JYU DISSERTATIONS 357

Praghajieeth Raajhen Santhana Gopalan

Attentional Subprocesses in Typical and Atypically Developing Children as Revealed Using Brain Electrical Activity

UNIVERSITY OF JYVÄSKYLÄ
FACULTY OF EDUCATION AND PSYCHOLOGY

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ABSTRACT

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Visual attention identifies and extracts relevant information from visual inputs and inhibits irrelevant information. Attention Network Theory proposes three functional subprocesses known as alerting, orienting, and inhibition. The aim of this dissertation is to investigate neural signatures, using electroencephalography (EEG) and brain event-related potentials (ERPs), of these attentional subprocesses in typically developing school-aged children, children with attentional problems (AP), and children with reading difficulties (RD) during the Attention Network Test (ANT). Study I aimed to investigate the reaction time (RT) performance, the target-related N1 amplitude associated with alerting and orienting, and the P3 associated with inhibition subprocesses, and to disentangle the neuronal sources related to these subprocesses of the attention network in typically developing children. RT performance in children was similar to typical ANT RT performance. The modulation of N1 amplitude for alerting and orienting subprocesses reflected the enhanced processing of the target stimulus followed by warning and spatial cues, respectively. The P3 amplitude modulation reflected the discriminability of the target stimulus from its flankers. Source-level analysis revealed reduced top-down control in children, compared to what is typically found in adults, for alerting and orienting subprocesses, evidenced by a lack of frontoparietal network activation. Study II evaluated how the attentional subprocesses differ in children with learning problems, i.e. attentional problems (AP) or reading difficulties (RD). The results of Study II did not show any differences in the RT performance and in the field potentials of ERPs between control children and children with learning problems. Neuronal source analysis of ERPs showed that children with AP had enhanced activity in the left occipital lobe compared to control and RD groups for the alerting network. The control children showed lower activity in the left occipital lobe compared to the AP and RD groups for the orienting network. This suggests a differential underlying functioning of attentional subprocesses in AP and RD children. Study III investigated the time-frequency power spectrum of ERPs in control children performing ANT. The results of Study III illustrated the different underlying spectral power mechanisms for attentional subprocesses in children. Overall, the findings of this dissertation confirm previous behavioural and ERP findings in children during ANT-task and, expand on these results by demonstrating atypical attentional subprocesses in children with AP and RD. In addition, the dissertation provides new knowledge of the neuronal sources and time-frequency indices of the attentional subprocesses to the growing body of literature on the attention network in children.

Keywords: attentional network, EEG, children, attentional problems, reading difficulties, source analysis, time-frequency analysis

TIIVISTELMÄ (ABSTRACT IN FINNISH)

Santhana Gopalan, Praghajieeth Raajhen
Tarkkaavaisuuden osaprosessit tyypillisesti ja epätyypillisesti kehittyvillä lapsilla aivosähkötoiminnan perusteella
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Visuaalinen tarkkaavaisuus kuuluu keskeisiin kognitiivisiin toimintoihin, joilla visuaalisista syötteistä tunnistetaan ja poimitaan relevanttia ja suljetaan pois epärelevanttia tietoa. Visuaalisilla tarkkaavaisuusongelmilla on tärkeä rooli kehityksellisissä oppimisvaikeuksissa, esimerkiksi tarkkaavaisuushäiriössä ja lukemisvaikeudessa. Yhdessä keskeisessä tarkkaavaisuuden teoriassa esitetään kolme visuaaliseen tarkkaavaisuuteen liittyvää toiminnallista osaprosessia: valppaus, orientointi ja inhibitio. Tämä tutkimus tarkastelee EEG:n ja aivojen tapahtumasidonnaisten jännitevasteiden (ERP) avulla näiden osaprosessien hermostollista perustaa tyypillisesti kehittyvillä kouluikäisillä ja niillä, joilla on tarkkaavaisuus- tai lukemisvaikeuksia ANT-testissä (Attention Network Test). *Tutkimuksessa I* tarkasteltiin reaktioaikoja, kohdeärsykkeen N1-vasteen voimakkuutta, joka liittyi valppauteen ja orientointiin, sekä inhibition osaprosesseihin liittyvää P3-vasteen voimakkuutta. Näihin osaprosesseihin liittyviä lähteitä aivoissa selvitettiin tyypillisesti kehittyvien lasten tarkkaavaisuusverkostossa. Lasten reaktioaika oli sama kuin tyypillinen ANT-reaktioaika aiemmissa tutkimuksissa. N1-vasteen voimakkuuden vaihtelu valppaus- ja orientointi-osaprosesseja mittaavan tehtävän aikana heijasteli kohdeärsykkeen parempaa prosessointia, jota edelsivät varoitus- ja spatiaaliset vihjeet. P3-vasteen voimakkuuden vaihtelu heijasteli inhibition vaikutusta häiriöärsykkeille ja kohdeärsykkeiden erottelua häiriöärsykkeistä. Lähdetason analyysi osoitti lasten tarkkaavaisuuden osaprosessien olevan heikompaa verrattuna aiemmissa tutkimuksissa havaittuihin aikuisten valppauden ja orientoinnin osaprosesseihin, mikä näkyi eroina frontoparietaalisen verkoston aktivaatiota mittaavissa vasteissa. *Tutkimuksessa II* verrattiin kontrolliryhmän ja tarkkaavaisuus- sekä lukemisvaikeusryhmien tarkkaavaisuuden osaprosesseja. Tuloksissa ei havaittu ryhmien välisiä eroja reaktioajassa eikä sensoritason ERP-vasteanalyyseissä. Lähdeanalyysi sen sijaan osoitti, että tarkkaavaisuusongelmaisten lasten aivotoiminta oli aktiivisempaa vasemmassa takaraivolohkossa kuin kontrolli- ja lukemisvaikeusryhmissä valppauteen liittyvässä verkostossa. Kontrolliryhmällä oli vasemmassa takaraivolohkossa vähemmän toimintaa kuin oppimisvaikeuksia (tarkkaavaisuus ja lukeminen) omaavilla lapsilla orientointiverkostossa. *Tutkimus III* kohdistui ERP:n aika-taajuus-analyysiin kontrolliryhmän suorittamassa ANT-testissä. Tulosten mukaan lasten tarkkaavaisuuden osaprosesseissa on erilaisia taajuusmekanismeja. Kaiken kaikkiaan väitöstutkimus vahvistaa aiemmat lasten ANT-testissä saadut käytös- ja ERP-tulokset sekä osoittaa, että oppimisvaikeuksia omaavilla lapsilla on epätyypillisiä tarkkaavaisuuden osaprosesseja. Tulokset tuovat tutkimuskirjallisuuteen uutta tietoa tarkkaavaisuuden osaprosessien hermostollisista lähteistä ja aika-taajuus-indekseistä.

Asiasanat: tarkkaavaisuusverkostot, elektroenkefalografia, lapset, tarkkaavaisuushäiriöt, lukemisvaikeudet, lähdeanalyysi, aika-taajuus-analyysi

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Taking into account the instructions given and the comments made by the co-authors, the author of this thesis contributed to the original publications as follows: the author analysed the data, wrote the manuscripts, and produced all the tables and figures for the three studies.

FIGURES

TABLES

ABBREVIATIONS

ACC	Anterior cingulate cortex
ADHD	Attention-deficit/hyperactivity disorder
ALLU	Ala-asteen lukutesti
AP	Attentional problems
ERP	Event-related potential
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
GLM	General linear model
MEG	Magnetoencephalography
MRI	Magnetic resonance imaging
RD	Reading difficulties
RSPM	Raven's standard progressive matrices
RT	Reaction time
TPJ	Temporal parietal junction
TSE	Temporal spectral evolution
WISC	Wechsler Intelligence Scale for Children

ACRONYMS

ANOVA	Analysis of variance
ANT	Attention network test
ATTEX	Attention and executive function rating inventory
CLARA	Classical LORETA analysis recursively applied
FEM	Finite element method
ILA	Internet lukemisen arviointi
LORETA	Low resolution electromagnetic tomography method
PAF	Principal axis factoring

CONTENTS

1 INTRODUCTION

"Everyone knows what attention is", said William James in 1890. Attention has been reported to play a major role in essential aspects of cognition, perception, and response selection (Johnson & Proctor, 2004). For example, when performing a task, we actively pay attention to task-relevant information and monitor our actions in order to provide appropriate responses. Attention can thus be described as a limited information processing capacity and that can be controlled intentionally (Desimone & Duncan, 1995).

Attention has been studied in a number of different experiments, and many theories and attentional mechanisms have been proposed in the literature (Broadbent, 1958; Eriksen & Eriksen, 1974; Fan et al., 2002; Posner, 1980; Treisman, 1964; Wolfe et al., 2000). Posner's theory of visual attention, with its three major subprocesses, has been one of the strongest influences on the attention network element. This theory encouraged us to consider and understand the attention network and its subprocesses in typically developing children and children with learning problems such as attentional problems (AP) and reading difficulties (RD). The first objective of the current research, therefore, was to investigate how the subprocesses of the attentional network manifest in typically developing children, as revealed using brain event-related potentials (ERPs) and their source localisation during the Attention Network Test (ANT). The second objective was to determine how these subprocesses differ between typically developing children and children with AP or RD. The third objective of this research was to examine the time-frequency power spectrum of ERPs in typically developing children performing ANT and how different frequency bands reflect distinct neuronal activity and their functional significance.

1.1 Visual attention

Visual attention is a process of selecting the relevant information for targeted actions and ignoring irrelevant information during ongoing behaviour

(Theeuwes, 2010). Broadbent's filter model and theory has proposed that physical characteristics of information are used to select the required information for further processing using the filter, with the loss of irrelevant information (Broadbent, 1958). One of the most recognised theories for the visual attention system in the human brain is the Attention Network Theory, developed by Posner and colleagues (Posner & Petersen, 1990). This theory describes three subprocesses of the attentional network: alerting, orienting, and response inhibition (Posner & Petersen, 1990). The Attention Network Test (ANT) is an experimental task used to study these attentional subprocesses simultaneously (Fan et al., 2002). The ANT is an integration of Eriksen's flanker test (Eriksen & Eriksen, 1974) and Posner's cued detection (Posner, 1980). During the ANT, the participant is asked to detect the direction of the middle target, surrounded by two flankers on either side. The stimulus is either preceded by a visual cue (double, centre, or spatial) or without a cue. During ANT, the direction of the target stimulus can be in the same direction (congruent) or in the opposite direction (incongruent) to the flankers.

1.2 Subprocesses of the visual attention network

Alerting is defined as the ability to prepare and sustain alertness to upcoming priority stimuli (Posner & Petersen, 1990). One of the approaches to studying alerting in the human brain is to use a warning or preparatory cue, which produces alertness to the target stimulus. The warning cue initiates the alert state to detect and respond to an expected upcoming stimuli. Using ANT, the alerting score can be calculated using the difference in reaction times (RTs) between trials with no cue and trials with double cue (Gamboz et al., 2010; Jennings et al., 2007; Neuhaus et al., 2010; Rueda, Fan, et al., 2004; Zhou et al., 2011). RT performance measured in adults (Fan et al., 2002, 2005; Neuhaus et al., 2010) and children (Konrad et al., 2005; Rueda, Fan, et al., 2004) has suggested that the warning cue helps to increase alertness by shortening the RT to the target stimulus. Furthermore, alertness in children (10 years old) has been shown to increase as age increases (Mezzacappa, 2004; Rueda, Fan, et al., 2004).

Orienting in the framework of attention is the ability to shift attention to incoming stimuli based on prior spatial information (Posner & Petersen, 1990). Orientation of attention comprises the engagement and disengagement of attention to a specific stimulus, and the shifting of visual attention between the stimuli (Posner & Petersen, 1990). The effect of orientation can be manipulated by providing a spatial cue that indicates the location of the upcoming target stimulus. The orienting score can then be calculated using the difference in RT between trials with centre cues and trials with spatial cue (Fan et al., 2002; Neuhaus et al., 2010). Spatial orientation has been seen to increase continuously between 5 and 14 years of age and improve further in adulthood, reflecting the development of spatial orientation of attention over time (Rueda, Fan, et al., 2004; Schul et al., 2003).

Inhibition is associated with higher-order cognitive processes, including response selection, error detection, stimulus conflict monitoring and decision-making (Posner & Rothbart, 2007). The inhibition score is measured by the difference in RT between incongruent trials and congruent trials (Fan et al., 2002; Neuhaus et al., 2010). In contrast to adults, children have had difficulty responding to incongruous trials, as evidenced by longer RTs (Rueda et al., 2005). However, RT improved significantly between 5 and 10 years of age. In later years, inhibition between 10-year-olds and adults appeared to have little or no development (Rueda et al., 2005; Rueda, Fan, et al., 2004).

1.3 Neuroimaging approaches to study the attention network

1.3.1 Brain event-related potentials

Event-related potentials (ERPs) have been widely used to assess the subprocesses of attention (Kaufman et al., 2016; Kratz et al., 2011; Neuhaus et al., 2010; Rueda, Posner, et al., 2004). Our main focus in this research is on visual-related ERP components such as N1 and P3. The visual-related N1 component generally peaks at 150–200 ms after visual target onset at the parietal and occipital cortices (Luck, 2014). The occipital N1 components tend to reveal the nature of the discriminative processing of the visual task (Hopf et al., 2002; Luck, 2014). The P3 component commonly appears in a range of 300–600 ms, which reflects the unpredictability, and inhibition of specific stimuli (Luck, 2014; Nobre, 2014). Specifically, N1 and P3 components reflect various attentional functions linked to stimulus processing in the brain (Kratz et al., 2011; Luck, 2014; Neuhaus et al., 2010).

The alerting effect modulates the posterior visual amplitude of N1 between 100 ms and 280 ms for the target stimulus (Kaufman et al., 2016; Neuhaus et al., 2010). The amplitude of N1 over the occipital lobe represents the visual processing of target stimulus characteristics and the influence of the warning cue conditions (Fan et al., 2005; Galvao-Carmona et al., 2014; Neuhaus et al., 2010).

Similarly, the orienting effect modulates the target-related N1 amplitude at 110–280 ms in children (X. Liu & Sun, 2017) and adults (Kaufman et al., 2016). The enhancement of N1 amplitude for orientation of attention over occipital and parieto-occipital regions suggests the engagement of spatial attention to the cued target location (Kaufman et al., 2016; Williams et al., 2016). Previous studies on orienting of visual attention have consistently shown that enhanced N1 implies the benefits of valid spatial cueing and subsequent processing of spatially cued target stimuli (Hopfinger et al., 2000; Neuhaus et al., 2010).

The inhibition effect modulates the P3 amplitude between 300 and 650 ms from target stimulus onset over the centro-parietal areas (Kratz et al., 2011; Neuhaus et al., 2010). The latency of P3 amplitude tends to appear in the later time window (400–500 ms) in children (10 years old) compared to adults, which suggests the late development of inhibitory function (Kratz et al., 2011). In the

ANT framework, P3 amplitude reflects the processing of conflicts in the visual stimuli and selection of response (Galvao-Carmona et al., 2014; Neuhaus et al., 2010; Polich, 2007).

1.3.2 Functional magnetic resonance imaging

Neuroanatomy of the attention network has been primarily studied using functional magnetic resonance imaging (fMRI) (Fan et al., 2005; Konrad et al., 2005; Posner & Rothbart, 2007; Posner & Petersen, 1990). The alerting network corresponds to the arousal and preparatory state with increased activity in the occipital, temporal parietal junction (TPJ), and prefrontal areas (Fan et al., 2005; Konrad et al., 2005; Xuan et al., 2016). In relation to the alerting effect, children tend to show maturational changes in the mid-occipital area extending towards the right superior temporal gyrus (Konrad et al., 2005). The increased neuronal activity in the occipital and temporal areas in children during alerting subprocesses suggests that these regions are associated with anticipation of the visual alerting and response preparedness for the upcoming target stimulus (Konrad et al., 2005; Xuan et al., 2016).

The orientation network examined in adults using fMRI has shown activity in the pulvinar, parietal lobe, superior colliculus and frontal eye fields (Fan et al., 2005; Xuan et al., 2016). Each region has a unique orientation-related functionality (Posner & Petersen, 1990). Pulvinar activity has been related to the involvement of visual attention in a spatially cued target stimulus. During disengagement of visual attention from the stimulus, the posterior parietal lobe has been enhanced along with the superior colliculus and frontal eye fields which are associated with the ability to shift visual attention from one stimulus to another (Petersen & Posner, 2012; Posner & Petersen, 1990). The orienting network in children has also shown activity in the superior frontal gyrus and bilateral occipital areas (Konrad et al., 2005). Furthermore, children showed reduced TPJ activity compared to adults, reflecting immature neuronal responses to invalid cues (target appears irrelevant to cue location) (Konrad et al., 2005).

The inhibition network in adults (Fan et al., 2005; Xuan et al., 2016) involves the activation of the anterior cingulate cortex (ACC), frontal eye fields, occipital cortex, and bilateral precentral gyrus. Evidence has shown activity in the ACC and the lateral frontal areas during the monitoring and resolving of resolving conflicts, respectively (Botvinick et al., 2001). In children, the inhibition network shows activity in the bilateral occipital cortex, bilateral parietal cortex, premotor cortex, and right superior temporal area with less prefrontal cortex activation, including inferior and medial frontal gyrus, in relation to adults (Konrad et al., 2005). These findings suggest immature development in the frontal areas for the inhibition network (Bunge et al., 2002; Konrad et al., 2005). In most of the above findings, fMRI has been used to study brain regions associated with attentional network subprocesses; EEG-based source localisation of attentional subprocesses in children is rare.

1.3.3 Time-frequency analysis

Time-frequency analysis is a technique that calculates the power spectrum of specific frequency bands at a given time interval. The most commonly defined frequency bands at which to perform time-frequency analysis on the attentional subprocesses are theta (4–8 Hz), alpha (8–14 Hz), beta (14–30 Hz), and gamma (30–80 Hz) (Albrecht et al., 2009; Fan et al., 2007). Time-frequency analysis is used to understand different neuronal subprocesses of attention and provide further insight into developmental problems related to attention, including attention-deficit hyperactivity disorders (ADHD) and behavioural disorders. Time-frequency analysis allows us to observe neural activation changes that are not phase-locked to a specific event. This complements the ERP approach, which is based on averaging EEG across stimulus events, that excludes events that are not phase-locked (Pfurtscheller & Lopes da Silva, 1999).

The alerting effect in adults, as measured by ANT, has been shown to result in a decrease in theta (4–8 Hz), alpha (8–14 Hz), and beta (14–30 Hz) power activity after 200 ms of a visual cue (Fan et al., 2007). This reduction has been related to the general preparatory state for the onset of any visual stimulus (Fan et al., 2007).

The orienting effect in adults, observed in the magnetoencephalography (MEG) study using Posner's cueing task has been shown to increase theta power activity following the visual cue and during target processing due to the disengagement of attention from the cued locations (Spooner et al., 2020). In another MEG study, the decrease in alpha power has been associated with anticipation of the upcoming stimulus based on the spatial cue (Marshall et al., 2015). Previous attention research (responding to the target based, whether the visual cue first appears on the left or on the right) (Gola et al., 2012) has indicated a decrease in beta (14–22 Hz) band power in older adults compared to younger adults following target stimulus onset. It has been suggested that this general decrease in beta power could be associated with the difficulty of maintaining attention on the cued location (Gola et al., 2012; Spooner et al., 2020). In both adult EEG (Fan et al., 2007) and MEG (Marshall et al., 2015) studies using the visual cueing experiment, an increase in gamma (30–100 Hz) band activity prior to onset of the spatial cue has been observed, suggested to be due to spatial orienting.

The inhibition effect in children, measured using ANT, has associated enhanced theta band activity with motor-related monitoring and error detection (Albrecht et al., 2009). In a letter-based flanker study (one central target letter with two flanker letters on either sides), alpha power for incongruent stimuli was high and linked to the active inhibition of irrelevant information and processing of relevant information (Janssens et al., 2018). A previous Go/No-Go study in adults showed an increase in event-induced theta power for the No-Go condition, which has been related to inhibition response (Harmony et al., 2009). An increase in gamma band power has been noted for incongruent stimuli compared to congruent stimuli; this has been related to response selection and monitoring (Fan et al., 2007; Fan, Raz, et al., 2003). The increase in gamma band power for the Go condition has been associated with the preparation and execution of the

motor response, while a decrease for the No-Go condition has been associated with inhibition (Harmony et al., 2009).

However, only a few studies in children have demonstrated how the time-frequency spectrum changes during alerting, orienting, and inhibiting subprocesses.

1.4 Subprocesses of the attentional network in attentional problems and reading difficulties

Attentional problems (AP) and reading difficulties (RD) are two of the crucial developmental issues that impair children's learning (American Psychiatric Association, 2013). These difficulties lead to an increased risk of academic, economic and psychological consequences (de Kieviet et al., 2012; Sexton et al., 2012). Attention-deficit/hyperactivity disorder (ADHD) is a common childhood disorder with genetic and neurobiological basis (Wender, 2001). The symptoms of ADHD, published by the American Psychiatric Association, include shortness of attention span, impulsivity, and excessive activity, and are similar to the symptoms of children with AP in our research (American Psychiatric Association, 2013). RD is frequently termed dyslexia. Individuals with RD have difficulties performing reading and/or spelling tasks despite their adequate educational provision and normal intelligence (Lyon et al., 2003; Rutter & Yule, 1975; Wender, 2001).

One characteristic of children with AP is a lack of ability to maintain alertness (Sergeant, 2000; Wender, 2001; Willcutt & Carlson, 2005). For example, during ANT, children with ADHD demonstrated longer response times for the alerting effect compared to the control groups. This highlights that children with AP experience a lower level of attention to the upcoming target stimulus (Booth et al., 2007; Konrad et al., 2006; Mullane et al., 2011). In contrast with the aforementioned studies, the alerting effect has shown no significant group differences between the control group, children with ADHD (Adólfsdóttir et al., 2008; Fabio & Urso, 2014; Kratz et al., 2011), and adults (Lundervold et al., 2011) except for a lower accuracy rate in children with ADHD. Similarly, there have been no differences in alerting effects between dyslexic and control children when stimulus is cued (Bednarek et al., 2004). Children with ADHD may have problems with spatial coordination and response inhibition, but not all exhibit these problems (Wender, 2001).According to the ANT framework, no differences in spatial orientation and inhibition have been observed between control children and children with ADHD (Adólfsdóttir et al., 2008; Kratz et al., 2011). In contrast, dyslexic adults have evidenced difficulties in maintaining spatial focus at the peripheral location (Buchholz & Aimola Davies, 2008). Studies of children with ADHD (Fabio & Urso, 2014) and dyslexic children (Bednarek et al., 2004), and dyslexic adults (Goldfarb & Shaul, 2013) have indicated a deficit in response inhibition in the form of longer RT to resolve the incongruence.

Brain-related ERP studies of alerting and orienting in adults with ADHD (Hasler et al., 2016; López et al., 2006) have shown that the modulation of target-related N1 amplitude follows the same pattern as that of control groups. Significantly, to my knowledge, there are no prior studies of target-related N1 alerting and orienting effects in children with AP or RD. However, inhibition effects in predominantly inattentive children (Kratz et al., 2011), adults with ADHD (Hasler et al., 2016), and dyslexic adults (Mahé et al., 2014) have shown smaller P3 amplitude compared to control groups. This suggests an impairment in processing the conflict in the target stimulus (Hasler et al., 2016; Mahé et al., 2014). Nonetheless, no studies have examined the inhibition effect using the child's version of ANT in children with RD. The investigation of ERP-level data in children with learning problems (i.e., AP or RD) could help to understand different underlying mechanisms for AP and RD.

Only a small number of fMRI studies have considered the alerting, orienting, and inhibition networks in children with AP and children with RD. Functional imaging studies on the alerting network have shown that control children are more active in the right ACC compared to children with ADHD, reflecting the top-down modulation in children (Konrad et al., 2006; Sturm & Willmes, 2001). Orienting networks in children with ADHD have shown atypical activation in the frontostriatal region, suggesting the involvement of altered brain mechanisms, including the dorsolateral prefrontal cortex and insular cortex (Bellman, 2002, p. 104; Konrad et al., 2006). Inhibition networks in children with ADHD have shown reduced frontostriatal activation compared to control children, linked to immature frontal development (Bunge et al., 2002; Durston et al., 2003; Konrad et al., 2006).

1.5 Aims of the research

This dissertation aimed to investigate the three attentional subprocesses (alerting, orienting, and inhibition) in typically developing children, children with AP, and children with RD. This included approaches such as RT performance, brain ERPs and their source localisation, and time-frequency power spectrum analysis of EEG for the subprocesses.

The aim of **Study I** was to investigate RT performance during the child version of ANT, the modulation of the target-related N1 amplitude (associated with alerting and orienting), and the target-related P3 amplitude (associated with inhibition). Further, spatio-temporal topographic maps and distributed source model (classical LORETA analysis recursively applied (CLARA)) were employed to identify and disentangle the neuronal sources related to the three subprocesses of the attentional network in typically developing children. **Study I** could therefore provide a reference point of attention network subprocesses for evaluating these in atypically developing children (i.e., children with AP or RD).

The aim of **Study II** was to examine subprocesses of attention in children with AP and children with RD. Previous studies have provided mixed results in

terms of RT performance in children with AP or RD, while knowledge is limited about the target-related N1 and target-related P3 amplitude in children with AP and RD. Further examination of neuronal sources in children with AP and RD, using a source model based on typically developing children, can help to identify the brain regions associated with these three attentional subprocesses.

The aim of **Study III** was to investigate the time-frequency power spectrum of different frequency bands (theta, alpha, beta, lower gamma, and higher gamma) associated with the three attentional subprocesses. This study demonstrated how different frequency bands reflect distinct neuronal activity and their functional significance. In this **Study III**, we employed the EEG data from **Study I** (i.e., neuronal brain activity measures using EEG in typically developing children). Time-frequency power spectrum analysis was carried out using the event-related phase-locked method (Temporal Spectral Evolution (TSE) to determine their association with attentional network subprocesses in children. Furthermore, a subtraction of the evoked activity from TSE was performed to calculate and explore the induced non-phase locked activity.

2 METHODS

2.1 Participants

The participants in **Studies I–III** were Finnish sixth-graders aged between 12 and 13 years with normal or corrected vision. Children with neurological problems or head injuries were excluded. Prior to the experiment, the participants and their parents or guardians signed an informed consent form, in accordance with the Declaration of Helsinki.

TABLE 1 Demographic information, attention and executive function rating inventory (ATTEX) score and reading fluency score of control children, children with attentional problems (AP) and children with reading difficulties (RD).

