UNIVERSITÀ DEGLI STUDI DI PADOVA

UNIVERSIDAD DE GRANADA

Department of General Psychology (University of Padua)
Department of Experimental Psychology (University of Granada)

Master Degree in Cognitive Neuroscience and Clinical Neuropsychology
Master Degree in Master in Behavioral and Cognitive Neuroscience

Final Dissertation

New Horizons in ADHD Treatment: Living Z-Score Neurofeedback Training from a Circadian Perspective

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Academic Year 2021-2022

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by alterations such as impulsivity, hyperactivity, and inattention. New techniques have been developed to overcome adversities that traditional established treatments entail. This is the case of neurofeedback. New clinical research lines are recently applying *Quantitative EEG* (QEEG) guided neurofeedback with promising results. One version of this use of QEEG is Z-Score training, which focus on Z-Scores by comparing data with a normative database capable of calculating standard deviations. Additionally, ADHD has a strong relationship with sleep disturbances and circadian rhythm alterations. A new circadian perspective is required to be taken to approach ADHD. Measuring ADHD symptomatology and executive vigilance, our study has a two-fold aim: i) to compare QEEG Z-Score (individualized training) to standard traditional training, and ii) to adapt the intervention to the circadian rhythm. Thus, an intervention proposal has been designed in which adults with ADHD were trained by using two different neurofeedback protocol (QEEG Z-Score vs. standard) in their optimum time of day or not (adjusted to the chronotype vs. no adjusted to the chronotype). It was predicted a better outcome in individualized QEEG Z-Score training with chronotype adjustment reducing ADHD symptomatology and executive vigilance in comparison to standard training with no adjustment. To clarify our hypotheses and data analyses, we simulated data from 300 adults with ADHD that would participate in the intervention. We can conclude from simulated data that individualized training can reach higher improvement than traditional interventions in neurofeedback.

Key Words

Adult ADHD, Chronotype, Circadian Rhythm, Neurofeedback, QEEG, TBR, Z-Score training.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a clinical neurodevelopmental condition generally characterized by over-emphasized areas for their age: inattention, hyperactivity, and impulsivity. One fhe latest worldwide estimate through regression meta-analysis resulted in a prevalence range between 5.01- 5.59% (Polanczyk et al., 2007), with some studies extending this range to 7% (Willcutt, 2012). This qualifies ADHD as one of the most prevalent disorders in the pediatric population. It is noteworthy that in the adult population, however, diagnostic criteria are only met in 2.5% of cases (Simon et al., 2009). The *Diagnostic and Statistical Manual of Mental Disorders* (5th edition; DSM-5) defines ADHD in children (younger than 17 years) as the existence of six or more symptoms associated with different domains: a persistent pattern of inattention, a hyperactive-impulsive pattern, or a mixed profile. Fewer symptoms (i.e., at least five in both domains) are required to meet the diagnostic criteria in adults.

The DSM-5, unlike its predecessor (4th edition, DSM-IV), makes special mention of the presence of symptoms rather than a classification into subtypes, taking into account that the set of symptoms that make up a profile may vary according to the period of development. It is important to note that maturity is likely to affect ADHD symptoms on a general scale by reducing defining features such as impulsivity. This is relevant as different longitudinal studies suggest at least four developmental milestones at which the onset of ADHD may mark its developmental trajectory: early onset (3-5 years), middle childhood onset with a persistent course (6-14 years), middle childhood onset with adolescent offset and finally, adolescent or adult onset (16 years and older; Krasner et al., 2018; Moffit et al., 2015; Sibley et al., 2018).

Moreover, ADHD can occur either as an isolated condition or in comorbidity with disruptive behavioral problems, anxiety and emotional dysregulation (Hartman et al., 2019), depression (Brunsvold et al., 2008), or learning disabilities (Taanila et al., 2014). Growing evidence also points to an important link between sleep problems and ADHD (Bondopadhyay, 2022; Coogan-McGowan, 2017; Zerón-Rugerio, 2020).

Treatment

Pharmacological Treatment

According to the *National Institute for Health and Care Excellence* (NICE) guidelines, stimulant medication is the first line of pharmacological treatment. The most commonly used are methylphenidate and amphetamines for long-term and short-term use (Posner et al., 2020). Adult treatment with stimulants such as methylphenidate only changes in dose quantity from 18-50 ml to 18-72ml (Posner et al., 2020).

As shown by several meta-analyses, both types of pharmacological treatment effectively reduce ADHD symptoms in both children and adults (Castells et al., 2011; Cortese et al., 2018; Faraone et al., 2010). It has even shown to reduce excessive motor activity later in the day, a characteristic symptom in ADHD patients compared to the healthy population (Sanabra et al., 2020). However, stimulant drug treatment can have side effects. These effects often involve reduced appetite*, Sleep Onset Insomnia* (SOI), dry mouth, and nausea, among the most studied symptoms in children and adults with ADHD (Schachter et al., 2001). SOI is a common problem in these patients reported in the literature (Ironside et al., 2010; van Veen et al., 2010). This is because the stimulant effect of drugs may be reduced during the evening and may lead to increased activity in the 0:00-7:00 am time frame (Sanabra et al., 2020). According to NICE, non-stimulant treatment is proposed only in cases where treatment with stimulants is ineffective or because of an excessive interference of side effects on the patient's life. They are therefore referred to as second-line medication. Non-stimulant medication is often less effective, but evidence shows that it is still effective, although treatment usually requires additional intervention (Cortese et al., 2018; Cunill et al., 2013; Schwartz et al., 2014). It is a fact that there are limitations to pharmacological treatment. In terms of academic outcomes in school, only methylphenidate has a small but inconsistent effect on educational outcomes. All other pharmacological therapies seem to give null results in this respect (Barbaresi et al., 2007; Molina et al., 2009; Kortekaas et al., 2019). In addition, long-term studies seem to question the persistence of effects throughout development, as they may generate tolerance with prolonged use (Greydanus et al., 2009). These limitations motivate research into non-pharmacological interventions.

Neurofeedback Training

One of the most studied non-pharmacological interventions is *Neurofeedback* (Bussalb et al., 2019; Cortese et al., 2016; Louthrenoo et al., 2021; Rahmani et al., 2022). This technique consists of recording the patient's brain activity to provide information and make the patient aware of their mental state so that they can modulate at will. The desired brain activity will be rewarded in such way that the patient will know which mental state is appropriate and will try to maintain it. This way of taking agency over one's brain activity has shown promising results without side effects in many studies (Aggensteiner et al., 2019; Arn et al., 2020; Cortese et al., 2016; Geladé et al., 2018; Liechti et al., 2012; Mohammadi et al., 2015; Rubia et al., 2019; Shereena et al., 2019). Neurofeedback has been proved using different tools from functional magnetic resonance imaging (fMRI; deBettencourt et al., 2015) to electroencephalography (EEG; Enriquez-Geppert, 2019). Despite all these clinical options, EEG has prevailed as the most economically available tool providing neurofeedback training based on frequency bands. Raw EEG data are filtered to get frequencies ranges. After years of study and literature, these frequency bands show a link with several cognitive processes (Cannon et al., 2014; Fellinger et al., 2011; Ray & Cole, 1985).

In this line, ADHD is characterized by several alterations in electrophysiological signals that make this population a good candidate to use EEG to counterbalance these deviations. One common feature is an excessive activity related to low frequency bands (2- 7 Hz), so-called *slow waves*, including *Delta* and *Theta* (Poil et al., 2014). After pharmacological treatment, slow waves show a decrease in children, which is linked with ADHD symptomatology reduction (Ogrim et al., 2014). In addition, abnormal low Beta frequency (15-25Hz) is also prevalent in this population, leading to one famous electrophysiological index of ADHD: *Theta/Beta Ratio* (TBR) (Lenartowicz & Loo, 2014).

