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State of the art and new directions of Quantitative Electroencephalography use in Differential Diagnosis of ADHD

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Abstract

Advances in technology in recent years have made the use of quantitative electroencephalogram more accessible to clinicians. The incorporation of normative databases in QEEG studies and the possibility of detecting different electroencephalographic patterns in patients with a given pathology, despite showing an apparent symptomatology homogeneity, make it an interesting source of information. The relationship of these patterns with a possible response to treatment or with prognostic estimates would justify its inclusion as a routine test in the process of the differential diagnosis of ADHD. In this paper, we present the possible benefits of the use of QEEG in the differential diagnosis of ADHD, the different electroencephalographic patterns associated with ADHD most common in the literature, and a case showcasing the use of the technique in a patient with ADHD.
Keywords: QEEG, ADHD, differential diagnosis, electroencephalographic patterns.

Resumen

Estado de la cuestión y uso de la electroencefalografía cuantitativa en el diagnóstico diferencial del TDAH. El avance de la tecnología en los últimos años ha hecho que el uso del electroencefalograma cuantitativo sea más accesible a los clínicos. La incorporación de bases de datos normativas en los estudios de QEEG y la posibilidad de detectar diferentes patrones electroencefalográficos en pacientes con una patología determinada, a pesar de mostrar una aparente homogeneidad sintomatológica, hacen que sea una fuente de información interesante. La relación de estos patrones con una posible respuesta a tratamientos o con estimaciones pronósticas justificarían su inclusión como prueba rutinaria en el proceso de diagnóstico diferencial del TDAH. En este trabajo se presentan los posibles beneficios del uso del QEEG en el diagnóstico diferencial del TDAH, los diferentes patrones electroencefalográficos asociados al TDAH más comunes en la literatura y un caso ilustrativo del uso de la técnica en un paciente con TDAH.
Palabras clave: QEEG, TDAH, diagnóstico diferencial, patrones electroencefalográficos.

Advances in technology in recent years have contributed to the improved use of the quantitative electroencephalogram (QEEG) in the study of patients with cognitive or learning disorders. New techniques, such as source localization methods and the use of normative databases, make this study even more accurate (Chiarenza, 2021; Pérez-Elvira, et al., 2021). It should also be noted that, in recent years, it has been observed that patients with the same diagnosis, and even an apparently homogeneous clinical presentation, have a different response to the treatments of choice for their condition (Arns, 2012a; Prichep et al., 1993).In fact, there is a positive response to the treatment of choice in only 60% of the cases (Prichep et al., 1993). This leads to think about the existence of heterogeneity within the same diagnostic labels and invites to explore individualized interventions. In those, the clinician has to have the tools that allow him to divide patients into groups according to profiles of some nature that help, in some way, to predict the response to treatment. This is the case of some of the approaches within the field of QEEG, in which the profiles or markers have been sought to predict patient suitability for treatment (Arns, 2012a; Arns et al., 2008, 2010; Arns & Olbrich, 2014; Pérez-Elvira, et al., 2021).

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed neuropediatric disorders (Faraone et al., 2021; Onandia-Hinchado et al., 2021). The essential feature of ADHD is a persistent pattern of impaired attention and executive functioning, which interferes with development and causes impairment in multiple settings such as home, school or work (Colomer et al., 2017; García & Rodríguez, 2021; Onandia-Hinchado et al., 2021).

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Neuroimaging studies have shown that ADHD patients show a pattern of hypoactivation of prefrontal and frontostriatal regions while performing cognitive tasks (Cortese et al., 2012; Rubia, 2018; Vieira de Melo et al., 2018). Despite the structural and functional differences that have been detected in ADHD patients, we do not have accurate biomarkers or a consensus on their use for its diagnosis (Conde et al., 2021).

Some authors have found different endophenotypes in ADHD using functional neuroimaging tests (SPECT, QEEG, fMRI) (Amen, 2013; Arns, 2012a; del Campo et al., 2012; Kropotov, 2016). These studies suggest that the current clinical classifications may not reflect all the neuropsychophysiological realities of this pathology and, therefore, they would lose the relevant information that could help to direct each case to the best therapeutic approach.

Although these technologies and studies (SPECT, fMRI) are promising in helping to better understand the physiological underpinnings of ADHD, they are not without methodological problems, such as inadequate sensitivity and specificity for psychiatric disorders. In addition, these techniques are of limited value in terms of establishing a diagnosis and are too expensive to be used for routine testing in clinical practice (Stormezand, 2021; Weyandt et al., 2013).