Study	Group	Number of participants	Mean age (M) years	Standard deviation (SD)	Inclusion criteria	
					ATTEX score	**Reading fluency score (percentile)**
I	Control	83 (40 boys, 43 girls)	12.38	0.48	below 30	above 10th
II	Control	77 (36 boys, 41 girls)	12.86	0.31	below 30	above 10th
	AP	15 (14 boys, 1 girl)	12.67	0.31	above 30	above 10th
	RD	23 (15 boys, 8 girls)	12.61	0.31	below 30	below 10th
III	Control	72 (36 boys, 41 girls)	12.87	0.31	below 30	above 10th

A total of 466 children from sixth-grade schools in rural and urban areas of Central Finland participated voluntarily in the eSeek study (Academy of Finland, TULOS-program project: eSeek–Internet and learning difficulties: Multidisciplinary approach for understanding information seeking in new media, number 274022. PI: Paavo H.T. Leppänen, Department of Psychology, University of Jyväskylä, Finland). 448 participants in total completed the internet reading assessment (Internet Lukemisen Arviointi (ILA) test (Kanniainen et al., 2019; Kiili,

Leu, Marttunen, et al., 2018; Kiili, Leu, Utriainen, et al., 2018). This test consisted of realistic closed internet tasks presented in a simulated web environment and it assessed participants' ability to (a) locate information, (b) evaluate information, (c) synthesise information, and (d) communicate information (Kiili, Leu, Utriainen, et al., 2018; Leu et al., 2013). 156 participants were invited to the EEG, eye tracking, and cognitive assessment based on the completion of the ILA test and the results of non-verbal reasoning measured by the RAVEN test (Raven & Court, 1998). AP and RD participants were included based on their attention and executive function teacher rating inventory (ATTEX) (Klenberg et al., 2010) and reading fluency (Principal Axis Factoring (PAF) scores, respectively (see **Table 1**). Reading fluency scores are discussed in detail below. Participants with a shortened RAVEN score of less than 15 and those with uncompleted ILA tests were not invited to the EEG measurements. Participants were also required to have Finnish as their primary language.

The control group participants in Study II were the same as in our Study I, with the exception of six participants, who were below the borderline of reading abilities required for inclusion in the control group on the basis of revised reading disorder criteria in the current study; this omission did not affect any of the results. Children with both AP and RD (comorbid group) were excluded from this study due to a smaller sample size ($n < 10$): these children had an ATTEX score above 30 and a reading fluency score below the 10th percentile. Study III consists of pre-processed EEG data from 72 control children. The details of the data pre-processing are discussed below.

2.2 Behavioural measures used in the dissertation articles

The criteria for the classification of children with AP and children with RD were assessed by reading fluency performance, ATTEX, and visuospatial reasoning ability subtest (RAVEN).

Reading fluency performance was measured using a factor score obtained from the following three subtests using PAF. The factor analysis was forced into one factor. The word identification test and word chain test were carried out in a group session. The oral pseudoword text-reading test was assessed individually.

> (1) The word identification test is a subtest of ALLU, the standardised Finnish reading test (Lindeman, 1998). It comprises 80 items, each having a picture and four phonologically similar words, only one of which semantically matches the picture. The task was to recognise and connect appropriate picture-word pairs as quickly as possible by drawing a line between word and picture. The maximum period of the task was two minutes. The score was the number of appropriately connected pairs completed within the time frame.

(2) The word chain test consists of 25 chains: each chain contains four words without spaces between them (Holopainen et al., 2004). The task was to insert a vertical line at the end of each word. The maximum time limit was 90 seconds. The score was given based on the number of correctly separated words completed within the time limit.

(3) The oral pseudoword text-reading test (Eklund et al., 2015) contains 38 pseudowords (277 letters). These pseudowords were presented as a paragraph. Children were instructed to read the paragraph aloud as quickly and accurately as possible. The score was given based on the correctly read pseudowords divided by the time (in seconds) spent reading them.

ATTEX (Klenberg et al., 2010) is a 55-items teacher rating scale used to measure difficulties of attention, inhibition, and executive function in school settings. The scale is grouped into ten clinical subscales (number of items per scale in parentheses): distractibility (4), impulsivity (9), motor hyperactivity (7), directing attention (5), sustaining attention (6), shifting attention (4), initiative (5), planning (4), execution of action (8), and evaluation (3). Teachers were instructed to rate the child's behaviour on a three-point scale ("not a problem"; "sometimes a problem"; and "often a problem").

Visuospatial reasoning ability was measured based on the following two subtests:

(1) Non-verbal reasoning ability was evaluated using Raven's Standard Progressive Matrices (RSPM) test, which consists of a visuospatial task (Raven and Court, 1998; John and Raven, 2003). This test was carried out in a group session. The full test comprises 60 items, of which a shortened version was used containing 30 items (every second item). The task was to complete a picture matrix by selecting the single correct option from six to eight choices to fill in a missing part. The maximum time limit was 15 minutes, and scores were based on the number of correctly responded items.

(2) A block design test (WISC-IV) (Lynne Beal, 2004) was used to assess visuo-spatial ability. The test presents nine red and white square blocks and a booklet of cards with different colour designs that can be made using the blocks. The task was to organise the blocks according to the design shown on cards (drawn by the examiner) as quickly and accurately as possible.

2.3 Experimental procedures: Attention Network Test for children

In Studies I–III, a modified version (adapted for children) of ANT (Neuhaus et al., 2010) was used to evaluate the three attentional network subprocesses: alerting, orienting, and inhibition. The stimulus consisted of a row of five horizontal fish (see **Figure 1)**. The centre fish was the target, and the two fish on

either side of the target were referred to as flankers. Throughout the experiment, participants were instructed to keep their eyes on the fixation cross and report the swimming direction of the target (centre fish) by pressing the corresponding button in the button box.

One of the four cues appeared prior to the target stimulus: no cue, double cue, centre cue, or spatial cue. For the double cue condition, two asterisks were shown simultaneously above and below the fixation cross. For the centre cue condition, an asterisk was presented on the fixation cross. For the spatial cue conditions, an asterisk was presented in the location of the upcoming stimulus.

The stimulus array appeared either above or below the fixation cross where the double cue or spatial cue appeared. Flankers and target in the same direction were termed congruent; flankers in the opposite direction to the target were termed incongruent.

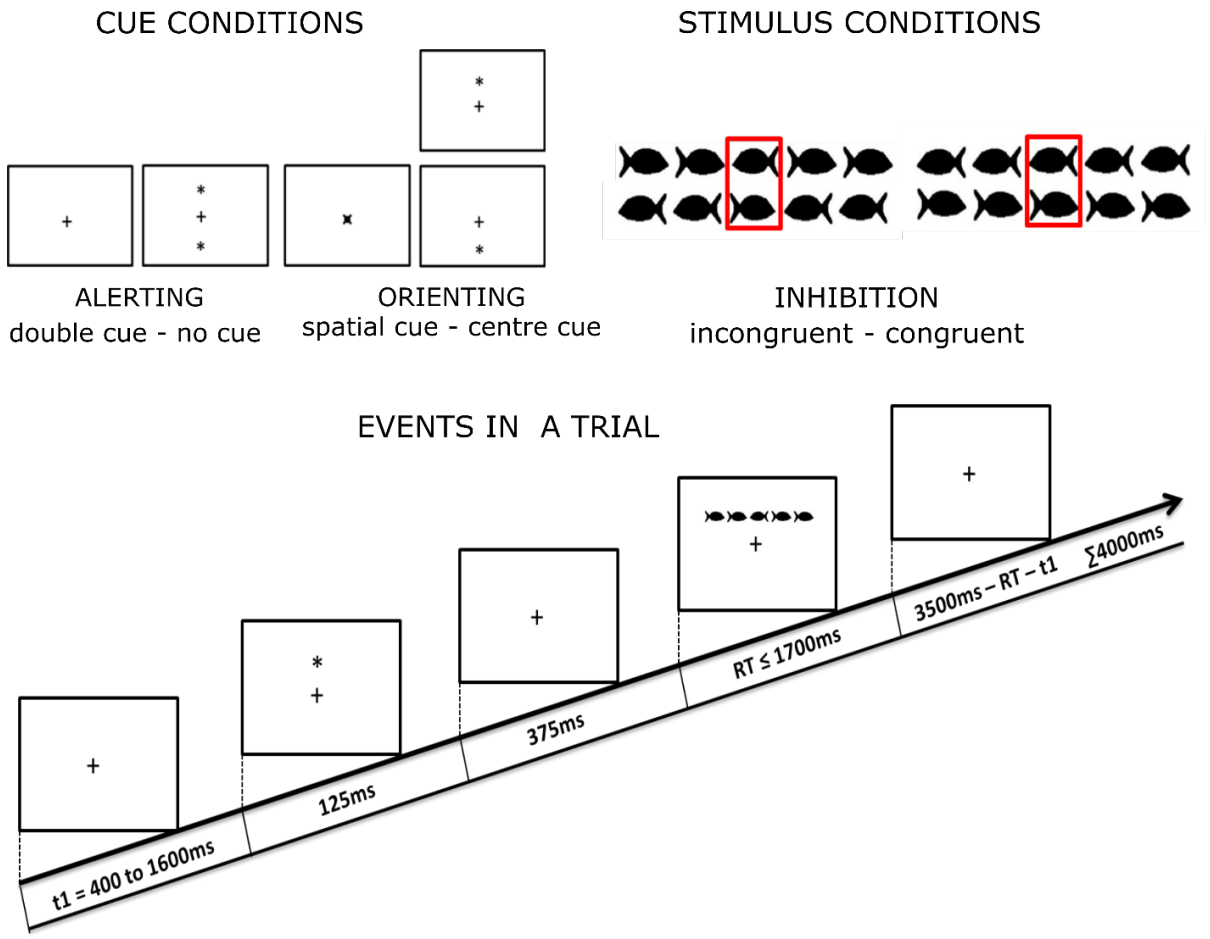


FIGURE 1 Schematic representations of the Attention Network Test for children. Cue conditions: no cue, double cue, centre cue, and spatial cue. Stimulus conditions: congruent target and incongruent target. Behavioural performance of the alerting effect is measured by reaction time (RT) differences between double-cued and non-cued trials; orienting effect is measured by RT differences between centre-cued and spatially cued trials; and inhibition effect is measured by RT differences between incongruent and congruent target trials. A sequence of events in a trial is shown below the cue conditions and stimulus conditions.

2.4 EEG and eye-tracker data acquisition

Electroencephalography (EEG) data were collected in a dim light room with sound attenuation at the University of Jyväskylä, Finland, with a high-density array of 128 Ag-AgCl electrodes in HydroCel Geodesic Sensor Nets (Electrical Geodesics Inc.). Based on the international electrode positions of the 10–10 system, electrode numbers 11, 55, 65, and 90 corresponded to Fz, CpZ, PO7, and PO8, respectively (Luu & Ferree, 2000). The ANT experiment was designed on a Dell Precision T5500 workstation using the Experiment Builder (1.10.1630) application. The EEG data were amplified using the NeurOne amplifier (Mega Electronics Ltd.). The impedance of the electrodes was kept below 50 kΩ throughout the measurement, and the performance of the EEG data was tracked during the EEG recording. EEG was referenced online to the Cz electrode and sampled at 1000 Hz. During EEG data recording an online high-pass filter of 0.16 Hz and a low-pass filter of 250 Hz were applied. In addition, eye movement data were collected for both eyes using a table-mounted Eyelink 1000 eye-tracking system at 1000 Hz (SR Research Ltd.).

2.5 Preprocessing of EEG data and eye tracking data

EEG data were pre-processed and analysed using MatLab R2014a, along with EEGLab (Delorme & Makeig, 2004) (Swartz Centre for Computational Neuroscience, San Diego) and FieldTrip (Oostenveld et al., 2011) toolboxes, BESA Research 6.1, and BESA Research 7.0 (BESA GmbH, Munich). The EEGLab add-on EYE-EEG was used to preprocess the raw eye tracking data (Dimigen et al., 2011). Using EEGLab, bad channels in the continuous raw EEG data were interpolated, and EEG and eye tracking data were synchronized using event triggers. The synchronisation quality was investigated by the linear regression line which quantifies the relationship between latencies of EEG data and eye tracking data. These are the common steps used in this dissertation to combine EEG and eye tracking data.

The pre-processing steps for Studies I and II were as follows. A 0.5 Hz high-pass filter (fifth-order, Butterworth zero-phase filter) was applied to the raw EEG data. Data were segmented into 1200 ms epochs (200 ms before cue onset and 1000 ms after cue onset) for no cue, double cue, centre cue and spatial cue trials, and 900 ms epochs (200 ms before and 700 ms after target stimulus onset) for congruent and incongruent target trials. A 30 Hz low-pass filter (sixth order, Butterworth zero-phase filter) was then applied. The baseline for filtered segmented data was set to -200 ms and 0 ms. If the gaze location on the display screen was outside the specified pixel region (860–1060, 440–640 (x , y), the trial was omitted from the further analysis. Trials with a difference between the maximum and minimum voltages exceeding 175 μV within the analysis time window (target N1 = 140–200 ms; target P3 = 480–700 ms) were rejected before

calculating the average. Accepted trials for each participant were averaged using the above criteria. The average ERPs were re-referenced to the averaged reference. Each group (control, AP, and RD) and each condition (no cue, double cue, centre cue, spatial cue, congruent target, and incongruent target) had a minimum of 30 trials for averaging, with the following exceptions: One participant had a minimum of 22 trials in the no cue and other cue conditions for averaging in the AP and RD groups, and two subjects had a minimum of 24 trials in the no cue condition. Additionally, the averaged data were visually inspected and compared to those of other participants.

The preprocessing steps for Study III were the same as in Study I and Study II except for filter settings. The raw EEG data was bandpass filtered in a range of 1–100 Hz (a fourth order, zero-phase Butterworth IIR filter). A notch filter of 50 Hz with a bandwidth margin of 1 Hz was applied to the bandpass filtered EEG data. The criteria for data segmentation, eye blink trial rejection, and amplitude threshold rejection were the same as in Studies I and II. Accepted trials using the above criteria were imported into BESA Research 7.0. Each condition (no cue, double cue, centre cue, spatial cue, congruent target, and incongruent target) in the control group had a minimum of 30 trials for time-frequency analysis. One participant had 27 trials for non-cued and double-cued stimuli, one participant had 27 for double-cued target stimuli, and one participant had 29 trials for non-cued target stimuli. Data quality of the data of these participants was not affected. Each participant dataset was visually inspected.

2.6 Source-level analysis

In Study I, ERP-based source analysis was performed in BESA Research 6.1 to estimate the brain sources associated with the three subprocesses of the attentional network (alerting: double-cued vs. non-cued trials; orienting: spatially cued vs. centre-cued trials; inhibition: incongruent vs. congruent target trials). The distributed source model classical LORETA analysis recursively applied (CLARA) and 12-year-old age-appropriate Finite Element Method (FEM) head model implemented in BESA Research 6.1 were selected. The latency of interest for the N1 and P3 periods of the post-target stimulus were 140–200 ms and 480–700 ms, respectively. These time windows were chosen based on the results of non-parametric, cluster-based permutation t-tests, which are discussed below. In the grand-averaged ERPs, all the conditions were combined and source analysis was carried out for the above-mentioned N1 and P3 time intervals. A regional source was fixed in the foci obtained from the CLARA estimation. Residual variances were calculated to examine the appropriateness of fit of the regional source in each condition and in each group. These sources were constructed as a spatial filter for the N1 and P3 periods to investigate alerting, orienting, and inhibition subprocesses of attention in control children, children with AP (Study II), and children with RD (Study II).

2.7 Time-frequency analysis

Pre-processed individual ERP trials from MatLab were imported into BESA Research 7.0 to compute the time-frequency. Dummy triggers were inserted (after 200 ms) in each trial in order to define the baseline and epoch time windows for each trial. For temporal spectral analysis, we applied the preprocessing trial setting in BESA Research 7.0. In BESA Research 7.0, time-frequency sampling was defined with a frequency sampling of 0.50 Hz and a time sampling of 100 ms. The lower and higher frequency cutoff range was set between 1 Hz and 90 Hz, respectively. Complex demodulation was performed for each trial to convert time-domain data into time based frequency domain (Papp & Ktonas, 1977). Time-frequency power spectrum analysis was carried out using the Temporal Spectral Evolution (TSE). TSE calculates the spectral amplitude density of each channel over time and frequency normalised relative to the baseline for each frequency. In addition, evoked activity from the analysed TSE data was subtracted to test the induced non-phase locked activity.

2.8 Statistical analysis

2.8.1 Statistical analysis of RT performance

In Studies I and II, paired-sample t-tests and repeated measures ANOVA were calculated using IBM SPSS Statistics version 24. Trials with incorrect responses, unattended trials, and trials excluded in the EEG data preprocessing were not included in the RT performance analysis. In Study I, the significance of RT performance between conditions in each subprocess (alerting: non-cued vs. double-cued trials; orienting: center-cued vs. spatially cued trials; inhibition: incongruent vs. congruent target trials) was calculated using paired-sample t-tests.

In Study II, the significance of RT performance between the groups (control, children with AP, children with RD) and subprocesses (alerting: non-cued and double-cued target stimuli; orienting: centre-cued and spatially cued target stimuli; inhibition: incongruent and congruent target stimuli) were calculated using repeated measures ANOVAs. The significance of RT between conditions in each subprocess within the groups was calculated using paired-sample t-tests.

2.8.2 Statistical analysis of ERP responses at sensor level and time-frequency power spectrum

In Study I, non-parametric cluster-based permutation t-tests were computed as a two-tailed test using BESA Statistics 2.0 (BESA GmbH, Munich) to evaluate the significance of the ERP field potentials across all the electrodes between conditions in each subprocess (alerting: double-cued vs. non-cued trials;

orienting: spatially cued vs. centre-cued trials; inhibition: incongruent vs. congruent target trials) within group (control). In Study II, the above t-tests were performed between conditions in each subprocess and group (control, AP, and RD). In Study III, non-parametric cluster-based permutation t-tests were computed to evaluate the statistical significance of the obtained event-related phase-locked values at each specific time-frequency band for each channel between conditions in each subprocess. The start and end frequencies for specific time-frequency bands were defined as follows: 4–8 Hz (theta), 8–14 Hz (alpha), 14–30 Hz (beta), 30–45 Hz (lower gamma), and 55–80 Hz (higher gamma). For alerting and orienting subprocesses, statistics were calculated between 200 ms before cue onset and 1000 ms after cue onset (target appears after 500 ms of cue onset). For the inhibition subprocess, statistics were calculated between 200 ms before target onset and 700 ms after target onset. The number of permutations was 1000, and the cluster alpha threshold level was 0.05. The neighbour distance between electrodes was 3 cm.

2.8.3 Statistical analysis of source-level data

In Study I, source-level paired t-tests were computed using a two-tailed test on the individual-level source waveforms associated with each neuronal source obtained from N1 and P3 time intervals between conditions in each subprocess (alerting: double-cued vs. non-cued trials; orienting: spatially cued vs. center-cued trials; inhibition: incongruent vs congruent target trials).

In Study II, t-tests were performed between conditions in each subprocess and groups (control vs. AP; control vs. RD; AP vs. RD) for residual variance using SPSS version 24. Each source activity was t-tested against zero to ensure the presence of an actual source. As a result, the left anterior temporal lobe in the alerting and orienting networks was omitted from further analysis. Source-level statistics were performed using 2 (conditions) x 3 (groups) repeated measures ANOVAs in SPSS version 24. The alpha level was adjusted using a false discovery rate method (Benjamini & Yekutieli, 2005) to correct the multiple comparisons of RT and neuronal sources.

3 RESULTS

3.1 Study I: Attentional subprocesses in typically developing children as revealed using brain ERPs and their source localisation

In Study I, RT performance, brain ERPs (see **Figure 2)**, and neuronal sources associated with the subprocesses of the attentional network were examined in typically developing children using a modified version of the Attention Network Test (ANT).

Significant alerting, orienting, and inhibition effects were observed in the RT performance level. The RT to the non-cued target stimuli was 64 ms slower than the RT for the double-cued target stimuli (alerting subprocess). RT for spatially-cued target stimuli was 55 ms faster than that for centrally-cued target stimuli (orienting subprocess). RT for congruent target stimuli was approximately 122 ms shorter than RT for incongruent target stimuli (inhibition subprocess).

Summary of the cluster-based permutation tests for ERPs and neuronal source localisation results are reported in the below **Figure 3 and Table 2**, respectively.

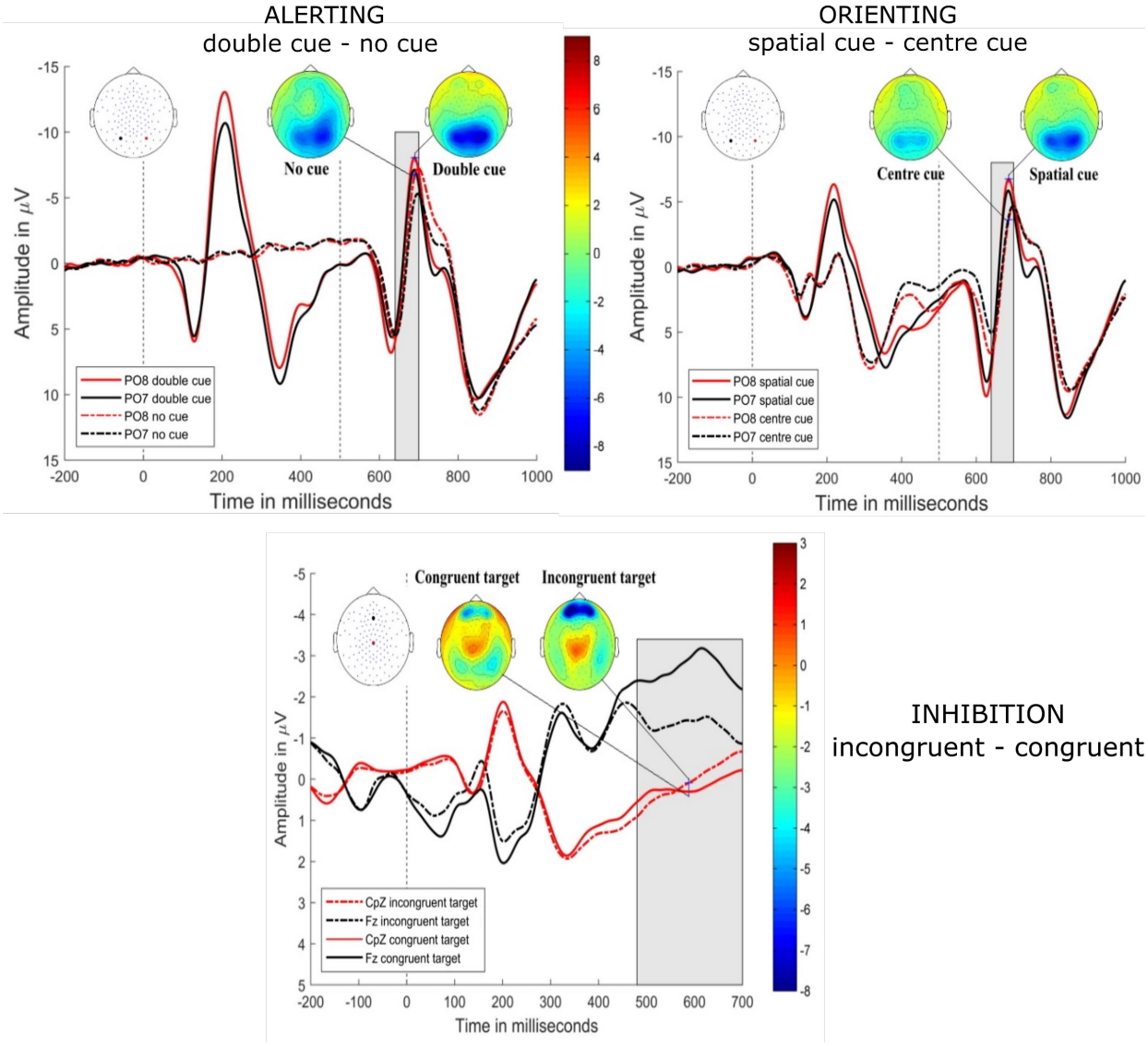


FIGURE 2 Grand-averaged ERP waveforms (n = 83) for double-cued (solid lines) vs. non-cued (dotted lines) trial; spatially cued (solid lines) vs. centre-cued (dotted lines) trials; and incongruent (dotted lines) vs. congruent (solid lines) target trials. For alerting and orienting effects, cue onset is at 0 ms and target onset is at 500 ms; waveforms are depicted from the posterior electrodes PO8 (right hemisphere) and PO7 (left hemisphere). Topoplots for each condition in alerting (double-cued and non-cued trials), orienting (spatially cued and centre-cued trials), and inhibition (incongruent and congruent target trials) are shown at 189 ms, 186 ms, and 612 ms, respectively, from the target onset period. For inhibition effect, target onset is at 0 ms; waveforms are depicted from the central electrode CpZ and frontal electrode Fz. Baseline is between -200 and 0 ms.

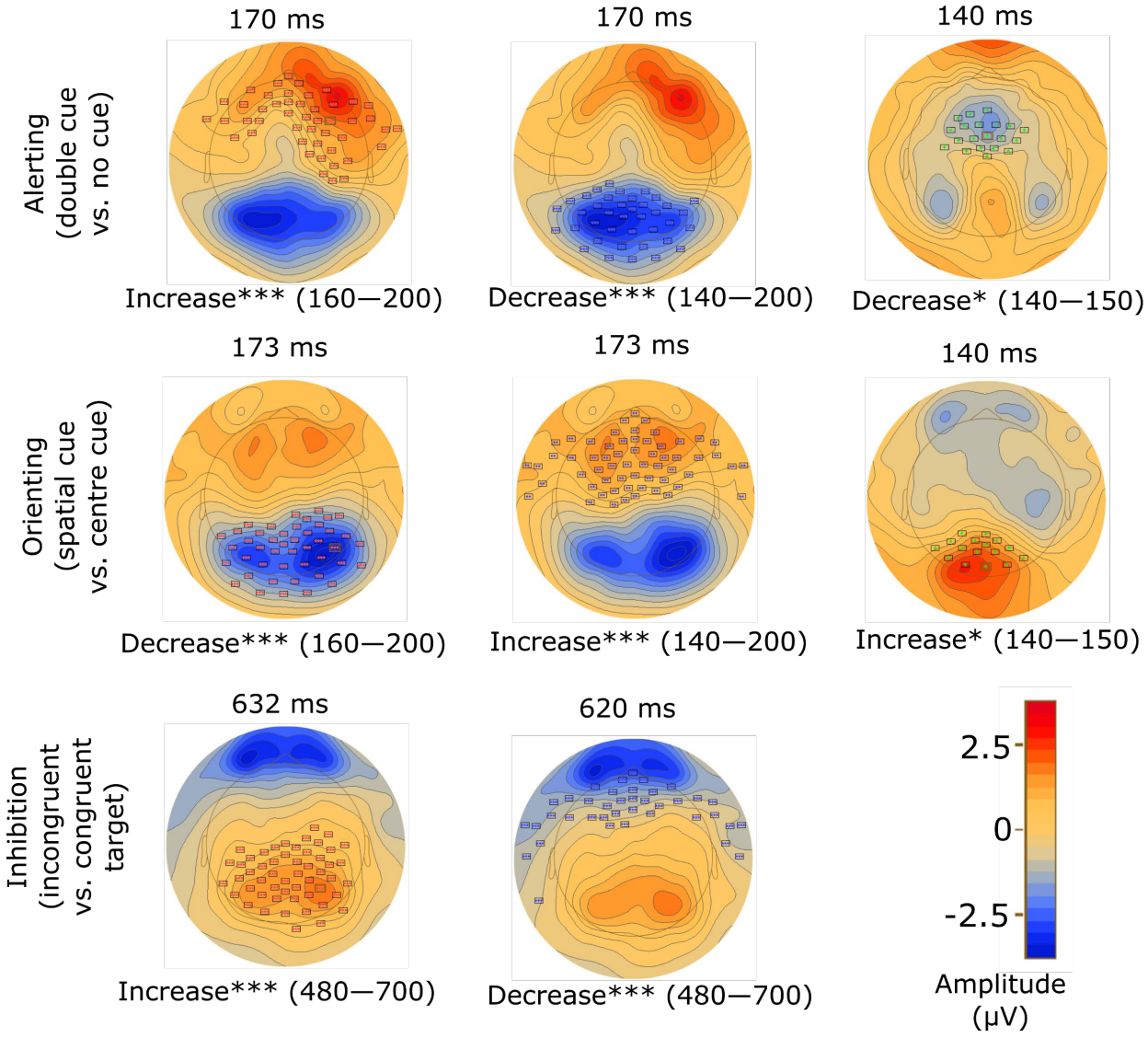
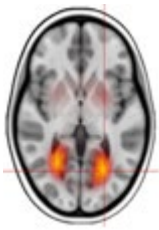
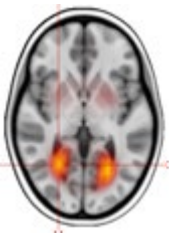


FIGURE 3 Cluster-based permutation results for ERPs and amplitude difference topographies for alerting (double-cued vs. non-cued trials; first row), orienting (spatially cued vs. centre-cued trials; second row), and inhibition (incongruent vs. congruent target trials; third row) in typically developing children (n = 83). The values at the top of each topoplot show the topographic distribution at the time point from target onset showing maximum amplitude difference. The latency range (in ms) of increase or decrease of amplitude difference is given below each topoplot: *** denotes $p < 0.0005$, ** denotes $p < 0.005$, and * denotes $p < 0.05$.

