PONTIFICIA UNIVERSIDAD CATÓLICA DE CHILE
Facultad de Medicina – Facultad de Ciencias Biológicas
Facultad de Ciencias Sociales – Facultad de Química y Farmacia

Doctorado en Neurociencias

Tesis Doctoral

Attentional networks in preschool children with and without early symptoms of attention deficit and hyperactivity disorder who participated in a working memory training program

Por

Felipe Andrés Oyarzún Gavilán

Diciembre 2021

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Tesis presentada a la Pontificia Universidad Católica de Chile como parte de los requisitos para optar al grado de Doctor en Neurociencias

Por

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Diciembre 2021

PONTIFICIA UNIVERSIDAD CATÓLICA DE CHILE
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Dedicated to all neurodiverse people.

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ABBREVIATIONS

ACC	: Anterior Cingulate Cortex
ADHD	: Attention-Deficit/Hyperactivity Disorder
ANT	: Attentional Networks Test
EEG	: Electroencephalogram
EFs	: Executive Functions
ERP	: Event-Related Potential
fMRI	: functional Magnetic Resonance Imaging
ICA	: Independent Component Analysis
PFC	: Prefrontal Cortex
RT	: Reaction Time
TD	: Typical development
WM	: Working Memory

1. ABSTRACT

Attention is an important cognitive process for daily life because it allows us to be expectant to situations in the environment and to select some information from many options that are presented simultaneously. It is a process that is affected in neurodevelopmental problems such as attention deficit and hyperactivity disorder (ADHD). There is a lot of knowledge about cognitive difficulties in children diagnosed with ADHD, but little is known about what happens during the development of this disorder, especially in the stages prior to being diagnosed or at preschool stages. For this reason, we decided to study the attention, based on the paradigm of attentional networks, in preschool children with both typical development and early symptoms of ADHD. As the brain regions that improve the activity after working memory training are similar to the regions that are activated in attentional tasks, we proposed that working memory training could improve attention. To achieve this objective we evaluate attention (Attentional network task, ANT) and working memory (verbal and visuospatial) before and after an intensive computer-based working memory training. The results of the study showed that children with early symptoms of attention deficit and hyperactivity disorder have a decrease in modulation of the orienting and executive attentional networks, but not the alerting network, in comparison with typical development children. Additionally, we found that working memory training can improve the modulation of executive attentional network in children with early symptoms of attention deficit and hyperactivity disorder, but not in typically developing children. These results show the importance of studying the course of abnormal development of attention, in stages prior to the diagnosis of ADHD. Additionally, we suggest working memory training as a method to improve some difficulties in modulating attention in children with early symptoms of ADHD.

2. INTRODUCTION

Attention deficit and hyperactivity disorder is a common neurodevelopmental disorder characterized by inattention, hyperactivity/impulsivity, or both. It affects 7% of the world population (Thomas et al., 2015), and a prevalence of 10% has been estimated in Chile (De la Barra et al., 2015). It has been described that people with ADHD can present during their life health problems, psychological dysfunction, social disability, risky behaviours, academic and occupational failure (Brunkhorst-Kanaan, et al., 2021, Faraone, et al., 2015). The risk factors for ADHD have been described as a combination of hereditary and non-hereditary multifactorial components, this means that multiple genes and non-hereditary factors contribute to the origin, development and/or persistence of ADHD. Prenatal and perinatal factors have been implicated as risks, but definitive causes are unknown (Thapar & Cooper, 2016). In the cognitive domain, it has been found that the greatest decrease in executive functions in ADHD is observed in response inhibition, vigilance, working memory, and planning (Willcutt et al., 2005). Studies of brain activity via fMRI have shown that people with ADHD have decreased executive/frontoparietal and visual-attentional/ventral attentional networks, and increased default mode and somatomotor networks (Cortese et al., 2012). Furthermore, it has been found that different components of attention are compromised. Based on Posner's attentional networks paradigm, it has been observed that people with ADHD have less brain activity in regions associated with the alerting, orientating and executive attentional networks (Konrad, et al., 2006).

Despite a great deal of knowledge about the general and specific deficits of people with ADHD, little is known about their abnormal course of development. Although it is known that ADHD is a neurodevelopmental problem, it is unknown what is happening in the brain development of children who are causing ADHD and developing this pathology. For this reason, it is very important to know what is happening at the brain level before the diagnosis of ADHD, in order to be able to find early intervention tools that can prevent or slow down the course of development of this disorder.

Studying the state of attention before the diagnosis of ADHD through the attentional networks paradigm is a good approach, since three attentional networks can be evaluated in a single task. In addition, there is a great accumulation of knowledge on behavioral, electroencephalographic and neuroimaging studies in people with typical development and ADHD (Abundis-Gutiérrez, et al., 2014, Fan, et al., 2007, Konrad, et al., 2006, Neuhaus, et al., 2010). For this reason, we propose in this thesis as the first research objective to determine the state of attentional networks in pre-school children, with and without ADHD symptoms, through the application of a pediatric version of the attentional networks test (ANT). Our hypothesis is that preschoolers with ADHD symptoms have less developed attentional networks than children without ADHD symptoms.

The question that arises from the first objective and hypothesis is what strategy could be used to improve attentional networks in children with symptoms of ADHD?
Currently there are pharmacological and non-pharmacological treatments for ADHD. As the medication of children under 6 years of age is highly restricted, we searched for a non-pharmacological treatment that could contribute to the improvement of attention in children with early symptoms of ADHD. Cognitive and Working memory training has been shown to have favorable results for the reduction of some ADHD symptoms in the children, adolescent and adult population (Cortese et al., 2014; C. T. Green et al., 2012; Klingberg et al., 2005; Klingberg, Forssberg, & Westerberg, 2002, Kollins, et al., 2020, Peñuelas-Calvo, et al., 2020). In terms of brain activity, working memory training has been shown to produce that prefrontal and superior parietal cortex increase hemodynamic activity after working memory training (Olsen et al., 2004). These brain regions also participate in the activation of attentional networks (Fan et al., 2005).

Despite the benefits of working memory training in people with ADHD, it is unknown whether changes in regions of the brain that involve working memory can lead to improvements in attention. More specifically, it is unknown whether improvements in brain regions from working memory training can produce improvements in cognitive processes that share those same brain regions, such as orienting and executive attentional networks. For this reason, we propose in this thesis as the second research objective, to study the role of working memory training and evaluate whether it produces benefits in the attentional networks in children with typical development and with early symptoms of ADHD.

To test our hypothesis, we designed and completed a double-blind study with 56 preschool children (mean age 67 months), 29 typically developing and 27 with early symptoms of ADHD. All preschoolers carried out a first evaluation session in which IQ and working memory were evaluated. Then, parents (or caregivers) and teachers completed the Spanish and short version of the Conners test 3rd Edition, in order to identify the presence of symptoms of ADHD. The total number of participants for each group was divided into two groups: intervention group and control group. The intervention group participated in working memory training and the control group carried out regular academic activities. Specifically, the experimental design consisted of carrying out a computer-based intervention of working memory training (3 times a week for 4 weeks) and to evaluate the performance of working memory and attentional networks both before and after the intervention. Working memory performance was evaluated using the Automated Working Memory Assessment (AWMA; Alloway et al., 2008). Attentional networks were evaluated using the Attentional Network Task (ANT; Abundis-gutierrez et al., 2014) during an electroencephalographic recording.

Our study showed that children with early symptoms of attention deficit and hyperactivity disorder have a decrease in modulation of the orienting and executive attentional networks, but not the alerting network, in comparison with typical development children. Additionally, we found that working memory training can improve the modulation of executive attentional network in children with early symptoms of attention deficit and hyperactivity disorder, but not in typically developing children. No improvements were found in alerting or orienting attentional networks in children with or without early symptoms of ADHD. These results show that children with early symptoms of ADHD already present difficulties in the attentional networks described in children and adults diagnosed with ADHD. This result highlights the need to focus future research on what is happening at the brain level before the diagnosis of ADHD, and the relevance of applying early interventions in order to avoid deviation in the course of typical development. Additionally, we suggest working memory training as a method to improve some difficulties in brain modulation of attention in children with early symptoms of ADHD.

3. BACKGROUND

Attention is an essential mechanism that makes it possible to select the relevant information present in the environment considering the individual's goals and expectations or the saliency and the potential danger posed by stimuli. Even though a consensual definition of the term *attention* has yet to be advanced, Michael Posner and Steven Petersen, in their well-known article *The Attention System of the Human Brain* (Posner & Petersen, 1990), collected the information available at the time and argued that attention is a neuro-anatomical system independent from other cognitive functions but which can interact with them. After the publication of this article, great efforts have been made to understand the origin and functioning of attention (Petersen & Posner, 2012). Nowadays, three attentional networks have been described: alerting, orienting, and executive network. These networks are involved in several processes, such as the maintenance of alert states, information selection, and the control of them (Fan & Posner, 2004; Posner, et al., 2014).

3.1 Alerting network

The alerting network makes it possible to regulate the state of vigilance in which the organism is engaged. Two types of alerting have been described: tonic alertness and phasic alertness. Tonic alertness makes possible the cognitive control of wakefulness and arousal. This general vigilance system can be affected by tiredness, the passage of time during the day, or even by the demands that characterize the task (Casagrande, et al., 2006). For its part, phasic alertness makes it possible to regulate the state of preparedness via signals. One way of studying phasic alert is to use a warning signal before a target stimulus, which generates a change of state that fosters detection and response in an expected task (Petersen & Posner, 2012). The alerting network has been associated with frontoparietal activation, predominantly in the left hemisphere (Fan, et al., 2005). When the alerting network is activated by signals originating in the external medium, activity is observed in the locus coeruleus, with the alert being modulated via norepinephrine (Aston-Jones & Cohen, 2005; Witte & Marrocco, 1997).

3.2 Orienting network

The Orienting network makes it possible to select relevant information according to the individual's goals or to its degree of saliency or dangerousness. In the selection process, attention can be oriented towards stimuli either voluntarily or involuntarily. Voluntary orientation depends on the goals and objectives of people, and makes it possible to orient attention in a top-down manner. It is composed of a dorsal attentional network which includes the frontal eye field, the intraparietal sulcus, and the superior parietal lobule (Petersen & Posner, 2012; Fan, et al., 2005; Thompson, et al., 2005) and is modulated by the cholinergic system (Fan & Posner, 2004). In the other hand, involuntary orientation depends on the properties of stimuli and makes is possible to orient attention in a bottom-up manner. It is composed of a ventral attentional network which includes the temporoparietal junction and the frontal-ventral cortex (Petersen & Posner, 2012).

3.3 Executive attentional network

The executive network refers how higher-order cognitive processes enable attentional control for directing behavior towards goals, regardless of the events that can distract the individual from the objective. It is necessary in situations that require planning or decision making (Fan & Posner, 2004). One way of studying executive attention is through the flanker test, which presents congruent (> > > > >) and incongruent targets (> > < > >); afterwards, the individual must indicate the direction of the central object, with response time and error rate being the indicators of executive control. The activation of the executive attentional network is associated with activity in the anterior cingulate gyrus and the prefrontal cortex (Botvinick, et al., 2001; Posner, et al., 2014, Fan, et al., 2005) and is modulated by the neurotransmitter dopamine (Green et al., 2008).

3.4 Attentional Network Test

The Attentional Network Test (ANT) makes it possible to evaluate the efficiency of each attentional network, and is a combination of flanker (Eriksen & Eriksen, 1974) and cued reaction time tasks (Posner, 1980). In this test, a target stimulus is presented which can be neutral, congruent, or incongruent, and the subject must state if the central arrow is pointing to the left or the right. Before the appearance of the target stimulus, cues will appear that may or may not predict where the arrows will come into view. These signals can be central, double, spatial, or no cue. Both the central and the double signals do not predict where the target stimulus will appear; in contrast, the spatial signal does predict where it will come into view (Fan, et al., 2002). The evaluation of each network is carried out by subtracting the means of the subject's reaction times (RT); for example, the alerting network is evaluated by comparing the RT for the double cue condition from the RT for the no cue condition. The orienting network is evaluated by comparing the RT for the spatial condition from the RT for the no cue condition. The conflict network is evaluated by comparing the RT for the congruent condition from the RT for the incongruent condition.

3.5 Neural correlate of attentional networks

During the ANT, a negative displacement of the ERP in posterior electrodes between 300 and 400 ms after the appearance of an alerting cue (Fan, et al., 2007) and an increase in the amplitude of posterior N1 between 150 and 250 ms, with this amplitude depending on the saliency of the stimulus, which suggests that N1 is modulated in a bottom-up manner (Neuhaus, et al., 2010). When auditory alert signals (tones) are applied, the N1 component can also be distinguished; in addition, it can be observed that, after the appearance of the tone in the electrode Fcz, the generation of evoked potentials P1 and P2 occurs, followed by the generation of a potential known as contingent negative variation (CNV), which has two phases: an early one between 400 and 600 ms, which represents anticipation, and a late one after the appearance of the target, which represents the motor effect (Abundis-Gutiérrez, et al., 2014). Regarding cerebral oscillations, when a visual alerting cue is presented, decreased activity is observed in the theta, alpha, and beta bands between 200 and 450 ms after the appearance of the cue (Fan, et al., 2007).

Studies that have investigated the electrophysiological correlate of the orienting of visuospatial attention have found an early posterior negativity between 200 to 400 ms or N1 (Fan, et al., 2007; Neuhaus, et al., 2010) and a more scattered positivity with less amplitude in the posterior area between 400 and 700 ms or P3 (Abundis-Gutiérrez, et al., 2014; Fan, et al., 2007; Talsma, et al., 2005). The increase in amplitude of N1 and the decrease in amplitude of P3 when orientation signals are presented are thought to facilitate early visual processing and evaluation processes, respectively (Abundis-Gutiérrez, et al., 2014). Concerning cerebral oscillations, an increase in gamma band activity is observed approximately 200 ms after the appearance of an orientation signal (spatial cue) which indicates the location of the target (Fan, et al., 2007).