In order to make a new contribution to the clinical utility of the QEEG, this article presents some evidence regarding ADHD, the applicability of the QEEG to the differential diagnosis of ADHD, and the different electroencephalographic patterns found in these patients –obtained from the application of the QEEG in both group and case studies–. The QEEG analysis of an unpublished ADHD case selected from the database of the International Center for Learning, Attention and Hyperactivity Disorders (CIDAAI) will also be shown for illustrative purposes.

Use of the QEEG in the differential diagnosis of ADHD

There are no univocal tests, neither imaging nor neuropsychological, for the diagnosis of ADHD (Wolraich et al., 2019); in fact, as Conde et al. (2021) state, the diagnosis is primarily clinical. For a diagnosis of ADHD to be made, it is also necessary to evaluate not only the child, but also to obtain information from parents, caregivers, and school environment, among others.

The use or the search for biomarkers has become commonplace, both in basic and in clinical science, although, in most cases, their validity should still be further evaluated (Strimbu & Tavel, 2010). In the case of the QEEG, it is not possible to affirm that with studies of this type an accurate diagnosis of ADHD can be reached, but, in most cases, they will provide information that clarifies certain possible strengths and weaknesses of the child. Yet there is reluctance to use brain mapping techniques in the diagnostic process of ADHD, despite the literature gathered in recent decades (Chiarenza, 2021). But what is the diagnostic accuracy that the EEG/QEEG approaches can provide in the diagnosis of ADHD by professionals? Quintana et al. (2007) showed that, compared to the use of rating scales –where the range of accuracy in the identification of ADHD was 55-79%, with a sensitivity of 81% and a specificity of 22% in the diagnosis–, with an overall accuracy of these scales being 60%, the QEEG showed a sensitivity of 94% and a specificity of 100%. According to these authors, the overall accuracy of the QEEG was 96%. These findings by Quintana et al. (2007) are in the same line as those provided by other authors (Kovatchev et al., 2001; Monastra et al., 1999, 2001).

Thus, although it does not constitute a diagnostic test per se for ADHD (Adamou et al., 2020), the QEEG could play a relevant role in its differential diagnosis, as well as other tests (Chiarenza, 2021; Lenartowicz & Loo, 2014; McVoy et al., 2019), and provide clinical information relevant to the patient's approach (Loo & Makeig, 2012). In addition, several studies have found patterns (Arns et al., 2008; Bong & Kim, 2021; del Campo et al., 2012) using the EEG spectral analyses that could –or could not– be considered as the electroencephalographic endophenotypes of ADHD and that, despite not having a clear diagnostic utility, would have a classificatory and even a prognostic utility. (Arns, 2012b; Arns & Olbrich, 2014; Slater et al., 2022). The following are some of the electroencephalographic patterns in ADHD which are most frequently reported in the literature.

EEG/QEEG patterns in ADHD

EEG with paroxysms and epileptiform findings

Between 12-15% of patients with ADHD have paroxysms compared to 1-2% of the population that does not present this pathology. These patients, who do not present seizures, respond to anticonvulsant medication. This response is similar to that of stimulants (Wood et al., 2007).

Frontal slowdown

Another common finding in ADHD patients is frontal pole EEG slowdown.

Since the 1990s, it has been noted that in some ADHD cases, the QEEG shows excesses of frontal slow activity, usually Theta. There are three main possible findings for this slowing: frontal Theta excesses, frontal Alpha excesses and/or elevated Theta/Beta ratio (Bussalb et al., 2019; Chabot et al., 1996; Swingle, 2015).

Monastra et al. (1999) were the first report that it was common among ADHD patients to show a frontal sluggish activity. These authors took the frontal Theta/Beta ratio (later known as the Monastra Ratio) as an attentional index; high ratios would indicate attention issues. Between 50-70% of ADHD patients would show an elevated Monastra Ratio, and this ratio would have a sensitivity –detection of cases– of 86% and a specificity, –exclusion of the healthy– of 96% (Monastra et al., 1999).

Paul Swingle (2015) found that about 60% of hyperactive patients have an elevated Theta/SMR ratio.

Arns et al. (2013) found in a meta-analysis that the Monastra Ratio differentiated between healthy and ADHD cases, but that this differentiation gets smaller while the age increases (6-13 years, ES0.75; 6-18 years, ES0.62). Ogrim et al. (2012) showed that Monastra's Ratio would only be relevant for a group of patients. Therefore, this would not be the main finding for all ADHD patients, suggesting that other subtypes or electroencephalographic findings may exist.