TABLE 2 Summary of neuronal source localisation in typically developing children (n = 83).

Source	 L Anterior temporal lobe	 L Occipital lobe (BA19)	 R Occipital lobe (BA19)	 R Anterior temporal lobe (BA38)	
Alerting (DC vs. NC)	NS	p = 0.002 (155–188) ms	p = 0.003 (140–177) ms	p = 0.009 (174–200) ms	
Orienting (SC vs. CC)	NS	p < 0.0001 (140–188) ms	p = 0.006 (162–193) ms	NS	
Source	 Medial frontal cortex (BA24)	 Medial prefrontal cortex (BA32)	 L anterior temporal lobe	 L medial temporal lobe (BA36)	 R medial temporal lobe (BA36)
Inhibition (Incon vs. Con)	NS	p < 0.001 (510–700) ms	p < 0.0001 (480–700) ms	NS	NS

Note: NS denotes not significant.

3.2 Study II: Attentional subprocesses in children with AP and children with RD as revealed using brain ERPs and their source localisation

In Study II, RT performance, brain ERPs, and their neuronal-level source analysis were investigated using the ANT task in control children (n = 77), children with AP (n = 15), and children with RD (n = 23). The neuronal-level source analysis in children with AP and children with RD was carried out based on the a priori region of the control children from Study I.

RT performance analysis using repeated measures ANOVA revealed a significant main effect of condition (alerting: non-cued vs. double-cued target stimuli; orienting: center-cued vs. spatially cued target stimuli; inhibition: incongruent vs. congruent target stimuli) and a significant main effect of group (control children, children with AP, and children with RD) for the three subprocess of attention. There was no significant interaction between conditions and groups. RT performance investigation using post hoc t-tests within group revealed significance between all conditions and no significance for between-group post hoc t-tests.

A non-parametric cluster-based permutation t-tests at sensor level revealed a significant difference between conditions in each subprocess within each group. The alerting (double-cued vs. non-cued trials) and orienting (spatially cued vs. centre-cued trials) effects showed significance in the interval between 140 and 200 ms from target onset. The inhibition effect showed significance in the time period between 480 and 700 ms from target onset. No significant group differences were observed in these sensor level analyses.

An interaction effect at the source-level was noted between alerting conditions (double-cued vs. non-cued trials) and groups (control and AP) in the left occipital lobe. This revealed that children with AP exhibited a larger alerting effect in the left occipital lobe in comparison to other groups. An interaction effect was observed between orienting conditions (spatially cued vs. centre-cued trials) and groups (control and RD) in the left occipital lobe. This showed that control children had a smaller orienting effect in the left occipital lobe in comparison with AP and RD group children (see **Figure 4)**. No significant differences were found between the groups in the inhibition subprocesses. A summary of the repeated measures ANOVA on neuronal sources for the three subprocesses of the attentional network is shown in Table **3.**

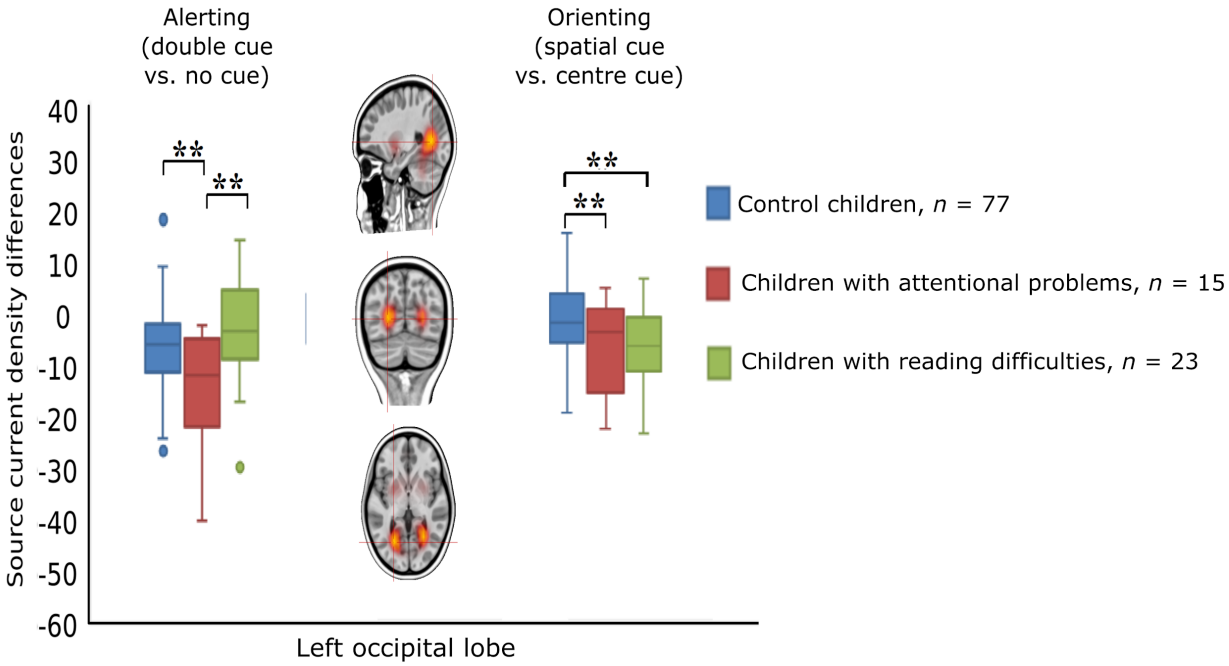


FIGURE 4 Boxplots of alerting (double-cued vs. non-cued trials) and orienting (spatially cued vs. centre-cued trials) for source current density differences for control children (n = 77), children with attentional problems (n = 15), and children with reading difficulties (n = 23). ** denotes $p < 0.005$. The FDR corrected alpha value is 0.012.

TABLE 3 Summary of p-values obtained from repeated measures ANOVA tests for alerting (double-cued vs. non-cued trials), orienting (spatially cued vs. centre-cued trials), and inhibition (incongruent vs. congruent target trials) sources between groups (control vs. children with AP, control vs. children with RD, children with AP vs. children with RD).

Control - *n* = 77 AP - *n* = 15 RD - *n* = 23	Control vs. AP	Control vs. RD	AP vs. RD	Control vs. AP	Control vs. RD	AP vs. RD	Control vs. AP	Control vs. RD	AP vs. RD	Control vs. AP	Control vs. RD	AP vs. RD			
Alerting (double cue vs. no cue)	**R anterior temporal lobe**			**L occipital lobe**			**R occipital lobe**			**L anterior temporal lobe**					
Main effect of condition	0.000	0.000	0.011	0.000	0.005	0.000	0.000	0.000	0.006	0.000	0.000	0.098			
Condition x group interaction	0.941	0.149	0.231	**0.002**	0.130	**0.004**	0.972	0.097	0.208	0.127	0.034	0.757			
Main effect of group	0.293	0.452	0.757	0.000	0.005	0.097	0.020	0.224	0.184	0.888	0.100	0.231			
Orienting (spatial cue vs. centre cue)	**R anterior temporal lobe**			**L occipital lobe**			**R occipital lobe**			**L anterior temporal lobe**					
Main effect of condition	0.926	0.021	0.381	0.186	0.165	0.009	0.001	0.001	0.005	0.370	0.099	0.377			
Condition x group interaction	0.420	0.212	0.157	**0.009**	**0.005**	0.947	0.153	0.135	0.972	0.909	0.424	0.737			
Main effect of group	0.834	0.624	0.853	0.022	0.011	0.848	0.100	0.096	0.851	0.301	0.254	0.954			
Inhibition (incongruent vs. congruent)	**Medial prefrontal cortex**			**Medial frontal cortex**			**L anterior temporal lobe**			**R medial temporal lobe**			**L medial temporal lobe**		
Main effect of condition	0.169	0.787	0.612	0.914	0.215	0.424	0.502	0.171	0.703	0.296	0.034	0.631	0.084	0.361	0.346
Condition x group interaction	0.418	0.334	0.174	0.028	0.292	0.355	0.451	0.755	0.647	0.246	0.048	0.026	0.033	0.647	0.071
Main effect of group	0.299	0.893	0.356	0.173	0.053	0.716	0.235	0.933	0.302	0.023	0.012	0.962	0.070	0.022	0.874

Note: AP – Children with attentional problems, RD – Children with reading difficulties, L – left, R – Right. The values in red color denote significant interaction effects and are less than 0.012 (alpha value of FDR correction).

3.3 Study III: Time-frequency analysis of attentional subprocesses in typically developing children

In Study III, we investigated the time-frequency power spectrum over a range of frequencies (theta, alpha, beta, lower gamma, and higher gamma) to determine their association with alerting, orienting and inhibition subprocesses of the attentional network in children.

The time-frequency power spectrum calculated by event-related phase-locked and induced non-phase locked methods followed the same pattern of results. **Figure 5** shows the cluster-based permutation results of the time-frequency power spectrum during the pre-target period for alerting and orienting subprocesses and during the post-target period for inhibition subprocesses. **Figure 6** shows the cluster-based permutation results of the time-frequency power spectrum during the post-target period for alerting, orienting, and inhibition subprocesses.

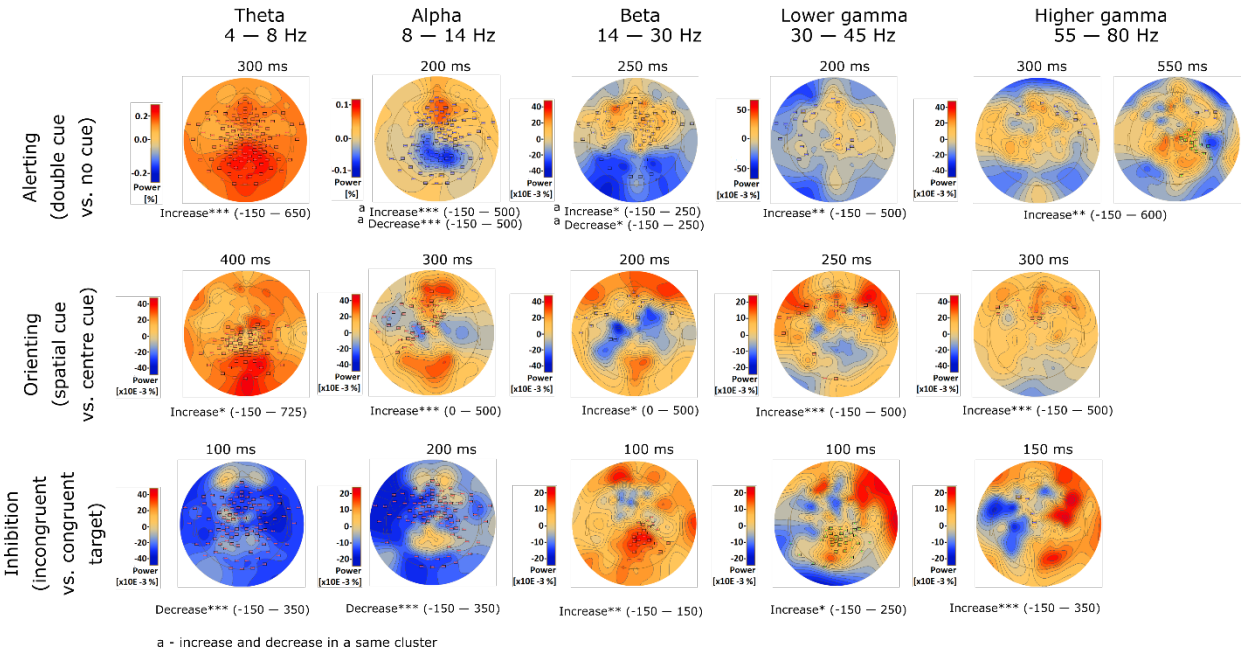


FIGURE 5 Cluster-based permutation tests of time-frequency power spectrum for alerting (double-cued vs. non-cued trial; first row), orienting (spatially cued vs. centre-cued trial; second row), and inhibition (incongruent vs. congruent target trial; third row) subprocesses in typically developing children (n = 77) over theta (4—8 Hz), alpha (8—14 Hz), beta (14—30 Hz), lower gamma (30—45 Hz) and higher gamma (55—80 Hz) bands. The topoplot is shown at the time point with maximum difference during the pre-target interval (0—500 ms) for alerting and orienting subprocesses and post-target interval (0—350 ms) for inhibition subprocesses. The values at the top of each topoplot show the topographic distribution of the power spectrum at the time point showing maximum difference. The latency range (in ms) of the increase or decrease of the power spectrum is given below each topoplot. *** denotes $p < 0.0005$, ** denotes $p < 0.005$, and * denotes $p < 0.05$. Baseline interval is between -200 ms and 0 ms. For alerting and orienting subprocesses, cue stimulus onset is at 0 ms, target stimulus onset is at 500 ms. For inhibition subprocesses, target stimulus onset is at 0 ms.

The alerting effect revealed an increase in theta band power (i.e., theta band power for the double-cued trials was greater than for the non-cued trials) between -150 ms (150 ms before cue onset) and 650 ms (150 ms after target onset) in the frontal and parieto-occipital areas. Increased frontal alpha power and decreased alpha power at the parieto-occipital site were observed between -150 ms (150 ms before cue onset) and 500 ms (target onset). Beta band power increased in the frontal area and decreased in the occipital region between between -150 ms (150 ms before cue onset) and 250 ms (250 ms after cue onset). Lower gamma power increased in the frontal and central areas between -150 ms (150 ms before cue onset) and 500 ms (target onset). An increase in the higher gamma band was observed in the frontal and right temporal areas between -150 ms (150 ms before cue onset) and 600 ms (100 ms after target onset).

The orienting effect revealed an increase in theta band power (i.e., theta band power for the spatially cued trials was greater than for the centre-cued trials) in the parieto-occipital areas between -150 ms (150 ms before cue onset) and 725 ms (225 ms after target onset). Increased frontal alpha and frontal beta band power were observed during the pre-target period (0–500 ms). Lower and higher gamma band power increased in the frontal area between -150 ms (150 ms before cue onset) and 500 ms (target onset).

The inhibition effect revealed a decrease in theta and alpha band powers (i.e., power for incongruent target trials was smaller than congruent target trials) in the bilateral parieto-occipital sites between -150 ms (150 ms before target onset) and 350 ms (350 ms after target onset). Beta band power increased in the parietal area between -150 ms (150 ms before target onset) and 150 ms (150 ms after target onset). Lower gamma band power increased in the parietal area (-150 ms to 250 ms). An increase of higher gamma band power was observed in the right centro-parietal areas between -150 ms (150 ms before target onset) and 350 ms (350 ms after target onset).

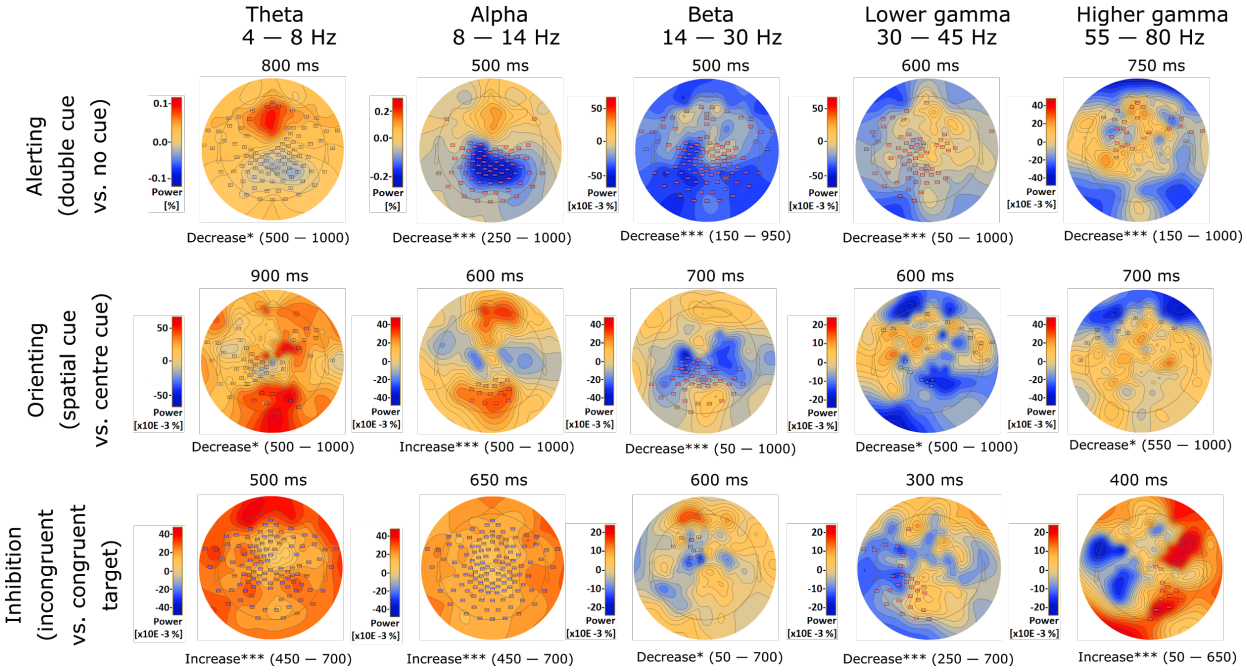


FIGURE 6 Cluster-based permutation tests of time-frequency power spectrum for alerting (double-cued vs. non-cued trial; first row), orienting (spatially cued vs. centre-cued trial; second row), and inhibition (incongruent vs. congruent target trial; third row) subprocesses in typically developing children (n = 77) over theta (4—8 Hz), alpha (8—14 Hz), beta (14—30 Hz), lower gamma (30—45 Hz) and higher gamma (55—80 Hz) bands. The topoplot is shown at the time point with maximum difference during the post-target interval (500—1000 ms) for alerting and orienting subprocesses and post-target interval (0—700 ms) for inhibition subprocesses. The values at the top of each topoplot show the topographic distribution of the power spectrum at the time point showing maximum difference. The latency range (in ms) of the increase or decrease of the power spectrum is given below each topoplot. *** denotes $p < 0.0005$, ** denotes $p < 0.005$, and * denotes $p < 0.05$. Baseline interval is between -200 ms and 0 ms. For alerting and orienting subprocesses, cue stimulus onset is at 0 ms, target stimulus onset is at 500 ms. For inhibition subprocesses, target stimulus onset is at 0 ms.

During the post-target period (500—1000 ms), the alerting effect showed a decrease in theta power (i.e., theta band power for the double-cued trials was smaller than for the non-cued trials) in the parieto-occipital areas. Alpha power decreased in parieto-occipital areas between 250 ms (250 ms before target onset) and 1000 ms (500 ms after target onset). A decrease of beta band power was found in the frontal and parieto-occipital regions between 150 ms (150 ms after cue onset) and 950 ms (450 ms after target onset). A decrease in lower gamma band power was observed in the left hemisphere and bilateral occipital areas between 50 ms (50 ms after cue onset) and 1000 ms (500 ms after target onset). Higher gamma showed a decrease in the frontal and bilateral occipital areas between 150 ms (150 ms after cue onset) and 1000 ms (500 ms after target onset).

The orienting effect revealed a decrease in theta band power (i.e., theta band power of spatially cued trials was lower than that of centre-cued trials)in the left centro-parietal area during post-target period (500—1000 ms). Increased alpha

power was observed in the occipital area during the post-target period (500—1000 ms). Beta band power decreased in the central and occipital areas between 50 ms (50ms after cue onset) and 1000 ms (500 ms after target onset). A decrease was found in lower gamma power in the frontal (500—1000 ms) and centro-parietal areas (500—950 ms) after target onset. Higher gamma power decreased in the frontal area between 550 ms (50 ms after target onset) and 1000 ms (500 ms after target onset).

The inhibition effect revealed an increase in theta and alpha bands power (i.e., the power of incongruent target trials was greater than those of congruent target trials) over both hemispheres between 450 ms and 700 ms after target onset. A decrease in beta power was observed in the left central and occipital areas between 50 ms and 700 ms after target onset. A decrease in lower gamma band power was found in the left hemisphere between 250 ms and 700 ms after target onset**.** Higher gamma band power increased in the right occipital and temporal areas between 50 ms and 650 ms after target onset.

4 DISCUSSION

This dissertation aimed to examine the subprocesses associated with the attentional network using EEG/ERP data from ANT task in typically developing children and children with learning problems (i.e., attentional problems, reading difficulties).

Study I includes the investigation of RT performance, ERPs, and their neuronal source activity related to the attentional network subprocesses in typically developing children at the sixth grade in school. RT data revealed that visual cues enhanced the children's performance, as observed in their faster RT. Alerting and orienting visual cues modulated the target-related N1 amplitude in the parieto-occipital areas. Inhibition showed P3 modulation at the mid-frontal and centro-parietal areas. Source level analysis of ERPs showed alerting network activation in the right anterior temporal lobe and bilateral occipital lobe; the orienting network showed activation bilaterally at the occipital lobe; and the inhibition network showed activation in the medial prefrontal cortex and left anterior temporal lobe.

Study II investigated how these attentional subprocesses differ between typical and atypical learners (i.e., children with AP or RD) in terms of RT, ERPs, and neuronal sources. No significant differences were observed between the groups in the RTs and the ERPs at the sensor level. However, neuronal-level source analysis of ERP showed that children with AP exhibited an enhanced alerting effect in the left occipital lobe compared to typically developing children and children with RD. Children in the typically developing group also showed a diminished orienting effect compared with atypical group children.

Study III examined the time-frequency power spectrum in typically children during ANT task. Analysis of the time-frequency power spectrum of the alerting subprocess showed decreased power over the frequency bands at the parieto-occipital and frontal regions during target processing followed by alerting cues. The orienting subprocess during the target period exhibited increased alpha power at the occipital area; decreased theta, beta, and lower gamma power at the central area; and decreased higher gamma power at the frontal area. Inhibition showed increased theta and alpha power in both

hemispheres and, higher gamma power in the right hemisphere, and decreased beta and lower gamma power in the left hemisphere. This suggests different underlying power spectral mechanisms for attentional subprocesses in the children compared to the adult findings in the literature.

4.1 Neuronal mechanisms of attentional subprocesses in typically developing children

In Study I, we investigated alerting (double-cued and non-cued trials), orienting (centre-cued and spatially cued trials), and inhibition (incongruent and congruent target trials) subprocesses of the attentional network in children using a modified version of ANT. RT performance showed spatially cued trial RTs were faster compared to those from centre-cued trials; RTs for congruent trials were faster than the RTs to those from incongruent trials. The modulation of target-related N1 amplitude associated with alerting and orienting subprocesses was observed between 140 and 200 ms in the parieto-occipital areas. The modulation of target-related P3 amplitude associated with inhibition in children was observed between 480 and 700 ms in the centro-parietal and mid-frontal areas. In addition, we carried out source localisation of ERPs related to these attentional subprocesses in children. Significant activation for the alerting network was observed bilaterally in the occipital areas and in the right anterior temporal lobes; the orienting network was activated in the bilateral occipital lobe; and the inhibition network was shown in the medial prefrontal cortex and left anterior temporal lobe.

RT performance data from the ANT task in Study I was inline with previous studies in children (Mezzacappa, 2004; Rueda, Fan, et al., 2004; Williams et al., 2016; Zhou et al., 2011) and adults (Fan et al., 2002; Galvao-Carmona et al., 2014; Neuhaus et al., 2010; Williams et al., 2016). Children responded approximately 64 ms faster to the double-cued trials compared to non-cued alerting trials. This revealed that alerting cues helped the children to increase their attentional engagement with the task (Posner et al., 2014; Rueda, Fan, et al., 2004). The use of spatial cues by the children was clearly observed in their faster RTs to spatially cued trials, which were 55 ms faster than centre-cued trials. This suggests that the spatial cue could have influenced children to maintain their spatial attention to the cued location prior to the target stimulus and to extract the required upcoming target information from the cued location (Mezzacappa, 2004; Rueda, Fan, et al., 2004). As expected, the children resolved the conflicts between target and flankers by responding approximately 122 ms faster to congruent trials compared to incongruent trials. Thus, the incongruence in the stimulus array delayed the response time of the children. Inline with previous findings (Fan et al., 2002; Neuhaus et al., 2010), our RT results here suggest that cueing improves performance across all three subprocesses of the attentional network in school-age children very similarly to the adults .

We also examined the effects of cueing and conflict resolution at the brain level with ERPs. Our results on the modulation of the target-related N1 amplitude for alerting and orienting cues in children were consistent with earlier findings in adults (Kaufman et al., 2016; Neuhaus et al., 2010; Williams et al., 2016). However, this is the first study to examine the target-related visual N1 amplitude in children (ANT). Alerting subprocesses showed the enhancement of the target-related N1 amplitude for double-cued trials (relative to non-cued trials) at the occipital areas between 140 and 190 ms from target onset. This suggests that children could efficiently process the visually alerted (double-cue) target stimulus. Similarly, orienting subprocesses showed target-related N1 enhancement at the occipital areas at 150–190 ms from target onset. This reflects the improved processing of the spatially cued target stimulus and the allocation of attention to the cued target location. Furthermore, our investigation of inhibition subprocesses revealed the modulation of the target-related P3 amplitude at the centroparietal and midfrontal areas in children between 480 and 700 ms from target onset. During the incongruent trials, children showed enhanced P3 amplitude compared to congruent trials which is inline with previous studies in children (Kratz et al., 2011; Rueda et al., 2012). The higher discriminability between the target and flankers during incongruent trials may have led to enhanced P3 amplitude in the centroparietal areas (Linden, 2005).