EEG Neurofeedback is now well established as a clinical intervention in children and adolescents with ADHD. A meta-analysis by Van Doren and colleagues (2019) showed that when comparing active (psychostimulants), semi-active (cognitive training), and neurofeedback treatments in a 6-month follow-up without booster sessions, the effects of neurofeedback were superior to semi-active interventions and had the same efficacy as active pharmacological treatments. Authors argued that this might occur because the impact of the pharmacological intervention diminishes over time, whereas the neurofeedback intervention is more resilient. However, despite promising results in reducing ADHD symptomatology, many inconsistencies have been found concerning executive functions training in meta-analyses conducted so far (Louthrenoo et al., 2021; Rahmani et al., 2022). These inconsistencies may be due to the diversity of designs, where blinded and double-blinded designs are rare. Taking such elements into account leads to a reduction in the effect size of the measured improvement (Cortese et al., 2016). Inconsistencies may also be due to the methodological misuse of the active control group (Arns et al., 2020), apart from the absence or poor considerations of circadian rhythm disturbances typical in the ADHD population. The study by Louthrenoo and colleagues (2021) found no effects of neurofeedback training on executive functions with a meta-analysis of 10 studies. The authors proposed several justifications for these inconclusive results. A small number of studies analyzed, the different measures used. Some of them were a difference in equipment or the number of sessions intensively applied, being the latter particularly pointed out. Furthermore, this study by Louthrenoo and colleagues (2021) was oriented to children as it is the population more affected by ADHD. However, as previously referred, there are slight differences in ADHD symptoms from childhood to adulthood. In particular, during childhood, hyperactive or combined profile is commonly diagnosed. On the contrary, there is a strong tendency to have an inattentive profile in adulthood due to reduction of symptomatology in the other dimensions (Faraone et et al., 2006). It is suggested that adolescent or adult ADHD onset does not present the same neurocognitive affection profile as childhood ADHD onset (Moffit, 2015). This makes us reflect on the possibility of successful neurofeedback training on executive functions in adulthood but not in childhood.

QEEG Guided Z-Score Training

After being aware of the current view of literature about neurofeedback, a new trend from clinical practice has been suggested. EEG is a measure widely used in clinical and basic neuroscience, but little is known about *Quantitative EEG* (QEEG). This way of using EEG as a quantitative measure based on individualized electrical activity has been studied concluding promising outcomes for neurofeedback training (Arns et al., 2012; Cannon et al., 2012; Collura, 2017; Hammer et al., 2011). QEEG consists in a basic recording of electrical activity with EEG during a brief period of time with eyes closed and the same sequence with open eyes. After this procedure, the data can be subjected to different techniques to make individualized indexes. *Z-Score* training has gained space in the clinical literature as a new way to develop tailored neurofeedback training. Data from each patient are compared with a common database generated by analyzing representative sample of the general population aged from 2 months to 82 years (NeuroGuide; Collura et al., 2009; Thatcher, 2001; Thatcher et al.,2003; 2005; 2009). This comparison allows to create an electrical activity profile using standard deviations for each frequency band and its location. And even more importantly, this index is based on a functional neuroscience perspective. QEEG-based protocols like live Z-Score training emphasize not only customized feedback based on amplitude but also their connectivity through indexes such as coherence, symmetry, or phase lag between electrodes (Collura et al., 2017; Hammer; 2011). By considering the brain a connected whole, this technique provides feedback from a modern line of intervention. Wigton and Krigbaum (2015) applied live Z-Score neurofeedback on a heterogeneous clinical sample to improve attention, executive functions, and behavioral problems. In this pilot study, all participants, including adults and children with ADHD, among other disorders, were divided into 4 groups; each group was assessed with different tools. In one group, attention was assessed with the *Visual and Auditory Continuous Performance Test* (IVA); in other group, executive functions were assessed with *Behavior Rating of Executive Functioning* (BRIEF), a different group evaluated behavioral disorders with the *Devereux Scale of Mental Disorders* (DSMD), and finally, one group undertook a QEEG to measure absolute power, relative power and coherence. All groups were assessed before and after Z-Score neurofeedback training with significantly beneficial outcomes in each dimension. In line with this study, Pérez-Elvira et al., (2020) compared *Theta/Beta Ratio* (TBR) standard protocol and Z-Score training to analyze the efficacy of both trainings in reducing the proper

TBR in ADHD population between 7 and 18 years. It turned out that Z-Score training was most efficient in reducing TBR than the standard protocol of the same name.

Despite results, these cited pilot researches require further analysis and new studies to build robust evidence. They leave us with the question of whether this new way of providing neurofeedback is the future of the clinical intervention in this field or, on the contrary, a mere scientific mirage. With that purpose, it is also essential to give importance to variables known for their influence on cognitive performance in ADHD population. It is remarkable that despite the evidence about how circadian rhythm and ADHD are linked (Bondopadhyay, 2022; Coogan-McGowan; Floros et al., 2020; 2017; Zerón-Rugerio, 2020), this relationship is not considered in ADHD treatment. This characteristic is particularly disruptive in the day-to-day life of ADHD patients and is not usually taken into account in the clinical intervention of this population.

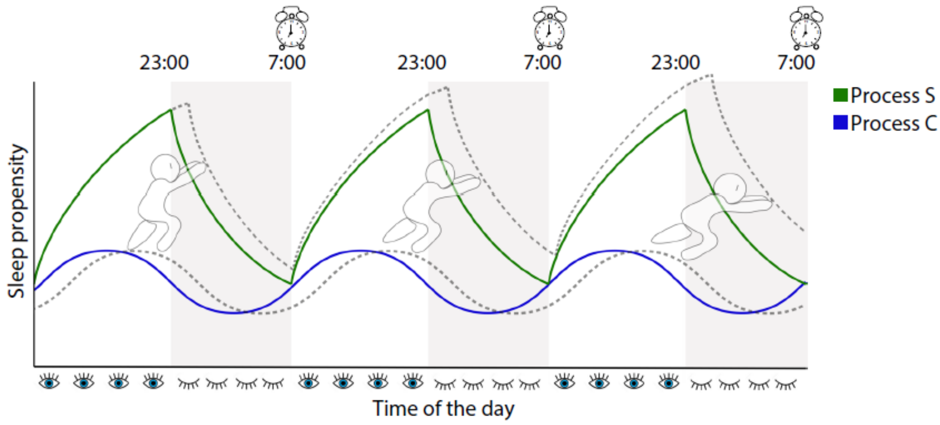
The Role of the Circadian Rhythm and Sleep in ADHD

A common feature in children and adults with ADHD is the presence of sleep disturbances such as parasomnias, sleep fragmentation, or chronic insomnia (Bijlenga et al., 2019; Bondopadhyay, 2022; Coogan-McGowan; Hvolby, 2015). Some recent studies have even linked the genetics of the disorder to sleep problems (Carpena et al., 2020). At the same time, ADHD symptomatology has been found in people with poor sleep quality. Studies such as Selvi and colleagues (2015) showed how shift work had an impact on attentional networks, with a greater increase in inattention and impulsivity in participants with night shifts. On the other hand, Floros and colleagues (2020) not only remarked that sleep loss interfered with executive functions in both healthy and clinical populations, but that those individuals with clinical traits had significantly higher cognitive conflict scores compared to the healthy population. For this reason, they conclude that the ADHD population is more vulnerable to the effects of poor sleep quality, sleep deprivation, or other disturbances than the neurotypical population.

In this line, it has been suggested that interference with sleep-wake cycles in this population is a particularly relevant factor. According to the two-process model by Borbély (1982) what we call circadian rhythm (*process C*) is one of the two oscillating mechanisms that determine sleep-wake cycles. The other mechanism is called homeostatic balance or sleep debt (*process S*). On the one hand, circadian oscillation refers to the complete physiological cycle in a day concerning sleep-wakefulness (Bijlenga et al., 2019; see Figure 1). This cycle depends on the suprachiasmatic nucleus of the hypothalamus, which creates a drive for wakefulness whose intensity is maximal at the end of the day, around the start of melatonin secretion. Immediately, the wakefulness drive tapers off, and the sleep drive appears in line with body temperature. Body temperature is an indicator for locating the peak of this sleep drive, coinciding with the minimum point of *Core Body Temperature* (CBT; Taillard et al., 2021).

Figure 1

Two-Process-Model of Sleep



Note. People are subjected to 2 different interactive processes that influence our behavior and cognitive state during wake-sleep cycles. Process S (green line) represents the amount of sleep debt accumulated over time. It is influenced by our routines and behavior being maximal at the end of the day, and it is reduced by a proportional amount of sleep. In contrast, Process C (blue line) is a regular oscillation that depends exclusively on physiological variables. Both processes are delayed in ADHD due to their interaction; delayed process C results in an increasing sleep dept accumulation, as it is shown in both dashed lines. From *The role of the circadian system in the etiology and pathophysiology of ADHD: time to redefine ADHD?* (p.6), by D. Bijlenga and colleagues, 2019, ADHD Attention Deficit and Hyperactivity Disorders, *11*(1), 5-19.