Patients exhibiting this pattern are the most likely to show a positive response to stimulant medication (Satterfield et al., 1973).

Beta excesses

Despite the high frequency of the frontal slowdown in the ADHD patients EGG (between 50-70%), there is another group of patients (between 13-20%) who show an EEG profile with excessive Beta activity (Arns, 2012a; Arns et al., 2012; Chabot et al., 1996; Clarke et al., 1998, 2001; Ogrim et al., 2012). These patients show different manifestations than those with frontal dulling. They respond to stimulants but without EEG changes –Beta activity neither increases nor decreases– indicating, therefore, that it is not simply a hyperarousal profile.

At the clinical level, this profile is observed mainly in the combined ADHD subtype, and is associated with hyperactivity and impulsivity, as well as with emotional dysregulation, but not necessarily with inattention.

We can include in this endophenotype, that is, at least initially, those patients who present beta spindles (beta spindles generally in the frontal pole), that rather than having a tonic, permanent excess of such activity, it is presented in a phasic way; in "bursts".

Slow Alpha Peak Frequency

The Alpha rhythm is predominantly posterior. Its behavior makes us recognize it even better than its frequency (theoretical frequency: 8-12Hz). It comes and goes describing spindles, and responds to ocular closure with an increase of its amplitude. This increase is at least 50% in posterior regions, otherwise it could be considered pathological (Demos, 2019; Swingle, 2015). This increase in Alpha's power at ocular closure causes the appearance of what we know as *individual Alpha Peak Frequency* (iAPF). The iAPF is the dominant frequency in the spectrogram in the eyes-closed condition at rest. This frequency changes with age, accelerating to 10Hz at around 12 or 13 years of age, and remaining stable until old age (Blum & Rutkove, 2007; Kondacs & Szabó, 1999). Research appears to show that it is also highly inheritable.

In some cases, the main finding on a patient with ADHD QEEG is a slow iAPF, (Arns, 2012a; Niedermeyer & Lopes da Silva, 2005) with a frequency lower than that which would correspond to their age. These patients, who are neurophysiologically distinct from those with Theta excesses, could mimic that group by showing a theoretical Theta excess that, in reality, would be Alpha, due to the overlapping of the Theta bands (Arns, 2012a).

Support for differentiation of comorbidities

In addition to these patterns shown in the literature, some studies have found biomarkers that could differentiate comorbidities in ADHD patients. Therefore, Chiarenza et al. (2018) found significant differences in two groups of children with ADHD; one showing comorbid oppositional defiant disorder and the other one did not. The latter group obtained higher elevations of Delta, Theta and Beta activity in the right frontal than those observed in the first group. Shephard et al. (2018) found in a study of children with ADHD, children with autism spectrum disorders (ASD) and children with both diagnoses that children with ASD showed reduced Theta and Alpha power compared to healthy children; however, children with ADHD showed a pattern of Delta activity deficits compared to healthy children. Finally, children with ADHD+ASD had an additive pattern of both entities. Ahmed et al. (2022) raise the interest of the electroencephalographic studies in patients with epilepsy and ADHD since, although both conditions can appear comorbidly –and ADHD is more prevalent among patients with epilepsy–, sometimes the core symptoms of ADHD in epileptic patients could be exclusively related to the epilepsy itself or to its treatment.

Illustrative case of the use of QEEG in ADHD

QEEG can be a useful tool, not only for diagnostic evaluation, but also for monitoring changes related to therapeutic interventions (Chiarenza, 2021; Galiana-Simal et al., 2020). We present here a case of a 12-year-old boy with combined ADHD who underwent a treatment with methylphenidate. The patient had problems in maintaining attention and significant problems in executive functioning. The SNAP-IV scale (Swanson et al., 2012) was administered to parents and teachers. In the version for teachers, the patient scored 2.66 (cut-off point = 2.56) in inattention and 1.8 (cut-off pont = 1.78) in impulsivity. On the scale completed by the parents, the patient scored 2.7 (cut-off point = 1.78) for inattention and 2.1 (cut-off point = 1.44) for impulsivity. The results of these scales, despite their psychometric limitations, were compatible with the patient's diagnosis. The patient's EEG was recorded, quantified, and analyzed prior to the initiation of the pharmacological treatment.