As a further step in the analysis, we investigated the subprocesses of the attentional network at the neuronal source-level in order to disentangle possible target-related N1 sources associated with alerting and, orienting and target-related P3 sources associated with inhibition. Source localisation of the target-related N1 period between 140 and 200 ms from target onset showed activation in the left and right occipital lobes, left anterior temporal lobe, and right anterior temporal lobe. The deep sources localised in the cerebellum and pons were excluded from further analysis: it is recognised that localisation of deep sources exhibits higher error and lower reliability (Dale & Sereno, 1993; Tyner et al., 1989).

The alerting effect showed significant activation in the left and right occipital lobes and the right anterior temporal lobe. The activation of left and right occipital lobes could be related to the increased visual processing of the target stimulus that appears in the cued area (Corbetta et al., 1998; Hopfinger et al., 2000; van Voorhis & Hillyard, 1977). The activation of the right anterior temporal lobe in our study was consistent with the results from previous fMRI studies (Fan et al., 2005; Konrad et al., 2005) and PET studies (Sturm et al., 1999; Sturm & Willmes, 2001) on intrinsic alertness. This lobe has been linked to an enhancement in alertness during target stimulus processing of the preceding warning cues (Amado et al., 2011; Thiel & Fink, 2007). Our results showed a lack of activation in the frontal and parietal areas in children as compared with the previous literature in children and adults which is discussed below.

For the orienting network the activation of the bilateral occipital lobe at 140–200 ms from target onset was associated with gaze shifts and eye movements during the appearance of the target stimulus with flankers (Corbetta et al., 1998). fMRI studies in adults have shown the orienting activation in the TPJ, bilateral

superior parietal lobe, and posterior parietal areas (Fan et al., 2005; Konrad et al., 2005; Xuan et al., 2016) and in children superior frontal gyrus, and occipital areas (Konrad et al., 2005). The findings of our orientation network support evidence from other functional neuroimaging studies in adults and children linked to the activation of the occipital lobe (Konrad et al., 2005; Xuan et al., 2016). As with alerting, the orienting network in our study showed a lack of frontal-parietal activation in children. Previous studies have suggested that frontal and parietal regions in adults could be linked to a state of preparedness for evaluating non-specific cued-target information (Fan et al., 2005; Périn et al., 2010). There are several possible explanations for the lack of activation in the frontoparietal areas in children. This may, for example, be because this state of preparedness develops after the age of 12 (Casey et al., 2004). However, the experimental design used in our study differs from the previous studies in adults, including the shape and size of the stimulus, the location of the target (vertical or horizontal to fixation cross), and the inter-stimulus interval duration between cue and target (Fan et al., 2005; Galvao-Carmona et al., 2014; Konrad et al., 2005). Earlier findings have suggested that these parameters may have an influence on task demands and network effects (Jennings et al., 2007; Ridderinkhof et al., 1997).

For the inhibition effect, the left anterior temporal lobe and medial prefrontal cortex showed significant activation in children. A previous fMRI study in children seems to support our finding in the activation of the left temporal lobe associated with response inhibition (Bunge et al., 2002). Our inhibition network results are consistent with several neuroimaging studies in children and adults, which link conflict resolutions to prefrontal cortex functionality, including the anterior cingulate gyrus. (Fan et al., 2005; Fan, Fossella, et al., 2003; Konrad et al., 2005; Rueda et al., 2012; van Veen & Carter, 2002). Ultimately, the combined study of RT performance, ERPs, and source analysis of ERPs provides a comprehensive view of neuronal mechanisms of the attentional network in children.

4.2 Differences in the attentional subprocesses of children with learning problems

In Study II, we extended our investigation of RT performance, ERPs, and neuronal source localisation to children with attentional problems (AP) and children with reading difficulties (RD), again using the ANT task to evaluate the alerting, orienting, and inhibition subprocesses of attention. The control children were the same as in the Study I. There were no significant differences between any of the groups (control , AP, and RD) in RT performance and ERP sensor-level analysis at the target-related N1 or P3 amplitudes. However, neural-level source analysis revealed that the left occipital lobe in children with AP had a larger alerting effect than for control and RD group children (i.e., the difference between the source strength for double-cued and non-cued trials was larger in the AP

group). The left occipital lobe in control children showed a lower orienting effect than AP and RD group children (i.e., the difference between the source strength for spatially cued and centre-cued trials was smaller in the control group). No group differences were observed for the neuronal sources associated with the inhibition subprocess (incongruent vs. congruent trials).

Previous studies of control vs. ADHD groups and control vs. dyslexia groups in children and adults have shown no group differences in RT performance for the alerting, orienting, and inhibition subprocesses (Adólfsdóttir et al., 2008; Kratz et al., 2011; Lundervold et al., 2011). In line with these studies, our RT results observed a lack of group differences indicating that these attentional subprocesses may not be affected in AP and RD group children or that these effects are too small to detect (Huang-Pollock & Nigg, 2003).

Similarly, the sensor-level analysis of ERPs revealed no group differences in the target-related N1 amplitude for alerting and orienting, or the target-related P3 amplitude for inhibition subprocesses. Our P3 amplitude findings in children with AP were contradictory to previous adult studies, although these have reported lower P3 amplitude for adults with ADHD compared to control groups (Hasler et al., 2016; Kratz et al., 2011). This has been linked to an ineffective allocation to stimulus processing and assessment (Hasler et al., 2016; Kratz et al., 2011). The lateralised ANT study in dyslexic adults supports our P3 amplitude findings in children with RD that inhibition of irrelevant information measured by P3 components is retained in the dyslexic group (Mahé et al., 2014).

As discussed above, our results on RT and ERPs at the sensor level reveal no group differences in any of the three attentional subprocesses. The use of cluster-based permutation statistics is one potential explanation: this could elicit overly conservative results compared to previous studies (Maris & Oostenveld, 2007; Pernet et al., 2015). One alternative is to use the ANOVA, but the arbitrary choice of channels in our high-density EEG electrode array is disadvantageous. Thus, we analysed information at the source level to distinguish neural origins in the AP and RD groups on the basis of the control group source model (Santhana Gopalan et al., 2019).

The target-related N1 sources were localised in the left and right occipital lobes, and left and right anterior temporal lobes between 140 ms and 200 ms. The left anterior temporal lobe was excluded from further analysis because it did not reveal any alerting or orienting effects that differed from zero. The target-related P3 sources were localised in the medial prefrontal cortex, medial frontal cortex, left anterior temporal lobe and left and right medial temporal lobes.

Children with AP showed enhanced neuronal activity for the alerting subprocess in the left occipital lobe (double-cued trials vs. non-cued trials). Similar evidence has been observed in structural and functional level studies of the left occipital lobe (lingual gyrus) in ADHD group and control children (Dickstein et al., 2006; Lei et al., 2015; Xia et al., 2014). Based on these previous findings, our results could be interpreted as suggesting that children with AP might have an atypical visual processing mechanism for the warned-target stimulus information. Children with AP also showed larger neuronal activity for

the orienting subprocess (centre-cued vs. spatially-cued trials) in the left occipital lobe compared to control children. A network of occipital lobe, centroparietal areas was speculated to be involved in top-down attentional control, as shown by research that suggest these areas are engaged in shifting attention towards the spatially cued target stimuli (Corbetta et al., 2008; Hopfinger & Ries, 2005; Zhao et al., 2017). This reduction in top-down attentional control reflects one possible explanation for the larger orienting differences between the control group and children with AP in our findings.

Our results on alerting subprocesses between the control and RD groups showed activation in the left occipital lobe that correlates with previous the structural and functional neuroimaging studies of dyslexia (Démonet et al., 2004; Pugh et al., 2000; Richlan, 2012; Xia et al., 2017). A recent review study on developmental dyslexia reported left posterior occipital temporal impairment as a secondary deficiency region in dyslexia. It has been suggested that the phonological processing deficits observed at the temporoparietal junction may lead to interference with the functioning of the left occipital temporal cortex (Kronbichler & Kronbichler, 2018). Thus, it would seem that atypical processing of visual information in the left occipital regions could be seen in children with RD, even for non-linguistic material.

A possible explanation for the non-correspondence results between RT performance and neuronal-level source analysis is that RT performance only reveals the variance in RT performance processes and that only a few cognition features that mediate task performance could be measured in this way (Konrad et al., 2005; Wilkinson & Halligan, 2004). Nevertheless, these findings suggest attentional subprocesses differ between control children and children with AP or RD.

4.3 Attentional subprocesses: Insight from time-frequency domain of ERPs in children

In Study III, we examined the time-frequency power spectrum of ERPs across each trial in typically developing 12- to 13-year-old children (same group as in the Study I) performing the ANT task in order to investigate the attentional subprocesses associated with stimulus-locked modulations in specific frequency bands. We employed event-related phase-locked and induced non-phase locked methods for the time-frequency power analysis of theta (4–8 Hz), alpha (8–14 Hz), beta (14–30 Hz), lower gamma (30–45 Hz) and higher gamma (55–80 Hz) bands associated with the three attentional subprocesses.

During the pre-target period (0–500 ms), the alerting subprocess showed an increase in power spectrum across various frequency bands. Alpha and beta bands showed a decrease in power in the occipital region. The orienting subprocess indicated a frontal increase in alpha but a decrease in the left centre-temporal region. During the post-target interval from 0 to 200 ms, the inhibition

effect revealed a decline in theta (both hemispheres) and alpha band power. Beta, lower gamma, and higher gamma band power increased at the right temporo-occipital site. During the post-target period (500–1000 ms), the power spectrum across the frequency bands decreased for the alerting and orienting subprocesses except for alpha band power. During the post-target period from 350 to 700 ms, the inhibition effect showed an increase in theta, alpha, and higher gamma power; beta and lower gamma band power decreased. However, the topography of these time-frequency effects was different across the frequencies. Furthermore, no changes were observed in the power spectrum that included the event-related phase-locked and induced non-phase-locked power spectrum. This indicated that attentional subprocesses examined by the event-related phase-locked activity are mostly driven by induced brain activity generated by internal processes.

Our findings for the alerting subprocess during the pre-target (0–500 ms) period indicated an increase in power at the frontal site over the different frequency bands (theta, alpha, beta, and gamma). Additionally, alerting showed decreased alpha and beta power in the centro-occipital areas. This is in contrast to a previous adult study (Fan et al., 2007), in which the power spectrum decreased in the entire region over theta, alpha, and beta bands except the left frontal area during the alerting subprocess (centre cue vs. no cue). During the alerting subprocess, the decrease in power spectrum of theta, alpha, and beta bands can be related to the general preparedness for the onset of any visual stimulus and attraction of attention towards the onset of the visual stimuli (Fan et al., 2007). Notably, the alerting cueing conditions differ between our current study (double cue vs. no cue conditions) and those of Fan and colleagues (who used centre cue vs. no cue conditions) (Fan et al., 2007). These cues nevertheless enabled the children to use the cueing information to evaluate the upcoming target equally well.

Similar to alerting, the orienting subprocess exhibited increased power over all the defined frequency bands during the pre-target period. The increase in theta power in the parieto-occipital areas for the orienting subprocess may be associated with focussed attention to the cued location where the target stimuli tended to appear (Basar, 2004, p. 80). Previous studies have indicated that an increase in theta activity is related to a combination of selective and narrowly focused attention processing (Basar, 2004; Schacter, 1977). It is thus possible that the enhancement of the power spectrum during the pre-target period in our study could have resulted from children's attention to the visual cues (Van der Lubbe & Utzerath, 2013). In an earlier adult study using EEG (in which the participant task was to respond to the target based on either a left or a right cue) increased gamma power was observed after cue onset and during visual target stimulus (Doesburg et al., 2008). Another adult study (Fan et al., 2007) also showed an increase in gamma power during the orienting subprocess (spatial cue vs. centre cue). Our findings supported this increase in gamma band activity during the cue period in the orienting subprocess. This may be linked to the

allocation of attention to a cued location even if it is not required to maintain attention at that location (Doesburg et al., 2008).

The inhibition subprocess showed a decrease in theta and alpha band power between 0 and 200 ms over the post-target period, which could be associated with the onset of visual target stimulus (Yantis & Jonides, 1984). A previous ANT study (Studer et al., 2014) in adults found increased beta power in inhibition during the target onset period, which was interpreted as an indicator of increased response speed to target stimulus evaluation. Increased gamma power was observed in the pre-target and target onset period (0 ms to 300 ms) during the inhibition subprocess. Another previous study of gamma synchrony during ANT in adults has suggested that an increase in gamma power resulted in improved selective attention to the target information processing (Doesburg et al., 2008).

The post-target (500–1000 ms) alerting effect revealed decreases of theta, alpha, and beta band power, predominately at the parieto-occipital scalp areas; lower gamma decreased in the left hemisphere, and higher gamma decreased in the frontal and occipital sites. The orienting subprocess also showed a decrease in theta power during the post-target period. Based on the previous literature, the decrease in theta power during target onset in the parieto-occipital areas might be attributed to focused attention, which diminishes the stimulus-related theta power (Basar, 2004; Nobre, 2014). A review study (Klimesch, 2012) on attentional alpha band oscillation has reported that alpha-band activity desynchronisation (decrease in alpha power) is typically related to the anticipation of upcoming target stimulus and engagement of the visual field with the incoming stimulus (Klimesch, 2012; Poeppel et al., 2020). The decrease in beta power in during the post-target period for alerting, orienting, and inhibition subprocesses of attention in our study might reflect the general state of movement preparation (Pfurtscheller, 1981; Tan et al., 2013; Tzagarakis et al., 2015). The gamma power spectrum for the alerting effect is discussed below, following a discussion of the orienting effect.

Orienting subprocesses during the post-target period showed an increase in alpha power relative to the target stimulus period at the occipital area in children, which could reflect inhibition of orientation towards the target (Poch et al., 2017). Earlier studies have also suggested an increase in alpha power as a marker of visuospatial orienting attention (Rihs et al., 2005; Thut et al., 2006). The interpretation of theta and beta power associated with the orienting subprocess is discussed above, along with the alerting effect. Our results showed a decrease in lower and higher gamma activity during the post-target period for alerting and orienting subprocesses. Previous research has suggested that the decrease in gamma power may be associated with the reduced activity of inhibition in children to the attended stimulus (Mangun, 2013, p. 35).

Previous studies have shown that theta enhancement is involved in processing conflicting information, selecting between alternative responses, motor-related monitoring, and error detection (Albrecht et al., 2009; Cavanagh et al., 2009; Cohen et al., 2008; Ridderinkhof et al., 2004). A prior flanker-task study

in children has shown an increase in theta power for inhibition (Albrecht et al., 2009). Our inhibition results showed higher theta band power for the incongruent stimulus (compared to the congruent target stimulus) around 450–700 ms, which is consistent with previous studies and could be interpreted to reflect the process of conflict between these stimuli (Albrecht et al., 2009). The increased alpha band power during inhibition has also been observed in a recent letter-based flanker study and was associated with active inhibition of irrelevant information and processing of relevant information (Janssens et al., 2018; Poch et al., 2017). Decrease in gamma power during the inhibition subprocess has been observed in a visual Go/No-Go study in young adults (Harmony et al., 2009); our results are in line with this earlier study. This, in turn, could be associated with reduced inhibition of irrelevant information processing (Harmony et al., 2009). A previous ANT study and visual Go/No-Go study showed an increase in the gamma band power spectrum (Fan et al., 2007; Fan, Raz, et al., 2003; Harmony et al., 2009). This suggests that it could be related to the preparation and execution of responses for the executive function of attention (Spagna et al., 2020).

4.4 General discussion

The central theme of this dissertation has been the examination of the three attentional subprocesses of alerting (non-cued vs. double-cued trials), orienting (centre-cued vs. spatially cued trials), and inhibition (incongruent vs. congruent trials) in control children, children with AP, and children with RD using EEG data from the ANT experiment.

In Study I, three attentional subprocesses were investigated as a combined study of RT, ERPs, and their neuronal sources in typically developing children. In Study II, attentional subprocesses were examined in children with AP, and children with RD. RT, ERPs, and neuronal analysis results from control children (Study I) were used to examine how the attentional subprocesses differ between typical and atypical children. Study III concentrated on investigating how various frequency bands represent distinct neuronal activity and their functional significance in these attentional network subprocesses in typically developing children.

In terms of RT performance, our studies aligned with previous research in both children (Mezzacappa, 2004; Rueda, Fan, et al., 2004; Williams et al., 2016; Zhou et al., 2011) and adults (Fan et al., 2002; Galvao-Carmona et al., 2014; Neuhaus et al., 2010; Williams et al., 2016). Studies I and II showed that RTs to non-cued trials were slower than the RTs to double-cued trials; RTs to centre-cued trials were slower than the RTs to spatially cued trials; and RTs to incongruent trials were slower than the RTs to congruent trials. On the one hand, no significant difference in RT was found between any of the groups (control = 77; children with AP = 15; children with RD = 23). On the other hand, RTs measure cognitive processes to a limited extent, revealing the outcome of these attentional subprocesses, but not the processes themselves as they unfold in time.

Studies I and II examined the ERPs related to the target N1 modulation for alerting and orienting subprocesses, and target P3 modulation for inhibition subprocesses which showed similarities in terms of time windows between control children, children with AP and children with RD. In other words, Studies I and II revealed the neuronal activity of the attentional subprocesses in the time domain. In addition, Study III analyzed the same ERPs in the frequency domain to investigate the time-frequency power spectrum of neuronal activity. For instance, the modulation of target-related N1 amplitude in the occipital region has been shown to be important for the visual processing of target stimulus characteristics and the influence of warning cue conditions (Fan et al., 2005; Galvao-Carmona et al., 2014; Neuhaus et al., 2010). The modulation of target-related P3 amplitude in the centro-parietal region, meanwhile, reflects the processing of conflicts in the visual stimuli and selection of response (Galvao-Carmona et al., 2014; Neuhaus et al., 2010; Polich, 2007). Our research has shown how the control children and children with AP or RD would reflect a similar pattern of neuronal processing during target processing. In Study III, the power spectrum of event-related phase-locked activity over theta, alpha, beta, lower gamma and higher gamma band points to the cognitive functions associated with these attentional subprocesses.

The EEG-based neuronal-level source analysis performed in Study I served as the reference point for Study II. For example, the spatial source model (with specific regional sources derived from the EEG data of the typically developing children) was employed as a spatial filter to test the validity of the sources related to alerting, orienting, and inhibition subprocesses in children with AP and children with RD. In Study I, the alerting effect (double-cued vs. non-cued trials) and orienting effect (spatially cued vs. center-cued trials) were observed in the left, and the right occipital lobes, and right anterior temporal lobe (only for the alerting effect). The findings in the occipital lobes suggested enhanced visual processing of the alerted target stimuli for the alerting effect (Corbetta et al., 1998; Hopfinger et al., 2000; van Voorhis & Hillyard, 1977) and modulation of gaze shift over the target and flankers for the orienting effect (Corbetta et al., 1998). The findings from Study II point to the important association of these occipital lobes (left hemisphere) with the alerting and orienting effects. This evidence showed that the left occipital lobe in children with AD and children with RD have atypical attentional visual processing of warning and spatially cued target stimuli.

In conclusion, the combined studies I, II, and III of RT performance, ERPs, neuronal sources, and the time-frequency power spectrum provide a comprehensive view of the attentional subprocesses in control children, children with AD, and children with RD. The findings of this thesis show that typical and atypical children exhibit the same level of RT performance during attention network tasks in a controlled experimental environment. Alerting enabled both typical and atypical children to increase their attentional engagement in the task. The spatial cue influenced the children to maintain their spatial attention to the cued location prior to the target stimulus. Moreover, children inhibited the

conflicts between target and flankers by responding more quickly to the congruent stimuli. The brain ERPs suggest that atypical group children also process the cued-target in a similar pattern to typical children. Neuronal source analysis revealed influences on the brain regions associated with the attentional subprocesses in children. Time-frequency power spectrum analysis showed how the power spectrum of different frequency bands could reflect the distinct neuronal activity and its functional significance. In the future, additional analysis of brain connectivity would provide a better understanding of the neural dynamics of attentional subprocesses in control children, children with ADHD, and children with dyslexia. Teachers and special educational workers could benefit from this research as a means of strengthening specific models in the curriculum, thereby enhancing children's learning efficiency.

4.5 Limitations

EEG is one of the most effective methods of examining amplitude and frequency modulations over time as part of comprehensive exploration of the temporal and limited spatial characteristics of measured brain signals. However, EEG based source imaging is known to have a poor spatial resolution, which makes it challenging to estimate the brain location of the neuronal activity from the scalp measurement. EEG source imaging may thus lead to more distributed source activation, which makes it difficult to differentiate near hemispheric areas and separate brain voxels or regions (Costa et al., 2015; Grech et al., 2008). High-density EEG measurement systems combined with sophisticated source localisation algorithms could enhance the reliability of EEG-based source localisation.

In Study I and Study II, we used child template MRI for EEG source localisation; individual MRI data were not measured due to limited resources. The use of this template may have resulted in loss of precision to a certain extent in our resulting source imaging (Brodbeck et al., 2011). However, template MRI-based source analysis has been employed previously (Duffy et al., 2013; Hämäläinen et al., 2011) and remains a preferred option for the use of adult MRI templates to estimate neuronal sources in children. In addition, examining the spatial correspondence between high-density EEG/ERP source localisation and fMRI activation in children (Brem et al., 2009; P. Liu et al., 2019) and individual-level MRI-constrained EEG source localization (Buzzell et al., 2017) could help ensure more precise source localisation.

In this research, the main objective is not exact source localisations (as the spatial resolution of EEG source localisation is at the millimetre scale at best in any case), but to approximate the brain regions for the ANT task related subcomponents across participants. As a result, we have presented the brain areas generating the ERP effects in less detail. The source analysis methodology in this study could provide additional information for use in future studies of individual-level source analysis of data with a high signal-to-noise ratio.

In Study II, we used the spatial filter source model based on the control group as prior information for neuronal activity during an ANT task; some neuronal sources associated with AP or RD may be activated outside these regions of interest. To overcome this limitation, neuronal source imaging could be estimated at an individual subject level mapped to corresponding MRI.

Furthermore, the difference in participant numbers (control = 77; AP = 15; RD = 23) represents an unbalanced design; mixed effects modelling may be more appropriate than the typical parametric tests used here. However, when the data is unbalanced, there are different ways to calculate the sums of squares for ANOVA, and in SPSS, the GLM repeated measures model handles the imbalance of the number of participants between groups by using the Type III sum-of-squares method. This limits the generalisability of the results and warrants further studies to verify the current findings. Another limitation in Study II is the unbalanced in the gender distribution of the groups compared. Most of the children with attention or reading difficulties were boys, while control groups consisted of approximately equal numbers of boys and girls. Further studies on gender-related differences in brain and RT performance associated with attentional subprocesses could be investigated to overcome this limitation.

Study III has its own limitations. First, only children were tested, leaving a potential gap in terms of which effects are unique between children and adults. Second, scalp distributions of the power spectrum give only a rough estimation of the scalp area. Time-frequency analysis at the neuronal source level could support further in understanding of the power spectrum of the functional attentional network in children (Fan et al., 2007). However, our interest here was in the power spectrum changes rather than the exact generator location of the effects.

In turn, the current paradigm was not designed to test the time-frequency power spectrum. For example, the cue and target interval in our experiment is relatively short (375 ms) compared to that of previous study (300–1450 ms) (Fan et al., 2007). This could affect the temporal resolution of time-frequency results. Therefore, we employed the BESA Research 7.0 software to perform the time-frequency analysis, in which zero padding (applied if the epoch or trial length is not sufficient to cover the wavelet width or low pass filter width required for the time-frequency transformation) helped to balance the region-of-interest time window without affecting the temporal resolution and spectral leakage.

Nonetheless, this study provides important additional information on attentional subprocesses in children and their link to frequency power spectra in the time domain. Future studies should test how a longer pre-target time period affects the time-frequency power spectrum.

4.6 Future directions

Future research could involve the classification of brain circuits that underlie attentional subprocesses in terms of the interaction between brain areas and their

frequency information. This could be implemented by performing advanced source localisation in the high-density EEG; the resulting source analysis information could be used for connectivity analysis (Anzolin et al., 2017). This could provide essential knowledge for a better understanding of cortical organisation and the developmental trajectory of the attention subprocesses in typical and atypical children. For instance, connectivity analyses could demonstrate the direction of the effect across regions, including insights as to whether the differences in occipital cortical function are triggered by or independent from top-down control from the frontal areas. Furthermore, the source analysis methodology in this study could serve as a starting point for future studies of individual-level source analysis for data with a high signal-to-noise ratio.

In Studies I and II, we observed a significant amplitude modulation between conditions in each subprocess and groups during ANT. While previous studies have examined the attentional subprocesses at the cue-related period in children (Kratz et al., 2011) and adults (Galvao-Carmona et al., 2014; Hasler et al., 2016) less is known about the neural subprocesses during the ANT cueing period in typically and atypically developing children. Future studies could, therefore, investigate brain-related ERPs during the cueing period to understand the neural mechanisms of attentional subprocesses. A further study on attentional subprocesses in children using MEG could open up new possibilities for the investigation of temporal and spatial characteristics associated with visual attention. Furthermore, the longitudinal follow-ups and examining how the attentional subprocesses affect the development of other areas of cognition, such as reading, speech perception, and auditory and social cognition. In turn, future research could extend our study on time-frequency analysis (Study III) to explore attentional subprocesses in children with AP or RD, and to consider developmental changes in attentional processes over a broader age range.

YHTEENVETO (SUMMARY)

Tarkkaavaisuuden osaprosessit tyypillisesti ja epätyypillisesti kehittyvillä lapsilla aivosähkötoiminnan perusteella

Tarkkaavaisuudella on keskeinen rooli kognitiossa, havaitsemisessa ja reaktion valinnassa. Esimerkiksi tehtävää suorittaessamme kiinnitämme aktiivisesti huomiota tehtävän kannalta relevanttiin tietoon ja tarkkailemme toimintaamme, jotta reagoisimme tarkoituksenmukaisella tavalla. Posnerin visuaalisen tarkkaavaisuuden teoria kolmine osaprosesseineen on vaikuttanut suuresti tarkkaavaisuuden tutkimukseen. Nämä kolme osaprosessia ovat valppaus, orientointi ja inhibitio ja niiden ajatellaan toimivan aivojemme etu- ja takaosien verkostoina Tässä väitöstyössä tutkittiin tarkkaavaisuutta ja sen osaprosesseja sekä tyypillisesti että epätyypillisesti kehittyvillä lapsilla, joilla on tarkkaavaisuushäiriöitä tai lukemisvaikeuksia.