On the other hand, from the moment we wake up and become active, we accumulate a need for rest that becomes evident at the end of the day; this second mechanism is also known as homeostatic balance. The demand for balance increases during waking hours and disappears during sleeping hours. This mechanism is governed by sleep-wake behaviours and sleep history, making it flexible and adapted to our activity profile. Sleep regulation depends on the interaction between the two oscillatory mechanisms. Individual differences in the population complement the two-process model. Differences can be found through physiological changes such as body temperature as an indicator of circadian rhythm or the time of awakening. When we look at the angle of the oscillation phases by measuring the distance between the point of lowest body temperature and the time of awakening, we see that there are people with a long and others with a short period of "sleep". These physiological analyses correlate with psychometric measures such as the *Munich Chronotype Questionnaire* (MCTQ), *Morning-Eveningness questionnaire* (MEQ), and *Composite Scale of*

Morningness (MCS). If we combine all this information, we see individual preferences in sleep/wake behaviour (Coogan-McGowan, 2017). This is why these chronological preferences are defined with the concept of chronotype. Chronotypes are usually measured in a dimensional form: on one side is the morning type (morning activity preference), and on the opposite side, the evening type (afternoon activity preference).

Social factors are one set of elements that drastically influences individuals' sleep period. This influence becomes evident when comparing sleep-wake behaviour (wake-up time, activity hours) between working days and days off (Taillard et al., 2021). It is very common to observe a mismatch between the sleep schedule imposed by our social responsibilities (work schedules, social events) and our sleep schedule. This mismatch is intrinsically associated with one's chronotype. A person with a morning chronotype usually wakes up at a similar time to what their work and social responsibilities would require, as these typically take place in the morning. In contrast, a person with an evening rhythm will suffer a greater mismatch between their biological clock and the required wake-up time on working days. These circumstances interfere with day-to-day performance. It is known that the quality of task performance and cognitive skills, mainly executive functions, are dependent on our circadian rhythm (Váldez & García, 2012).

Accordingly, ADHD population and its relationship with circadian rhythm have been studied in depth. Evidence suggests that there is a tendency for the ADHD population to have more evening rhythm than the general population in their respective age range (Bondopadhyay, 2022; Coogan-McGowan, 2017; Floros et al., 2020; van Andel, 2022; Zerón-Rugerio et al., 2020) This circadian rhythm delay is translated into sleep problems. 73% of ADHD children report any type of sleep disturbance, and 42% have day-time sleepness (Langberg et al., 2017; Hysing et al., 2016). This circadian diphase is also consistent in adults (Bijlenga et al. 2013; van Veen et al., 2010). Measuring *Dim Light Melatonin Onset* (DLMO) showed that this delay has an objective prevalence of 78% of the adults diagnosed with ADHD (Craig et al., 2017; van Veen et al., 2010). In addition, one study showed that from 17-to 23h, children with ADHD had higher motor activity than their healthy counterparts. Furthermore, this excessive activity in the afternoon is consistent with greater symptomatology of hyperactivity and inattention. However, this symptomatology was associated with the characteristics of the ADHD profile that the subjects had (Zerón-Rugerio et al., 2020).

Evidence suggests that this population tends to have a circadian rhythm shift towards an evening chronotype, that sleep disturbances are strongly linked to this condition, and that both characteristics influence their symptomatology. Knowing this, chronotherapy has started to be investigated at the clinical level from different dimensions. Research with treatments aimed at circadian rhythm regulation has proven how the use of bright light and melatonin can affect the circadian rhythm by advancing the circadian cycle (van Andel et al., 2020; van Geijlswijk et al., 2010) suggesting a reduction of ADHD symptoms (Fargason et al., 2017; Rybak et al., 2006; van Andel et al., 2020). However, little is known about adapting the intervention to patients' chronotypes.

Present Study

For the present study, Posner and colleagues' theoretical model of attention (Petersen & Posner, 2012) has been used. This model separates the attentional system into three interacting but independent dimensions or attentional networks: the alerting network, the orienting network, and the executive network. The model first proposes the alerting network as the network that regulates arousal as well as the maintenance of performance over time. The orientation network is responsible for prioritizing and selecting a stimulus from any sensory modality or location in space or time. Finally, the executive network is responsible for monitoring behavior and goal-directed responses. The latter has been supported by the evidence as a critical element to build executive functions (Kane et al., 2007) some studies even suggest that common mechanisms underlie executive attention and executive control (Tiego et al., 2020). Consequently, to some degree, a great number of studies suggest that executive attentional network and executive skills are parts of the same whole, executive functions (Rueda, 2021). We know that several investigations have been devoted to studying the functioning of these attentional networks in the ADHD population. The evidence suggests an alteration especially in the alerting and executive networks (Arora et al., 2020; Barkley, 1997; Coll-Martín et al., 2021; Martella et al., 2020; Sergeant, 2000).

This is why increasingly more accurate measurement tools have been developed, such as the Attentional *Networks Test for Interactions and Vigilance - executive and arousal components* (ANTI-Vea; Luna et al., 2018). ANTI-Vea has been shown to record measures of *Executive Vigilance* (EV) and *Arousal Vigilance* (AV) for sufficient time (~33min) to reliably see the evolution of performance over time (Luna et al., 2018; 2020). Of relevance for the present proposal, a recent study has shown a significant correlation between EV and ADHD symptom severity in adulthood (Coll-Martín, Carretero-Dios, Lupiáñez, 2021) by using a variant of the ANTI-Vea. Consequently, the intervention of this study will be especially directed to improve EV and ADHD symptomatology.

From a neurofeedback point of view, the intervention has focused on computerized sustained attention tasks where the goal is concentration to achieve desired mind states induced by rewards (e.g., changing the color of a stimulus or moving a virtual character; Gevensleben et al., 2009). Novel neurofeedback training methodology combining motor response with EEG or using others neuroimaging techniques (e.g, fMRI or EMG) has been proposed in recent literature (Bazanova et al., 2018; deBettecourt et al., 2015; Mishra et al., 2021). However, the most studied protocols with the most favorable evidence are EEG neurofeedback: TBR, Slow Cortical Potential (SCP), and Sensorimotor rhythm (SMR), which have come to be called the standard protocols (Arns et al., 2020; Cortese et al., 2016; van Doren et al., 2017). In this range of protocol, the literature indicates that the type of training protocol used is not a relevant factor for a better outcome (Cortese et al., 2016; Gevensleven et al.; 2009). Conversely, it has been shown that neural mechanisms that each training protocol makes use of may be different (Arns & Kenemans, 2014; Arns et al., 2014; Enriquez-Geppert et al.; 2019). For our study, TBR training is desired not only because of support from the literature but also because of its relationship with the regulation of abnormal electrical signals in ADHD and its impact on executive functioning and ADHD symptomatology (Arns et al., 2013; Lenartowitwicz, 2014; Miranda et al., 2020; Zhang et al., 2019) including sleep quality (Arns et al., 2014). Studies such as Arns, Feddema, and Kenemans (2014) managed to investigate the effects between the TBR protocol and the SMR protocol. The results were similar both in terms of clinical benefits reducing ADHD symptomatology and improving sleep quality at different moments during the intervention. Nevertheless, TBR intrinsic correlation with executive functions in children and adolescence (Zhang et al., 2019) is a criterion for which TBR neurofeedback seems to be indicated for this study, as particular importance is given to variables related to these processes.

In this intervention, we want to investigate whether QEEG guided Z-Score neurofeedback training adapted to the adults ADHD patient's chronotype can improve the quality of executive vigilance, and their respective symptomatology, compared with TBR neurofeedback training with a random schedule. To this aim, adults with ADHD were trained by means of two different neurofeedback protocol (standard TBR vs QEEG Z-Score) in their optimum time of day or not (adjusted to the chronotype vs. no adjusted to the chronotype). EV and ADHD symptomatology will be measured before and after the different types of neurofeedback trainings.