Among the multiple functions attributed to executive attention, the ANT through the flanker test, can measure response inhibition. This aspect of executive attention has been a key object of study in the last decade, and has been correlated with the appearance of the evoked potential P3 or positivity which appears at 300 ms and which has two subcomponents: frontal P3a, provoked by novel stimuli, and temporoparietal P3b, which reflects cortical activity associated with the processing of incoming sensory information (Neuhaus, et al., 2010; Polich, 2007). It has also been observed that the frontoparietal N2 component between 200 and 400 ms displays greater amplitude when an incongruent stimulus is presented, which represents a greater effort to suppress relevant information (Abundis-Gutiérrez, et al., 2014). Regarding cerebral oscillations, after the appearance of incongruent flanks in comparison with congruent ones, an early increase is observed in gamma band activity along with a late decrease in the beta and low gamma bands. In addition, before the response, a decrease is observed in all frequency bands; after the response, all frequency bands increase (Fan, et al., 2007).

3.6 Development of attentional networks

Research on attention development indicates that the alerting, orienting, and executive attentional networks are present in childhood, but that their functions and connectivity change during development (Posner, Rothbart, & Rueda, 2014). From the behavioral point of view, studies on attention development in childhood reveal that, both in children and adults, the alerting, orienting, and executive attentional networks function independently (Rueda, et al., 2004). In addition, it has been advanced that response inhibition, associated with executive attention, may develop less markedly than response activation (Band, et al., 2000). Behavioral evidence obtained through ANT indicates that executive network scores stabilize at age 7, in contrast with alerting network scores, which become stable after age 10. On the other hand, the orienting network remains relatively unchanged during development because attentional changes in response to exogenous signals differ only slightly between children and adults; instead, it is voluntary attention that is thought to improve with age (Rueda, et al., 2004).

Abundis-Gutiérrez ,et al. (2014), in their study of the neural mechanisms that underlie the development of attentional functions during childhood, used electroencephalography while conducting a version of the ANT for children. In this study, participants were grouped into four age ranges (4-6, 7-9, and 10-13 years and adults) whose attentional networks were compared with each other, which revealed differences between children and adults in terms of the activation of the three attentional networks. Younger children seem to have less early alerting cue processing than children aged 10 to 13 and adults, a situation that is revealed by the low amplitude of components N1 and P2. In addition, less amplitude was observed for N1 and P3, which suggests less processing of orientation signals. Regarding to executive network does not seem to be fully mature at 13 years old, a situation that is suggested by the lack of modulation associated with component N2.

3.7 Attentional deficit hyperactivity disorder

Attentional deficit hyperactivity disorder (ADHD) is considered to be a neurological development disorder characterized by a lack of attention and/or hyperactivity-impulsiveness which can manifest itself in contexts such as school, the home, or the workplace (American Psychiatric Association, 2013). Therefore, according to the DSM-V, people can suffer from ADHD predominantly inattentive (ADHDin), hyperactive/impulsive (ADHDhyp), or a combination of both (ADHDcom). This attentional disorder is highly prevalent in the population, and affects 7% of school-age children and adolescents (Thomas et al. 2015). According to the study by Vicente, et al. (2012), the prevalence for ADHD in Santiago de Chile is 12.6%. This value is much higher than the world prevalence that indicates a rate of 5.3%. According to the epidemiological study by De la Barra et al. (2015), the national prevalence of ADHD in children and adolescents in Chile is 10% and the subtype with the highest prevalence is hyperactive / impulsive, without gender differences.

ADHD generates academic as well as social difficulties which have an impact on individuals' adult lives and those of their families (Barkley, 2002; Harpin, 2005). According to the Unifying Theory of ADHD proposed by Barkley (1997), this disorder in characterized by a behavioral inhibition deficit, which depends on four executive functions: working memory, self-regulation of affect-motivation-arousal, internalization of speech, and reconstitution (behavioral analysis and synthesis). Although the etiology of this neuropsychological disorder is heterogeneous (Sonuga-Barke, 2002), it is thought that the executive network deficiencies of ADHD sufferers have a relevant role in the origin of their lack of attention (Castellanos et al., 2006; Sonuga-Barke, 2003).

Based on the paradigm of attentional networks, differences have been described in the alerting and the executive networks, but not in the orienting network, when comparing children with ADHD and typical development (TD) (Berger & Posner, 2000; Johnson et al., 2008; Konrad et al., 2006; Mullane et al., 2011). An electrophysiological study conducted with children aged 8-10 which compared the performance of participants with and without ADHD while conducting an ANT (Kratz et al., 2011), reveals that children with ADHD compared with those who suffer from TD display more variable response times during the ANT, as well as cue-P3 and target-P3 amplitude. These results appear to support the hypothesis that ADHD sufferers have deficiencies in orienting modulation and executive attention. Additionally, in terms of hemodynamic activity, it has been suggested that people with ADHD are affected by alerting, orienting ant executive attentional networks (Konrad, et al., 2006).

3.8 Working memory training and ADHD

Working memory is a cognitive function that allows the maintenance and manipulation of information for short periods of time, during the performance of a specific task. Lesion studies have associated WM with the prefrontal cortex (PFC) and this link has been confirmed by electrophysiological recordings that revealed neural correlates of WM in the PFC of monkeys (Constantinidis & Klingberg, 2016).
FMRI studies have associated working memory with prefrontal cortex, inferior and middle temporal cortex, and superior parietal regions (Fang et al., 2016, Emch et al., 2019). Specifically dorsolateral prefrontal cortex has been related to maintenance

and manipulation, and the anterior cingulate cortex with executive control and error detection (Chai et al., 2018). It is important to emphasize that the regions involved in the executive attention system include midline frontal structures such as the anterior cingulate cortex and the lateral prefrontal area (Botvinick et al., 2001, Fan et al., 2005). The functions associated with the executive attentional network include conflict resolution and response inhibition, in which the anterior cingulate cortex has a key role; in addition, the parietal areas activated during working memory tasks (Bush, et al., 2000) are regions shared with the orienting attentional network (Fan et al., 2005).

Because working memory is a central cognitive function for learning, memory, and performing daily life tasks, attempts have been made to improve its performance through cognitive training. Several studies have shown that training working memory allows improving the performance of trained tasks and other different tasks that require working memory. However, it is not known whether working memory training can produce improvements in cognitive functions other than those directly related to working memory. In terms of brain activity, working memory training has been shown to produce that prefrontal and superior parietal cortex increase hemodynamic activity after working memory training (Olsen et al., 2004).

Sonuga-Barke (2014) proposes that executive deficits are a measure of causal risk of ADHD, and for this reason, the training of working memory should reduce ADHD symptoms. Previous research has provided evidence supporting this notion through the application of several working memory training programs such as Cogmed, Cognifit, Jungle Memory, and N-back Training (Cortese et al., 2014; C. T. Green et al., 2012; Klingberg et al., 2005; Klingberg, Forssberg, & Westerberg, 2002). Klingberg et al. (2002 and 2005), after carrying out a working memory training program (Cogmed) for children with ADHD aged 7 - 15, observed a performance improvement in working memory tasks, considering both trained and untrained aspects of WM, with the latter being regarded as a close transference effect; consequently, they suggest that the training program may be clinically useful for reducing ADHD symptoms. Considering several studies, Spencer-Smith & Klingberg (2015) conducted a systematic review and a meta-analysis to determine whether the WM training method that they employed (Cogmed) improved attentional problems in daily life. The analysis revealed a significant effect of training on inattention in the daily lives of children and adults with and without ADHD. The studies that involved a follow-up assessment showed that this effect persisted over time.

4. HYPOTHESES AND OBJECTIVES

4.1. Hypotheses

4.1.1. General Hypothesis

Preschoolers with ADHD symptoms have less developed attentional networks than children without ADHD symptoms. Such differences can be attenuated through working memory training.

4.1.2. Specific Hypotheses

1. There are behavioral and electroencephalographic differences between children with and without ADHD symptoms in pre-school stage.

2. The plasticity induced by working memory training in preschoolers with and without ADHD symptoms makes it possible to attenuate the symptoms and improve performance in attentional tasks compared with children who do not receive training.

4.2. Objectives

4.2.1. General Objective

To study, in preschoolers with and without ADHD symptoms, the state of the alerting, orienting, and executive attentional networks, and to determine the effects of a working memory training program on these attentional networks.

4.2.2. Specific Objectives

4.2.2.1. Objective Nº1: To determine the state of attentional networks in children aged 5 years, with and without ADHD symptoms, through the application of a pediatric version of the attentional networks test (ANT).

> **1.** To compare ANT performance by attentional group (with and without ADHD symptoms) in order to establish similarities and differences at the behavioral level.
>
> **2.** To establish the neural correlate according to ANT performance for attentional groups through the analysis of event-related potentials (ERP) associated with each attentional network.

4.2.2.2. Objective Nº2: To determine the immediate effects of a working memory training program on the attentional networks of preschoolers with and without ADHD symptoms.

> **1.** To determine the behavioral effects of the working memory training program on the ANT performance of preschoolers with and without ADHD.

2. To establish the neural correlate according to ANT performance before and after the working memory training program for each group through the analysis of event-related potentials (ERP) associated with each attentional network.

5. PARTICIPANTS AND METHODS

5.1. Subjects

Fifty-six, right-handed, Spanish speaking preschool children (mean age = 67,05 months; SD = 5,46; range 52 to 76 months; 52% female) participated in this study. According to what their caregivers and teachers reported, all participants had normal hearing and corrected-to-normal vision, and reported neither current nor past neurological and/or psychological conditions. All procedures, including EEG records and interventions, were carried out in three schools with a high vulnerability index, above 75% according to the classification of Ministry of Education of Chile. Informed consents were obtained from all parents or caregivers and teachers. Before any procedure the verbal assent of the participating children was requested. All procedures were approved by the ethics committee of the Pontificia Universidad Católica de Chile.

The fifty-six preschoolers carried out a first evaluation session in which IQ and working memory were evaluated (Table Nº1). The IQ was evaluated in order to establish that there were no differences for this parameter between groups that could explain the results obtained later. This index was calculated as a measure of the WISC-IV Digits Backward subtest. Then, parents (or caregivers) and teachers completed the Spanish and short version of the Conners test 3rd Edition, in order to identify the presence of symptoms of ADHD. This test has been shown to have high levels of reliability applied to the Chilean population (Ocampo, 2018). The applied version of this test corresponds to a form in which 39 behaviors are indicated and the caregivers and teachers must answer how often it has occurred in the last month according to a scale from 0 to 3 where 0 is that it never occurred and 3 if it happened very often. Then, the data is processed with the software provided by the developer of the test (MHS / Conners 3®), in which the ADHD indices are obtained according to the responses of caregivers and teachers. Twenty-seven children had symptoms of ADHD and twenty-nine had typical development, according to the following criterion:

> **a) Symptoms of Attention Deficit Hyperactivity Disorder (ADHD-S):** Score over 65 for inattention and / or hyperactivity, consistent between parents and teachers.
>
> **b) No symptoms of ADHD or Typical development (TD):** Score lower than 65 for inattention and / or hyperactivity, congruent or incongruent between parents and teachers.

The ADHD index was calculated by averaging the indices of inattention and hyperactivity of parents and teachers (Table Nº1). Regarding the subtypes of ADHD symptoms, 59.3% of the children presented symptoms of a combined subtype, 22.2% only hyperactivity and 18.5% only inattention.

	TD Children	ADHD-S Children	
n	29	27	
Females	12	17	
	Mean ± *SD*	**Mean ± *SD***	***t* value (*p* value)**
Age (months)	67 ± 4,53	67,11 ± 6,40	0,08 (0,94)
IQ	3,20 ± 0,61	3,22 ± 0,57	0,09 (0,92)
ADHD index	52,75 ± 7,87	73,36 ± 7,41	10,06 (< 0,0001)

Table Nº1: Characteristics of the participating children according to objective Nº1.

In order to achieve the objective Nº 2, the total number of participants for each group was divided into two groups: Intervention group and Control group (Table Nº2). The intervention group participated in working memory training and the control group carried out regular academic activities. ANOVA analysis showed that there are no differences by symptoms (ADHD-S, TD) or group (Intervention, control), for age and IQ. There were also no differences within group (intervention, Control) in ADHD index, verbal WM and visual-spatial WM. However, there are differences for ADHD index (F(5,27) p = 0,06) between symptoms (ADHD-S and TD).

	TD Children		ADHD-S Children	
	Control	Intervention	Control	Intervention
n	14	15	13	14
Females	6	6	9	8
Age (months)	66,5 ± 3,45	67,46 ± 5,43	66 ± 5,88	68,14 ± 6,9
IQ	3,14 ± 0,66	3,26 ± 0,59	3,15 ± 0,37	3,28 ± 0,72
ADHD Index	54 ± 7,43	51,58 ± 8,35	75,96 ± 6,87	70,94 ± 7,29
Verbal WM	101,64 ± 14,62	99,93 ± 15,82	92,69 ± 12,93	86,92 ± 13,3
Visuo-spatial WM	110 ± 9,24	105,86 ± 14,62	102,30 ± 13,33	94,07 ± 9,2

Table 2: Characteristics of the participating children according to objective Nº2.

5.2. Experimental Design and Procedure

The experimental design consisted of carrying out a computer-based intervention of working memory training and to evaluate the performance of working memory and attentional networks both before and after the intervention. Working memory performance was evaluated using the Automated Working Memory Assessment (AWMA; Alloway et al., 2008). Attentional networks were evaluated using the Attentional Network Task (ANT; Abundis-gutierrez et al., 2014) during an electroencephalographic recording. The details of each procedure is explained below.

5.2.1. Working memory training

The computer-based intervention comprised twelve 30-min sessions (three per week) in which the children played with a WM training program. The intervention program used is the same one used by Rojas-Barahona et al. (2015), and consisted of four activities for stimulating phonological working memory and four for visuospatial working memory. Each activity was a game that began with an introduction with instructions, followed by a period of practice to ensure that children understood what to do during the game, and finally five trials of the same activity. At the end of both trial and activities there was positive visual and auditory reinforcement, and only at the end of the activities, the number of points obtained was indicated and then moved on to the next activity. If the child could not complete the activity in a time span of 15 minutes, the program automatically proceed to the next activity to ensure that each session exposed the child to the same amount of time of phonological and visuospatial stimulation. If the child fails to answer an activity, the instruction is repeated until the correct answer is provided. The intervention had three levels of complexity that increased through the different sessions by expanding the number of elements to remember and by expanding the number of objects from which the objects must be chosen to generate the answer.