Ensimmäisenä tavoitteena (Tutkimus I) oli selvittää, kuinka tarkkaavaisuusverkoston osaprosessit näyttäytyvät tyypillisesti kehittyvillä lapsilla. Tätä tutkittiin aivojen tapahtumasidonnaisilla jännitevasteilla (ERP) ja niiden lähteiden paikannuksella ANT-testin (Attention Network Test) aikana. Toisena tavoitteena (Tutkimus II) oli verrata kontrolliryhmän ja tarkkaavaisuus- ja lukemisvaikeusryhmien tarkkaavaisuuden osaprosesseja. Kolmantena tavoitteena (Tutkimus III) oli määrittää erilaisia lasten tarkkaavaisuuden osaprosessien taustalla vaikuttavia mekanismeja aika-taajuusanalyysien avulla.

Tutkimuksessa I tutkimme lasten tarkkaavaisuuden verkoston osaprosessien valppautta (testeissä kaksoisvihje tai ei vihjettä), orientointia (sentraalinen ja spatiaalinen vihje) ja inhibitiota (epäkongruentti ja kongruentti kohdeärsyke) ANT-testin lapsille mukautetulla versiolla ja elektroenkefalografialla (EEG). Lasten reaktioajat kohdeärsykkeisiin, joissa oli spatiaalisia vihjeitä, olivat lyhyempiä kuin vihjeettömiin kohdeärsykkeisiin. Kongruenttien ärsykkeiden reaktioajat olivat lyhyempiä kuin inkongruenttien. Kohdeärsykkeen N1-vasteen voimakkuutta, joka liittyi lasten valppauden ja orientoinnin osaprosesseihin, tarkkailtiin välillä 140 ja 200 ms parietaali-oksipitaalisilla alueilla. Lasten inhibitioon liittyvää kohdeärsykkeen P3-vasteen voimakkuutta tarkasteltiin välillä 480 ja 700 ms päälaen ja otsalohkon alueilla. Lisäksi suoritettiin näihin osaprosesseihin liittyvä ERP:n lähdepaikannus. Merkitseviä vaikutuksia valppauteen liittyvässä verkostossa havaittiin bilateraalisti takaraivolohkossa ja oikeanpuoleisessa anteriorisessa temporaalilohkossa; orientointiverkosto näkyi bilateraalisesti takaraivolohkossa ja inhibitioverkosto mediaalisessa prefrontaalisessa aivokuoressa sekä vasemmassa anteriorisessa temporaalilohkossa. Huolimatta aikuisten tuloksia vastaavistakäyttäytymistason tuloksista lasten ERP- ja lähdetulokset eroavat aikuisten vastaavista. Tulokset viittaavat lasten heikompiin tarkkaavaisuuden hallintamekanismeihin valppauden ja orientoinnin osaprosesseissa. Tämä näkyi frontoparietaalisen verkoston aktivoinnin puutteena.

Osatutkimuksessa II tutkittiin tarkkaavaisuuden (valppauden, orientoinnin ja inhibition) osaprosesseihin liittyviä reaktioaikoja, ERP:tä ja lähteiden paikannusta tarkkaavaisuushäiriöitä sekä lukemisvaikeuksia omaavilla lapsilla ANT-tehtävän aikana. Ryhmät eivät eronneet merkitsevästi toisistaan eikä kontrolliryhmästä reaktioajoissa eikä ERP:n sensoritason analyysissä tutkittaessa kohdeärsykkeen N1- tai P3-vasteen voimakkuutta. ERP:n lähdeanalyysi kuitenkin osoitti tarkkaavaisuushäiriöisillä muita kohderyhmiä suurempaa valppautta heijastavaa aktivaatiotavasemmanpuoleisessa takaraivolohkossa. Kontrolliryhmän lähteen voimakkuus vasemmassa takaraivolohkossa oli puolestaan pienempi orientointikoetilanteessa kuin kahdella muulla ryhmällä. Ryhmien välillä ei havaittu eroja inhibition osaprosesseihin liittyvissä lähteissä. Tulokset osoittavat, että tarkkaavaisuusprosessit ovat pitkälle samanlaisia tarkkaavaisuushäiriöitä ja lukemisvaikeuksia omaavilla lapsilla, poiketen kuitenkin valppauden ja orientoinnin osaprosesseissa. Vaikeuksien taustalla vaikuttavat siis erilaiset mekanismit. Nämä reaktioajoista ja hermostollisista lähteistä saadut tulokset tuovat lisäävät ymmärrystämme tarkkaavaisuuden osakomponenteista ja tukevat aiempaa tutkimusta, jonka mukaan tarkkaavaisuusverkosto on hyödyllinen kognitiivinen malli lasten tarkkaavaisuus- ja lukemisongelmien ymmärtämisessä.

Tutkimuksessa III keskityttiin aika-taajuusanalyysiin tyypillisesti kehittyvien lasten ANT-testissä käyttäen tapahtumasidonnaisia, vaihelukittuja sekä indusoituja, vaihelukittumattomia menetelmiä. Valppauden osaprosessin aika-taajuus-analyysi osoitti taajuuskaistojen alentunutta tehoa parietaali-oksipitaalisilla ja frontaalisilla alueilla prosessoitaessa kohdeärsykettä valppausvihjeiden esittämisen jälkeen. Orientoinnin osaprosessissa näkyi kohdeärsykkeen prosessoinnin aikana lisääntynyttä alfa-tehoa oksipitaalisella alueella, vähentynyttä theeta-, beeta- ja matalaa gamma-tehoa keskialueella sekä vähentynyttä korkeaa gamma-tehoa frontaalialueella. Inhibitio osoitti lisääntynyttä theetaa ja alfaa molemmissa aivopuoliskoissa, korkeampaa gammaa oikeassa aivopuoliskossa sekä vähentynyttä beetaa ja matalaa gamma-tehoa vasemmassa aivopuoliskossa. Tämän mukaan lasten tarkkaavaisuuden osaprosesseissa on erilaisia taajuusmekanismeja.

Kaiken kaikkiaan osatutkimusten I, II ja III reaktioajoista, ERP:stä, hermostollisista lähteistä ja aika-taajuusanalyysistä saadut tulokset antavat kokonaiskuvan kontrolliryhmän sekä tarkkaavaisuushäiriöitä ja lukemisvaikeuksia omaavien ryhmien tarkkaavaisuuden osaprosesseista. Väitöstutkimuksen perusteella tyypillisten ja tarkkaavaisuus- tai lukipulmia omaavien lasten reaktioajat ovat samantasoisia tarkkaavaisuusverkostotehtävissä. Tämän mukaisesti sekä tyypillisesti kehittyvät lapset että lapset, joilla oli tarkkaavaisuuden tai lukemisen pulmia, pystyivät valppauden avulla lisäämään tarkkaavaisuuttaan tehtävää suorittaessaan. Spatiaalinen vihje auttoi lapsia säilyttämään spatiaalisen tarkkaavaisuutensa vihjeeseen liittyvän paikan suhteen ennen kohdeärsykettä. Aivojen tapahtumasidonnaiset jännitevasteet viittaavat siihen, että kognitiivisia pulmia omaavan ryhmän lapset myös prosessoivat vihjeeseen liittyviä kohdeärsykkeitä pääosin samalla tavalla kuin tyypilliset lapset. Lähdeanalyysi toi esille aivojen eri alueisiin kohdistuvia vaikutuksia, jotka olivat yhteydessä lasten tarkkaavaisuu-

den osaprosesseihin. Aika-taajuus-analyysi osoitti, kuinka eri taajuuskaistojen tehospektri voi heijastaa erilaista hermostollista toimintaa. Aivojen toiminnallisten yhteyksien lisätutkimus voisi tuoda lisätietoa tarkkaavaisuuden osaprosessien hermostollisesta dynamiikasta kontrolliryhmässä sekä lapsilla, joilla on ADHD tai dysleksia. Esimerkiksi opettajille ja erityispedagogiikan parissa toimiville on hyötyä tästä tutkimuksesta, joka osaltaan auttaa laatimaan oppimista edistävän opetussuunnitelman.

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ORIGINAL PAPERS

I

ATTENTIONAL PROCESSES IN TYPICALLY DEVELOPING CHILDREN AS REVEALED USING BRAIN EVENT-RELATED POTENTIALS AND THEIR SOURCE LOCALIZATION IN ATTENTION NETWORK TEST

by

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Attentional processes in typically developing children as revealed using brain event-related potentials and their source localization in Attention Network Test

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Attention-related processes include three functional sub-components: alerting, orienting, and inhibition. We investigated these components using EEG-based, brain event-related potentials and their neuronal source activations during the Attention Network Test in typically developing school-aged children. Participants were asked to detect the swimming direction of the centre fish in a group of five fish. The target stimulus was either preceded by a cue (centre, double, or spatial) or no cue. An EEG using 128 electrodes was recorded for 83 children aged 12–13 years. RTs showed significant effects across all three sub-components of attention. Alerting and orienting (responses to double vs non-cued target stimulus and spatially vs centre-cued target stimulus, respectively) resulted in larger N1 amplitude, whereas inhibition (responses to incongruent vs congruent target stimulus) resulted in larger P3 amplitude. Neuronal source activation for the alerting effect was localized in the right anterior temporal and bilateral occipital lobes, for the orienting effect bilaterally in the occipital lobe, and for the inhibition effect in the medial prefrontal cortex and left anterior temporal lobe. Neuronal sources of ERPs revealed that sub-processes related to the attention network are different in children as compared to earlier adult fMRI studies, which was not evident from scalp ERPs.

Visual attention identifies and selects information that is relevant to ongoing behaviour, and ignores information that is irrelevant[1]. Several studies have described the development of sub-components of visual attention in children and adults using behavioural paradigms; these studies have also mapped the time course of brain activity across brain areas related to attention networks[2–6]. However, to the best of our knowledge, there are no electroencephalography (EEG) investigations of both event-related potentials (ERPs) and their underlying neuronal sources related to attention networks in children in a single study. In this study, we examined reaction times (RTs), brain ERPs, and neuronal sources associated with attention network sub-components using a modified attention network test (ANT)[7] in typically developing school-aged children.

ANT is an experimental task which measures three sub-components of attention: alerting, orienting, and inhibition[7,8]. ANT[9] is a combination of Posner's cued detection[10] and Eriksen's flanker task[11]. In this test, participants are asked to detect the direction of a middle target item out of a group of five items, often an arrow[5] or, in studies with children, a fish[6]. The target stimulus is either preceded by a cue (centre, double, or spatial) or without a cue (no cue), in order to manipulate the alerting and orienting sub-components of attention[12]. In addition, the direction of the target item can either be congruent or incongruent in relation to the flanker items, thereby manipulating the inhibition sub-component of attention.

Alerting in the framework of attention refers to achieving and maintaining a state of sensitivity to incoming stimulus[8]. Alerting effects can be measured by the difference in RTs to a target stimulus, with a cue versus without a cue. Previous studies showed that a warning cue helps increase alertness and decrease RTs to the target stimulus[5,12,13].

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This alerting effect is also observed in children, although their RTs vary with age and are slower than those of adults. For example, a previous study found that in response to a target with an alerting cue, five-year-old children tended to have longer RTs than seven-year-old children[14]. Similarly, RTs for the ANT in both 10-year-old children and adults have shown significant improvements in behavioural alerting scores as age increases[12].

The functioning of the attentional processes at the brain level has been investigated using ERPs in both children[6,15] and adults[5,16]. The behavioural effects for alerting (visual cue vs no cue) are accompanied by modulations to the posterior visual N1 amplitude at 100–280 ms for the target stimulus[5,16–19]. Previous research showed that both hemispheres exhibit alerting effects, but that they may be stronger in the right hemisphere[7,20]. Generally, in adults, N1 amplitude over the occipital and parietal regions reflects visual processing of target stimulus properties, and is modulated by cue conditions[5,21,22]. However, to the best of our knowledge, there are no studies that employ visual cue manipulation of the N1 alerting effect in typically developing children.

Adult functional magnetic resonance imaging (fMRI) studies have shown that the alerting network is associated with increased activity in the thalamus, temporal parietal junction (TPJ), and prefrontal cortex[13,22]. Recently, a slightly modified experimental design produced results that revealed additional brain areas being activated by alerting in the anterior cingulate cortex (ACC), frontal eye fields (FEF), occipital, and visual areas[23]. These findings imply that the activation of these areas is associated with response preparation and anticipation based on the visual warning cue[23]. The alerting network in children shows neuronal activity in the middle occipital cortex, which extends towards the right superior temporal gyrus. It is suggested that the differences in neural correlates of alerting effects between children and adults are due to maturational changes in neuronal network organization that occur during development[13].

The second sub-component of interest, orientation, is associated with spatial selection. Spatial orienting has three distinct sub-functions: the engagement of visual attention to a particular stimulus, the disengagement of visual attention from a stimulus, and the shifting of visual attention from one stimulus to another[7]. Like alerting effects, orienting effects can be measured by a difference in RTs between centre-cued and spatially-cued target stimuli. This ability to shift attention between stimuli tends to improve between 5 and 14 years of age, and improves further into adulthood, thereby showing progressive development in orienting effect over an extended age period[12,24,25].

Orientation of attention to a cued target stimulus location enhances the N1 ERP amplitude between 110 ms and 280 ms in children[26] and adults[16,19]. Consistently, studies on adults have shown that spatially-cued target stimuli elicit larger N1 amplitude than centre-cued target stimuli, which suggests stronger engagement and lasting effects for the spatial cue with regard to the target stimulus[16,27]. Further, studies have suggested that both the right and left hemispheres of the brain are involved in orienting attention[20]. In addition, the N1 enhancement for orienting to the cued target stimulus location has been observed over occipital and parieto-occipital scalp areas[5], which is similar to the alerting effects described above.

The topography of ERP responses that reflect the orientation effect is partially consistent with the network nodes found in adult fMRI studies, particularly at the TPJ. fMRI studies related to orienting also found other regions, such as the bilateral superior parietal lobe, FEFs, pulvinar, and superior colliculus[13,22,23]. Further, the pulvinar has also been shown to be active during the engagement of visual attention at a particular stimulus in specific spatial location; the posterior parietal lobe is involved in the disengagement of visual attention from a stimulus, while the superior colliculus along with the FEFs and interparietal sulcus are related to the ability to shift visual attention from one stimulus to another[2,7]. A study examining the orienting network in children found responses in the superior frontal gyrus and bilaterally in the occipital cortex[13].

The third sub-component of interest, inhibition, includes mechanisms for resolving conflicts, detecting errors, and selecting actions in response to target stimuli[8]. The inhibition effect, as it relates to conflict resolution, can be demonstrated by the RT difference between incongruent and congruent target stimuli[9]. Previous studies on children[13,14] and adults[5,9] have suggested that such conflicts could increase inhibition of competing visual information and produce interference to response selection.

As with the other sub-components of attention, children show longer RTs than adults when resolving incongruence, but children's RTs improve from 4 to 7 years of age[28]. However, the development of inhibition does not appear to be linear, as there is a larger improvement in RTs from 5 to 10 years of age, while there is a smaller change or no difference between 10-year-olds and adults[12,29].

Inhibition effects can be observed as a modulation of the P3 segment of the ERP amplitude[5,6,15,16]. In the context of the ANT, P3 reflects neural activity related to the processing of cueing information and response control (motor selection)[30]. The time window of P3 is 300–650 ms from target stimulus onset[5,6,16], with a maximal amplitude typically over the centro-parietal scalp area[5,31]. In the ANT, target stimulus-generated P3 amplitudes tend to appear at later latencies in children (10 years old)[6] as compared to adults[16], thereby reflecting a developmental trend in the evaluation of target direction[32] and suggesting a rather late development of inhibitory processes[33].

fMRI sources of an inhibition network have been examined in both children[13,15,34] and adults[22,23,35]. In adults, inhibition appears to include activation of the right ACC, bilateral precentral gyrus, intraparietal sulcus, anterior insular cortex, FEFs, as well as right, middle, and left inferior occipital corteces[23]. In particular, the ACC plays an important role in resolving conflicts[4]. Two theories based on computational models suggest that the ACC is engaged in monitoring conflict, and the lateral frontal areas are involved in resolving the conflict[36]. Large developmental differences exist between children and adults during effective response inhibition[34]. In children (aged 8–12 years), inhibition processes involve the right superior temporal gyrus, bilateral parietal cortex, bilateral occipital cortex, and premotor cortex; however, these processes show less prefrontal cortex activation (inferior and medial frontal gyrus) as compared to that in adults[13,34]. These results suggest an immature development, particularly in the frontal area, in children for the inhibition network[34,37].

Previous studies that employed the ANT used EEG[5,6,27] and fMRI[13,15,22,23] to demonstrate the time course of attention-related brain activations. Yet, ERP studies on attentional processes utilizing attention network test

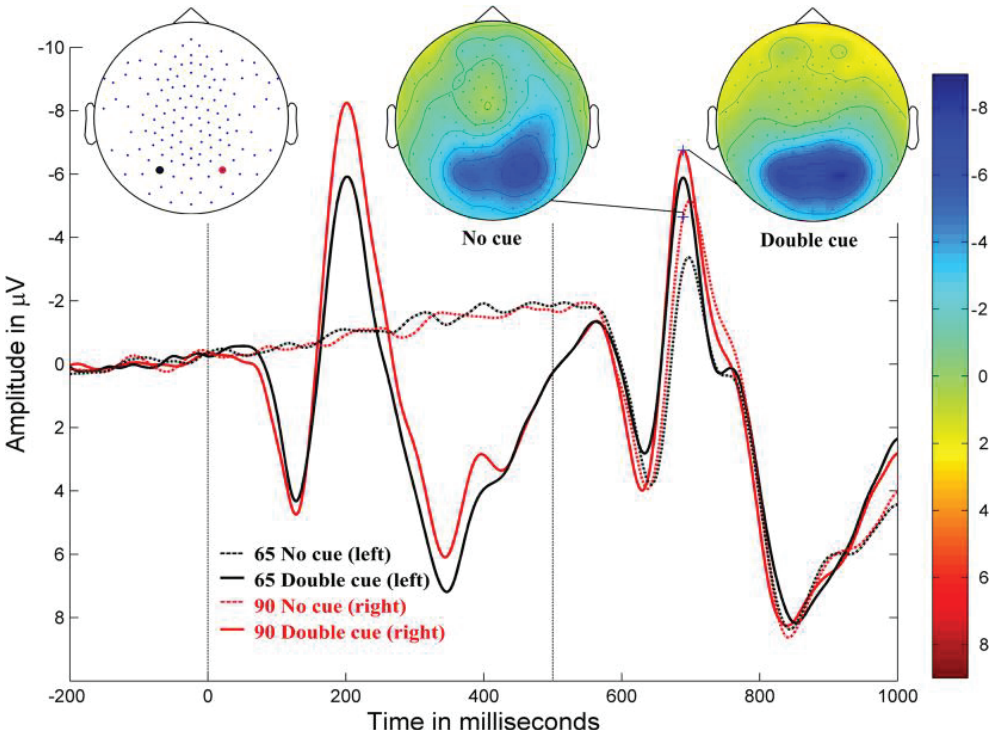

Figure 1. Alerting. Grand-averaged ERP waveforms for the double-cued stimulus (solid lines) and non-cued stimulus (dotted lines) for posterior electrodes (90, red, right hemisphere; 65, black, left hemisphere) in typically developing children (negativity up). Cue onset is at 0 ms and target stimulus onset is at 500 ms. Amplitude topographies for double-cued and non-cued target stimuli at 689 ms (i.e., 189 ms after target stimulus onset).

(ANT) paradigm in school-aged children are rare. Although orienting and inhibition sub-processes have been examined before in children, there is a lack of knowledge on target stimulus N1 in children in the form of a visual alerting cue (double vs non-cued). Further investigation of neuronal sources using high-temporal resolution EEG in typically developing children to identify the brain areas associated with the three attentional sub-processes would help us to understand the time course of activations in the different brain regions involved in the attention network. Our study could provide a reference point, for example, to evaluate attention network sub-components related to linear text reading[38] in children at the brain level, and how this relationship is different in children with attentional problems[6,39].

Based on previous EEG-based studies[5,6,15,16], we expect that alerting and orienting in children would produce larger N1 amplitude for double-cued vs non-cued target stimulus and spatially-cued vs centre-cued target stimulus, respectively, which are potentially associated with efficient processing of stimulus[5]; we also expect that inhibition would produce larger P3 amplitude for a congruent target stimulus, which is associated with the evaluation of target stimulus[21]. Further, based on previous fMRI studies[13,22,23], we also expect that alerting effects would modulate activity in the bilateral occipital lobe, right temporal lobe, FEFs, and prefrontal cortex; orienting effects would modulate activity in the bilateral occipital, parietal, and frontal lobes, and FEFs; and inhibition effe cts[13,15,22,23,34,35] would modulate activity in the bilateral occipital and parietal lobes, right temporal lobe, FEFs, and the medial and prefrontal cortices.

In this study, we investigated the modulation of the N1 amplitude to the target stimulus for both the alerting and orienting networks, and the modulation of target stimulus P3 for the inhibition network in typically developing children aged between 12 and 13 years as part of a larger project[38] (eSeek—Internet and Learning Difficulties: A multidisciplinary approach for understanding reading in new media). We used spatio-temporal topographic maps and the classical LORETA analysis recursively applied (CLARA[40]) distribution model to separately identify the activation of neuronal sources in these three networks. We also performed dipole source modelling using spatial constraints provided by CLARA solutions.

Results

Reaction-time performance. *Event-related potentials.* The grand-averaged ERP waveforms and amplitude topographies for alerting, orienting, and inhibition in typically developing children are illustrated in Figs 1, 2, and 3, respectively.

Cluster-based permutation tests showed significant differences for each attention network contrast (Fig. 4). Significant alerting effects ($p < 0.001$) were presented in a negative cluster (i.e., the negative amplitude of double-cued

Conditions		Accuracy mean (standard deviation)	RT mean (standard deviation) in milliseconds	Paired t-test		
				M (SD)	t-value: df (82)	Cohen's D_z
Alerting	Non-cued	0.96 (0.03)	790 (99)	63.95 (40.26)	14.47***	1.59
	Double-cued	0.95 (0.04)	726 (85)			
Orienting	Centre-cued	0.96 (0.04)	762 (95)	54.31 (48.65)	10.17***	1.12
	Spatially-cued	0.96 (0.03)	707 (88)			
Inhibition	Incongruent	0.98 (0.02)	812 (98)	121.47 (51.85)	21.34***	2.35
	Congruent	0.94 (0.05)	690 (82)			

Table 1. Summary of the accuracy and reaction time (RT) results and statistics. Accuracy (mean and standard deviation) and RT (mean and standard deviation) of each stimulus condition of the ANT. In the paired t-tests, M and SD denote the average difference and standard deviation of the difference between the RTs for two target stimuli, respectively. ***$p < 0.0005$ (two-tailed). The t-values denote test statistics with degrees of freedom (df) of 82. Cohen's D_z denotes the effect size between RTs for different target stimuli.

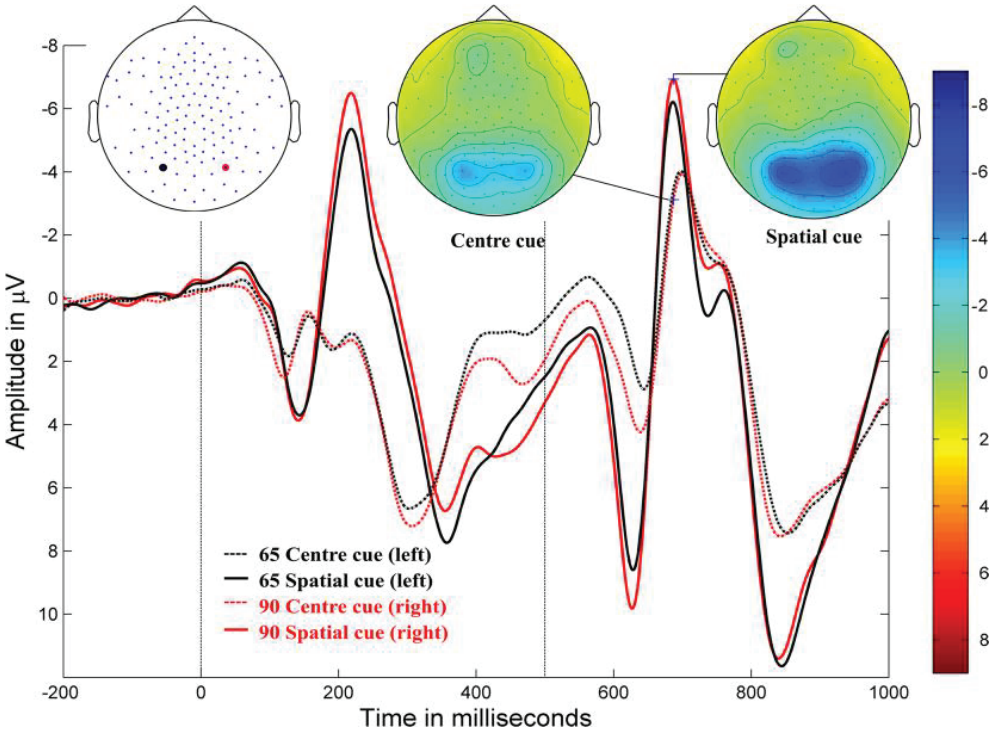

Figure 2. Orienting. Grand-averaged ERP waveforms for the spatially-cued stimulus (solid lines) and centre-cued stimulus (dotted lines) at posterior electrodes (90, red, right hemisphere; 65, black, left hemisphere) in typically developing children (negativity up). Cue onset at 0 ms and target stimulus onset at 500 ms. Amplitude topographies for spatially-cued and centre-cued target stimuli at 686 ms (i.e., 186 ms after target stimulus onset).

target stimulus was larger than the negative amplitude of non-cued target stimulus) in the bilateral occipito-parietal areas, extending from approximately 140–200 ms following target stimulus onset, with a peak at approximately 170–180 ms; the difference between conditions was greater in the left hemisphere. There was also a negative cluster ($p < 0.0001$) over the central region from 140–150 ms, and a positive cluster ($p < 0.0001$) that originated in the frontal region and travelled to the right temporal region from 160–200 ms, with a greater difference in the right hemisphere.

A significant orienting effects ($p < 0.0001$) were evident in a negative cluster (i.e. the negative amplitude of the spatially-cued target stimulus was larger than the negative amplitude of the centre-cued target stimulus) in the bilateral occipital and right temporo-parietal areas, extending from approximately 150–200 ms after target stimulus onset, with a peak at approximately 160–180 ms; the difference between conditions was greater in the right hemisphere. The positive cluster ($p < 0.0001$) moved from the occipital to the mid-frontal area over the time range of 140–200 ms, with a greater difference in the left hemisphere.