Thus, taking all the previous evidence together, the present study has a twofold aim: On the one side, we want to find out whether an evidence-based neurofeedback intervention applied at the moment of maximum cognitive performance according to the patient's chronotype (Valdez et al., 2012) can improve clinical and behavioral outcomes in comparison to standard procedures. Additionally, we have the intention to compare a well-studied neurofeedback protocol to a new clinical QEEG-guided protocol in patients with ADHD to see possible differences. 3 main hypotheses have been made: (1) We expected to find a main effect of training protocol showing better outcome in adapted protocol compared to standard. (2) We also sense that we are going to find effect of chronotype by which groups with an adjusted training will show better outcome than non-adjusted training. (3) Finally, we have no solid evidence to hypothesized interaction effect between variables according to previous literature. In consequence, we expect additive effects between training protocol and chronotype.

Methods

Participants

According to the aim of our study, the required sample for our intervention are adults aged 18 to 65 years old and diagnosed with ADHD. The number of participants has been estimated by setting the parameters of interest for this research. To get a target effect size in randomized controlled trials we have based our research on the study by Rothwell and colleagues (2018), they calculated the average standardized effects size (Cohen´s *d*= 0.3-0.35) in clinical literature. Using this reference, we have simulated the number of participants required to detect this target size-effect with 80% of statistical power. This sample was found by running a statistics-related computer program, R. From this analysis, we concluded an estimated sample size of 75 participants per group (*n*=300): adjusted TBR training, non-adjusted TBR training, adjusted Z-Score training and non-adjusted Z-Score training.

This number of participants would only be possible to be recruited under a national plan of recruitment in collaboration with *Federación Española de Asociaciones de Ayuda al Déficit de Atención e Hiperactividad* (FEAADAH), *University of Granada* (UGR) and ADHD organizations around Spain provinces. Announcements of our proposal would be distributed by FEAADAH and it would be also supported in platforms attached to UGR and social media, explaining the importance of participation and benefits from these treatments. Clinics in contact with these associations will provide the suggested training from their locations. Participation will be rewarded with 10 euros per hour which will be given to participants after the whole procedure is completed. In case of significant differences between training, participants assigned to the less effective intervention will be allowed to take advantage of the training with the best outcome.

Participants would be assessed to know their chronotype and disposal to develop our training at different day-times. As soon as we know the participant's disposal, we will randomly divide them into four groups. Two will be treated with standard TBR neurofeedback protocol, and the other two will be trained with QEEG guided Z-Score neurofeedback. TBR and Z-Score training would have an adjusted chronotype and non-adjusted chronotype group with training that would take place at different day-time (morning or evening).

All participants will be included after being diagnosed with ADHD following clinical procedure in each clinic. For the present study, according to research previously referred (Coll-Martín, 2021; Moffit, 2015), we decided to exclude the DSM-5 criterion of having ADHD before 12 years. Participants won´t be included if they have some of the following characteristics: 1) Ongoing pharmacological treatment; 2) A different age from the established age range, 18-65 years; and 3) To have completed the whole training procedure.

Behavioral and Psychometric Instruments

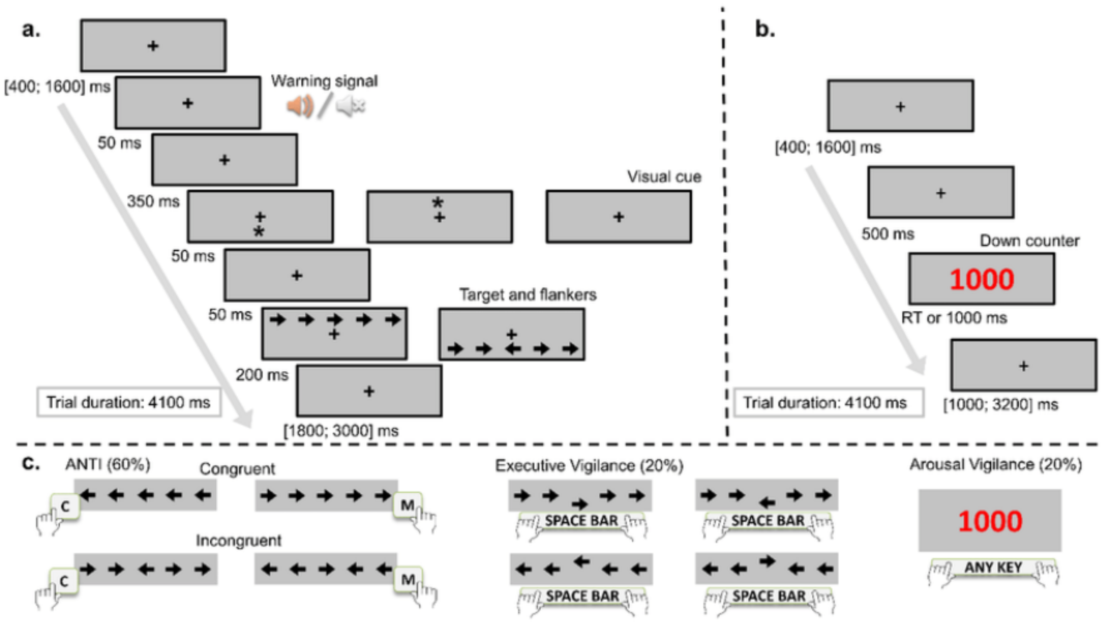
To get a reliable measure of the presence of ADHD symptoms in each participant, we used the BAARS-IV (Barkley, 2011). This scale allows us to display an adult version to get information about the concurrent symptomatology in adulthood. In the present study, we have the intention to use BAARS-IV, as it has demonstrated a good validity in identifying individuals with a high risk of ADHD in adults (Barkly, 2011). This scale has 18 items (9 for inattention symptomatology and 9 hyperactive-impulsivity symptomatology) with a Likert scale from 0 to 3 in each of them, reaching a maximal score of 54 points. The recommended cut-off is 95th percentile to identify as high-risk ADHD individuals.

For measuring chronotype, *Morning-Eveningness Questionnaire* (MEQ; Horne & Ostberg, 1976) is the most commonly used tool for analyzing circadian preference. This is an easy and reliable procedure for acquiring the chronotype information of patients (Natale et al., 2006). It consists of 19 items approaching different dimensions: habits for rising and going to bed, preference for physical and mental performance, and finally, alertness after rising or prior to going to bed. It can distinguish between morning-type, intermediate type, and evening-type. In the case of intermediate chronotype, the participants will be excluded due to the possibility of creating bias in the chronotype effect.

Additionally, for measuring attention and vigilance across the day, ANTI-Vea will be used online (https://ugr.es/~neurocog/AntiResults.html). This validated computer-based task is capable of measuring executive attention and arousal, both components being mainly altered in ADHD. With this task, we have the intention to focus on the EV index. This index shows the decrement in EV over the course of the task computed through responses to an infrequent (20% of probability) stimulus (one arrow below or above the arrow line, see Figure 2). By comparing this index across groups before and after training we can see the improvement in task requiring EV across time. Additionally, evidence points to a relationship between the decrement in EV and executive control (Luna et al., 2022). That is why, by using ANTI-Vea, we can study vigilance and executive attention together with a broader cognitive profile to acquire as much information as possible for future analysis. Finally, we intend to support the hypothesis of using neurofeedback as a cognitive enhancement tool for these cognitive functions. ANTI-Vea will enable us to know the difference between one training and the other in this regard. Task description is depicted in Figure 2.

Figure 2

Tasks in Attention Network Test for Interaction and Vigilance – Executive and Arousal Components *(ANTI-Vea)*



Notes. (**A**) Temporal sequence in *Attention Network Test for Interaction* (ANTI) and *Executive Vigilance* (EV) trials. Target and flankers will appear above or below the fixation point. Visual cue could appear in the same location as the target (valid cue), in the opposite location (invalid cue), or could not appear (no cue). (**B**) *Arousal Vigilance* (AV) time sequence of trials. (**C**) Arrow location and procedure to follow by pressing the correct key in every case. From *Attentional networks functioning and vigilance in expert musicians and non-musicians (p.7),* by R. Román-Caballero and colleagues, 2019, Psychological Research, *85*(3), 1121-1135.