5.2.2. Automated Working Memory Assessment (AWMA)

Before and after training, each child's short-term and working memory ability was assessed using the short Spanish version of Automated Working Memory Assessment (AWMA; Alloway et al., 2008). The short version includes four tasks, two for verbal memory and two for visuospatial memory. Verbal short-term memory was assessed using a digit recall task in which the child listens to a digit sequence and tries to remember its correct order. Verbal working memory was assessed using a listening recall task in which the child listens to a series of oral statements and must verify whether they are true or false while also remembering the final word of each. Visuospatial short-term memory was assessed using a dot matrix task in which the child is shown the position of a red dot in a series of 4 × 4 matrices and must remember its position by pointing to the correct square in an empty matrix shown on the computer screen. Visuospatial working memory was assessed using a spatial recall task in which the child looks at a picture with two asymmetrical figures, with the one on the right displaying a red dot on one of its sides. The figure may be rotated.

The child must identify whether the figure on the right is the same as the one on the left or its opposite and indicate in which of three possible positions the red dot was.

For each of the four tasks, the program provides a raw score and an equivalent percentile according to the age of the child. For the analysis of this study, the percentile value was used.

5.2.3. Attentional network task (ANT)

Before and after training all participants performed a child version of the ANT (Abundis-Gutierrez, 2014) during an electroencephalographic recording. In this task, the participants had to respond in which direction a target or central fish is oriented. This target could be preceded by an alerting cue that predicted when the target would appear and / or by an orientating cue that predicted or not where the target would appear. All participants completed one o more practice blocks of 12 trials, until it was clear that the instructions were fully understood. The practice block was run as many times as necessary until it was clear that the instructions were fully understood. After the practice period, the participants carried out the task that consisted of four blocks of 36 trials each. The sequence of events in each trial is displayed in figure Nº1. Each trial started with a fixation point in the center of the screen of variable duration, which was randomly selected between 400 and 1600 ms. In half of the trials an alerting cue appeared, a 2000 HZ sound of 100 ms long. Afterwards, an orienting cue (an asterisk), could appear above or below the fixation point for 100 ms. The orienting cue could predict where the target would appear (valid cue), it could not predict where the target would appear (invalid cue), or it could not present the asterisk signal (no cue). Each of these three orienting cues appeared in one-thirds of the trials. Finally, a row of five fish located above or below the fixation cross was presented horizontally. Fish flanking the central fish could point in the same direction (congruent target) or in the opposite direction (incongruent target). Half of the trials were congruent and the other half incongruent. Participants were asked to indicate the direction of the center fish by pressing the right or left button on a keyboard as quickly and accurately as possible. The target was presented until a response was given or up to 2500 ms. After answering a feedback appeared for 500 ms showing a happy fish (blowing bubbles) and saying "wooh" if the answer was correct and showing a sad fish (tears coming down the eye) and saying "oh" if the answer was incorrect. To make the task more child-friendly, they were told that the fish in the middle was hungry and that they should feed it by pressing the corresponding button. Response times and accuracy were recorded to determine performance during the task.

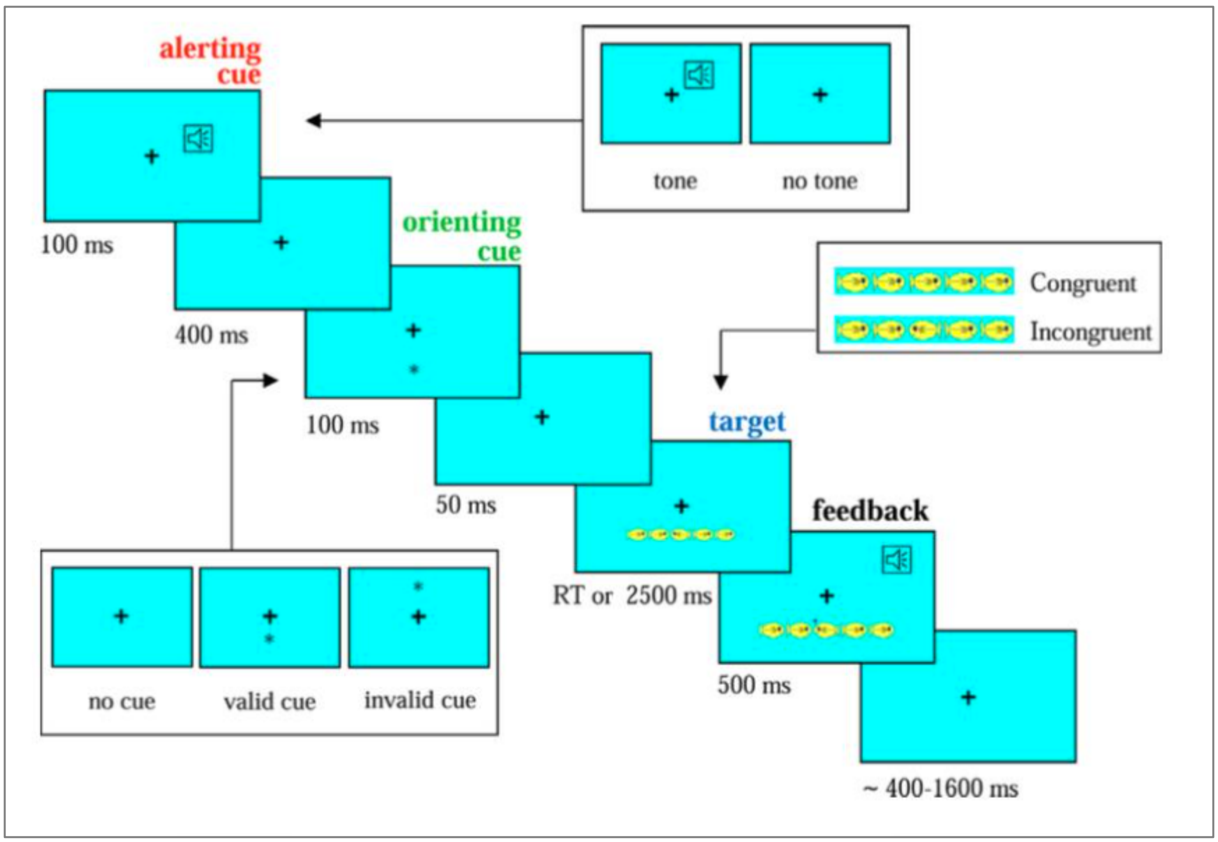

Figure Nº1. Sequence of events in each trial. Each trial started with a fixation cross followed by one of two alerting cues, then one of three orienting cues and finally one of two target conditions. The structure of the trial is based on Abundis-Gutierrez (2014).

5.3. EEG Data Acquisition

The acquisition of electroencephalographic data was performed in the participating children's schools with NuAmps Neuroscan equipment with 40-channel. The sampling rate was 1KHz with an impedance less than 5 kΩ and referenced to mastoid. During the breaks in the EEG session, electrode impedance levels were checked and reduced if necessary.

5.4. Data Analyses

5.4.1. Behavioral Data Analyses

The behavioral variables collected for each trial were percentages of correct answer (accuracy) and reaction time (RT). These variables were obtained for the global performance of the task and for each alert condition (tone, no tone), orientation (valid, invalid, no cue) and executive (Congruent and incongruous). Group differences for each attentional network were assessed with one-way ANOVAs using SPSS software (IBM SPSS Statistics 20). Additionally, a 2 (Group: TD, ADHD-S) x 2 (Alerting cue: Tone, No tone) x 3 (Orienting cue: Valid, Invalid, no cue) x 2 (Target congruency: Congruent, incongruent) ANOVA with median accuracy as dependent measures were carried out.

In order to achieve the objective Nº 2, a series of one-factor ANOVAs was carried out to determine the differences in working memory performance for each session (pre and post training) and group (ADHD and TD) using SPSS software (IBM SPSS Statistics 20). Additionally treatment (Intervention and control) differences for each group (ADHD-S and TD) per attentional network were assessed with a series one-way ANOVAs. Moreover, a 2 (treatment: Intervention, control) x 2 (Session: Pre and post training) x 2 (Alerting cue: Tone, No tone) x 3 (Orienting cue: Valid, Invalid, no cue) x 2 (Target congruency: Congruent, incongruent) ANOVA with median accuracy as dependent measures were carried out for each group (ADHD-S and TD).

5.4.2. EEG Data Analyses

The pre-processing of the continuous signal was performed on matlab (EEGLAB) using a high pass filter of 0.5 Hz and a low pass filter of 30 Hz. Component removal was performed through an independent component analysis (ICA) and three types of segmentation were applied (one per attentional network). For the alerting network, data were segmented into alerting cue-locked, -200 ms to 800 ms around presentation of the alerting cue. For the orienting and executive attentional networks, data were segmented into target cue-locked, -200 ms to 1000 ms around presentation of the target. Bad channels were rejected and replaced by interpolation from neighbor channels. A visual inspection of the segmented signal was performed to manually remove artifactual segments. Segment for correct responses were averaged across conditions to obtain the ERPs for each participant. The grand average ERPs was obtained for each group and / or session, and the effects of each attention network were calculated through a paired or unpaired t-test (as appropriate), with or without FDR correction, where compares the amplitude per condition for each time point.

6. RESULTS

6.1 Objective Nº1

6.1.1 Behavioral outcomes

According to the global accuracy values of the ANT task, TD children show a higher percentage of correct answers than children with early symptoms of ADHD (t-test, p=0,013) (Table Nº3). Although the average reaction time is slightly shorter in the TD group, no significant differences were found in the comparison between groups (Table Nº3). No correlation was found between index of ADHD and global accuracy (T = -1,53 ; p-value = 0,13; Cor -0,20) nor reaction time (T = -0,19; p-value = 0,84; cor = -0,02).

The comparison of accuracy between conditions for the same attentional network showed that TD children decrease the accuracy in the conditions of higher attentional demand (Figure Nº2 A), that is, they present lower accuracy for the non-tone condition in the alerting network, the invalid condition for the orienting network and the incongruent condition for the executive attentional network. However, a significant difference was only found between conditions in the executive network when comparing the congruent condition with the incongruent condition (t-test, p=0,003). Similar results were found when comparing the accuracy of ADHD-S children (t-test, p=0,0005) (Figure N2º B).

To compare the performance in each network, three different 2x2 ANOVA analysis were carried out. For reaction time in the alerting network, differences were found per conditions (Tone and no tone) (F(3,9) = 0,06; p = 0,053) but not interaction for group and conditions ((F(0,88) = 0,016; p=0,352) .

For accuracy in the alerting network differences were found per conditions (Tone and no tone) ($F(5,749) = 0,09$; $p = 0,02$) and interaction for group and conditions (($F(4,36) = 0,075$; $p=0,043$). For reaction time in the orienting network, differences were found per conditions (Valid and Invalid) ($F(11,9) = 0,18$; $p = 0,001$) but not interaction for group and conditions (($F(0,01) = 0$; $p=0,971$).

For accuracy in the orienting network no differences were found per conditions (Valid and Invalid) ($F(1,11) = 0,01$; $p = 0,29$) nor interaction for group and conditions (($F(0,87) = 0,16$; $p=0,355$). For reaction time in the executive attentional network differences were found per conditions (Congruent and Incongruent) ($F(30,7) = 0,36$; $p = 0,000$) but not interaction for group and conditions (($F(0,38) = 0,007$; $p=0,539$).

For accuracy in the executive attentional network, differences were found per conditions (Congruent and Incongruent) ($F(49,82) = 0,04$; $p = 0,000$) but not interaction for group and conditions (($F(2,716) = 0,04$; $p=0,105$).

A 2 (Group: TD, ADHD-S) x 2 (Alerting cue: Tone, No tone) x 3 (Orienting cue: Valid, Invalid, no cue) x 2 (Target congruency: Congruent, incongruent) ANOVA with median accuracy as dependent measures were carried out. The main effects for alerting ($F(5,9) = 0,099$; $p = 0,018$) and execute attentional network ($F(51,86) = 0,49$; $p = 0,000$) were significant, but not for the orienting network ($F(0,44) = 0,016$; $p = 0,652$). Additionally, There was no interaction between group and alerting ($F(3,97) = 0,068$; $p = 0,051$), group and orienting ($F(1,79) = 0,063$; $p = 0,17$), or group and executive attentional network ($F(2,70) = 0,048$; $p = 0,106$). However, interaction was found between Alerting and executive network ($F(4,97) = 0,08$; $p = 0,030$), orienting and executive network ($F(3,79) = 0,12$; $p = 0,029$), and alerting, orienting, executive network and group ($F(3,73) = 0,123$; $p = 0,03$).

	TD	**ADHD-S**	**t-value (p-Value)**
Accuracy	0.798 (0.12)	0.69 (0.17)	**-2.55 (0.013)***
Reaction time	1419 (201)	1423 (208)	0,06 (0,951)

Table Nº3 Comparison of global reaction times and global accuracy between typically developing children and children with early symptoms of ADHD. The numerical values in the table correspond to the average of the accuracy and reaction time of the complete task. the values in parentheses represent the standard deviation. TD: typical development group ; ADHD-S: group with early symptoms of attention deficit and hyperactivity.

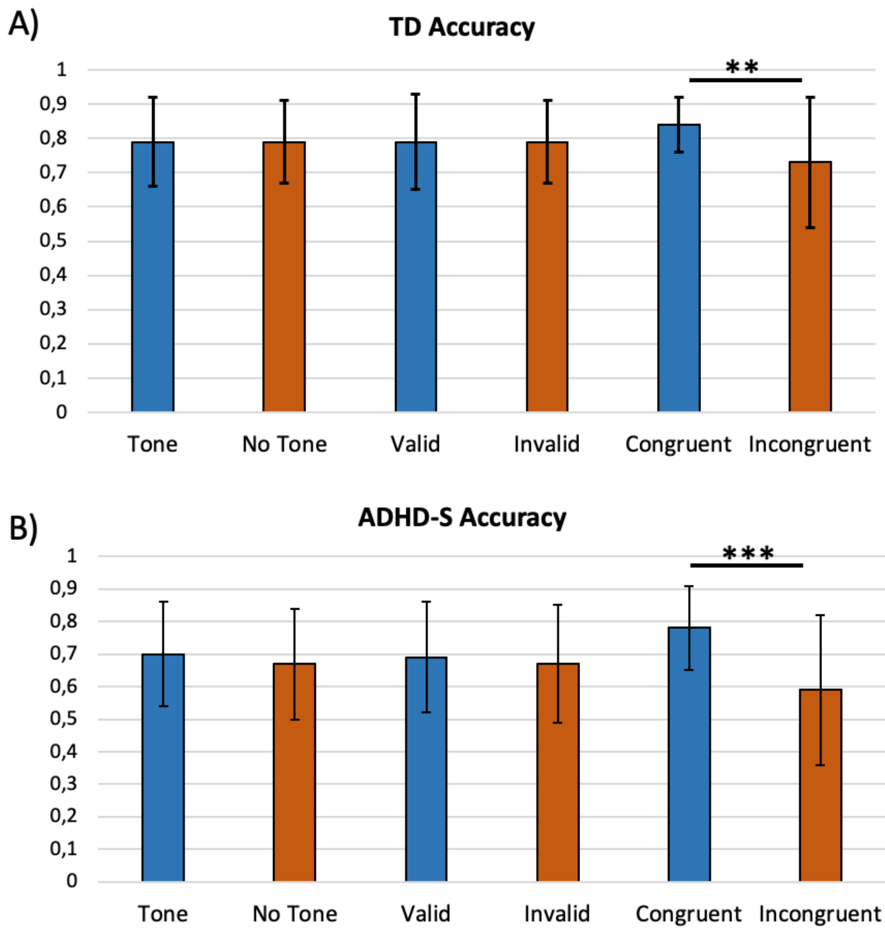

Figure Nº2 Comparison between conditions of global accuracy in typically developing children and children with early symptoms of ADHD. The graphs represent the percentage of correct answers (accuracy) for each attentional condition for typically developing children or TD group (A) and children with early symptoms of ADHD or ADHD-S group (B). Error bars represent the standard deviation. The asterisks represent the level of significance in the comparison.