Significant inhibition effects ($p < 0.0001$) were shown in a positive cluster (i.e. the positive amplitude of incongruent target stimulus was larger than the positive amplitude of congruent target stimulus) in the mid area and spread over the parietal and occipital areas, extending from approximately 480–700 ms after target stimulus onset,

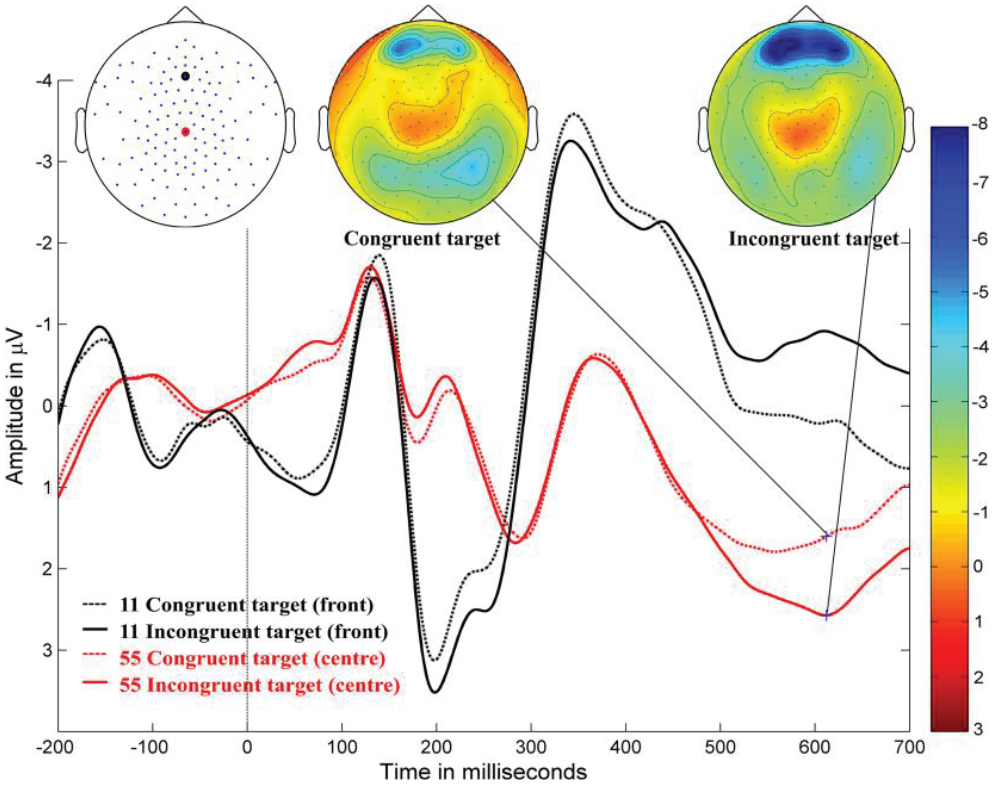

Figure 3. Inhibition. Grand-averaged ERP waveforms for congruent stimulus (dotted lines) and incongruent stimulus (solid lines) at the central electrode (55, red, behind Cz) and the frontal electrode (11, black, at Fz) in typically developing children (negativity up). Target stimulus onset is at 0 ms. Amplitude topographies for the congruent and incongruent target stimulus conditions at 612 ms after target stimulus onset.

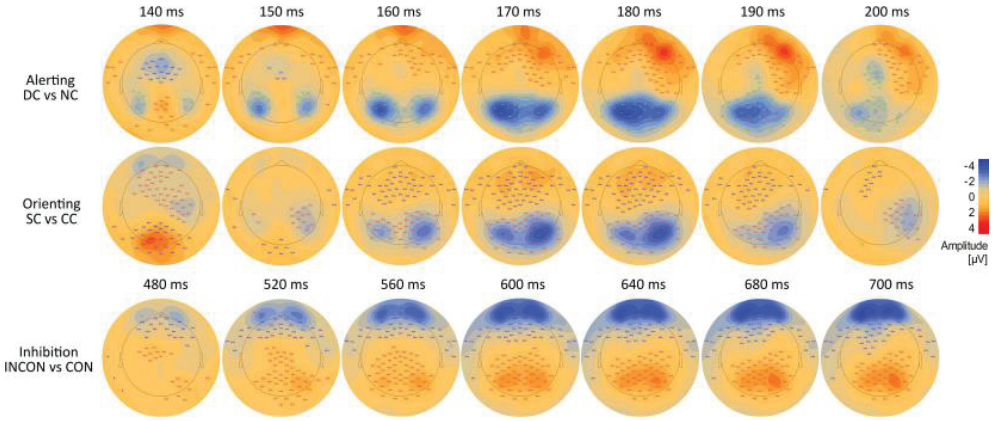

Figure 4. Cluster-based permutation tests for ERPs and amplitude difference topographies between conditions. Alerting: ERPs for the double-cued (DC) vs non-cued (NC) target stimulus (first row); orienting: ERPs for the spatially-cued (SC) vs centre-cued (CC) target stimulus (middle row); and inhibition: ERPs for the incongruent (INCON) vs congruent (CON) target stimulus (last row). Target stimulus onset is at 0 ms. Significant clusters were labelled with stars within the rectangles. ***p-values < 0.0005, **p-values between 0.005 and 0.0005. Blue and red colours indicate negative and positive amplitude values, respectively, from −4 to 4 µV.

with a peak at approximately 560–640 ms; the difference between conditions was greater in the right hemisphere. Further, a negative cluster ($p < 0.0001$) was spread along the mid-frontal and left-central areas between 480 ms

Source	Brodmann area	Talairach coordinates (mm)			*p*-value (latency in ms)	
		X	Y	Z	Alerting (DC vs NC)	Orienting (SC vs CC)
L Anterior temporal lobe		−31.5	−2.9	−11.3	NS	NS
L Occipital lobe	BA19	−24.5	−65.9	2.7	= 0.002 (155–188)	< 0.0001 (140–188)
R Occipital lobe	BA19	24.5	−58.9	2.7	= 0.003 (140–177)	= 0.006 (162–193)
R Anterior temporal lobe	BA38	31.5	4.1	−18.3	= 0.009 (174–200)	NS

Table 2. Talairach coordinates of sources during the N1 period of the target stimulus (140–200 ms). The table presents the *p*-values for alerting (double-cued vs non-cued stimuli) and orienting (spatially-cued vs centre-cued stimuli) sources and the latency of their effects. NS denotes not significant.

and 700 ms, with a greater difference in the left hemisphere. It is important to note that all these clusters did not have equal amplitudes across all time points.

Neural source localization analysis. Figure 5 illustrates the locations of source activations of grand-averaged ERPs collapsed across all conditions (congruent and incongruent stimuli with no cue, double cue, centre cue, and spatial cue) over the time points of the N1 period of the target stimulus (140–200 ms) using CLARA. Brain activations were found bilaterally in the anterior temporal and occipital lobes. Source-level statistics were calculated across individual participant source waveforms, based on the activation strength of the regional sources in the time window (140–200 ms after onset of target stimulus), thereby showing statistically significant effects at the electrode level. As shown in Table 2, for the alerting network, a significant effect was found in the left occipital lobe ($p = 0.002$) between 155 ms and 188 ms as well as in the right occipital lobe ($p = 0.003$) in the time window of 140–177 ms. The right anterior temporal lobe showed a significant response ($p = 0.009$) between 174 ms and 200 ms. For the orienting network, a significant effect was found in the left occipital lobe between 140 ms and 188 ms ($p < 0.0001$), and in the right occipital lobe from 162 ms to 193 ms ($p = 0.006$).

Figure 6 illustrates the locations of source activations of grand-averaged ERPs collapsed across all conditions (congruent and incongruent stimuli with no cue, double cue, centre cue, and spatial cue) over the time points of the P3 period of the target stimulus (480–700 ms) using CLARA. Brain activations were found in the left anterior temporal lobe, medial prefrontal cortex, bilateral medial temporal lobe, and medial frontal cortex. As shown in Table 3, for the inhibition network, significant effects were found in the medial prefrontal cortex ($p < 0.001$) from 510 ms to 700 ms and in the left anterior temporal lobe ($p < 0.0001$) from 480 ms to 700 ms.

Discussion

In this paper, we studied three attentional sub-processes derived from a modified version of the ANT for children. We examined (1) RT performance related to three attention networks: alerting, orienting, and inhibition in 12- and 13-year old typically developing children; (2) modulation of the visual N1 amplitude to the target stimulus by alerting and orienting sub-processes, and modulation of the P3 amplitude to the target stimulus by the inhibition sub-process; and (3) EEG-based neuronal sources related to these three sub-processes. We observed that visually cueing the stimulus enhanced performance; children responded faster in this case than in the absence of a cue. Further, we found that RTs to incongruent target stimuli were slower than those to congruent target stimuli. Alerting and orienting visual cues modulated the N1 amplitudes of target stimulus in the occipital and parietal areas. Further, P3 was modulated by target-to-flanker congruency across the centro-parietal and mid-frontal areas. Furthermore, EEG-based source-level statistics showed significant effects for alerting (double cue vs no cue) in the bilateral occipital lobe and right anterior temporal lobe, orienting (spatial cue vs centre cue) in the bilateral occipital lobe, and inhibition (incongruent vs congruent target stimuli) in the medial prefrontal cortex and left anterior temporal lobe.

The behavioural results of our study replicated those of existing research in both children[12,14,27,41] and adults[5,9,21,27] in terms of RT performance in the ANT. RTs to non-cued target stimuli were approximately 64 ms slower than RTs for double-cued target stimuli. Previous studies have suggested that alerting tends to improve from 10 years of age into adulthood[4,14,42]. RTs for spatially-cued target stimuli were approximately 55 ms faster than those for centrally-cued target stimuli. This shows that, like adults, children utilise orienting cues to extract the specific spatial location of an incoming target, and focus their spatial attention to the location prior to the onset of the target stimulus[12,14]. Our results are in line with previous studies, demonstrating that orienting tends to mature at an early stage of childhood[4,41,42]. The effect of inhibition manifested in faster RTs to a congruent target stimulus compared to an incongruent one, with a delay in response latency of approximately 122 ms for a target stimulus that is not aligned with its flankers. Overall, our results showed that cueing helps to enhance performance in children, while incongruence of the stimuli impedes performance, which follows Fan's[9] and Neuhaus's[5] findings on adults.

The effects of cueing and congruency manipulations were also reflected in the ERPs. Alerting and orienting effects were observed over occipital areas between 140–190 ms and 150–190 ms following target stimulus onset, respectively; whereas alerting effects in adults have shown centro-parietal topography[5]. Further, we found that orienting effects in children align with prior research in terms of effect timing and topographic differences in adults[5]. Inhibition effects were observed at 520–700 ms in the centro-parietal areas. The topographic differences in our study demonstrated a reversed polarity to that from a previous study on adults[5], likely because of a higher P3 amplitude for incongruent stimuli in children, which has also been demonstrated in other studies[6,39]. This developmental effect is further discussed below.

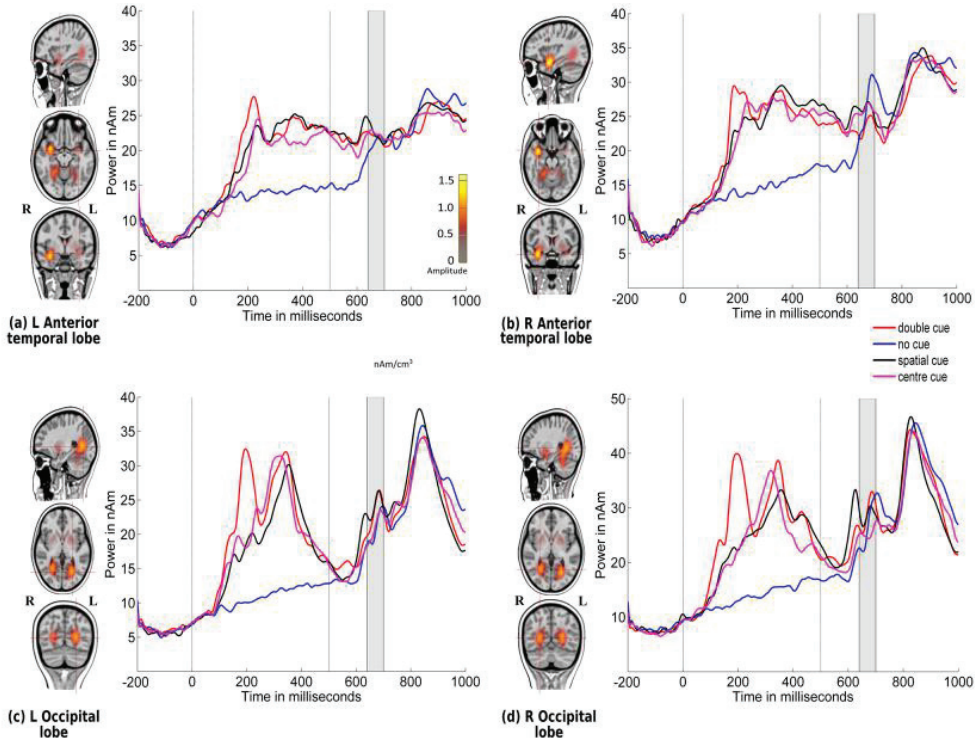

Figure 5. Source locations of grand-averaged ERPs collapsed across all conditions (congruent and incongruent stimuli: no cue, double cue, centre cue, and spatial cue) over time points of the N1 period of the target stimulus (140–200 ms) using CLARA in typically developing children. Cue onset is at 0 ms and target stimulus onset is at 500 ms. Brain activations were localized in the (**a**) left anterior temporal lobe, (**b**) right anterior temporal lobe, (**c**) left occipital lobe, and (**d**) right occipital lobe. Grand-averaged source waveforms for double-cued (red), non-cued (blue), spatially-cued (black), and centre-cued (magenta) stimuli, extracted using regional sources at the foci revealed by CLARA, are shown on the right side of each source. The colour bar denotes source amplitude. The shaded grey area denotes the source analysis time window.

In our study, the modulation of the visual N1 amplitude to the target stimulus by alerting and orienting cues in children was consistent with prior findings in adults[5,16,27]. However, no previous studies examine a cueing effect on the visual N1 for the target stimulus with flanker stimuli in children. Our finding of enhanced N1 for the double-cued target stimulus in the alerting sub-process may indicate more efficient processing of the target stimulus following specific warning cues (double cue). Similar to alerting, orienting manipulation enhanced the N1 when spatially cued. This again reflected enhanced processing of the target stimulus, with attention allocation to the correct spatial location.

As a final stage of the analysis, we examined our source-level information to disentangle possible neural sources beyond the scalp potentials. The N1-related sources of the target stimulus were localized to the right anterior temporal lobe, left and right occipital lobes, and left anterior temporal lobe. We excluded deep sources (pons, cerebellum) because these sources make a smaller contribution to the scalp recording of ERPs than cortical sources[43,44]; therefore, they can be less reliable.

For the alerting network, a significant effect was shown across multiple neuronal sources between 140 ms and 200 ms. These sources were the left and right occipital lobes and the right anterior temporal lobe. Our results showed activation in both hemispheres for alerting and orienting networks. The activity in the left and right occipital lobes could be interpreted as enhanced visual processing of a target stimulus appearing in the cued location[45–47]. Modulation of activity in the right anterior temporal lobe, which has been found in previous fMRI studies[13,22] and in other experiments[48] on intrinsic alertness using PET data, replicated in our findings in more anterior temporal areas. This region is generally thought to be involved in the facilitation of alertness in the brain in response to warning cues[49,50]. The lack of an alerting effect in the activity of frontal and parietal areas in children is discussed below, along with the orienting effect.

For orienting, a significant effect was shown in the bilateral occipital lobe between 140 ms and 200 ms. Bilateral occipital lobe activity was shown to be modulated by gaze shifts and direction of eye movement over the target stimulus and its flankers[47]. Our findings regarding the orienting network in children are in accordance with functional neuroimaging studies on children[13] and orienting effects in adults[23] that relate to the activation of the occipital lobe. In this study, similar to alerting, the orienting network showed reduced or absence of frontal and parietal activation in children. Prior studies have shown that the adult attention network utilises frontal-parietal

Source	Brodmann area	Talairach coordinate (mm)			*p*-value (latency in ms)
		X	Y	Z	Inhibition (INCON vs CON)
Medial frontal cortex	BA24	−3.5	4.1	30.7	NS
Medial prefrontal cortex	BA32	−3.5	46.1	2.7	<0.001 (510–700)
L Anterior temporal lobe		−31.5	4.1	−25.3	<0.0001 (480–700)
L Medial temporal lobe	BA36	−31.5	−30.9	−11.3	NS
R Medial temporal lobe	BA36	24.5	−30.9	−11.3	NS

Table 3. Talairach coordinates of the sources for the target stimulus P3 period (480–700 ms) The table presents the *p*-values of the inhibition (incongruent vs congruent stimuli) sources and the latency of their effects. NS denotes not significant.

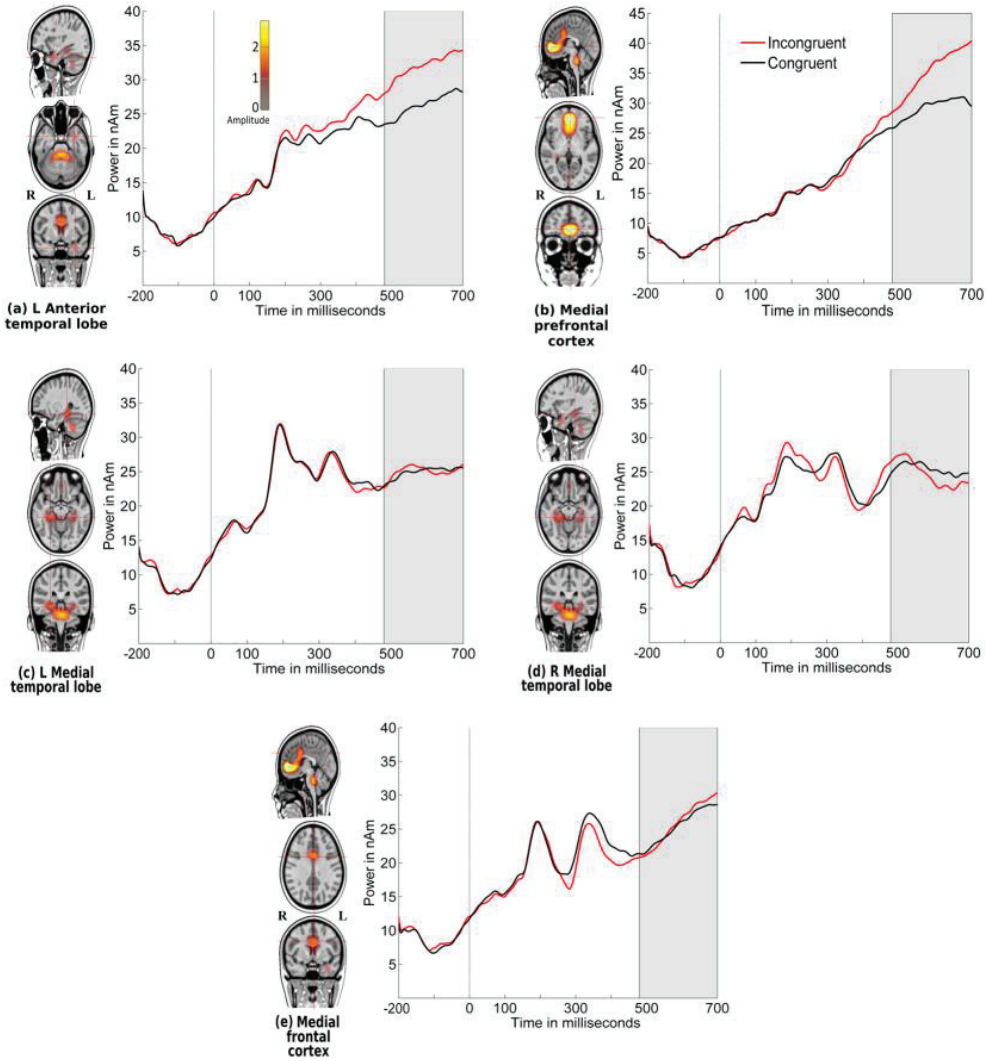

Figure 6. Source locations of grand-averaged ERPs collapsed across all conditions (congruent and incongruent stimuli with no cue, double cue, centre cue, and spatial cue) over time points of the target stimulus P3 period (480–700 ms) using CLARA. Target stimulus onset is at 0 ms. Brain activations were localized in the (**a**) left anterior temporal lobe, (**b**) medial prefrontal cortex, (**c**) left medial temporal lobe, (**d**) right medial temporal lobe, and (**e**) medial frontal cortex. The grand-averaged source waveforms for incongruent (red lines) and congruent (black lines) stimuli, extracted using regional sources at the foci revealed by CLARA, are shown on the right of each source. The colour bar denotes source amplitude. The shaded grey area denotes the source analysis time window.

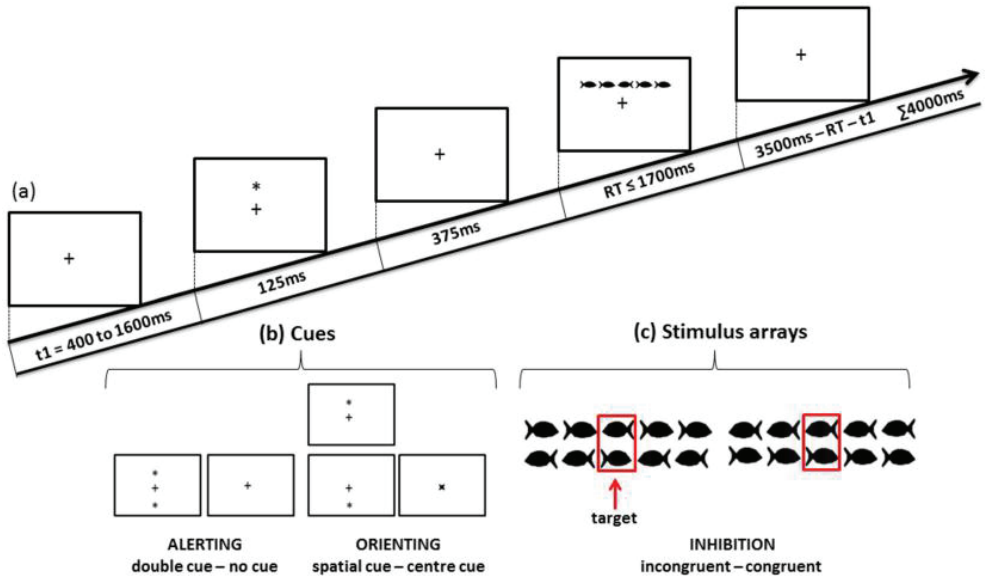

Figure 7. (**a**) Schematic illustration of the sequence of events in the modified ANT; t1 denotes a fixation period of a random duration between 400 and 1600 ms, (**b**) the four cue conditions used in ANT, and (**c**) the two congruency conditions for which the children had to decide the swimming direction of the middle fish.

areas to maintain a state of readiness for processing of non-specific cueing target information[22,51]. Thus, it appears that this maintenance of readiness matures only in late childhood, after 12 years of age, and fronto-parietal activity in adults might reflect more top-down control of attention that is not utilised by children in the ANT[37]. On the other hand, in previous studies on adults that employed the ANT, the experimental design differs from that in the current study in a number of ways: longer cue-to-target interval and random variation of the duration of this interval[22], appearance of the target on either the left or right of a fixation cross[13], and size and shape of the target stimulus[21]. Previous studies have suggested that these specific parameters might have an effect on task demands and network effects[29,42]. Further, in our study, there was no significant correlation between observed RT performance and neuronal source strength. Along with the finding of expected RT pattern, this suggests that RT performance reflects the sum of differences in the processes produced by RT performance, and that the processes measured in this study might be sensitive only to a few of the attributes of cognition that mediate task performance[13,52].

Further, we found that the modulation of the P3 amplitude to the target stimulus associated with the inhibition response in children had significant effects in the centro-parietal and mid-frontal areas. P3 amplitudes for incongruent target stimuli at the centro-parietal electrodes were considerably higher than for congruent target stimuli. This increase in the P3 amplitudes of incongruent target stimuli in children is consistent with previous ANT studies on children[6,15,39]. A possible interpretation could be higher discriminability of the target stimulus from its flankers, which led to a higher P3 amplitude in the centro-parietal areas[53]. However, ANT studies on young adults show decreased amplitudes in response to incongruent versus congruent targets for the P3 component[5,21]. This discrepancy between the results for children and adults might be better interpreted based on the source analysis.

For inhibition, source-level statistics showed significant activation in the medial prefrontal cortex and left anterior temporal lobe. A large number of neuroimaging studies have revealed that the prefrontal cortex (ACC) is involved in the inhibition network in both children[13,15] and adults[22,54–56]. Evidence from a previous fMRI study on children showed that the left temporal lobe is strongly associated with response inhibition[34], although our source localization was more anterior. The increased ERP amplitude to incongruent versus congruent target stimuli is in line with source analysis results and with the involvement of the ACC region in conflict resolution[4,22]. The lack of modulation of other cortical regions by the congruency of the target stimulus (e.g. the fusiform gyri[22]) might explain the different direction of the P3 effect between children and adults.

In a developmental study of attention networks in children and adults, significant lateralization differences were found in the temporal lobe (superior temporal gyrus)[13]. One explanation for activation of this area in children relates to their verbal strategies[34]. However, it is challenging to define a single function for the temporal lobe or prefrontal cortex, because they include higher-order cortical regions (i.e. superior temporal gyrus and ACC) that are involved in several cognitive processes[57]. However, our study suggests that these areas also play an important role in children's inhibition networks.

Overall, our study has certain limitations. The first is the fact that current EEG/ERP source imaging is an estimation of brain activity with rather limited spatial resolution. The distributed source imaging could produce more source activation spread[58,59], which would make it difficult to distinguish between close hemispheric areas

and specific brain voxels or regions. Second, we used a child template MRI rather than individual MRIs for our participants, which likely resulted in some loss of precision in source imaging[60]. However, this method has been used in previous source analysis studies and remains a better option than using adult templates for studies on children[61,62]. Further, by examining the spatial correspondence between high-density EEG/ERP source localization and fMRI activation in children[63,64] and individual level MRI-constrained EEG source localization[65] could help to more precise source localization.

In summary, our study demonstrated that children replicated classic attentional behavioural RT performances using a modified version of the ANT. Our study shows significant modulation of the visual N1 amplitude to a target stimulus by the alerting and orienting sub-processes of attention, and modulation of the P3 amplitude to the target stimulus by the inhibition sub-process. However, despite their classic behavioural performance pattern, ERP and source results for children are different from those for adults. Thus, our results indicate reduced top-down control mechanisms in children for the alerting and orienting sub-processes, evidenced by a lack of fronto-parietal network activation, which could at least partially be explained by differences in fMRI and EEG experimental designs. The combined study of RTs, ERPs, and their neuronal sources provides a comprehensive view of the mechanisms that underlie attentional networks in children. Future studies could extend our findings to explore attentional processes in children with attentional problems and other developmental difficulties.

Methods

Participants. Eighty-three Finnish children aged between 12 and 13 years (43 girls, 40 boys; mean age 12.38 years, SD: 0.48) and studying in the sixth grade participated in this study. All children had normal or corrected vision, with no history of neurological problems or head injuries. They were recruited to the eSeek project (Internet and Learning Difficulties: A Multidisciplinary Approach for Understanding Reading in New Media). The study was conducted in compliance with the Declaration of Helsinki, and study protocols were approved by the ethics committee of the University of Jyväskylä, Finland. All methods were performed in accordance with the relevant guidelines and regulations. The participants and their parents provided signed informed consent prior to the study. The analysed data sets from this study are available from the research group upon request.