QEEG Acquisition and Z-Scores

Quantitative EEG data acquisition will perform following a well-established methodology described by Wigton and Krigbaum (2015). It consists in an EEG recording using a 19-channel cap (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2) distributed as it is suggested by 10-20 international system in a controlled room. This number of channels is optimum and economically accessible for clinical purposes. Skin resistance will be lower than 10kW for each electrode. Brainmaster-Discovery 24E (Brainmaster Technologies, Inc., Bedford, OH; Discovery version 1.4) was the selected amplifier with an EEG bandwidth of 0.43-80Hz. The signal sample rate would be set at 256 samples per second to the computer using 1000 GΩ. The frequency range of interest would be filtered with a high pass filter of 0.5 Hz and a low pass filter of 50 Hz, as it is referred in Neuroguide (Collura et al., 2009; Thatcher, 2001; Thatcher et al.,2003; 2005; 2009) normative database.

EEG is registered essentially during the resting state, as it has been suggested in literature due to the discrimination that this condition can make between disorders such as ADHD (Angelidis et al., 2016; Keizer, 2021). The usual procedure varies from 1 to 4 min registration, in this study, we opted to record a 4-min Eyes Open condition and 4-min Eyes Closed condition as it did Cannon and colleagues (2012) analyzing its reliability. Instructions will be given to avoid muscle activity from the forehead, neck, and jaw apart from detected blinks. To exclude technical and biological artifacts, it will be followed the EEG selection method by Thatcher (2012) and a computational analysis program to remove artifacts (BrainAvatar 4.6.4). After a fast Fourier transformation procedure, the filtered frequency bands we intend to work with as metrics of absolute power, relative power, and coherence will be as follows: Delta (1-4 Hz), Theta (4-8Hz), Alpha (8-12 Hz), Beta1 (12-15 Hz), Beta2 (15-18 Hz), Beta3 (18-25 Hz), and high Beta (25-30 Hz).

Acquired data will be systematically compared to a Normative Database available for clinical practice, *Neuroguide* (Collura et al., 2009; Thatcher, 2001; Thatcher et al.,2003; 2005), which has been used as a normed dataset for both eyes open and eyes closed conditions with a controlled healthy sample of 625 participants from ages of 2 months to 82 years. QEEG Z-Scores are representations of functional electrocortical activity about the mean. Deviations of absolute power, relative power, or coherence values from the mean are statistically standardized when the comparison is made. Each Z-Score builds an individualized profile of sites of interest, Z-Scores above 1 *Standard Deviation* (*SD*) in absolute value are targeted by location and frequency (see Figure 3). These Z-Scores are averaged to generate a unique value for each participant representing the distance from the mean for that metric.

Theta/Beta Protocol

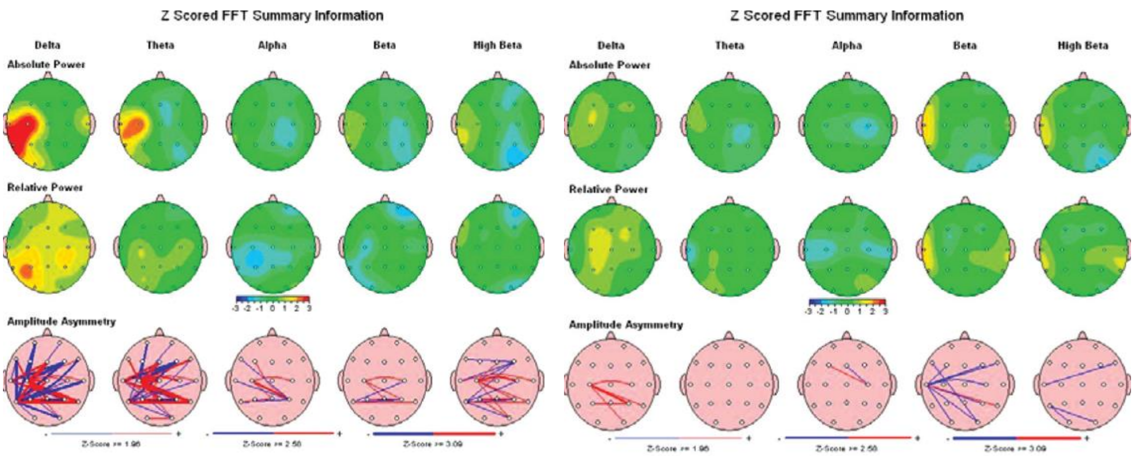
For groups destined to perform a standardized training with the TBR protocol, a baseline was previously analyzed to adapt each frequency band to its particular range with 2 mins of resting state. Each threshold needs 30 seconds to codify ongoing information to calculate the percentage of reward or inhibition that each frequency band of interest has.

There is no evidence-based standard number of sessions to apply but based on previous research and considering the minimal number of sessions to have differential effects we opted to apply 30 sessions of 30 mins, twice a week as it is frequently used (Bussalb et al., 2019; Cortese et al, 2016; Louthrenoo et al., 2021; Rahmani et al., 2022). The protocol will focus on enhancing Beta 1-2 (12-18 Hz) and, on the other side, inhibiting Theta (4-8 Hz). The participants will select short videos to provide feedback. When the criteria are met, the video is visualized with high quality and good audio, otherwise, the video image will be blurred, and audio will be muted.

Figure 3

Individualized Pre-Training and Post-Training Profile with Z-Score Neurofeedback

A **B**



Note. This figure shows (**A**) individualized pre-training absolute and relative power profile in each frequency band together with amplitude asymmetry as a measure of functional connectivity. (**B**) Z-Score training effect after 20 sessions can normalize excessive standard deviations in each profile metric. From *EEG biofeedback case studies using live Z-Score training and a normative database (p.32)*, by T. F. Collura and colleagues, 2010, Journal of Neurotherapy, *14*(1), 22-46.

Z-Score Neurofeedback Training

Z-Score training will be provided based on QEEG findings orienting the training to normalization of Z-Score average, in other words, improving standard deviations towards *SD*=0. The training threshold is adjusted automatically depending on the percentage of Z-Scores within the stablished limits. For our study, previous literature has selected the limits at one standard deviation as upper and lower threshold (Perez-Elvira et al., 2020; Thatcher & Lubar, 2015). Following this literature, we have the intention to set the same limits. The participants will select short videos to provide feedback. When the criteria are met, the video is visualized with high quality and good audio, otherwise, the video image will be blurred, and audio will be muted.

Procedure

Clinics will be contacted based on their knowledge about neurofeedback, in case of no experience, experts in EGG neurofeedback and QEEG will be sent to the clinics with the appropriate material for their use and transportation. A training course will be implemented for the clinical staff and the training of the participants will be under expert supervision.

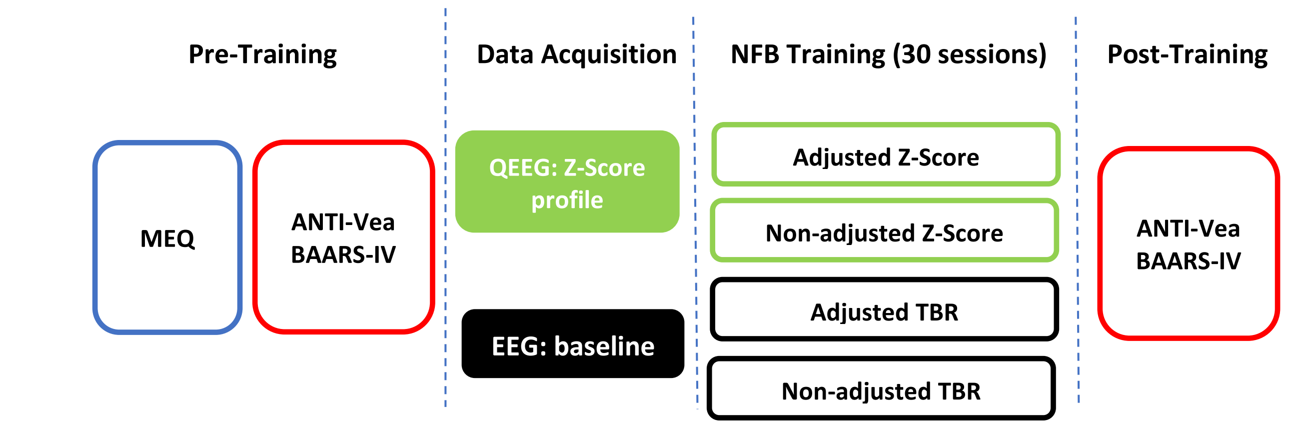
Prior to the intervention, all selected participants will complete the MEQ and the aBAARS-IV. After displaying these questionnaires, we proceed to use the ANTI-Vea in order to know how they perform it as baseline. Participants will be randomly distributed and counterbalanced to have a similar number of people with different chronotype in each training group.