6.1.2 EEG outcomes

6.1.2.1 Typically developing children and children with early symptoms of ADHD show an alerting network effect.

Cue-locked ERP per alerting condition (tone and no tone) for each group (TD and ADHD-S) are presented in figure Nº3. In both groups, 4 characteristic components are observed in the alerting network, specifically in the tone condition, P1 at 100 ms, N1 at 150 ms, P2 at 200 ms and CNV between 300 and 600 ms. The CNV component in CZ channel shows the effect of the alerting network, that is, a significant difference between tone and non-tone conditions. In typical development group (TD), the effect of the alerting network ranges between 246 ms and 554 ms, with an average significance p-value of 0.0054 (paired t-test with FRD correction for multiple comparisons). In attentional deficit and hyperactivity disorder symptoms group (ADHD-S), the effect of the alerting network ranges between 242 ms and 437 ms, with an average significance p-value of 0.0157 (paired t-test with FRD correction for multiple comparisons). Differences between groups for each condition were not found. Topographic maps show a typical frontoparietal distribution of the CNV component (see figure Nº4). The alerting effect can be observed throughout the entire distribution of the CNV component and not just in CZ electrode.

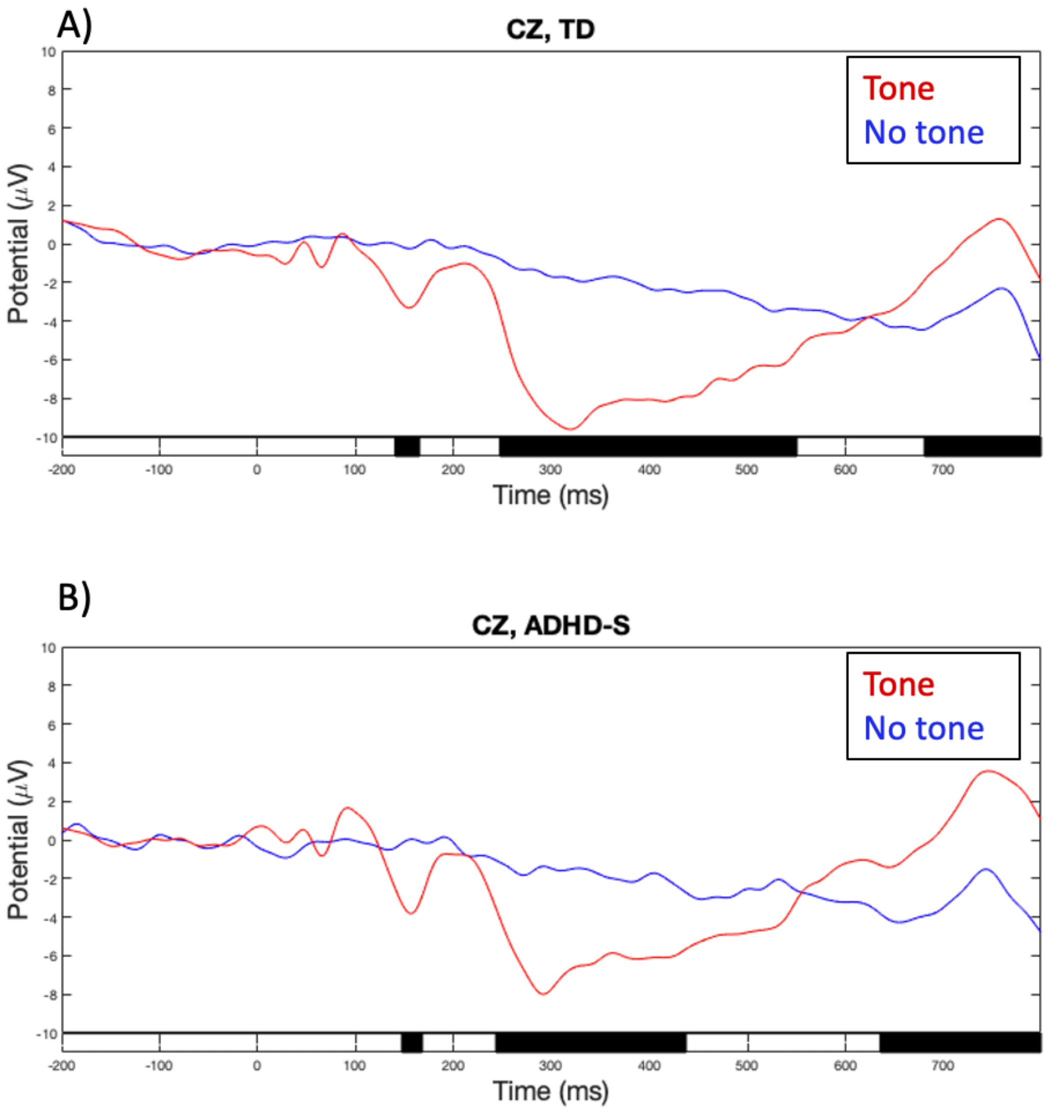

Figure Nº3: Alerting effects on electrophysiological data. Graphs representing cue-locked ERPs on the CZ Channel for each condition and group. In both graphs the red line represents tone condition and the blue line no tone condition. The upper graph (A) represents alerting ERP to TD or typ
ical development group, and the lower graph (B) represents alerting ERP to ADHD-S or attention deficit and hyperactivity disorder symptoms group. The black bar below the X axes indicate time windows with significant differences between conditions ($p < 0.05$) by t-test corrected for multiple comparisons using the false discovery rate procedure.

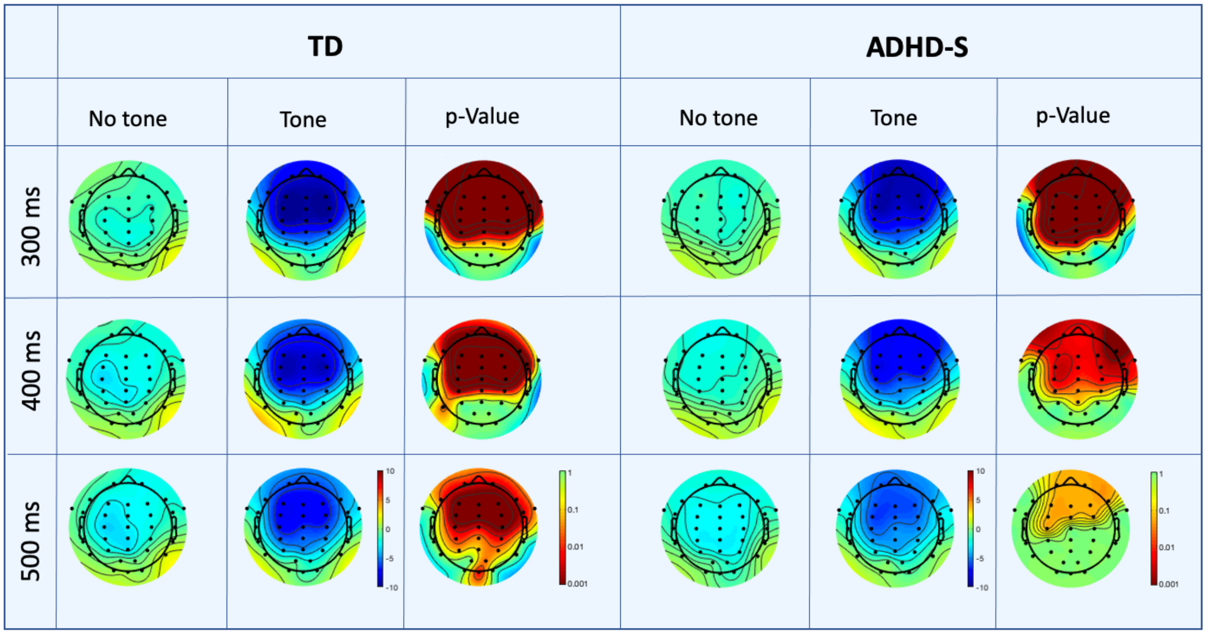

Figure Nº4: Alerting effect on topographic maps per group for CNV component. Graphs representing amplitude for ERPs on topographic maps for each condition (No tone and tone) and group (TD and ADHD-S) at three different times (300, 400 and 500 ms). In tone and non-tone columns, the distribution of the amplitude of the evoked activity is represented in a range between -10 **µV** (blue color) and 10 **µV** (red color). The P-Value columns shows the level of significance when comparing both conditions (No tone and Tone), and the color bar shows the scale in the levels of significance, from $p = 1$ for the green, $p < 0.05$ for the light red and $p < 0.001$ for the intense red color, by t-test corrected for multiple comparisons using the false discovery rate procedure.

6.1.2.2 Typically developing children show an orienting network effect and children with early symptoms of ADHD do not.

Target-locked ERP per orienting condition (Valid and Invalid) for each group (TD and ADHD-S) are presented in figure Nº5. In both groups, 3 characteristic components are observed in the orienting network, P1 at 50 ms, N1 at 200 ms, and P3 from 300 ms. In typical development group (TD) the P1 and P3 components in CPZ channel shows the effect of the orienting network, that is, a significant difference between valid and invalid conditions. The P1 component presents greater amplitude for the valid condition compared to the invalid condition, and the significant differences extend in the time range between 41 ms and 63 ms with an average significance p-value of 0.0462 (paired t-test with FRD correction for multiple comparisons). The P3 component presents greater amplitude for the invalid condition compared to the valid condition, and the significant differences extend in the time range between 433 ms and 489 ms, with an average significance p-value of 0.0171 (paired t-test with FRD correction for multiple comparisons). In attentional deficit and hyperactivity disorder symptoms group (ADHD-S), does not present an orienting effect for any component. Differences between groups for each condition were not found. Topographic maps show a typical mid-frontal distribution of the P1 component at 50 ms in TD and ADHD-S group (see figure Nº6). The orienting effect can be observed throughout the entire distribution of the P1 component and not just in CPZ electrode only, and this effect were only found in TD group but not in ADHD-S group. Also, P3 component show a typical frontoparietal distribution between 430 ms and 500 ms in TD and ADHD-S groups. However, the orienting effect were only found in the TD group but not in the ADHD group.

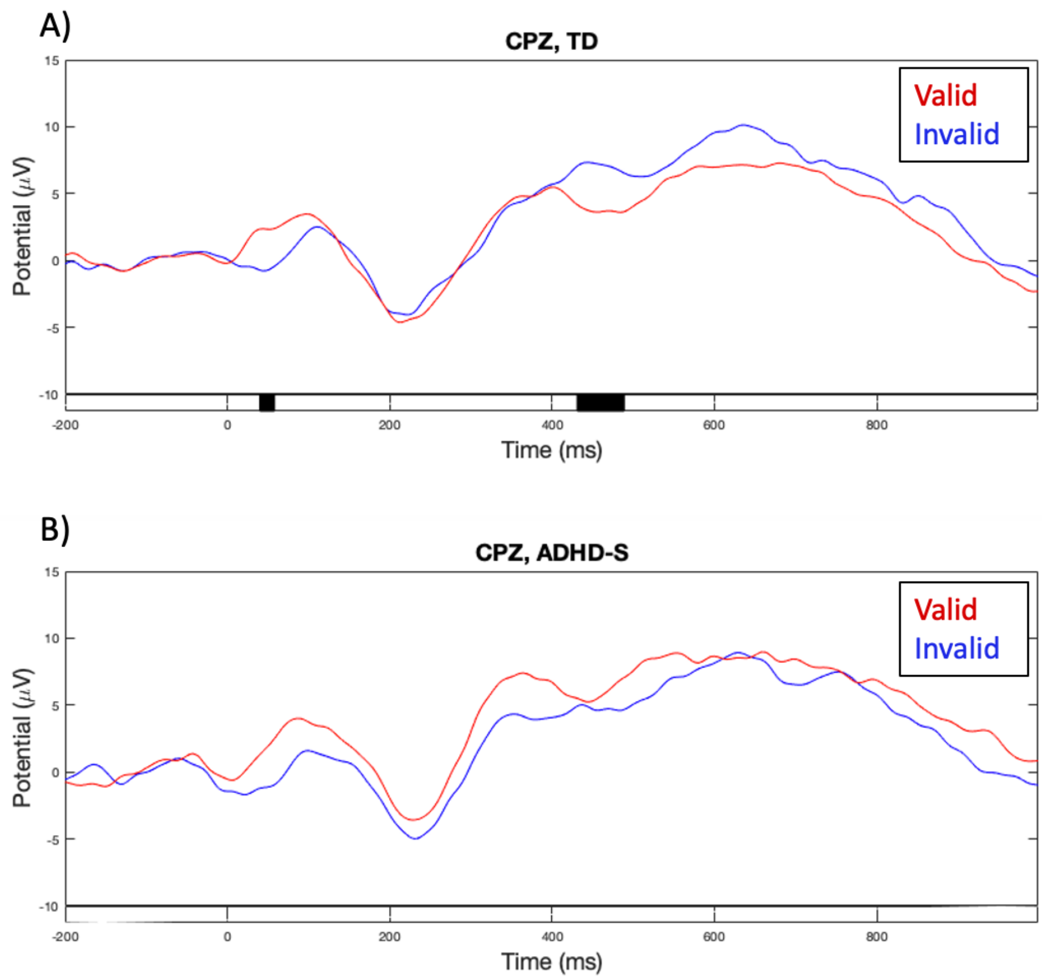

Figure Nº5: Orienting effects on electrophysiological data. Graphs representing target-locked ERPs on the CPZ Channel for each condition and group. In both graphs the red line represents valid condition and the blue line invalid condition. The upper graph (A) represents orienting ERP to TD or typical development group, and the lower graph (B) represents orienting ERP to ADHD-S or attention deficit and hyperactivity disorder symptoms group. The black bar below the X axes indicate time windows with significant differences between conditions ($p < 0.05$) by t-test corrected for multiple comparisons using the false discovery rate procedure.

