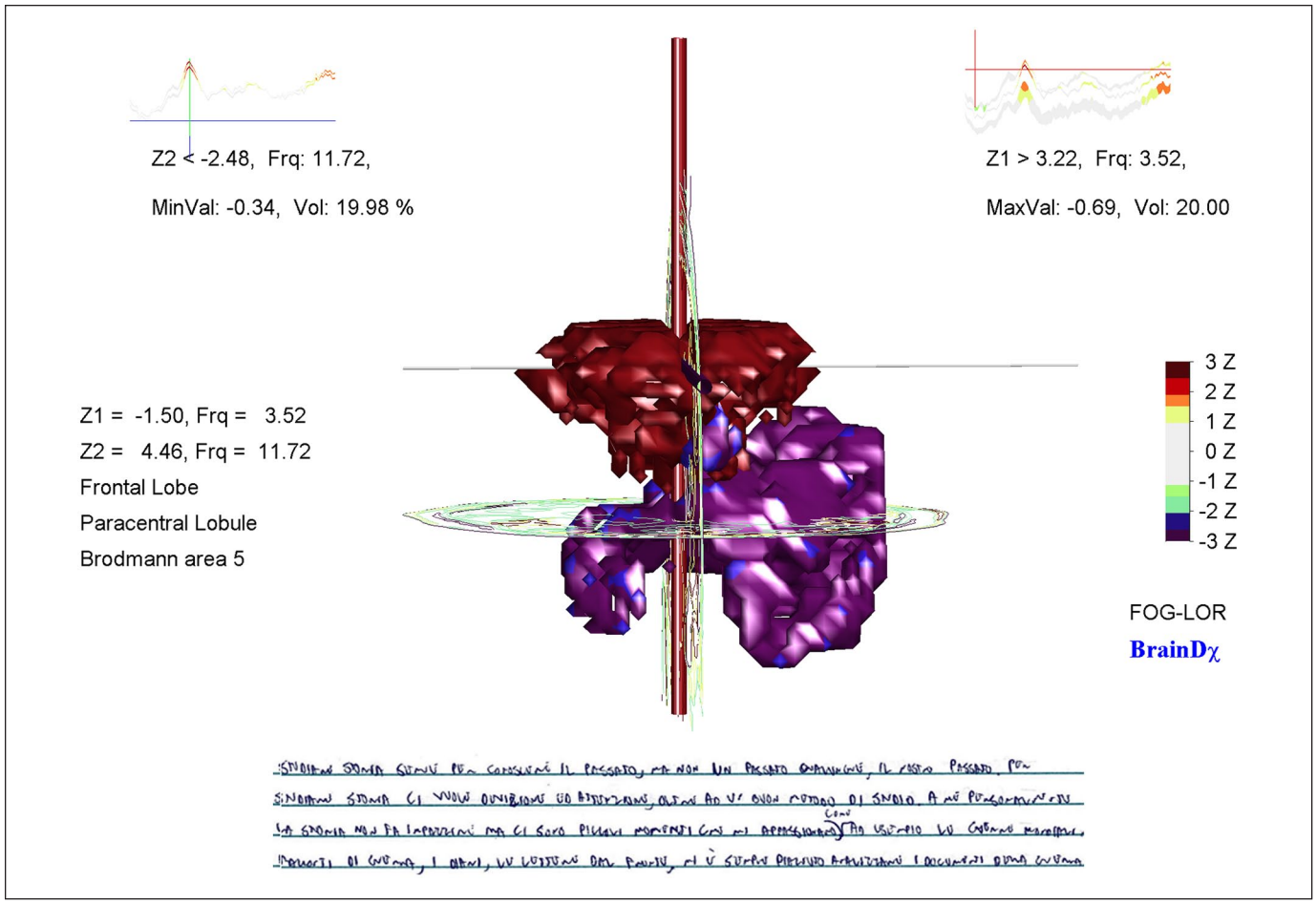


**Figure 5.** Volumetric 3-dimensional LORETA (standard low-resolution brain electrotomography) images and the writing of the subject. The current source density analysis showed an hypoactivation at 3.5 Hz. The 3D sources localization (sLORETA) showed that the most probable sources with minimum value (blue colors) (z score = −3.9) were located at temporal lobe, fusiform gyrus, Brodmann area 37 bilaterally. In addition, an hyperactivation at 11.7 Hz was observed: the most probable sources with maximum value (red color) (z score = 4.8) were located at frontal lobe, paracentral lobule, Brodmann area 5. Vol, volume; Frq, frequencies; Z1 and Z2, z scores. Age-dependent z-score spectra of the EEG at the sources were used in this study. The z scores were calculated using the Braindx data and software.

## Appendix

### *EEG Data Acquisition and Analysis*

The EEG was recorded at 19 leads of the 1020 International Positioning System (S10-20), using Electro-caps referenced to linked earlobes. Twenty minutes of eyes closed resting EEG were recorded. A differential eye channel (diagonally placed above and below the eye orbit) was used for detection of eye movements. All electrode impedances were <5000 ohm. The EEG amplifiers were set to a bandpass from 0.5 to 70 Hz (3 dB points). All EEG data were collected on the same digital system to achieve amplifier equivalence. Data were sampled at a rate of 256 Hz with 12-bit resolution. All the patients were recorded in the morning and instructed to keep their eyes closed and stay awake. This allowed to control for drowsiness during EEG recordings and to guarantee similar conditions throughout the different sessions. The technician was also aware of the subject's state to avoid drowsiness. Additionally, patients were monitored with a closed-circuit television system, during the recording.

The author visually edited the raw EEG data to select EEG epochs free of either biological (eg, muscle movement, EMG) as well as nonbiological (eg, electrical noise in the room) artifacts. This was augmented by a computerized artifact detection algorithm. A minimum of 30 epochs of 2.56 minutes (256 time points, since the sampling rate was 100 Hz) of artifact-free data were selected for each subject and submitted to frequency analysis. The EEG spectra were calculated using the high-resolution spectral (HRS) model[92,94] for all the channels by means of the fast Fourier transform (FFT), in a frequency range from 0.39 to 9.11 Hz, with a frequency resolution of 0.39 Hz. The selection of these frequency parameters was made on the basis that they match the available parameters from the Cuban Normative Database[95] to transform the raw EEG spectra into *Z*-probabilistic measurements, age corrected. The spectra were log-transformed, to approach them to Gaussianity[96,97] and the *Z*-transform was calculated against the Cuban Normative Database. Significant test-retest reliability for these measures has been demonstrated.[18,98,99]

To obtain the raw spectra at the EEG generators, the variable resolution electrical tomography (VARETA) method[15] was used for the source localization analysis. Same as with the spectra at the electrodes, the source density localization analysis was performed for frequencies between 0.39 and 19.11 Hz and for all the sources in the cerebral cortex for a grid of 3244 sources. VARETA is an already known technique for estimating the distribution of the primary current in the source generators of EEG data. VARETA is a discrete spline distributed solution, like LORETA.[92] This technique was used in all the studies reported above except for the 2 case reports where the LORETA technique was applied. For more details about these techniques, please read Bosch-Bayard et al[15,25] and Pascual-Marqui.[92]

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