Process of sample collection and analysis of the patient´s EEG: EEG Recording, quantification, and analysis.

An EEG was obtained before starting the metylphenidate intervention, and after 3 months of treatment. To obtain the EEG, the patient was fitted with a 19-channel (Electro-cap International) according to the International 10–20 System with Linked Ears montage (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). For 10 minutes, the EEG signals were obtained and collected simultaneously over these 19 channels with a Discovery20 amplifier from BrainMaster Technologies, Inc. The impedances were kept below 5kOhm in all channels. Data were sampled at a rate of 256Hz. The EEG recordings were recorded in eyes-closed condition, using Brain Avatar 4.6.4 from Brain Master Technologies.

The EEG signals were then imported into the NeuroGuide v. 2.9.1 software for quantification and analysis, where artifacts (i.e., activity collected from the EEG that is not produced by the brain) were visually inspected and removed, retaining at least 50 seconds with a test retest value above of .90. The EEG was processed with Linked Ears Montage and compared with the normative database NeuroGuide, and Z-Score values were obtained in order to identify the patient´s brain waves that were out of normal range. NeuroStat software from Neuroguide was later used to analyze the significance of changes in QEEG.

Results of QEEG analysis

The initial study of the patient's spectral analysis showed excessive Theta activity, expressed in Z scores, mainly frontal (Figure 1). Theta excesses in frontal regions are a commonly reported finding in patients with combined subtype ADHD. Moreover, these frontal Theta excesses usually result in an elevated Theta/Beta ratio, as in the case of our patient, a finding that has been postulated as a biomarker of combined ADHD (Arns et al., 2013; Monastra et al., 1999; Ogrim et al., 2012).

The patient was pharmacologically treated with stimulants (metylphenidate) with the appropriate regimen. Three months later, he was evaluated again by QEEG and showed the same electroencephalographic pattern (Figure 2), but with a significant reduction of frontal Theta activity (Figure 3) and remarkable clinical improvement.

The literature indicates that the administration of stimulants to patients with ADHD produces a global shift of the QEEG in the direction of normalization by reducing Theta activity (Chiarenza, 2021; Loo et al., 1999), and that this response to medication, when it appears in this pattern, is accompanied by clinical improvement (Loo et al., 1999, 2004).

Figure 1. Pre-treatment QEEG maps showing frontal Theta excesses expressed as Z-scores.

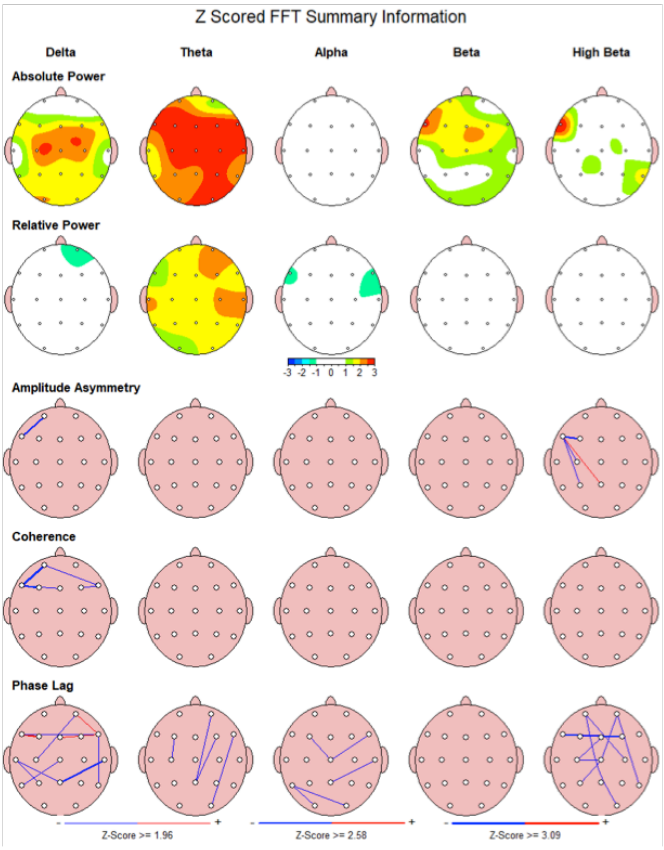
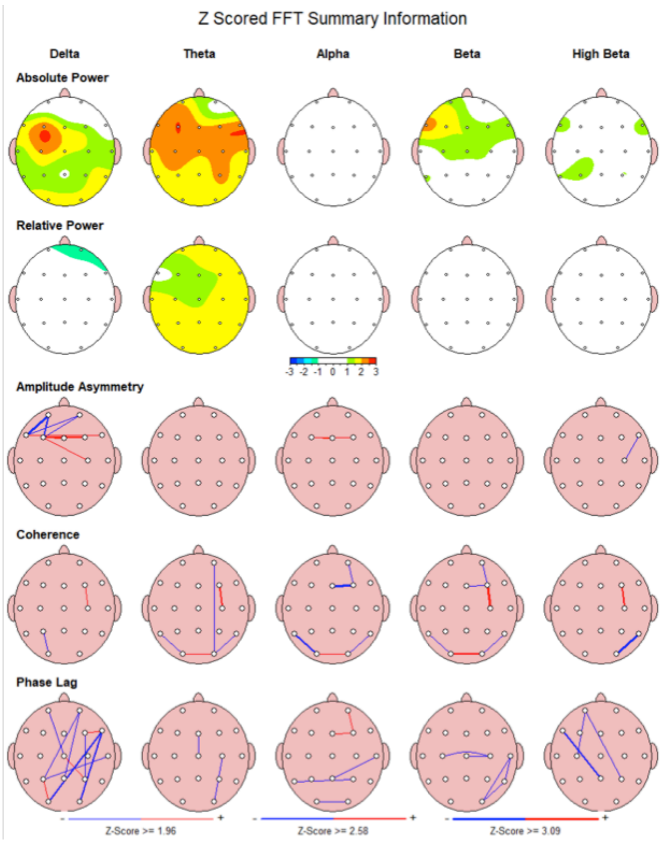