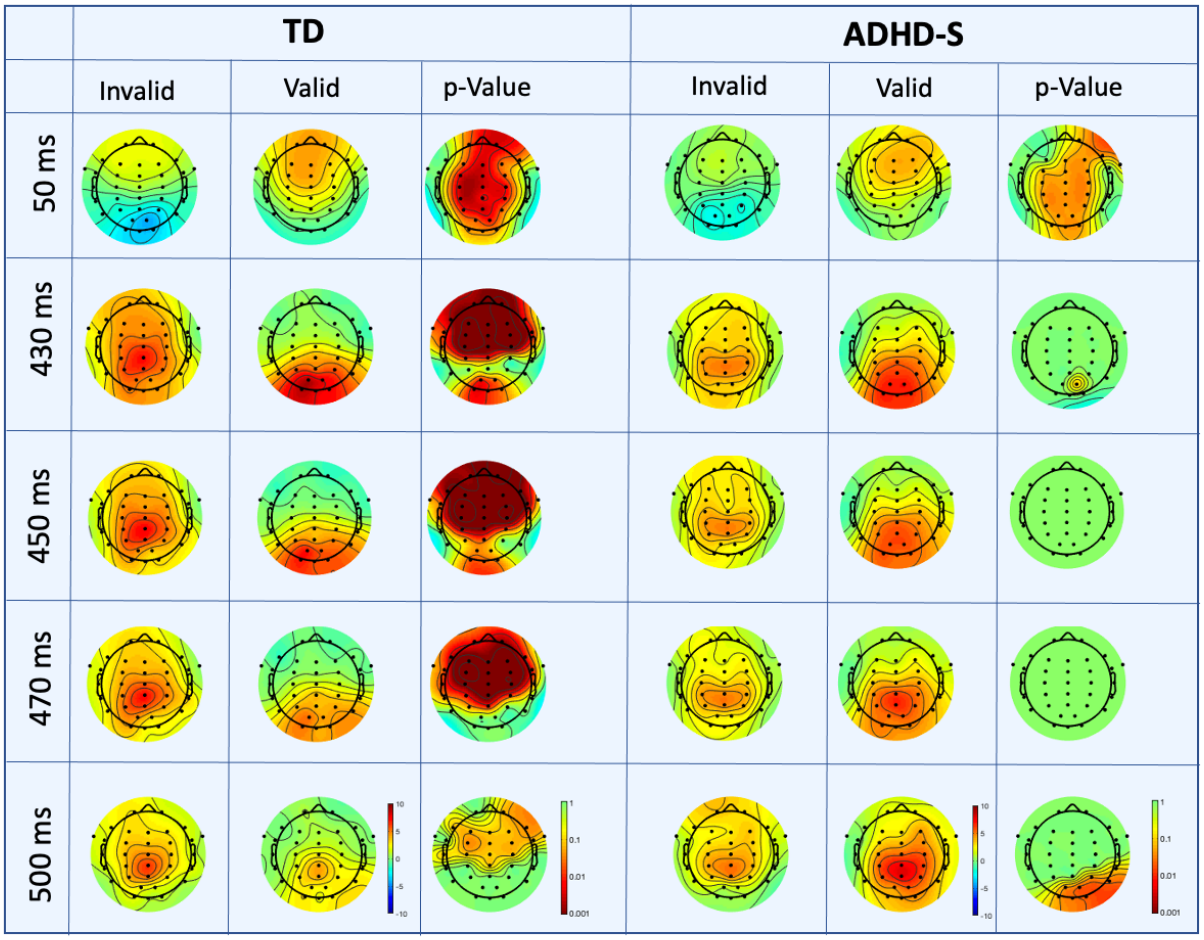

Figure Nº6: Orienting effect on topographic maps per group for P1 and P3 components. Graphs representing amplitude for ERPs on topographic maps for each condition (Invalid and Valid) and group (TD and ADHD-S) at five different times 50 ms for P1 component, and 430 , 450, 470 and 500 ms for P3 component. In Invalid and Valid columns, the distribution of the amplitude of the evoked activity is represented in a range between -10 **µV** (blue color) and 10 **µV** (red color). The P-Value columns shows the level of significance when comparing both conditions (valid and invalid), and the color bar shows the scale in the levels of significance, from p = 1 for the green, p < 0.05 for the light red and p < 0.001 for the intense red color, by t-test corrected for multiple comparisons using the false discovery rate procedure.

6.1.2.3 Typically developing children show an executive attentional network effect and children with early symptoms of ADHD do not.

Target-locked ERP per target condition (congruent and incongruent) for each group (TD and ADHD-S) are presented in figure Nº7. In both groups, 3 characteristic components are observed in the executive attentional network, P1 at 100 ms, N2 at 200 ms, P3 from 300 ms. In typical development group (TD), the P3 component in PZ channel presents greater amplitude for the incongruent condition compared to the congruent condition, and shows the effect of the execute attentional network, that is, a significant difference between congruent and incongruent conditions. This effect is in a discontinuous time range between 289 and 1000 ms, with an average significance p-value of 0.0270 (paired t-test with FRD correction for multiple comparisons). In attentional deficit and hyperactivity disorder symptoms, group (ADHD-S), does not present an executive attentional effect for any component. Differences between groups for each condition were not found. Topographic maps show an occipitofrontal distribution of the P3 component from 400, 600 and 800 ms in both groups (see figure Nº8). However, differences between target conditions were only found in the TD group but not in the ADHD group.

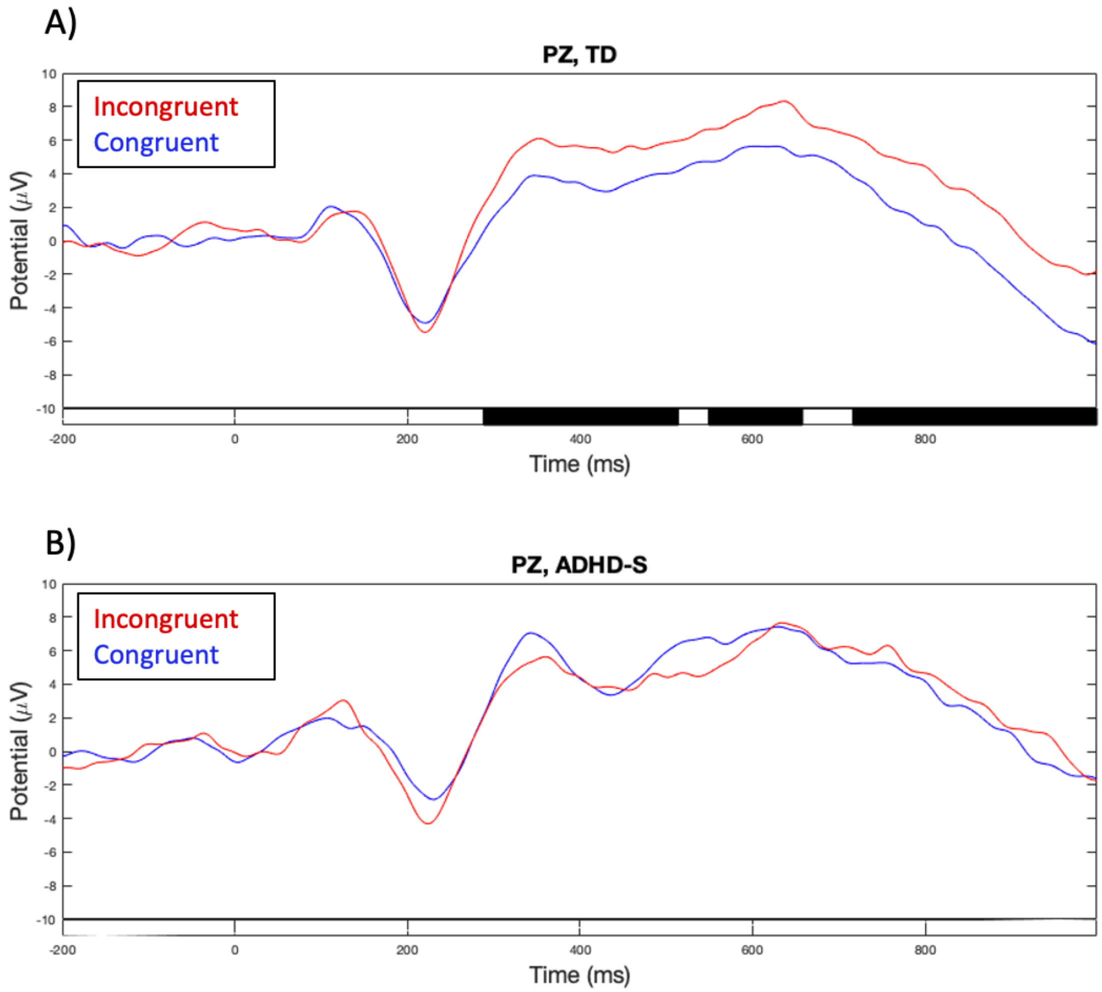

Figure Nº7: Executive attention effects on electrophysiological data. Graphs representing target-locked ERPs on the PZ Channel for each condition and group. In both graphs the red line represents incongruent condition and the blue line congruent condition. The upper graph (A) represents executive attention ERP to TD or typical development group, and the lower graph (B) represents executive attention ERP to ADHD-S or attention deficit and hyperactivity disorder symptoms group. The black bar below the X axes indicate time windows with significant differences between conditions ($p < 0.05$) by t-test corrected for multiple comparisons using the false discovery rate procedure.

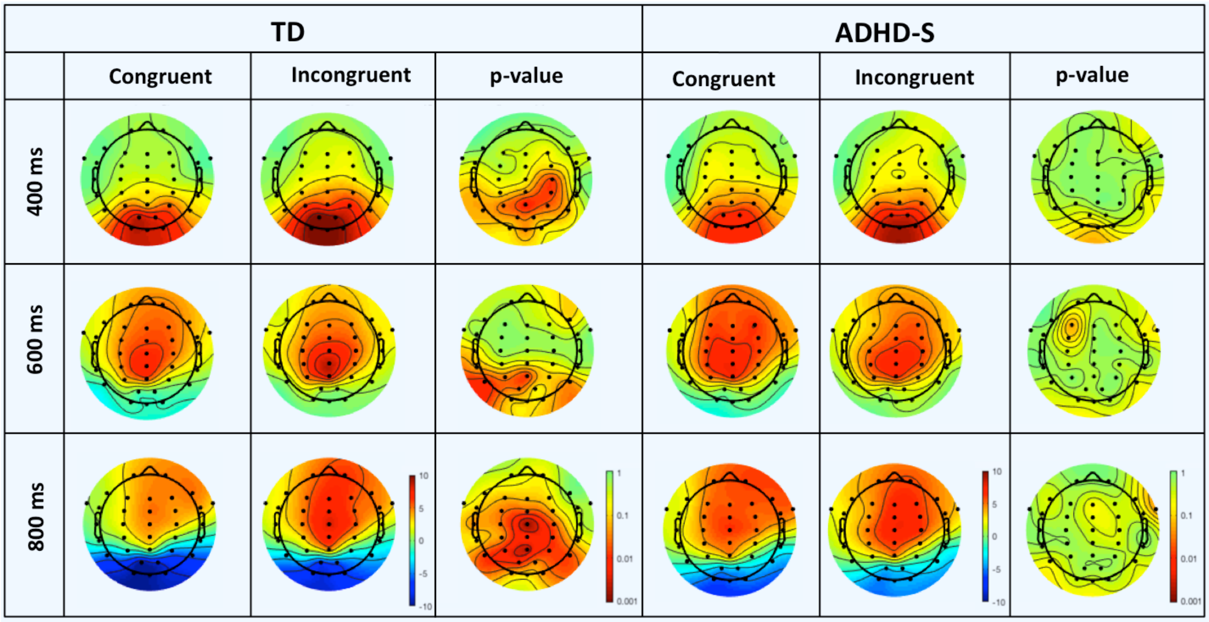

Figure Nº8: Executive attentional effect on topographic maps per group for P3 component. Graphs representing amplitude for ERPs on topographic maps for each condition (Congruent and Incongruent) and group (TD and ADHD-S) at three different times 400, 600 and 800 ms for P3 component. In congruent and incogruent columns, the distribution of the amplitude of the evoked activity is represented in a range between -10 **µV** (blue color) and 10 **µV** (red color). The P-Value columns shows the level of significance when comparing both conditions (congruent and incongruent), and the color bar shows the scale in the levels of significance, from p = 1 for the green, p < 0.05 for the light red and p < 0.001 for the intense red color, by t-test corrected for multiple comparisons using the false discovery rate procedure.

6.2 Objective Nº2

6.2.1 Behavioral outcomes

To determine if training had effect on working memory performance, one-way ANOVAs were carried out for each Group (ADHD-S and TD) and type of working memory (Verbal and visual-spatial). Figure Nº9 shows that there is a significant difference between sessions (pre and post training) in the performance of verbal working memory in the ADHD-S intervention group ($F(7,57)= 0,23$; $p= 0,011$) and not in the ADHD-S control group (See Figure Nº9 A). Furthermore, there is a significant difference between sessions (pre and post training) in the performance of visuo-spatial working memory in the ADHD-S intervention group ($F(7,54)= 0,23$; $p= 0,011$) and not in the ADHD-S control group (See Figure Nº9 B). No differences were found per session (pre and post training) in working memory performance in the TD intervention or TD control group in verbal working memory ($F(1,74)= 0,061$; $p= 0,197$) (See figure Nº9 C) or visuo-spatial working memory ($F(0,29)= 0,11$; $p= 0,59$) (See figure Nº9 D).