Later on, QEEG guided Z-Score training group will go through an assessment period to adapt neurofeedback to Z-Scores. In case of TBR training group, they would be previously measured to know EEG baseline activity. Broth training groups will be divided into two groups. One group will train at their optimum cognitive moment and the other group will train at a time of day that is not in sync with their chronotype. Both groups will undergo 30 neurofeedback training sessions.

When each training is completed, each participant will repeat an ANTI-Vea at the same moment they registered the previous one and BAARS-IV with the purpose of comparing the total improvement between one training and the others without chronotype effect (Procedure is depicted in Figure 4).

Figure 4

Proposed Procedure to Be Followed in this Study



Note. It will be assessed prior to training chronotype through MEQ, ADHD symptoms with BAARS-IV and EV together with other attentional indexes by means of ANTI-Vea. They will go through a period of acquisition of data different for each training, QEEG will build a Z-Score profile for each participant of one training and a standard EEG baseline will be used to adapt parameters in the other. Finally, it will be measured again ADHD symptoms and attentional performance after training. The whole duration is 30 sessions of 30 mins, twice a week: 15 hours in total.

Analysis of Data

Our design comprises 2 independent variables with 2 levels each one: type of training protocol (standard TBR and QEEG guided Z-Score training) and chronotype adjustment (Adjusted /Non-adjusted). We intend to measure two dependent variables: ADHD symptomatology in pre-training condition versus post-training condition, and the performance in the ANTI-Vea (EV) in pre-treatment condition versus post-treatment condition. Consequently, we would present a 2 x 2 x 2 design: TRAINING X CRONOTYPE X TIME. We will take into account that baseline score is not significantly different in all experimental groups. For the sake of simplicity, we underwent a calculation of pre and post differences to manage the data analyses in each dependent variable. First, we transformed BAARS-IV punctuation before and after neurofeedback training into one common dependent variable calculating the improvement in BAARS-IV scale subtracting pre-treatment score to post-treatment score (see Table 1). Then, we also transformed ANTI-Vea EV index by subtracting post-training performance to pre-training performance to get a measure of improvement for EV hits and decrement in performance across time.

This procedure will restructure our design which will be 2x2 for our statistic model. the four groups will be compared through Analysis of variance (ANOVA), and with the final purpose of studying the possible differences between groups, we are going to apply a comparison of simple contrasts (T-Student).

Results

Our expected results are developed from the same baseline with groups of participants that do not differ from each other. Our measures intend to evaluate how effective is QEEG guided Z-Score and chronotype adjustment in reducing ADHD symptoms and enhancing EV compared to standard procedures.

ADHD Symptoms

BAARS-IV scale would be used before and after training. Average scores in the BAARS-IV scale for each group would have no difference prior to training. As shown in Table 1, we start from the same baseline in each group regarding ADHD symptomatology. Our model was programmed to get the same mean in BAARS-IV punctuation through random scores among participants. Having the same mean and same standard deviation in our groups let us avoid analysis to be sure that these groups are not different before training. This makes us conclude that differences after training are due to our experimental condition.

Table 1

Descriptive of the BAARS-IV Score Before and After Training with the Improvement Value of Each Training

Protocol	**TBR Standard Training**						**Z-Score Training**					
Chronotype	**Adjusted**			**Non-Adjusted**			**Adjusted**			**Non-Adjusted**		
Time	**B**	**A**	**I**	**B**	**A**	**I**	**B**	**A**	**I**	**B**	**A**	**I**
Mean Score	44	43	1	44	41.4	2.6	44	39.2	4.8	44	40.5	3.5
SD	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2

Notes. Before training (B), after training (A) and improvement value of the training (I). It is shown that each simulated group has the same mean and the same standard deviation previous to training. Expected results according to our hypothesis regarding ADHD symptoms will show differential changes post-training. Imp: Improvement.

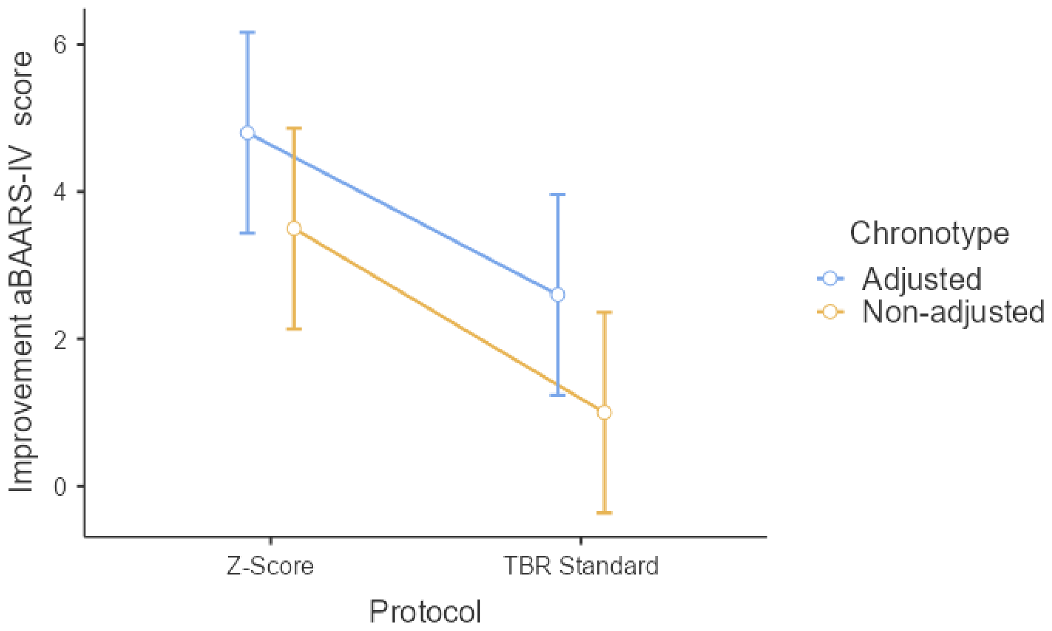
Effects and differences between trainings are visually represented in Figure 5. Firstly, ANOVA shows main effect of training protocol (F=11.50; p<0.001; η_p^2=0.037; d=0.392). Our model indicates significant differences between ADHD symptomatology in people who have been treated with one neurofeedback training and the other, with a larger reduction (reflected as greater improvement) in ADHD symptomology in the QEEG guided Z-Score training group as compared to the standard group. The size effect is moderate but clinically meaningful (Rothwell et al., 2018).

ANOVA also shows main effect of chronotype (F=4.38; p<0.037; η_p^2=0.015; d=0.247). Patients trained at their optimum time of day can differ from those trained not adapting their chronotype. Larger reduction of ADHD symptoms is presented in people with training adjusted to chronotype compared to non-adjusted. This chronotype effect has projected a side effect around d = 0.25 which is interpreted as a small effect but clinically interesting to take into account.

Regarding our third hypothesis, our model suggests no interaction effect between independent variables (F= 0.0469; p<0.829). There is no significant difference between the influence of one variable over the other. The effects would be added in the same proportion to each variable.

Figure 5

Representation of Protocol and Chronotype in Relation to ADHD Symptomatology Based on BAAARS-IV Score



Note. Z-Score neurofeedback is expected to produce better outcome with regard to ADHD symptomatology reduction, when chronotype is adjusted, patients increase their improvement. In turn, TBR standard protocol is not expected to have great results, when chronotype is taken into account, improvement is expected to increase proportionally.

Simple contrasts were applied to analyze differences between groups. After correction only one comparison between training groups showed significant differences. Z-Score neurofeedback training with chronotype adjustment showed significantly higher improvement in ADHD symptomatology than standard TBR training with no chronotype adjustment (p<0.001; d= 0.633; see Appendix A for more information about post-hoc analysis with ADHD symptomatology).

Executive Vigilance

Regarding EV data, we start from data described in Table 2. Findings are plotted in Figure 6. In first place, ANOVA shows main effect of training protocol (F=11.50; p<0.001; η_p^2=0.037; d=0.392) in EV improvement. Our model suggests significant differences between the capability to maintain EV across time in people who have been treated with one neurofeedback training and the other. They will present a larger reduction of EV slope of decrement in the QEEG guided Z-Score training group compared to the standard group. The size effect is again moderate but clinically interesting nonetheless (Rothwell et al., 2018).