Figure 2. Post-treatment QEEG maps showing a reduction in frontal Theta excesses expressed as Z-scores.



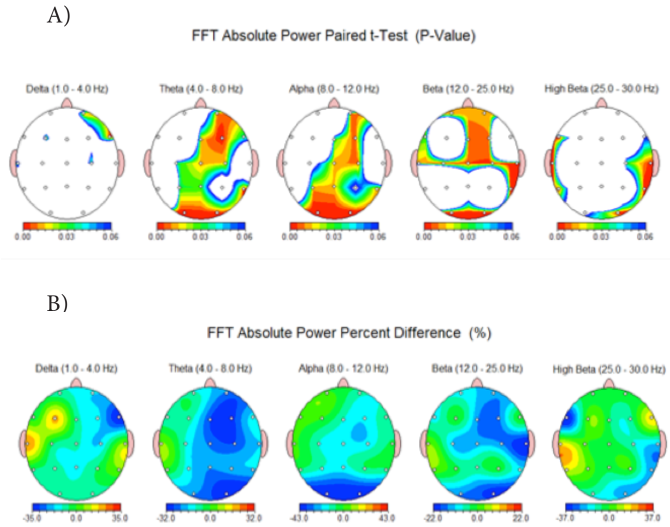


Figure 3. Statistical comparison (NeuroStat) of pre- and post-treatment QEEG maps. A) significance of post-treatment change. B) percentage change post-treatment, showing an approximate reduction in frontal Theta activity of 30%.

Conclusions

The clinical use of QEEG is receiving great interest thanks to the precision that the technique has acquired in recent decades and the current focus on personalized medicine in healthcare. It is of interest to the clinicians to be able to add information in their evaluations that will allow them to classify patients for future interventions or predict their responses to treatments.

Despite the more or less generalized reluctance to use the QEEG in the process of an ADHD differential diagnosis, studies with QEEG have shown the possibility of identifying different subtypes or electroencephalographic patterns, which sometimes serve as markers of response to certain treatments. This is particularly interesting since it allows for the personalization of healthcare, with decisions and treatments that can be tailored to the patient. Moreover, in neuropsychophysiological terms, this classificatory capacity offered by the QEEG in the ADHD cases provides the clinician with an additional source of information on the pathophysiological mechanisms of their patients.

The recognition of electroencephalographic patterns in ADHD patients can be helpful in the differential diagnostic process by providing extra data on the possible existence of comorbidities. The use of the QEEG in patients with ADHD also offers new possibilities to study the response to treatment and thus to establish prognostic assessments.

The safety of the technique, the cost-benefit efficiency and the relative ease of application make QEEG a good candidate to be included as a routine test in the evaluation of children with ADHD.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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