ANOVAs for accuracy values were carried out for each group (ADHD-S and TD) and attention network (Alert, orientation and executive). In ADHD-S group, the alerting network it was found a main effect on session ($F(15,01)= 0,35$; $p= 0,001$) and alerting condition ($F(14,14)= 0,36$; $p= 0,001$). In the orienting network it was found a main effect on session ($F(17,59)= 0,413$; $p= 0,000$). In the executive attentional network it was found a main effect on session ($F(13,78)= 0,355$; $p= 0,001$) , a main effect on executive attentional condition ($F(28,37)= 0,532$; $p= 0,000$), and interaction between session and executive attentional condition ($F(6,51)= 0,207$; $p= 0,017$). In TD group the alerting, orienting and executive attentional network it was not found a main effect on session, condition or interactions, except for the executive network where a main effect was found in executive attentional condition ($F(18,80)= 0,41$; $p= 0,000$).

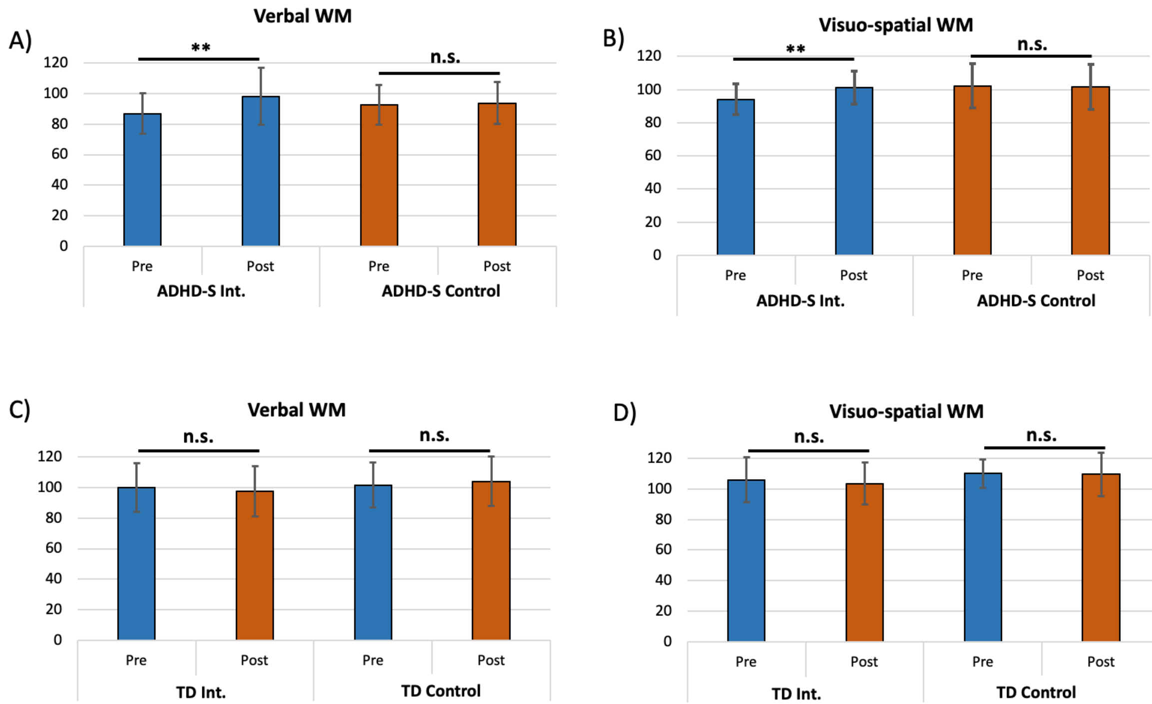

Figure Nº9: Effect of working memory training on verbal and visuo-spatial working memory performance. (A) shows the verbal working memory performance for children with early symptoms of ADHD for intervention group (ADHD-S Int.) and control group (ADHD-S Control), before (Pre) and after (post) working memory training. In the same way, (B) shows the visuospatial working memory performance for the ADHD-S groups, (C) shows the verbal working memory performance for the TD groups and (D) shows the visuospatial working memory performance for TD groups.

6.2.2 EEG outcomes

6.2.2.1 Effect of working memory training on executive attentional network in children with and without early symptoms of ADHD.

Target-locked ERP in CPZ Channel per target condition (congruent and incongruent) for ADHD-S group Pre and Post training are presented in figure Nº10. The P3 component for the two target conditions was obtained both before and after training in control and intervention groups. However, the P3 component in CPZ channel shows no effect of the executive network in both groups (ADHD Control and ADHD intervention) before training. After training, the effect of the executive network is observed in the ADHD-S intervention group and not in the ADHD-S control group. The P3 component post intervention for ADHD-S Intervention group presents greater amplitude for the incongruent condition compared to the congruent condition, and shows the effect of the execute attentional network, that is, a significant difference between congruent and incongruent conditions (see figure 10 B) . This effect is in a discontinuous time range between 593 ms and 1000 ms, with an average significance p-value = 0.0392 (uncorrected t-test). Topographic maps for ADHD-S Intervention and ADHD-S Control group show an occipitofrontal distribution of the P3 component from 600 and 800 ms in pre and post training (see figure Nº11 and Nº12). However, the differences after training between target conditions were only found in the ADHD-S Intervention group, but not in the ADHD-S control group.

In TD group, the executive attentional network effect can be observed in both groups (TD Control and TD intervention) pre training (see figure 13). Post-training there were no improvements in the executive attentional effect of the P3 component. However, in the TD intervention group the effect of the executive attentional network was not observed post training (See figure 13 B).

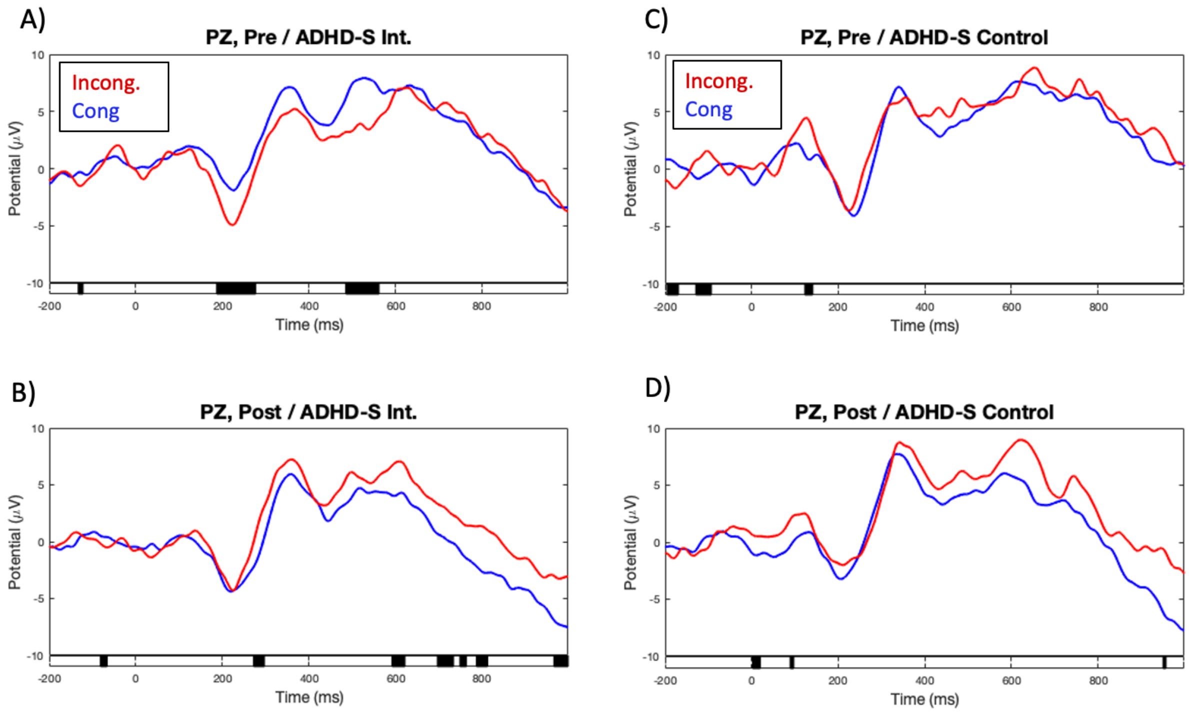

Figure Nº10: Effect of working memory training on executive attentional network in children with early symptoms of ADHD. Graphs representing target-locked ERPs on the PZ channel for ADHD-S children for each condition (Congruent and Incongruent), session (Pre and post training) and groups (Intervention and control). The red line represents incongruent condition and the blue line congruent condition. The upper left (A) and lower left (B) graphs represent the ERPs of the executive attentional network for ADHD-S children in intervention group, before and after training respectively. Similarly, the upper right (C) and lower right (D) graphs represent the ERPs of the executive attentional network before and after training, for ADHD-S children belonging to the control group. The black bar below the X axes indicate time windows with significant differences between conditions ($p < 0.05$) by uncorrected t-test.

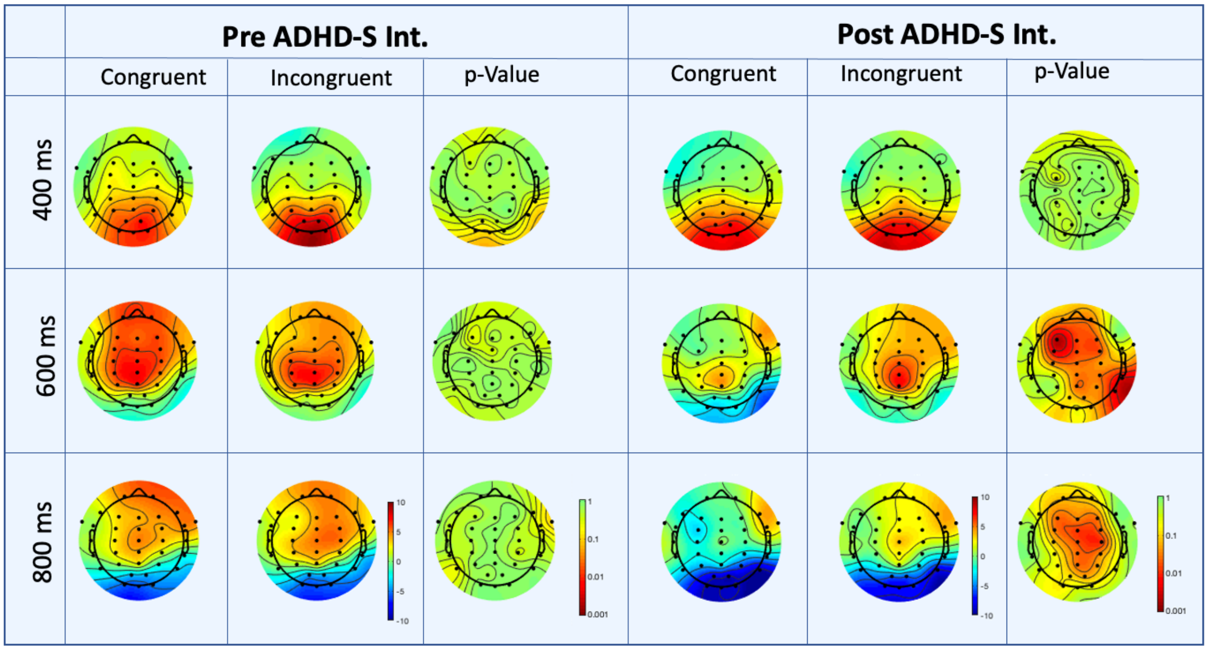

Figure Nº11: Executive attentional effect on topographic maps for ADHD-S intervention group per sessions. Graphs representing amplitude for ERPs on topographic maps for each session (Pre and Post training) per condition (congruent and incongruent) at three different times 400, 600 and 800 ms for P3 component. In congruent and incongruent columns, the distribution of the amplitude of the evoked activity is represented in a range between -10 **µV** (blue color) and 10 **µV** (red color). The P-Value columns shows the level of significance when comparing both conditions (congruent and incongruent), and the color bar shows the scale in the levels of significance, from $p = 1$ for the green, $p < 0.05$ for the light red and $p < 0.001$ for the intense red color, by uncorrected t-test.

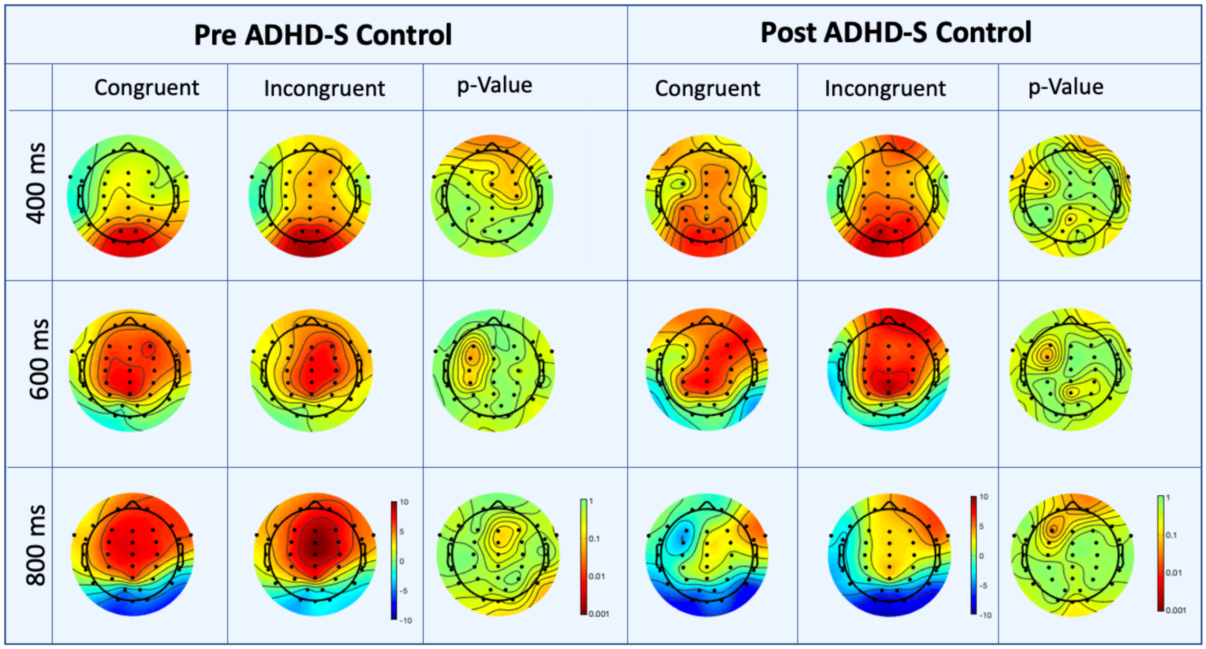

Figure Nº12: Executive attentional effect on topographic maps for ADHD-S control group per sessions. Graphs representing amplitude for ERPs on topographic maps for each session (Pre and Post training) per condition (congruent and incongruent) at three different times 400, 600 and 800 ms for P3 component. In congruent and incongruent columns, the distribution of the amplitude of the evoked activity is represented in a range between -10 **µV** (blue color) and 10 **µV** (red color). The P-Value columns shows the level of significance when comparing both conditions (congruent and incongruent), and the color bar shows the scale in the levels of significance, from p = 1 for the green, p < 0.05 for the light red and p < 0.001 for the intense red color, by uncorrected t-test.