Procedure: Attention Network Test for Children. In this study, we used the modified version of the ANT[5] to measure the three sub-components of the attention network: alerting, orienting, and inhibition. Participants were required to lean on a chinrest located 60 cm from a 24-inch computer screen (resolution of 1920 × 1080 and a refresh rate of 60 Hz). A fixation cross was visible in the centre of the white-colour screen (960, 540 (x, y)) during the entire testing period (i.e. not during eye-tracker calibration). The participant's task was to look at the fixation cross and report the direction of the middle fish as quickly and accurately as possible by pressing a corresponding button.

As shown in Fig. 7, the stimulus (a group of fish) was preceded by one of the four cue conditions (no cue, double cue, centre cue, or spatial cue). The fixation period of a random duration was between 400 ms and 1600 ms before cue appearing. The duration of the cue was 125 ms, which was followed by 375 ms of waiting time before the stimulus was presented (a total of 500 ms prior to stimulus presentation). In the double cue trial, two asterisks were presented simultaneously at a 1° angle above and below the fixation cross. In the centre cue trial, an asterisk was presented on the fixation cross. In the spatial cue trial, a single asterisk appeared in the position of the upcoming stimulus.

To make the experiment more child-friendly, black fish drawings were used as stimulus. The stimulus comprised a row of five horizontal fish. Each fish was subtended to 0.7°, and adjacent fish were separated by 0.3° each. The size of the entire stimulus array was 4.7°. The centre fish in the stimulus was the target, and the two fish on either side of the target were referred to as flankers. The stimulus array in each trial was presented above or below the fixation cross, at the same location where the double cue or spatial cue appeared. The maximum duration of each trial was 4000 ms. The maximum duration of the stimulus array in each trial was 1700 ms, until a response was detected; thereafter, if there was no response, it was considered an unattended trial and terminated. The maximum duration between the offset of the stimulus and the start time of the next trial was 3500 ms, which varied according to the duration of the stimulus array. For congruent stimuli, the flankers were in the same direction as the target and for incongruent stimuli, the flankers were in the opposite direction. Participants were instructed to keep their gaze on the fixation cross throughout the experiment and report the swimming direction of the centre fish by pressing a left or right corresponding direction button in the button box.

One ANT session consisted of 288 pseudo-randomized trials, which were divided into 4 experimental blocks, with 72 trials in each block. Each block consisted of all eight possible conditions in equal proportions: four cue conditions (no cue, double cue, centre cue, and spatial cue) × two stimulus conditions (congruent, incongruent).

EEG and eye-tracker recording. The experiment was designed using the Experiment Builder (1.10.1630) software on a Dell Precision T5500 workstation. EEG data were recorded using a high-density array of 128 Ag-AgCl electrodes in HydroCel Geodesic Sensor Nets (Electrical Geodesics Inc.). The EEG was amplified using a NeurOne amplifier (Mega Electronics Ltd.). During measurement, the impedance of most electrodes was kept below 50 kΩ, and the quality of the EEG data was monitored throughout the EEG recording. EEG was referenced to Cz online and sampled at 1000 Hz. An online high-pass filter of 0.16 Hz and low-pass filter of 250 Hz were applied during EEG data recording. Further, eye movement data were recorded with a table-mounted Eyelink 1000 eye tracking device at 1000 Hz for both eyes (SR Research Ltd.). EEG and eye movements were recorded simultaneously through the combination of triggering via Ethernet messages and TTL pulses. The entire experiment was conducted in a dimly lit sound-attenuated room in a laboratory at the University of Jyväskylä, Finland.

Pre-processing of EEG data and eye tracking. EEG data were pre-processed using MatLab R2014a, with toolboxes EEGLab[66] (Swartz Centre for Computational Neuroscience, San Diego) and FieldTrip[67] (version 20160110), and BESA Research 6.1 (BESA GmbH, Munich, Germany). The raw eye-tracking data were converted and stored into a MatLab-structured array using the EEGLab add-on EYE-EEG[68]. The continuous raw EEG data file was imported into EEGLab, in which bad channels were interpolated and the EEG was synchronized with the eye-tracking data. The quality of synchronization was checked by comparing eye-tracking event latencies against EEG event latencies.

A high-pass filter of 0.5 Hz (fifth order, zero-phase Butterworth filter) was applied to the raw EEG data. It was segmented into 1200 ms (200 ms before cue onset and 1000 ms after cue onset) for non-cued, double-cued, centre-cued, and spatially-cued stimuli, and 900 ms (200 ms before and 700 ms after the onset of target stimulus) for congruent and incongruent stimuli. Then, a low-pass filter of 30 Hz (sixth order, zero-phase Butterworth filter) was applied to the high-pass filtered, segmented EEG data (trials). The baseline was set to −200 ms and 0 ms of the filtered segmented data. Gaze positions in each trial were examined in order to ensure that participants maintained their gaze in the optimal position for stimulus presentation. As such, if there was an eye blink, the gaze position value was recorded as zero, which was outside the defined area (860–1060, 440–640 (x, y)) on the display screen; such trials were eliminated. Trials with muscular and other artefacts were rejected using a threshold rejection approach. Moreover, trials with a difference between the maximum and minimum voltages within an ERP epoch that exceeded 175 μV were rejected prior to calculating the average. Accepted trials using the above criteria were averaged for each participant. The averaged ERPs were re-referenced to average reference in BESA Research 6.1 (BESA GmbH, Munich, Germany). Each condition (non-cued, double-cued, centre-cued, spatially-cued, congruent, and incongruent) had a minimum of 30 trials for averaging. The average number of correctly responded trials for both cued (double, centre, and spatial) and non-cued conditions were 65; the average number of correctly responded trials for incongruent and congruent target stimuli were 134 and 128, respectively. The EEG data of 12 participants were excluded from the analysis because of eye blinks (11 participants) and physical movement artefacts (1 participant).

Data analysis. *Statistical analysis of RT data*. The RTs of each trial were calculated from target stimulus onset time to button response time. Unattended trials, trials with incorrect responses, and trials which were not accepted for ERP averaging were excluded from calculations of the mean RTs. All participants maintained a high level of accuracy (see Table 1). Paired-sample t-tests were performed in IBM SPSS Statistics Version 24 to determine significant differences in RTs between conditions. There were no outliers, and the data was approximately normally distributed.

Statistical analysis of the EEG and eye-tracking data. Nonparametric, cluster-based permutation t-tests were performed as a two-tailed test in BESA Statistics 1.0 (BESA GmbH, Munich, Germany) for revealing significant effects across all the electrodes in alerting (double-cued vs non-cued target stimulus), orienting (spatially-cued vs centre-cued stimulus), and inhibition (incongruent vs congruent target stimulus). For alerting and orienting conditions, ERP statistics were calculated between 500 ms (the onset of target stimulus) and 1000 ms from the onset of the cue. For the inhibition condition, ERP statistics were calculated from the onset of the target stimulus to 700 ms. The number of permutations was set to 1000, and cluster alpha (the significance threshold level for data to enter a cluster) was set to 0.05. For spatial clustering, the neighbour distance between electrodes was set to 3 cm. (Permutation testing is a non-parametric statistical approach that uses the arbitrary division of groups or conditions to evaluate the distribution of the effect of interest. By comparing the original test statistic with the permutation distribution, it is possible to compute a p-value for the effect[69–71]).

Source analysis. Source analysis was performed in BESA Research 6.1 to estimate source areas in the brain that were responsible for the alerting, orienting, and inhibition sub-components of attention. The source areas associated with alerting were calculated by the difference in response between double-cued and non-cued target stimuli, those in orienting by the difference between spatially-cued and centre-cued target stimuli, and those in inhibition by the difference between incongruent and congruent target stimuli. The distributed source model CLARA[40] was used to localize neuronal sources. For effective forward-head modelling, an age-appropriate FEM head model for 12-year-olds implemented in BESA Research 6.1 was selected. The time window of interest for the N1 period of the target stimulus was between 140 ms and 200 ms, and the time window for the P3 period of the target stimulus was between 480 ms and 700 ms. Source locations were calculated for N1 and P3 target stimuli periods of the grand-averaged ERPs, which were collapsed across all the conditions (congruent and incongruent conditions for no cue, double cue, centre cue, and spatial cue). The source analysis time interval was selected on the basis of the significant time window from the cluster-based permutation tests of the ERPs. A regional source was considered as three single dipoles at the same location, with three orthogonal orientations[40]. This source was fitted in the foci obtained from the CLARA solution. The source strength at each time point was estimated as a combined sum of the power of the three orthogonal orientations of the regional sources. These regional sources were used as a spatial filter for source modelling for each of the three effects. Source-level paired t-test statistics were calculated using a two-tailed test based on the individual-level source waveforms associated with the locations of the neuronal sources obtained from N1 and P3 periods of the collapsed grand-averaged ERP between conditions.

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Author Contributions

O.L., J.A.H. and P.L. designed the experiment. Research assistants, O.L. and P.L. recruited the participants and collected the data. P.R.S.G. analysed the data, wrote the main manuscript and created all the figures. All authors commented on and reviewed the manuscript.

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ATTENTIONAL PROCESSES IN CHILDREN WITH ATTENTIONAL PROBLEMS OR READING DIFFICULTIES AS REVEALED USING BRAIN EVENT-RELATED POTENTIALS AND THEIR SOURCE LOCALIZATION

by

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Attentional Processes in Children With Attentional Problems or Reading Difficulties as Revealed Using Brain Event-Related Potentials and Their Source Localization

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Visual attention-related processes include three functional sub-processes: alerting, orienting, and inhibition. We examined these sub-processes using reaction times, event-related potentials (ERPs), and their neuronal source activations during the Attention Network Test (ANT) in control children, attentional problems (AP) children, and reading difficulties (RD) children. During the ANT, electroencephalography was measured using 128 electrodes on three groups of Finnish sixth-graders aged 12–13 years (control = 77; AP = 15; RD = 23). Participants were asked to detect the direction of a middle target fish within a group of five fish. The target stimulus was either preceded by a cue (center, double, or spatial), or without a cue, to manipulate the alerting and orienting sub-processes of attention. The direction of the target fish was either congruent or incongruent in relation to the flanker fish, thereby manipulating the inhibition sub-processes of attention. Reaction time performance showed no differences between groups in alerting, orienting, and inhibition effects. The group differences in ERPs were only found at the source level. Neuronal source analysis in the AP children revealed a larger alerting effect (double-cued vs. non-cued target stimuli) than control and RD children in the left occipital lobe. Control children showed a smaller orienting effect (spatially cued vs. center-cued target stimuli) in the left occipital lobe than AP and RD children. No group differences were found for the neuronal sources related to the inhibition effect. The neuronal activity differences related to sub-processes of attention in the AP and RD groups suggest different underlying mechanisms for attentional and reading problems.

Keywords: attention, ANT, event-related potentials, N1, P3, source analysis, attentional problems, reading difficulties

INTRODUCTION

Attentional problems (AP) and reading difficulties (RD) are two of the most common developmental problems that hinder learning in children (American Psychiatric Association, 2013). These difficulties increase the risk of serious academic, economic, and psychosocial consequences (de Kieviet et al., 2012; Sexton et al., 2012). Visual Attention Network Test (ANT) studies are

increasingly used to understand these difficulties in typically and atypically developing children (Bednarek et al., 2004; Mezzacappa, 2004; Rueda et al., 2004a, 2012; Adólfsdóttir et al., 2008; Kratz et al., 2011; Mullane et al., 2011; Liu and Sun, 2017). However, there is a lack of neuronal-level brain information related to ANT in children with AP and children with RD in the same study. In this study, we examined reaction time (RT) performance, scalp topography of event-related potentials (ERPs), and their neuronal sources associated with attention network sub-processes using an Attention Network Test (ANT) (Santhana Gopalan et al., 2019) in AP and RD children.

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood psychiatric disorder with a strong genetic and neurobiological basis (National Collaborating Centre for Mental Health (UK), 2018). The symptoms of AP defined here are similar to those of ADHD, and they include short attention span, excessive activity, and impulsivity (American Psychiatric Association, 2013). The bottom-up theories of neurobiology of ADHD propose disturbances in subcortical regions such as the thalamus, hypothalamus, and striatum. It has been suggested that these brain regions play an important role in ADHD groups during motor inhibition (Matthews et al., 2014; Singh et al., 2015). The top-down theories attribute dysfunction to frontal and prefrontal cortices (Singh et al., 2015). These regions seem to be associated with spatially focusing attention, resisting distractions, and developing an awareness of self and of time (Bellman, 2002, 104). Individuals with ADHD show deviant activation patterns in the anterior and frontal cortices (dorsolateral prefrontal cortex and orbitofrontal cortex) with greater involvement of the right hemisphere (Posner and Raichle, 1994) and parietal cortex (Konrad et al., 2006; Booth et al., 2007).

Reading difficulties, commonly referred to as dyslexia, are characterized by a number of difficulties (Wagner and Torgesen, 1987; Wimmer, 1993; Wagner et al., 1994; Feinberg and Farah, 2003, 802; Lyon et al., 2003; Vellutino et al., 2004; Wimmer and Schurz, 2010; Rose and Rouhani, 2012). Individuals with dyslexia are often considered poor readers despite their normal intelligence and adequate educational provision (Rutter and Yule, 1975; Lyon et al., 2003; Vellutino et al., 2004). Some studies have interpreted the impaired performance of dyslexic children in visual tasks as evidence of a deficit in visual processing (Facoetti et al., 2006, 2008; Bosse et al., 2007). In reading, the dorsal stream (occipito-parietal pathway) allocates attention to appropriate areas of text (spatial location), providing sufficient feedback to the ventral stream (occipito-temporal pathway) for processing or analysis of letters (Jones et al., 2008). A dorsal stream deficit might therefore impede smooth attentional focus on orthographic items, disrupting the visual recognition of letters that is accomplished by the ventral stream. The late stages of dorsal stream functioning involve the parietal cortex, which serves to deploy and control visual attention across different regions of the visual field. In line with these observations, individuals with dyslexia might have visual deficits that originate in the dorsal processing stream (Pammer and Vidyasagar, 2005). These findings suggest some common attentional deficits in RD and AP.

Previous studies involving random and clinical samples have consistently shown that ADHD and dyslexia overlap and are inter-related (Mayes et al., 2000; Carroll et al., 2005; Maughan and Carroll, 2006; Germanò et al., 2010). The overlap of these difficulties is described as co-occurring rather than involving comorbidity, which implies that the background factors are not causally related (Dykman and Ackerman, 1991; Kaplan et al., 2006). Children with co-occurring ADHD and dyslexia seem to share common neuropsychological deficits (slower naming speed for letters, impaired phonological processing, and poor word identification or reading), behavioral deficits (impulsivity and inattention), and inhibition deficits (Wolf and Bowers, 1999; American Psychiatric Association, 2000; Donfrancesco et al., 2005; Tiffin-Richards et al., 2008; Laasonen et al., 2012).

Posner and his team proposed in the 1990s that the attention network has three separate main networks associated with attention. These are known as the alerting, orienting, and inhibition networks (Posner and Petersen, 1990; Posner and Raichle, 1994). More recent studies have shown that this theoretical model provides a good fit for examining the potential cognitive mechanisms underlying attentional problems (Berger and Posner, 2000; Mullane et al., 2011) and reading difficulties (Bednarek et al., 2004; Goldfarb and Shaul, 2013). The Attention Network Test (ANT) is a reaction time (RT) task designed to measure these three attention networks in the same task (Fan et al., 2002; Rueda et al., 2004a). In the ANT, the participant must determine the direction of the central arrow or fish (target) surrounded by congruent or incongruent arrows or fish (flankers). The array of arrows or fish is preceded by either an alerting visual cue or a spatially orienting cue. Although the literature on these three attention networks shows some evidence of group differences between controls and individuals with AP (Konrad et al., 2006; Booth et al., 2007; Kratz et al., 2011; Mullane et al., 2011; Fabio and Urso, 2014; Hasler et al., 2016) in terms of reaction time, ERPs, and fMRI (BOLD signal), the results remain somewhat contradictory, as will be described in the following sections.

The alerting sub-processes of attention can be defined as a network associated with arousal and vigilance involved in the attainment and maintenance of a state of sensitivity to subsequent stimuli (Posner and Petersen, 1990). The alerting effect is measured by differentiating stimuli preceded by non-informative visual warning cues and informative cues (Fan et al., 2002). On the other hand, orientation is associated with spatial selection (Neuhaus et al., 2010). Orienting effects can be measured (similar to that for alerting effects) by an RT difference between center-cued and spatially cued target stimuli (Neuhaus et al., 2010). Spatial orientation has three distinct sub-functions: the engagement of visual attention to a particular stimulus, the disengagement of visual attention from a stimulus, and the shifting of visual attention from one stimulus to another (Posner and Petersen, 1990).

Individuals with attentional problems tend to have impairment in the alerting process (Sergeant, 2000; Swaab-Barneveld et al., 2000; Willcutt and Carlson, 2005; Konrad et al., 2006). In line with this, children with the combined subtype (attention deficit and hyperactivity) of ADHD and aged between 7 and 13 years showed a larger alerting effect relative to control

children (Booth et al., 2007; Mullane et al., 2011), suggesting that their general level of alertness is lower (Mullane et al., 2011). In contrast, previous ANT studies between ADHD and control children (Adólfsdóttir et al., 2008; Kratz et al., 2011; Fabio and Urso, 2014) and adults (Lundervold et al., 2011) did not show significant group differences in the alerting process but did reveal lower accuracy (as measured by number of correct responses) and higher omission errors in the ADHD group, which indicates a higher level of inattention than vigilance. The orienting effect in 7−13-year-old children (Booth et al., 2007; Adólfsdóttir et al., 2008; Kratz et al., 2011; Fabio and Urso, 2014) and adults (Lundervold et al., 2011) with ADHD did not differ from control groups. The lack of difference between the groups suggests that either the orienting effects might not be affected in children with ADHD, or that the effect was too small to be detected in the previous studies (Huang-Pollock and Nigg, 2003).

The alerting effect observed in the 10-year-old children with dyslexia (Bednarek et al., 2004) and adults with dyslexia (Buchholz and Aimola Davies, 2008) was not significantly different from the control groups, suggesting that both the dyslexia and control groups tend to have an increased level of readiness when a target stimuli is cued (Bednarek et al., 2004; Buchholz and Aimola Davies, 2008). Similarly, dyslexic and control children (10-year-olds) did not show any evidence of a deficit in the orienting effect (Bednarek et al., 2004). In contrast, in the adult studies (Buchholz and Aimola Davies, 2008; Goldfarb and Shaul, 2013) there was a significant group difference in the orienting effect between the dyslexic and control groups. A study with dyslexic adults showed that such individuals have difficulties in the adjustment and maintenance of attentional focus and peripheral spatial location (Buchholz and Aimola Davies, 2008).

The functioning of the attentional processes at the brain level has been widely investigated using the ANT paradigm coupled with ERPs in children (Kratz et al., 2011; Santhana Gopalan et al., 2019) and adults (Neuhaus et al., 2010; Kratz et al., 2011; Rueda et al., 2012; Kaufman et al., 2016). Generally, alerting (non-cued vs. visually cued target stimuli) and orienting visual cues (center-cued vs. spatially cued target stimuli) enhance the modulation of the posterior visual N1 amplitude at 100–280 ms for the target stimulus (Hillyard and Anllo-Vento, 1998; Neuhaus et al., 2010; Luck, 2014; Kaufman et al., 2016). In children and adults (Fan et al., 2005; Neuhaus et al., 2010; Galvao-Carmona et al., 2014), target stimulus-related N1 was modulated by cue conditions (double, spatial, and center) over the occipital and parietal regions, reflecting the visual attentional processing of target stimulus properties in relation to the cue context. Studies in adults have consistently shown that spatially cued target stimuli elicit a larger N1 amplitude than center-cued target stimuli, which suggests stronger engagement and lasting effects for the spatial cue with regard to the target stimulus (Kaufman et al., 2016; Williams et al., 2016). Alerting and orienting N1 amplitudes in adults with ADHD follow a similar pattern as that for control adults, which corroborates the reaction time studies on adults with ADHD (López et al., 2006; Hasler et al., 2016). However, there are no studies showing how N1-alerting and orienting effects for a visually cued target stimulus are processed in AP and RD children.

Functional magnetic resonance imaging studies have revealed that several brain sources are activated during the attention network test. The alerting network in adult fMRI studies has been shown to have increased neuronal activity in the thalamus, temporal parietal junction (TPJ), and prefrontal cortex (Fan et al., 2005; Konrad et al., 2005). A recent adult fMRI study produced results with additional brain areas in the anterior cingulate cortex (ACC), frontal eye fields (FEF), occipital, and visual areas (Xuan et al., 2016). The alerting network in an fMRI study of children showed increased neuronal activity in the bilateral occipital lobe and temporal lobe (i.e., the middle occipital cortex extending toward the right superior temporal gyrus), suggesting that these regions enhance the anticipation of the visual warning cue and response preparation toward the upcoming target stimuli (Konrad et al., 2005; Xuan et al., 2016). There is some evidence from fMRI studies that the alerting network might activate differently in children with ADHD. In control children, the right ACC showed greater activation compared to ADHD children, suggesting that neural activity is modulated with a top-down bias in control children, thereby assisting in the processing of stimuli at the attended location (Sturm and Willmes, 2001; Konrad et al., 2006).

The orienting network in fMRI studies with adults has shown neuronal activity in the TPJ, bilateral superior parietal lobe, FEFs, pulvinar, and superior colliculus (Fan et al., 2005; Konrad et al., 2005; Xuan et al., 2016). Previous ANT studies with children found orienting network responses in the superior frontal gyrus and bilaterally in the occipital cortex (Konrad et al., 2005; Santhana Gopalan et al., 2019). A previous fMRI study also showed that children with ADHD have atypical activation in the frontostriatal region compared to control children (Bellman, 2002, 104). This altered brain activation could be due to an alternative function (brain functions to solve a problem and not necessarily to an overt or volitional approach used by the children) during reorienting, which includes the dorsolateral prefrontal cortex and insular cortex (Bellman, 2002, 104; Konrad et al., 2006). No studies have investigated the neural sources associated with the alerting or orienting networks in individuals with RD using fMRI.

The third attention network tapped by the ANT is related to inhibition. Inhibition involves a number of mechanisms for resolving conflicts, detecting errors, and selecting actions in response to target stimuli (Michael, 1998; Posner and Rothbart, 2007). The inhibition effect in the ANT is measured by the RT difference between incongruent and congruent target stimuli (Fan et al., 2002; Neuhaus et al., 2010).

Several studies with children (involving 7−13-year-olds) (Booth et al., 2007; Adólfsdóttir et al., 2008; Kratz et al., 2011) and adults (Lundervold et al., 2011) have shown that ADHD children and control groups do not differ with respect to the inhibition effect in ANT. However, one study with ADHD children showed larger inhibition effects (i.e., more time to change the focus when the stimulus is incongruent) relative to a control group (Fabio and Urso, 2014). According to the authors, this indicates that ADHD children could have a deficit in inhibition processes (Fabio and Urso, 2014). The inhibition effect in the 10-year-old dyslexic children (Bednarek et al., 2004) and

adults (Goldfarb and Shaul, 2013) showed slower reaction time performance compared to their respective control groups. These findings were interpreted as representing an executive control deficiency in the inhibition of distracting information (Bednarek et al., 2004; Goldfarb and Shaul, 2013).

At the brain response level in ERP studies, inhibition effects have been associated with a P3 response in the time window between 300–650 ms from target stimulus onset (Neuhaus et al., 2010; Kratz et al., 2011; Mahé et al., 2014; Hasler et al., 2016; Kaufman et al., 2016). In the context of ANT, the P3 response represents the neural activity related to the processing of cueing information for target detection (Neuhaus et al., 2010) and response control processes to target stimuli (motor selection and inhibition) (Polich, 2007). In ANT, a target stimulus-generated P3 response is generally observed with delayed latency in children (4–12 years old) (Rueda et al., 2004b; Kratz et al., 2011) compared to adults (Neuhaus et al., 2010; Kaufman et al., 2016), which suggests a developmental trend in the evaluation of the target direction (Falkenstein et al., 1994). Furthermore, previous studies have shown that the target P3 in ANT has smaller amplitudes in predominantly inattentive 10-year-old children (Kratz et al., 2011), ADHD adults (Hasler et al., 2016), and dyslexic adults (Mahé et al., 2014) compared to control groups, which suggests an impairment in attentional resource allocation leading to decreased target stimulus evaluation and processing capabilities for a difficult task (Mahé et al., 2014; Hasler et al., 2016). No studies have used the children's version of the ANT to examine inhibition effects in children with RD.

Attention Network Test studies on adults using fMRI have revealed activation related to inhibition in the right ACC, bilateral precentral gyrus, intraparietal sulcus, anterior insular cortex, FEFs, and bilateral occipital cortex (Xuan et al., 2016). In children eight to 12 years old, inhibition processes (ANT experiment) activated the right superior temporal gyrus, bilateral parietal, occipital, and premotor cortices but involved less prefrontal cortex activation (inferior and medial frontal gyrus) compared to adults (Bunge et al., 2002; Konrad et al., 2005). In line with the reaction time and ERP studies, fMRI studies also show differences between children with ADHD and control children with respect to inhibition networks. Specifically, ADHD children (8−12 years old) showed typical left superior parietal cortex and posterior parietal cortex activations (Durston et al., 2003; Konrad et al., 2006) and reduced frontostriatal activation compared to control children. Together, the results provide strong evidence that in children with ADHD, there is decreased activation or immature frontal development of the inhibition network (Bunge et al., 2002; Durston et al., 2002, 2003; Konrad et al., 2006). With respect to the examination of regions associated with the inhibition network, there have been no fMRI studies of children with RD that have assessed attentional processing using the visual attentional task.

In summary, Posner's model of attention (Posner and Raichle, 1994) and previous neuroimaging studies show that the alerting network involves the thalamus, TPJ, prefrontal cortex, occipital and visual areas associated with readiness, arousal, and vigilance (Fan et al., 2005; Konrad et al., 2005; Booth et al., 2007). Neuroimaging studies of control groups have consistently shown the occipital cortex and TPJ to subserve the orienting of attention (Corbetta and Shulman, 2002). Neurologically, the right TPJ receives information from various brain areas about stimuli in the environment and inhibits spatial orientation (Goldfarb and Shaul, 2013). Developmental changes in the right TPJ have been linked to reading acquisition in normally developing children, and some studies have observed differences in the activation of the right TPJ in dyslexics (Grünling et al., 2004; Hoeft et al., 2006). The inhibition network involves the prefrontal cortex (including ACC and FEFs) and the parietal cortex associated with conflict resolution appears to be deficient in individuals with ADHD (Konrad et al., 2006; Booth et al., 2007). These findings provide a basis for examining the three attentional networks in AP and RD groups.

Some studies using ANT have utilized EEG (Neuhaus et al., 2010; Kratz et al., 2011; Williams et al., 2016) and fMRI (Fan et al., 2005; Konrad et al., 2005; Rueda et al., 2012; Xuan et al., 2016) to demonstrate the time course and network of attention-related brain activations. However, EEG-based studies of attentional sub-processes in school-aged children with AP and RD groups are rare (Kratz et al., 2011). Although reaction time performance in AP and RD children and the target stimulus P3 in AP children have been examined, there remains a lack of knowledge about the target stimulus N1 in AP and RD children as it relates to alerting (double-cued vs. non-cued target stimuli) and orienting (spatially cued vs. center-cued target stimuli) processes. This is also the case for target stimulus P3 in RD children (incongruent vs. congruent target stimuli). Further investigation of neuronal sources in AP and RD children that capitalizes on high temporal resolution EEG by using source models based on typically developing children to identify the brain areas associated with these three attentional networks would address this knowledge gap. This would help us to understand the time course of activation in the different brain regions involved in the attention network of children with RD or AP.