Table 2

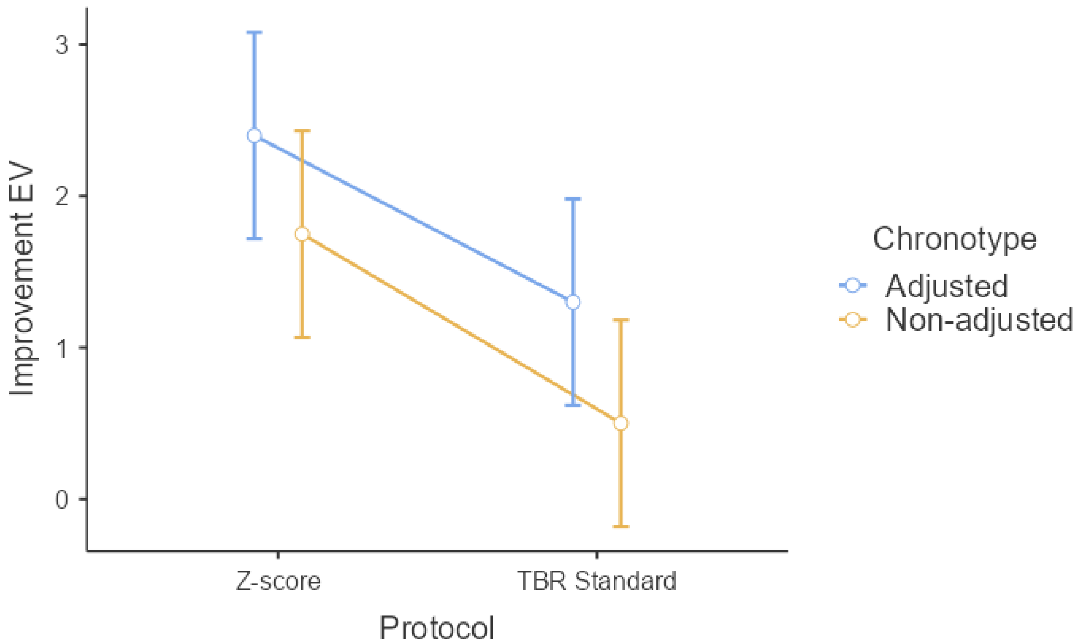
Descriptive of EV Decrement Slope Before and After Training

Protocol	**TBR Standard Training**						**Z-Score Training**					
Chronotype	**Adjusted**			**Non-Adjusted**			**Adjusted**			**Non-Adjusted**		
Time	**B**	**A**	**I**	**B**	**A**	**I**	**B**	**A**	**I**	**B**	**A**	**I**
Mean Score	-4	-2.70	1.30	-4	-3.50	0.5	-4	-1.60	2.40	-4	-2.25	1.75
SD	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00

Notes. Before training (B), after training (A) and improvement value of the training (I). It is shown that each simulated group has the same mean and the same standard deviation previous to training. Expected results according to our hypothesis regarding ADHD symptoms will show differential changes post-training.

Figure 6

Representation of Protocol and Chronotype in Relation to EV Decrement Across Time Based on ANTI-Vea Score



Note. Z-Score neurofeedback is expected to produce better outcome with regard to maintain EV across time, when chronotype is adjusted, patients increase their improvement. In turn, TBR standard protocol is not expected to have great results, when chronotype is taken into account, improvement is expected to increase proportionally.

In connection with previous analyses, ANOVA also shows main effect of chronotype (*F*=4.38; *p*<0.037; η_p^2=0.015; *d*=0.247). Participants trained at their optimum time of day differ from those trained not adapting their chronotype. Larger reduction of EV decrement slope is presented in people with training adjusted to chronotype compared to non-adjusted. Again, chronotype effect has shown a side effect around *d* = 0.25 which is interpreted as a small effect but interesting enough to take into account.

With respect our third hypothesis, no interaction effect between independent variables was suggested by our model (*F*= 0.0469; *p*<0.829). Effects would be added in the same proportion to each variable.

We expect that better outcome will be observed in the most adapted neurofeedback training group. EV improved when Z-Score training protocol was applied and this training was performed adjusting their chronotype. To see differences between groups, simple contrasts were applied. After correction only one comparison between training groups showed significant differences. Z-Score neurofeedback training with chronotype adjustment showed significantly higher improvement in EV than standard TBR training with no chronotype adjustment (*p*<0.001; *d*= 0.633; see Appendix B for more information about Post-Hoc analysis).

Discussion

The present intervention proposal aims to test whether an individualized QEEG guided Z-Score training and/or a chronotype adjustment of the treatment can determine an improvement of both ADHD symptomatology and EV in adults with ADHD.

As far as we know, QEEG is a promising tool highly known in the clinical community and growing literature supports this protocol as the next step in neurofeedback intervention (Arns & Drinkenburg, 2012; Cannon et al., 2012; Collura, 2017; Hammer et al., 2011). This study would be the first random control trial to study QEEG capabilities to improve ADHD condition. In addition, it is strongly proposed from literature a new circadian perspective on ADHD, taking into account variables such as chronotype and sleep quality as it is referred in previous research (Bijlenga et al., 2019; Bondopadhyay, 2022; Carpena et al., 2020; Coogan-McGowan, 2017). This study embraces this new perspective giving rise to evidence for new lines of research in order to improve not only the mechanism by which we can reduce symptomatology but also the way we apply the intervention having a better quality of life as the ultimate goal.

Our hypothesis has been translated into a model that allows us to visualize how would have been this research in case this study was done. We have calculated the number of participants required to get a targeted size effect. With that simulated sample we have applied 4 conditions following the hypothesis this research is based on.

On account to our first hypothesis, our study suggests that QEEG guided Z-score training would have the best improvement regarding symptomatology and executive vigilance compared to standard protocol TBR. In each training group, chronotype has shown an effect creating a difference between tailored and untailored conditions where a better outcome appears in the chronotype-adjusted group. These data support our second hypothesis. However, effects from protocol and chronotype seem to be independent. Despite our data showing an improvement when protocol and chronotype were adjusted to individuals, both variables have no interaction effect. We could think that maximal training individualization can potentiate enhancement to the point of a possible interaction effect. However, no studies have been done in this respect and it would be a risky hypothesis because literature gives no solid reason to think these variables can interact with each other so far. Subsequently, our model represents the measured variables with additive effects. The same difference will show in both neurofeedback training. Having said that, to find an interaction effect among these variables would be worthwhile and really interesting to open new question about individualized therapy.

Previous studies have showed that a 10 sessions training of QEEG Z-Score neurofeedback is more effective than standard TBR in reducing electrophysiological signals of ADHD, such as Theta/Beta ratio (Pérez-Elvira, 2020). Our findings support this result and shed light on the efficacy and efficiency of Z-score neurofeedback training. According to previous research, Z-Score training can reach optimum normalization within 30 sessions of training (Perez-Elvira, 2018; 2019; 2020). On the contrary, standard protocol are suggested to reach optimum effects within 40 sessions as metanalysis strongly highlights (Bussalb et al., 2019; Cortese et al, 2016; Louthrenoo et al., 2021; Rahmani et al., 2022). This leads to new research questions about whether these benefits are a matter of efficiency rather than efficacy. Maybe these new procedures are faster reaching clinical benefits but not better with regard to standard protocol benefits. Having said this, several differences separate one from the other. Standard protocols, including TBR, only focus on absolute or relative power. By contrast, QEEG guided trainings such as Z-Score neurofeedback provides individualized information that considers connectivity and functional EEG indexes, making us reach a more realistic EEG profile to modulate. Z-Score training in this research would create not only the opportunity to get benefits earlier but also these benefits will be based on functional and personalized information about the patients leading to a better quality of benefits. This QEEG profile can be treated on the one hand by holistic treatments as Z-Score training making a total mean of Z-Score deviations or even using a very well-known program, *Loreta,* that is capable of triangulating accurately standard deviation scores in each region from electrodes information (Cannon et al., 2012). On the other hand, QEEG has also used for partially individualized training. Once we have a standard deviation profile, we can choose which neurofeedback training is more appropriate for each patient, as demonstrated before (Arns et al., 2012; Hammond, 2009; Walker, 2009). Clinical evidence suggests that either of previous options can be functional in short and long-term.