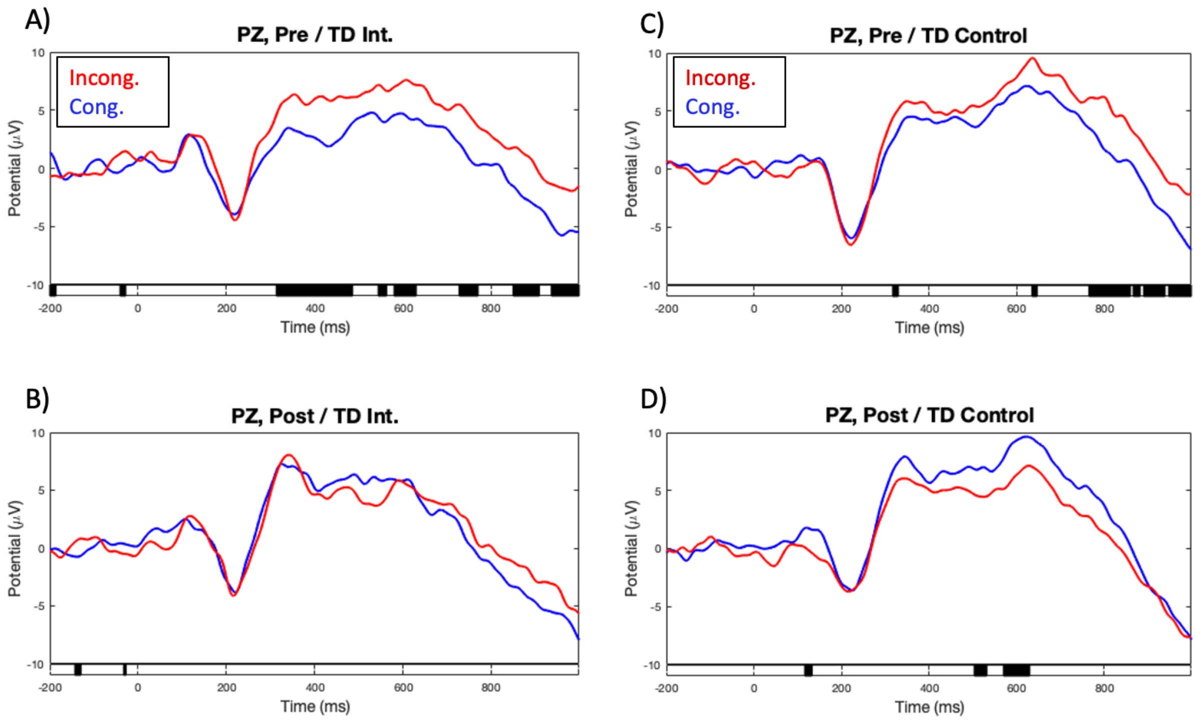

Figure Nº13: Effect of working memory training on executive attentional network in children without early symptoms of ADHD. Graphs representing target-locked ERPs on the PZ channel for TD children for each condition (Congruent and Incongruent), session (Pre and post training) and groups (Intervention and control). The red line represents incongruent condition and the blue line congruent condition. The upper left (A) and lower left (B) graphs represent the ERPs of the executive attentional network for TD children in intervention group, before and after training respectively. Similarly, the upper right (C) and lower right (D) graphs represent the ERPs of the executive attentional network before and after training, for TD children belonging to the control group. The black bar below the X axes indicate time windows with significant differences between conditions ($p < 0.05$) by uncorrected t-test.

6.2.2.2 Effect of working memory training on orienting network in children with and without early symptoms of ADHD.

Target-locked ERP in CPZ Channel per orienting condition (Valid and Invalid) for ADHD-S group Pre and Post training are presented in figure Nº14. The P3 component for the two orienting conditions was obtained both before and after training in control and intervention groups. The P3 component in CPZ channel shows no effect of the orienting network in both groups (ADHD Control and ADHD intervention) both before and after training (Pre and Post). In TD group, the orienting network effect can be observed in both groups (TD Control and TD intervention) pre training (see figure 15). Post-training there were no improvements in the modulation of the P3 component, however, in the TD intervention group the effect of the orientation network was not observed post training.

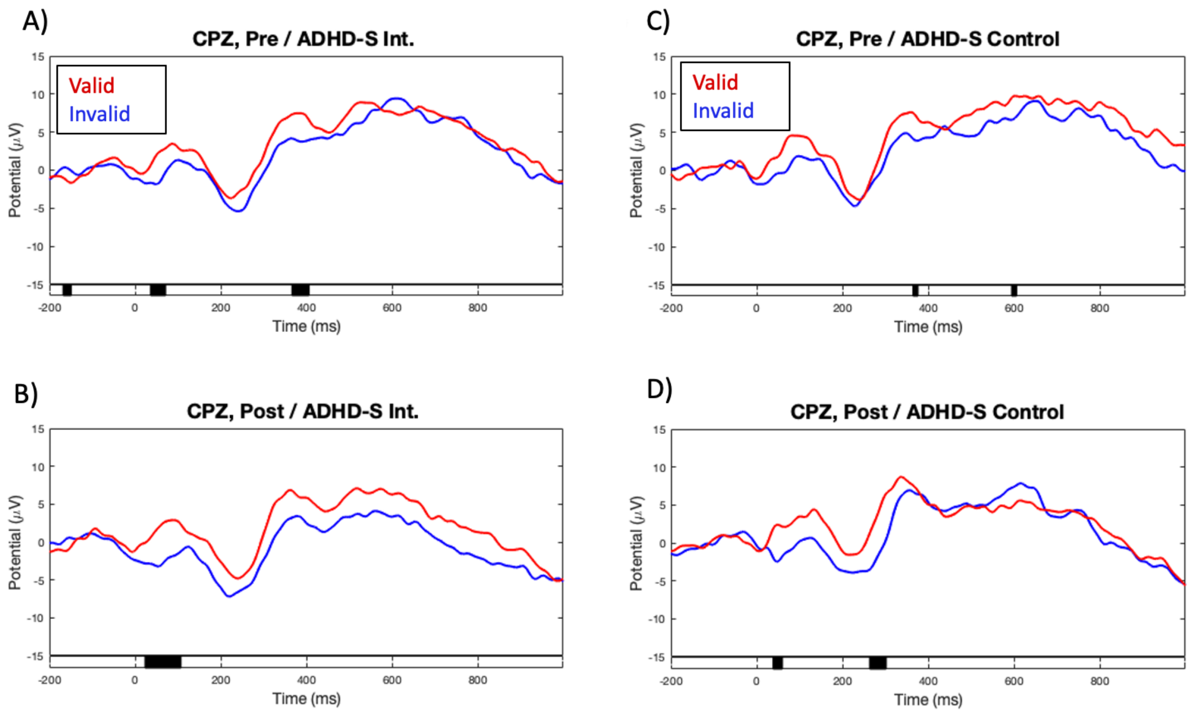

Figure Nº14: Effect of working memory training on orienting network in children without early symptoms of ADHD. Graphs representing target-locked ERPs on the CPZ channel for TD children for each condition (Valid and Invalid), session (Pre and post training) and groups (Intervention and control). The red line represents valid condition and the blue line invalid condition. The upper left (A) and lower left (B) graphs represent the ERPs of the orienting network for TD children in intervention group, before and after training respectively. Similarly, the upper right (C) and lower right (D) graphs represent the ERPs of the orienting network before and after training, for TD children belonging to the control group. The black bar below the X axes indicate time windows with significant differences between conditions ($p < 0.05$) by uncorrected t-test.

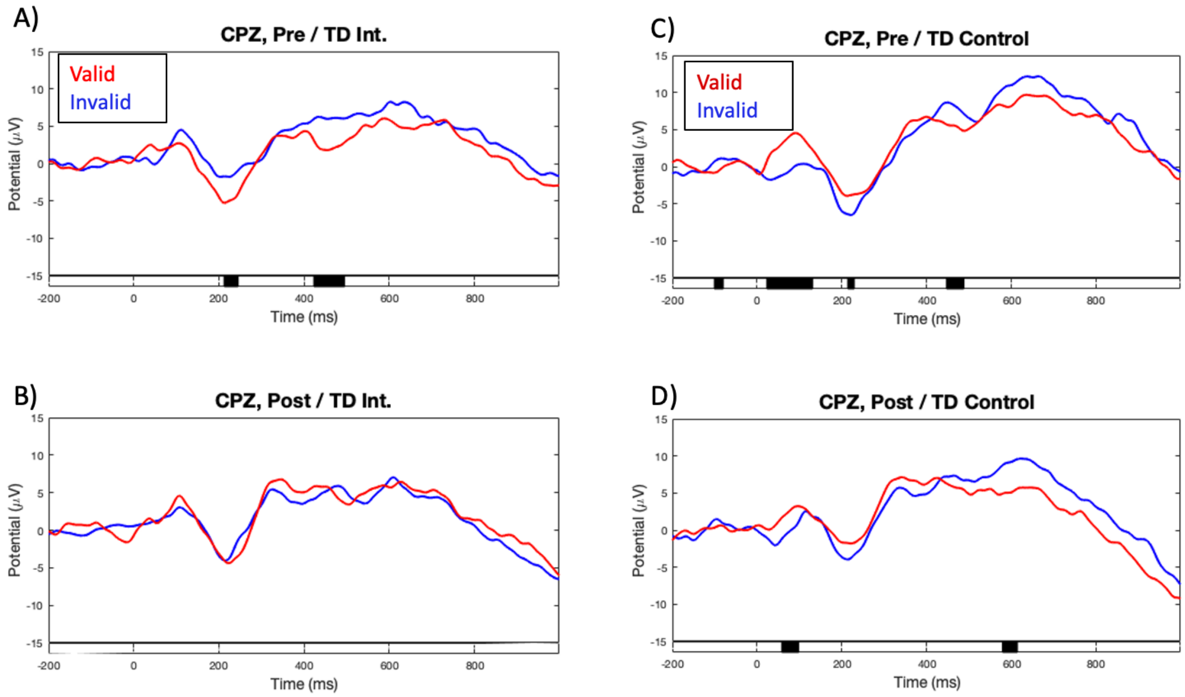

Figure Nº15: Effect of working memory training on orienting network in children with early symptoms of ADHD. Graphs representing target-locked ERPs on the CPZ channel for ADHD-S children for each condition (Valid and Invalid), session (Pre and post training) and groups (Intervention and control). The red line represents valid condition and the blue line invalid condition. The upper left (A) and lower left (B) graphs represent the ERPs of the orienting network for children with early symptoms of ADHD in intervention group, before and after training respectively. Similarly, the upper right (C) and lower right (D) graphs represent the ERPs of the orienting network before and after training, for children with early symptoms of ADHD belonging to the control group. The black bar below the X axes indicate time windows with significant differences between conditions ($p < 0.05$) by uncorrected t-test.

6.2.2.3 Effect of working memory training on alerting network in children with and without early symptoms of ADHD.

Cue-locked ERP in CZ Channel per alerting condition (tone and no tone) for ADHD-S group Pre and Post training are presented in figure Nº16. The CNV component for the tone condition was obtained both before and after training in control and intervention groups. The CNV component in CZ channel shows the effect of the alerting network, that is, a significant difference between tone and non-tone conditions. The alerting network effect found can be observed in both groups (ADHD Control and ADHD intervention) both before and after training (Pre and Post). Similar results were found in TD control and TD intervention groups before and after training (See figure 17).

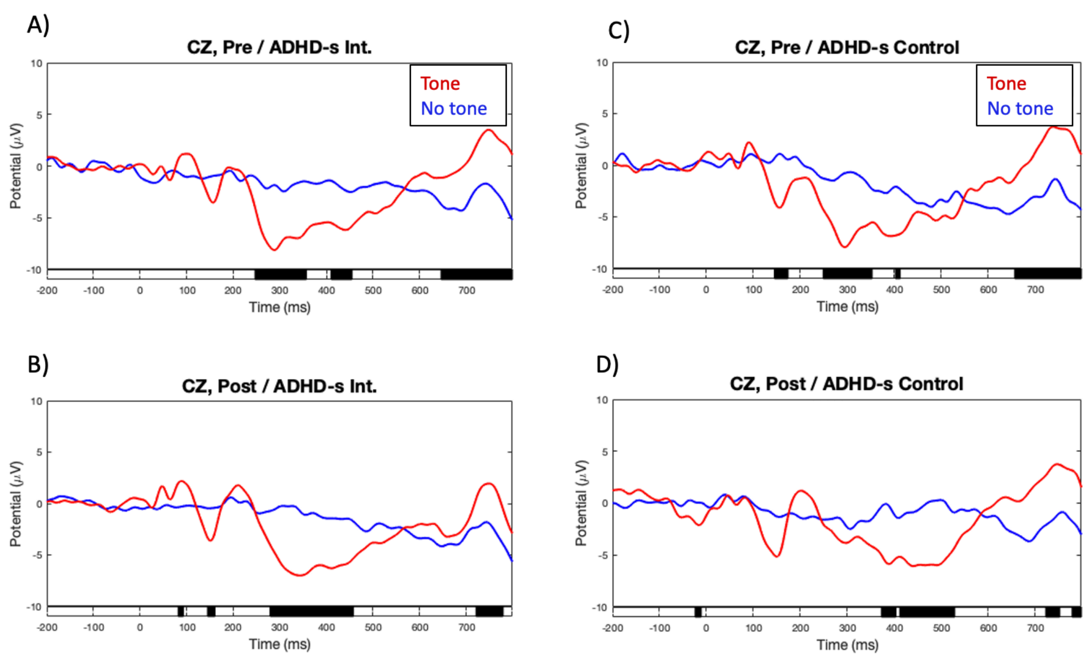

Figure Nº16: Effect of working memory training on alerting network in children with early symptoms of ADHD. Graphs representing cue-locked ERPs on the CZ channel for ADHD-S children for each condition (Tone and no tone), session (Pre and post training) and groups (Intervention and control). The red line represents tone condition and the blue line no tone condition. The upper left (A) and lower left (B) graphs represent the ERPs of the alerting network for children with early symptoms of ADHD in intervention group, before and after training respectively. Similarly, the upper right (C) and lower right (D) graphs represent the ERPs of the alerting network before and after training, for children with early symptoms of ADHD belonging to the control group. The black bars below the X axes indicate time windows with significant differences between conditions (p <0.05) by uncorrected t-test.

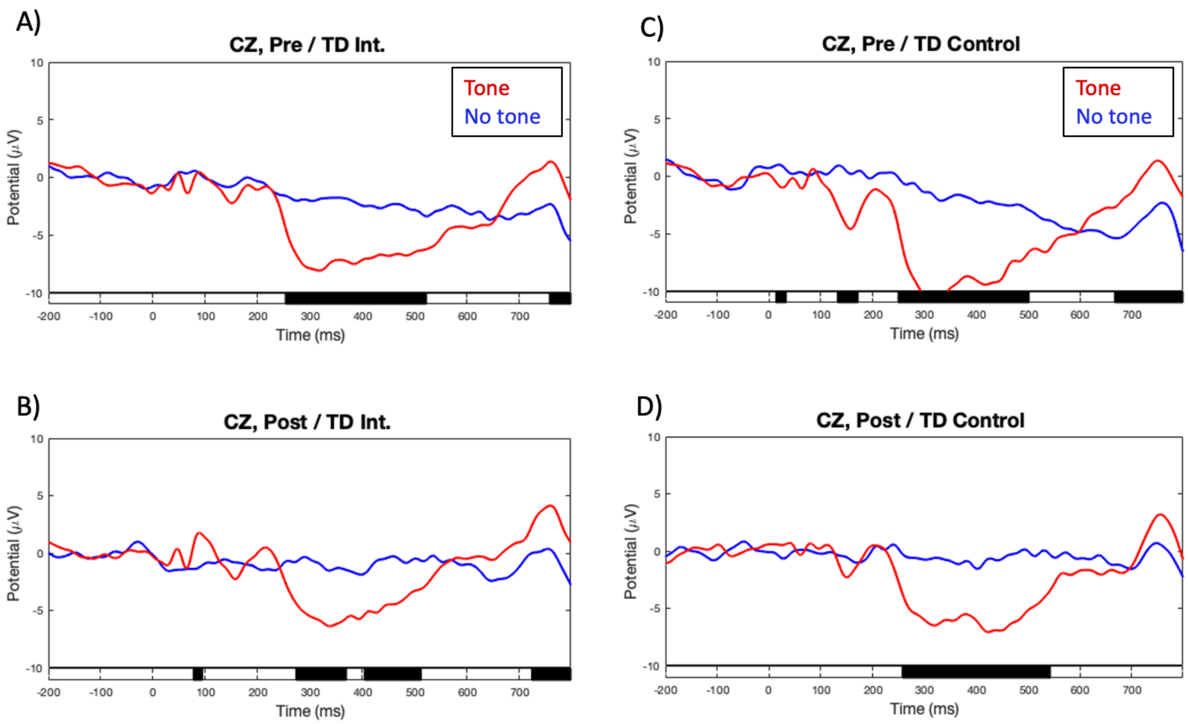

Figure Nº17: Effect of working memory training on alerting network in children without early symptoms of ADHD. Graphs representing cue-locked ERPs on the CZ channel for TD children for each condition (Tone and no tone), session (Pre and post training) and groups (Intervention and control). The red line represents tone condition and the blue line no tone condition. The upper left (A) and lower left (B) graphs represent the ERPs of the alerting network for TD children in intervention group, before and after training respectively. Similarly, the upper right (C) and lower right (D) graphs represent the ERPs of the alerting network before and after training, for TD children belonging to the control group. The black bar below the X axes indicate time windows with significant differences between conditions (p <0.05) by uncorrected t-test.

7. DISCUSSION

In this thesis we sought to investigate the state of attentional networks in the preschool stage and try to determine if there are differences in these networks between children with typical development and early symptoms of attention deficit and hyperactivity disorder. Additionally, we sought to investigate the effect that working memory training can produce on the performance and modulation of the attentional networks in both groups of children. Our main hypothesis was that preschoolers with ADHD symptoms have less developed attentional networks than children without ADHD symptoms, and such differences can be attenuated through working memory training. To test our hypothesis, we designed and completed a double-blind study based on a computer intervention of working memory training and we evaluated the performance of working memory and attentional networks, both before and after the intervention. 56 children completed the study, of which 29 presented typical development (ADHD-Index: 52,75 ± 7,87) and 27 presented early symptoms of ADHD (ADHD-Index: 73,36 ± 7,41). Of the group with typical development, 14 belonged to the control group (ADHD-Index: 54 ± 7,43) and 15 to the intervention group (ADHD-Index: 51,5 ± 8,35). In the group with early symptoms of ADHD, 13 belonged to the control group (ADHD-Index: 75,9 ± 6,87) and 14 to the intervention group (ADHD-Index: 70,94 ± 7,29). For all participants working memory performance was evaluated using the Automated Working Memory Assessment (AWMA; Alloway et al., 2008), and attentional networks were evaluated using the Attentional Network Task (ANT; Abundis-gutierrez et al., 2014; see figure Nº1), and only the ANT during an electroencephalographic recording.

At behavioral level, our results show that children with early symptoms of ADHD present lower accuracy for the global performance of the ANT task, compared to children with typical development (table Nº3). Results from the 2x2x3x2 ANOVA analysis reveal a decrease in accuracy for alerting, orienting and executive attentional networks. These results are related to research in children and adults diagnosed with ADHD that show that the three attentional networks are affected (Konrad et al. 2005, Johnson et al. 2008, Mullane et al. 2011). Our results are important because it shows that even before ADHD diagnosis, preschool children with high ADHD index already have the three attentional networks affected.

On the other hand, our electroencephalographic results show that the alerting network is not affected in children with early symptoms of ADHD. The figures 3 and 4 show the presence of the same alerting components for TD and ADHD-S. The effect of the alerting network (significant differences between tone and no tone condition) for the CNV component is present in both groups too. However the duration time is slightly shorter for ADHD than TD. Perhaps in future studies it could be compared if the duration of this effect is different between groups and if it is correlated with the behavioral performance of the task. Therefore, the question remains open, whether the duration of the alerting effect in CNV component could be a maturing indicator of the alerting network in children with symptoms or diagnosed with ADHD. In other tasks, such as CPT and Go / No Go tasks, less modulation of the CNV component in patients diagnosed with ADHD has been found (Banaschewski, et al, 2008; Benikos and Johnstone, 2009). This information is interesting because it would suggest that in ADHD the deviation in the development of the alert network occurs later, even after the age of diagnosis. In fact, the study by Doehnert et al. (2010) showed that there is less modulation of the CNV component in children diagnosed with ADHD, a difference found in groups of children with an average age of 12 years but not in groups of children with an average age of 10 years.

Our results show that the orienting network is affected in children with early symptoms of ADHD. Although the P1, N1 and P3 components described in the literature for the orienting network (Abundis-Gutierrez, et al. 2014) are present in children with and without early symptoms of ADHD, there is no difference between valid and invalid conditions in children with early symptoms of ADHD (see figure 5 y 6). The absence of an orienting effect between valid and invalid condition in P1 and P3 components in children with early symptoms of ADHD reveals that the orienting network is affected. These results are consistent with the results obtained by Kratz et al. (2011), in which it shows a lower modulation of the cue-P3 component for children diagnosed with ADHD compared to typically developing children in an attentional network task.

Similarly, our results show that the executive attentional network is affected in children with early symptoms of ADHD. Although the P3 component described in the literature for the executive attentional network (Abundis-Gutierrez, et al. 2014) are present in children with and without early symptoms of ADHD, there is no difference between congruent and incongruent conditions in children with early symptoms of ADHD (see figure 7 y 8). The absence of an executive attentional effect between congruent and incongruent condition in P3 component in children with early symptoms of ADHD reveals that the executive attentional network is affected. These results are consistent with the results obtained by Kratz et al. (2011), in which it shows a lower modulation of the P3 component for children diagnosed with ADHD compared to typically developing children in an attentional network task. These results are consistent with previous research that show a detriment of the executive attentional network by lower modulation of target-P3 component in an attentional network task (Kratz et al. 2011).

Both behavioral and electroencephalographic results confirm our initial hypothesis, and show that even before the age allowed for the diagnosis of ADHD, there is already less performance and modulation of the attentional networks. This is a key point, not to diagnose earlier according to age, but to highlight the importance of understanding ADHD as a neurodevelopmental problem, which is developing even before the age of clinical diagnosis. For this reason, we propose the need to generate early intervention strategies in children with early symptoms of ADHD, to mitigate the problems that already exist in the preschool stage. These strategies that could positively impact the course of development of this disorder.

According to the second hypothesis we proposed to study the effect of working memory training on the performance and modulation of each of the three attentional networks in children with and without early symptoms of ADHD. Our results support the hypothesis that the plasticity induced by working memory training in preschoolers with and without early symptoms of ADHD makes it possible to attenuate the differences and improve performance in attentional tasks compared with children who do not receive training.

At behavioral level, our results show that children with early symptoms of ADHD present an improvement for working memory performance, and children of typical development do not (Figure Nº9). Additionally, only children with early symptoms of ADHD who participated in working memory training showed an increase in their verbal and visuospatial working memory performance. The group with early symptoms of ADHD that did not participate in working memory training and did regular academic activities did not show improvement in working memory.

Through multiple ANOVA analyzes, our behavioral results did not show differences in accuracy by conditions, sessions or groups for the three attentional networks. These results suggest that working memory training does not produce behavioral improvements in the alerting, orienting, or executive network, both for children with early symptoms of ADHD and for typically developing children.

Regarding the electroencephalographic results, the target-P3 component is present for each condition in both groups of children with and without ADHD symptoms (Figure Nº10 y Nº13). In the target-P3 component, the incongruent condition presents a greater amplitude than the congruent condition. This can be seen in typically developing children before training but not in children with early symptoms of ADHD pre training. These finding are related to the results described for objective 1, which suggest that modulation of the executive network is affected in children with early symptoms of ADHD. Additionally, it is observed that only in the ADHD-S intervention group does the effect of the executive attentional network arise after working memory training, that is, a significant difference between the incongruent condition (greater amplitude) and the congruent condition (smaller amplitude). That change is not present in control ADHD-S children who did not receive the training program, suggesting that working memory training produces an improvement in the modulation of the executive attentional network.

The improvements observed in the modulation of the executive attentional network after working memory training in children with early symptoms of ADHD, are not observed for the orienting or alerting networks, both for children with or without early symptoms of ADHD (See figure Nº15 and Nº16).

Behavioral and electroencephalographic results suggest that typically developing children do not improve performance or modulation of alerting, orienting, and executive attentional networks. Although children with early symptoms of ADHD do not show improvements in the alerting or orienting networks, they do show an improvement in the modulation of the executive attentional network.

Working memory training has been seen to improve brain activity in dorsolateral prefrontal cortex, anterior cingulate and inferior frontal gyrus (Olsen, et al., 2004, Al-Saad et al., 2021). Some of these regions are shared with orienting and executive attentional networks and not with the alerting network (Fan, et al, 2005). We propose that despite this, there is only an improvement in the executive attentional network and not in the orienting network, since working memory training has been shown to produce changes at the dopaminergic level (McNab, et al., 2009), a neurotransmitter that modulates the executive network and not the orientation network (Posner, et al., 2016). Some of the changes described are an increase in dopamine receptor density and increased dopamine release from the caudate nucleus (Constantinidis & Klingberg, 2016).

If the reason for the improvement in executive attention is the increase in dopaminergic activity in prefrontal regions, then we could have found an improvement in the executive attentional network also in children with typical development. This result was not found since precisely these children did not show improvement in working memory. It would be interesting to investigate the reasons why typically developing children did not improve their working memory performance. We propose that perhaps it is because despite the interest generated by the computer training program, the level of difficulty was not challenging enough for typically developing children. In this way, by not challenging working memory sufficiently, the benefit is not produced in prefrontal and anterior cingulate cortex activity and consequently there is no improvement in the executive attentional network. It would be interesting to be able to answer this problem in order to determine if the benefits of working memory training can also be transferred to the executive attention of typically developing children.

Finally, according to a neurodevelopmental theory called development fractionation theory, we propose that the benefits of improved attention when training working memory is due to the fact that at an early age the prefrontal cortex does not yet differentiate the subregions for the regulation of each cognitive process (Tsujimoto, 2008). For this reason, the changes in connectivity and cytoarchitecture of a greater part of the prefrontal cortex, induced by working memory training, would improve executive attention. This hypothesis could be verified by training working memory in adults (with mature prefrontal cortex) and evaluating whether, despite the benefit in working memory, they do not obtain benefit in executive attention.

Some questions that arise from the results are:

How long does the effect of working memory training on the executive attentional network last?

Will the benefit in executive attentional network be enough to attenuate some of the clinical symptoms in the future?

Can the benefits in attention and working memory translate to improvements in aspects of daily life?

Will similar results be obtained when conducting this study with children and adolescents clinically diagnosed with ADHD?

8. CONCLUSION

The results of this research show that the ANT task allows evaluating the performance of attentional networks in preschool children, and specifically evaluating the state of alerting, orienting and executive attentional networks in children with typical development and children with early symptoms of attention deficit and hyperactivity. From the electroencephalographic analysis we show that preschool children with early symptoms of attention deficit and hyperactivity disorder already have orienting and executive attentional networks affected.

Our research shows that computer-based working memory training produces direct improvements in working memory performance but also produces improvements in brain modulation of the executive attentional network only in children with early symptoms of attention deficit and not in children with typical development.

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