Our data manifest not only a better outcome for ADHD symptomatology, we also expect better improvement in EV. People with ADHD have difficulty maintaining attention focused on the objective in mind and therefore they have an altered capability to keep attentional resources under control. From the Resource-Control theory point of view (Thompson et al., 2015), mind-wandering state is, by default, increasingly consuming cognitive resources as the task goes on. This is not due to a depletion in the amount of resources, but rather to the loss of control over such resources. Luna and colleagues (2022), by studying executive control in relation to decrement in vigilance, found a correlation between both indexes giving evidence supporting the Resource-Control theory. This interesting model allow us to explain difficulties in EV across ADHD population (Coll-Martín et al., 2021). That is why, our expected results are really interesting not only because we would train executive vigilance, we also have the opportunity to study later on this relationship between executive vigilance and executive control in ADHD population thanks to the range of measures that ANTI-vea has.

Considering all the possibilities, reduced effects in TBR protocol can be due not exclusively to the comparison with QEEG guided training, it could include some variables that also influence the data. Evidence has investigated certain differences in TBR across ADHD population. TBR as a standard protocol has been widely studied in children. Arns and colleagues (2013) developed one metanalysis that concluded in consistent capability of discrimination between ADHD and healthy control people with an effect size between *d*=0.75 (from 6 to 13 years old) and *d*=0.62 (from 6 to 18 years old). It is even suggested to be a characteristic index of the ADHD EEG profile. It is defined by significantly higher Theta and lower Beta than healthy control. However, several studies support the high level of heterogeneity within ADHD population; this variability increases even more with age (Arns et al, 2014; Lenartowitwicz, 2014; Miranda et al., 2020). Loo and colleagues (2013), compared children and adult ADHD with their respective healthy control groups, concluding that TBR difference was decreased in adults. This evidence suggests that it is possible a different neural basis for each neurodevelopmental stage of ADHD. Following this argument, TBR is arguably not consistent enough between ages to apply the same training in children and adults. It is possible that interventions studied in children do not apply to adults, or at least not in the same way.

Another reason to distinguish between adulthood and childhood when applying the same treatment or protocol is neural plasticity. Adults are more neurologically rigid in their learning than children (Brehmer et al., 2007; Giannakopoulou et al., 2013). Childhood offers a time window in which they can modify their brain connections more easily than adults. This difference can indeed be crucial to successful neurofeedback treatments. However, this tool provides neuromodulatory training capable of changing brain activity, not only brain activity but also brain connectivity. Studies like Gaziri and colleagues (2013) have found evidence of changes in white matter myelinization and grey matter volume after EEG neurofeedback in healthy young adults. Nonetheless, there is almost no evidence about effects of neurofeedback in adults with ADHD. On this account, it is strongly encouraged to personalize therapy to avoid problematic generalizations in such diverse disorders as it is ADHD.

Certain lines of research about cognitive training state that neurofeedback which is considered so far a cognitive enhancement tool could work differently as we originally thought. Von Bastian and colleagues (2022) showed in their review that there is a lack of solid evidence pointing to cognitive enhancement capability after cognitive training. By contrast, robust support from evidence highlights a training-induced improvement in cognitive efficiency. This would mean that neurofeedback as a cognitive training tool among other brain-enhancing strategies are suggested to be techniques that improve performance optimization within a limited cognitive capability. In other words, cognitive training makes people more efficient with their diminished cognitive resources. This idea could explain the possibility of no cognitive enhancement after our training, instead, cognitive efficiency would improve in this condition showing a better management of resources and strategies to cope with their limits. In any case, this study will be useful to disentangle functionality of this cognitive training tool and its relation with executive control over attentional resources in ADHD population.

Consequently, this new line of research opens the door to new hypothesis based on efficiency of cognitive training. Some of them based on chronotherapy, it is possible that the number of sessions required to get the maximal effect in patients with neurofeedback can be reduced when we manage to create optimal context. By recruiting more cognitive resources during training, we could reduce the number of standard sessions in ADHD population, among others. The effect we hypothesized in this research is indeed small. With regard to chronotype, and from the clinical point of view we must make the question. Is it worth investing in this minimal effect? Would this investment be more profitable in other lines of clinical benefits in which we can focus on? To build consistent evidence, further research in the future will be needed. However, the possibility of reducing the number of sessions can potentiate adherence in neurofeedback treatment which is difficult to achieve with a 38% of dropouts nowadays (Moreno et al., 2013).

One point that must be discussed in our research is the statistic model we have applied. Based on our model, we would need a great number of participants. Taking this limitation in the recruiting process into account, we have decided to develop research on equilibrium between ideality and reality. By reducing a substantial statistical capability to detect our smallest effect size of interest, we wanted to sustain realistic research. Having a control group would increase the number of people required for the analysis which is especially complex in the clinical field due to external conditions that are needed to be considered. We opted to make a simpler analysis by recruiting a more realistic number of participants.

Additionally, another limitation in our research is the absence of a control group as a measure of change through time without treatment. We have followed the idea of DSM-5 which states that ADHD in adulthood is a prolonged childhood condition still in adults. We assumed this disorder has the same dysfunctional mechanism in different developmental stages. Neurofeedback has been supported by evidence in the childhood population, and following the explained principle, we based our hypothesis on the continuity from one stage to the other. As it was a supported treatment by the clinical community, we focused our attention on improving this tool assuming it was clinically operative. Despite differences in cognitive profile between ADHD in adulthood and childhood, both share cognitive deficit which would explain improvement after neurofeedback training in both cases.

Conclusion

We can expect from this research new evidence about individualized treatment with QEEG guided neurofeedback. We will have information on the efficacy of promising techniques as Z-Score training in reducing ADHD symptomatology and improving EV compared to standard protocols such as TBR. We also want to include circadian variables to complete ADHD conceptualization making use of their chronotype to study their improvement in ADHD symptoms and EV if the training is ergonomically adjusted to their preference. This study will reveal new horizons in the clinical approach to this population.

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Appendices

Appendix A. Post-Hoc Simple Contrast to See Differences Between Groups

Comparison												
Protocol	Chronotype		Protocol	Chronotype	Mean Difference	SE	df	t	p	p_{tukey}	Cohen's *d*
Z-Score	Adjusted	-	Z-Score	Non-adjusted	1.300	0.980	296	1.327	0.186	0.547	0.217
		-	TBR Standard	Adjusted	2.200	0.980	296	2.245	0.025	0.114	0.367
		-	TBR Standard	Non-adjusted	3.800	0.980	296	3.878	< .001	< .001	0.633
	Non-adjusted	-	TBR Standard	Adjusted	0.900	0.980	296	0.919	0.359	0.795	-0.150
		-	TBR Standard	Non-adjusted	2.500	0.980	296	2.552	0.011	0.054	0.417
TBR Standard	Adjusted	-	TBR Standard	Non-adjusted	1.600	0.980	296	1.633	0.104	0.362	0.267

Note. There is only one comparison that is significantly different. Z-Score training with chronotype adjustment differs significantly from TBR standard protocol with no chronotype adjustment. The rest of the groups do not have significant differences between each other.

Appendix B. Post-Hoc Simple Contrast to See Differences Between Groups

Post Hoc Comparisons - QEEG ✻ Chronotype

Comparison										
QEEG	Chronotype		QEEG	Chronotype	Mean Difference	SE	df	t	p_{tukey}	Cohen's *d*
Adapted	Adjusted	-	Adapted	Non-adjusted	0.650	0.490	296	1.327	0.547	0.217
		-	Standard	Adjusted	1.100	0.490	296	2.245	0.114	0.367
		-	Standard	Non-adjusted	1.900	0.490	296	3.878	< .001	0.633
	Non-adjusted	-	Standard	Adjusted	0.450	0.490	296	0.919	0.795	-0.150
		-	Standard	Non-adjusted	1.250	0.490	296	2.552	0.054	0.417
Standard	Adjusted	-	Standard	Non-adjusted	0.800	0.490	296	1.633	0.362	0.267

Note. There is only one comparison that is significantly different. Z-Score training with chronotype adjustment differs significantly from TBR standard protocol with no chronotype adjustment. The rest of the groups do not have significant differences between each other.