In this study, we investigated reaction time performance during the ANT (as modified for children) and the modulation of the target-stimulus-driven N1 amplitude related both to the alerting and orienting networks, the modulation of the P3 amplitude related to the inhibition network, and their neural sources in children with attentional and reading difficulties. We employed source models derived from the data of control children (Santhana Gopalan et al., 2019) as a spatial filter for the source localization of the three network effects in AP and RD children.

Based on previous ANT reaction time studies, we could assume that the alerting and inhibition effects in AP children (Konrad et al., 2006; Booth et al., 2007; Fabio and Urso, 2014) and the inhibition effect in RD children (Bednarek et al., 2004), would be different compared to a control group. Previous studies have not found such group effects (Adólfsdóttir et al., 2008; Kratz et al., 2011; Lundervold et al., 2011) and have emphasized the importance of replication. We expected that differences in inhibition effect in AP children would produce reduced P3 amplitude associated with target-related attentional processes. This could reflect the atypical function of the TPJ and ventral frontal cortex involved in the processing of the stimulus

(Szuromi et al., 2011; Vossel et al., 2014; Hasler et al., 2016). Furthermore, in line with previous fMRI studies (Fan et al., 2005; Konrad et al., 2005; Xuan et al., 2016) and our previous EEG investigation (Santhana Gopalan et al., 2019), we assumed that alerting effects in children with AP would modulate atypical activity in the bilateral occipital lobe and temporal lobe compared to control children. Orienting would modulate atypical activity in the bilateral occipital lobe compared to controls, and inhibition would modulate atypical activity in the bilateral occipital lobe, parietal lobe, and prefrontal cortices as compared to a control group. We did not hypothesize brain regions for any of the three attention sub-networks in children with RD because we did not find any literature on this issue.

MATERIALS AND METHODS

Participants

The data consist of 115 (65 boys, 50 girls) Finnish sixth-graders with normal visuospatial reasoning ability aged between 12 and 13 years. Inclusion criteria for the attentional problems (AP) group (N = 15; 14 boys, 1 girl) (mean age: 12.67 years, SD: 0.31) were as follows: an ATTEX score above 30 (Klenberg et al., 2010) and a reading fluency score above the 10th percentile [which is a composite score of three reading tasks created using Principal Axis Factoring, PAF (see detailed description below)]. For the reading difficulties (RD) group (N = 23; 15 boys, 8 girls) (mean age: 12.61 years, SD: 0.31), an ATTEX score below 30 and a reading fluency score below the 10th percentile were the criteria for inclusion. Inclusion criteria for the control group (N = 77; 36 boys, 41 girls) (mean age: 12.86 years, SD: 0.31) were an ATTEX score below 30 and a reading fluency score above the 10th percentile (see **Figure 1**). The control sample used in this study was the same as in our previous study (Santhana Gopalan et al., 2019) with the exclusion of six participants because they were below the borderline in their reading skills to be included in the control group based on the updated criteria for the reading disorder in the current study. This exclusion did not alter any of the results. Children with both AP and RD were excluded in this study because of sample size (n < 10) (these children had an ATTEX score above 30 and a reading fluency score below the 10th percentile). All children had normal or corrected vision and no history of neurological problems or head injuries, which was reported by parents or guardians. The study was conducted in compliance with the Declaration of Helsinki, and protocols were approved by the ethics committee of the University of Jyväskylä, Finland. All methods were performed in accordance with relevant guidelines and regulations. The participants and their parents signed a letter of informed consent prior to the experiment.

In this study, 466 participants were recruited from sixth grade schools in Central Finland during the years 2014–2015. Schools from both rural and urban areas participated voluntarily in this study. Participants (numbering 448) finished the ILA test (Kiili et al., 2018a,b; Kanniainen et al., 2019). The test comprises simulated closed internet environmental tasks that measure an individual's ability to: (1) locate information, (2) evaluate information, (3) synthesize information, and (4) communicate

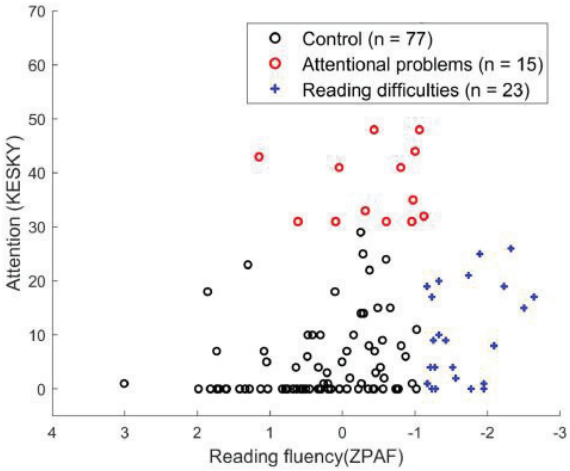

FIGURE 1 | Distribution of control (N = 77; 36 boys, 41 girls), attentional problems (N = 15; 14 boys, 1 girl), and reading difficulties (N = 23; 15 boys, 8 girls) groups based on the reading fluency score (as evaluated using a composite score derived from the word identification test, the word chain test, and the oral pseudoword text reading test) and attention score (ATTEX). Symbols for each group are as follows: control (black circle), AP (red circle), and RD (blue cross).

information (Leu et al., 2013; Kiili et al., 2018b). One hundred and fifty-six participants were invited to the EEG measurement based on the completion of the ILA test and performance in the RAVEN test (Raven and Court, 1998). The AP and RD participants were included based on ATTEX and reading fluency (PAF) scores. Detailed selection criteria are described below. The participants who did not complete the ILA test and whose shortened RAVEN score was less than 15 were not invited to the individual EEG measurements. Participants with a native language other than Finnish were not included in this study.

Behavioral Measures

Reading fluency, attention, and visuospatial reasoning ability of the children were assessed during the sixth grade (see **Table 1**).

Reading fluency performance was evaluated using a composite score derived from the following three subtests using PAF with Promax rotation. The factor analysis was forced into one factor. The word identification test and word chain test were conducted as a group session. The oral pseudoword text-reading test was conducted as an individual session.

(1) The word identification test, which is a subtest of the standardized Finnish reading test ALLU (Lindeman, 1998), consists of 80 items, each consisting of a picture and four phonologically similar words, one of them semantically matching the picture. The purpose of the task was to identify and connect correct picture-word pairs as quickly as possible by drawing a line between a word and the picture. The maximum duration of the task was 2 min. The score was the number of correctly connected pairs completed within the time limit. The Kuder-Richardson

TABLE 1 | Summary of reading fluency, attention, and executive function rating inventory (ATTEX), Raven's Standard Progressive Matrices test, block design test, and their statistics between groups.

Group	Reading fluency			ATTEX			RAVEN			Block design		
	df	*t*-value	*p*-value	Cohen's d	*t*-value	*p*-value	Cohen's d	*t*-value	*p*-value	Cohen's d	*t*-value	*p*-value	Cohen's d
Control vs. AP	90	2.914	0.004	0.822	−16.342	0.000	−4.612	1.589	0.115	0.448	3.454	0.001	0.975
Control vs. RD	98	10.451	0.000	2.483	−2.906	0.005	−0.691	1.953	0.054	0.464	1.270	0.207	0.302
AP vs. RD	36	6.567	0.000	2.179	9.651	0.000	3.203	−0.023	0.982	−0.008	−1.496	0.143	−0.496
		M	***SD***		***M***	***SD***		***M***	***SD***		***M***	***SD***	
Control		0.283	0.851		4.82	7.150		23.34	3.059		46.60	8.367	
AP		0.401	0.719		40.80	10.665		21.93	3.494		38.13	10.225	
RD		1.654	0.461		10.04	8.860		21.96	2.671		43.78	12.060	

The t-values denote test statistics with degrees of freedom (df). AP denotes the attentional problems group, RD denotes the reading difficulties group, and control denotes the typically developing group. Cohen's d denotes the effect size between groups. M and SD denotes the mean and standard deviation of each test score in the three groups. The FDR corrected alpha value is 0.012.

reliability coefficient for the original test is 0.97 (Lindeman, 1998). The factor loading of the test for the reading fluency factor is 0.683.

(2) The word chain test (Holopainen et al., 2004) consists of 25 chains, each consisting of four words written without spaces between them. The task was to insert a vertical line at the word boundaries. The maximum duration was 90 s, and the score was the number of correctly separated words within the time limit. The test-retest reliability coefficient for the original test varied between 0.70 and 0.84. The factor loading of the test for the reading fluency factor is 0.872.

(3) The oral pseudoword text-reading test (Eklund et al., 2015) consists of 38 pseudowords (277 letters). These pseudowords were given as a short passage, which children were instructed to read aloud as quickly and accurately as possible. The reading performance of the students was audio recorded for scoring. The score was the number of correctly read pseudowords divided by the time (in seconds) spent on reading. The inter-rater agreement for scoring the original test is 0.95. The factor loading of the test for the reading fluency factor is 0.653.

Attention and executive function rating inventory (ATTEX) (Klenberg et al., 2010) is a teacher rating scale with 55 items to measure difficulties of inhibition, attention, and executive function in school settings grouped into ten clinical subscales (number of items per scale in parentheses): distractibility (4), impulsivity (9), motor hyperactivity (7), directing attention (5), sustaining attention (6), shifting attention (4), initiative (5), planning (4), execution of action (8), and evaluation (3). The teachers were instructed to rate the child's behavior on a three-point scale ("not a problem," "sometimes a problem," and "often a problem"). The internal consistency reliability of ATTEX and its scales varies between 0.67–0.98 and criterion validity varies between 0.68–0.95 (Klenberg et al., 2010).

Visuospatial reasoning ability was evaluated based on the following two subtests:

(1) Non-verbal reasoning ability was assessed using the Raven's Standard Progressive Matrices (RSPM) test, which is a visuospatial task (Raven and Court, 1998; John and Raven, 2003). This was conducted as a group testing session. The test consists of 60 items, of which a shortened version was used containing 30 items (every second item from the complete test). The task was to select the one correct option among six to eight choices to fill in a missing part and complete a picture matrix. These choices were always similar in shape, but they varied from each other with respect to their pattern. The total score was the number of items correctly responded to. The maximum duration of the task was 15 min. In another large-scale project with more than 800 sixth graders from the same area in Finland, the same shortened version was used with a Cronbach's alpha reliability coefficient of 0.81 (Kanerva et al., 2019).

(2) A block design test (WISC-IV) (Lynne Beal, 2004) was used to measure spatial ability. It consists of nine red and white square blocks and a booklet of cards with different color designs that can be made with the blocks. The task was to arrange the blocks to match the design formed by the examiner (or as shown on cards) as quickly and accurately as possible. This test was used to further characterize the groups and was not used as an inclusion or exclusion criterion.

Experimental Procedure: Attention Network Test for Children

In this EEG experiment, a modified version of the ANT (Neuhaus et al., 2010) was used to measure the three sub-processes of the attention network: alerting, orienting, and inhibition. Participants were required to lean on a chinrest located 60 cm from a 24-inch computer screen (resolution of 1920 × 1080 and a refresh rate of 60 Hz). A fixation cross was visible in the center of the white screen [960, 540 (x, y)] during the entire testing period. The participant's task was to look at the fixation cross and report the direction of the middle fish as quickly and accurately as possible by pressing a corresponding button.

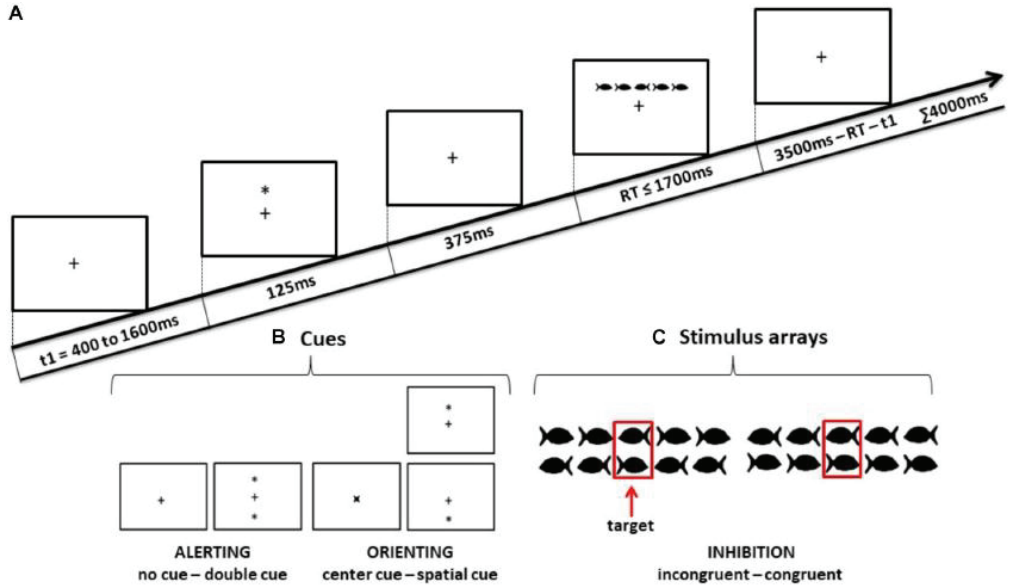

FIGURE 2 | Schematic illustrations of **(A)** the sequence of events in the Child-Attention Network Test (ANT), **(B)** the four cue conditions used in ANT, and **(C)** the two target stimulus conditions for which the children had to decide the swimming direction of the middle fish.

As shown in **Figure 2**, the stimulus (a group of fish) was preceded by one of the four cue conditions (no cue, double cue, center cue, or spatial cue). The fixation period of a random duration was between 400 ms and 1600 ms before the cue appeared. The duration of the cue was 125 ms, which was followed by 375 ms of waiting time before the stimulus was presented (a total of 500 ms prior to stimulus presentation). In the double cue trial, two asterisks were presented simultaneously at a 1° angle above and below the fixation cross. In the center cue trial, an asterisk was presented on the fixation cross. In the spatial cue trial, a single asterisk appeared in the position of the upcoming stimulus.

To make the experiment more child-friendly, black fish drawings instead of arrows were used as stimuli. The stimulus comprised a row of five horizontal fish. Each fish was subtended to 0.7°, and adjacent fish were separated by 0.3° each. The size of the entire stimulus array was 4.7°. The center fish in the stimulus was the target, and the two fish on either side of the target were referred to as flankers. The stimulus array in each trial was presented above or below the fixation cross at the same location where the double cue or spatial cue appeared. The maximum duration of each trial was 4000 ms. The maximum duration of the stimulus array in each trial was 1700 ms until a response was detected; thereafter, if there was no response, it was considered an unattended trial and terminated. The maximum duration between the onset of the stimulus and the start time of the next trial was 3500 ms, which varied according to the duration of the stimulus array. For congruent stimuli, the flankers were in the same direction as the target and for incongruent stimuli, the flankers were in the opposite direction. Participants were instructed to keep their gaze on the fixation cross throughout the experiment and report the swimming direction of the center fish by pressing a left or right corresponding direction button in the button box.

One ANT session consisted of 288 pseudo-randomized trials, which were divided into four experimental blocks with 72 trials in each block. Each block consisted of all eight possible conditions in equal proportions: four cue conditions (no cue, double cue, center cue, and spatial cue) × two target stimulus conditions (congruent, incongruent).

EEG and Eye-Tracker Recording

The ANT experiment was designed using the Experiment Builder (1.10.1630) software on a Dell Precision T5500 workstation. Electroencephalography data were recorded using a high-density array of 128 Ag-AgCl electrodes in HydroCel Geodesic Sensor Nets (GSN; Electrical Geodesics Inc.). The electrode positions for 128 channel HydroCel GSN approximate the correspondence with the international 10–10 system electrode positions. The electrode numbers 11, 55, 65, and 90 plotted in **Figure 3** correspond to Fz, CpZ, PO7, and PO8, respectively, based on the international 10–10 system (Luu and Ferree, 2000). The EEG data were amplified using a NeurOne amplifier (Mega Electronics Ltd.). During measurement, the impedance of the electrodes was intended to be kept below 50 kΩ, and the quality of the EEG data was monitored throughout the EEG recording. Electroencephalography was referenced to the Cz electrode online and sampled at 1000 Hz. An online high-pass filter of 0.16 Hz and a low-pass filter of 250 Hz were applied during EEG data recording. Eye movement data were recorded with a table-mounted Eyelink 1000 eye-tracking device at 1000 Hz for both eyes (SR Research Ltd.). Eye movements and EEG were

recorded simultaneously through the combination of triggering via ethernet messages and TTL pulses. The entire experiment was conducted in a dimly lit sound-attenuated room in a laboratory at the University of Jyväskylä, Finland.

Pre-processing of EEG Data and Eye Tracking

Electroencephalography data were preprocessed using MatLab R2014a, with EEGLab (Delorme and Makeig, 2004) (Swartz Centre for Computational Neuroscience, San Diego), FieldTrip (Oostenveld et al., 2011) (version 20160110) toolboxes, and BESA Research 6.1 (BESA GmbH, Munich, Germany). The raw eye tracking data were converted and stored into a MatLab structured array using the EEGLab add-on EYE-EEG (Dimigen et al., 2011). The continuous raw EEG data file was imported into EEGLab, in which bad channels were interpolated. In EEGLab, the events observed in EEG and eye tracking were used for synchronization. One event at each of the beginning and end of the eye-tracking data record were linearly interpolated to match the number of EEG sampling points recorded during the same time interval. The quality of synchronization was assessed by examination of the linear regression line for the regression of latencies of eye-tracking events on the latencies of EEG events.

A high-pass filter of 0.5 Hz (a fifth order, zero-phase Butterworth filter) was applied to the raw EEG data. Data were segmented into 1200 ms epochs (200 ms before cue onset and 1000 ms after cue onset) for non-cued, double-cued, center-cued, and spatially cued target stimuli, and 900 ms epochs (200 ms before and 700 ms after the onset of target stimulus) for congruent and incongruent stimuli. Trials with incorrect responses were excluded from the data analyses. A low-pass filter of 30 Hz (sixth order, zero-phase Butterworth filter) was then applied to the high-pass filtered, segmented EEG data. The baseline was set to −200 ms and 0 ms of the filtered segmented data. Gaze positions in each trial were examined in order to ensure that participants maintained their gaze in the optimal position for stimulus presentation. If there was an eye blink, the gaze position value was recorded as zero, or if the gaze position was outside the defined area [860–1060, 440–640 (x, y)] on the display screen, the trial was excluded. Trials with muscular movement and other artifacts were rejected using a threshold rejection approach. The value of threshold rejection was 175 μV. The average percentages of rejected trials for all conditions in control, AP, and RD groups are given in **Supplementary Table 1**. Accepted trials using the above criteria were averaged for each participant. The averaged ERPs were re-referenced to the average reference. In the control group, each condition (non-cued, double-cued, center-cued, spatially cued, congruent, and incongruent target stimuli) had a minimum of 30 trials for averaging. In the attentional problems and reading difficulties groups, one subject had a minimum of 22 trials in the non-cued and cued stimulus conditions for averaging, while two participants had a minimum of 24 trials in a no-cue condition for averaging. The remainder had a minimum of 30 trials. The averaged data were visually inspected and comparable to that of other participants.

Statistical Analysis of Reaction Time Data

The RTs of each trial were calculated from the target stimulus onset time to the button press response time. The unattended trials, trials with incorrect responses, and trials that were not accepted for ERP averaging were excluded from calculations of the mean RTs. All participants maintained a high level of accuracy (see **Supplementary Table 3**). There were no participants excluded due to poor performance. Repeated measures ANOVAs were performed in IBM SPSS Statistics version 24 to determine significant differences in RTs between conditions and groups. Separate Repeated measures ANOVAs for alerting, orienting, and inhibition {3 (group) × 2 (condition)} were calculated with repeated measures to determine the significance of the reaction time performance between the groups (control, AP, RD) and conditions (alerting: non-cued and double-cued target stimuli; orienting: center-cue and spatially cued target stimuli; inhibition: incongruent and congruent target stimuli). Paired-sample t-tests were calculated in IBM SPSS Statistics version 24 to determine the significant differences in RTs between conditions within the groups. Cohen's D_z was calculated to determine the effect size between RTs for different target stimuli within a group.

Statistical Analysis of ERP Responses at the Sensor Level of Field Potentials

Non-parametric, cluster-based permutation tests were calculated as a two-tailed test using BESA Statistics 2.0 (BESA GmbH, Munich, Germany) to determine significant effects for the field ERP field potentials across all the electrodes between conditions (alerting: double-cued vs. non-cued target stimuli; orienting: spatially cued vs. center-cued target stimuli; inhibition: incongruent vs. congruent target stimuli) within the groups. The difference waveform was calculated between the conditions (alerting: double-cued vs. non-cued target stimuli; orienting: spatially cued vs. center-cued target stimuli; inhibition: incongruent vs. congruent target stimuli) using BESA Research 6.1. Non-parametric, cluster-based permutation tests were then calculated as a two-tailed test to determine the significant effects for the difference in wave ERP field potentials across all the electrodes between groups (control vs. AP; control vs. RD; AP vs. RD). Based on our previous study (Santhana Gopalan et al., 2019), the time window for cluster-based permutation tests between groups was set to 140–200 ms after target onset (alerting and orienting conditions) and 480–700 ms after target onset (inhibition conditions). The number of permutations was set to 1000, and cluster alpha (the significance threshold level for data to enter a cluster) was set to 0.05. For spatial clustering, the neighbor distance between electrodes was set to 3 cm.

Source-Level Analysis

Source analysis was performed in BESA Research 6.1 to estimate source areas in the brain related to the sub-processes of attention. In our previous study (Santhana Gopalan et al., 2019), we reconstructed the source representation of scalp data based on the control children ($N = 83$) using the classical LORETA analysis recursively applied (CLARA) distributed source analysis method.

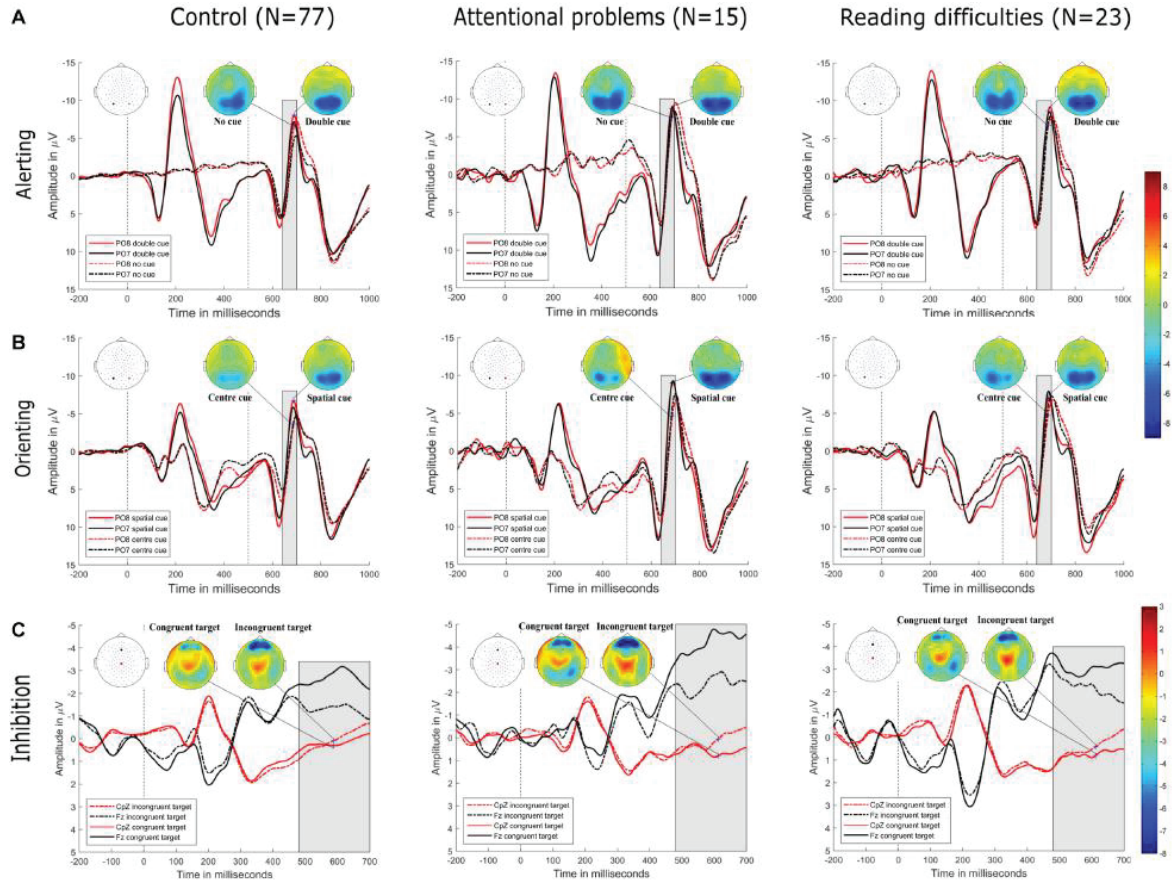

FIGURE 3 | (A) Alerting. Grand-averaged ERP waveforms for the double-cued target stimulus (solid lines) and non-cued target stimulus (dotted lines) at posterior electrodes (PO8, red, right hemisphere; PO7, black, left hemisphere) in control (top row-left), attentional problems (top row-center), and reading difficulties (top row-right) groups. Cue onset is at 0 ms and target stimulus onset is at 500 ms. Amplitude topographies for double-cued and non-cued target stimuli are at 689 ms (i.e., 189 ms after target stimulus onset). **(B)** Orienting. Grand-averaged ERP waveforms for the spatially cued target stimulus (solid lines) and center-cued target stimulus (dotted lines) for posterior electrodes (PO8, red, right hemisphere; PO7, black, left hemisphere) in control (middle row-left), attentional problems (middle row-center), and reading difficulties (middle row-right) groups. Cue onset is at 0 ms and target stimulus onset is at 500 ms. Amplitude topographies for spatially cued and center-cued target stimuli are at 686 ms (i.e., 186 ms after target stimulus onset). **(C)** Inhibition. Grand-averaged ERP waveforms for the congruent stimulus (dotted lines) and incongruent stimulus (solid lines) at central electrode (CpZ, red) and frontal electrode (Fz, black) in control (bottom row-left), attentional problems (bottom row-middle), and reading difficulties (bottom row-right) groups. Target stimulus onset is at 0 ms. Amplitude topographies for congruent and incongruent target stimuli are at 612 ms after target stimulus onset. Negativity is upward.

A regional source was fitted in the foci obtained from the CLARA solution. A regional source was considered as three single dipoles at the same location, with three orthogonal orientations (Hoechstetter et al., 2010). The source strength at each time point was estimated as a combined sum of the power of the three orthogonal orientations of the regional sources. These regional sources were used as a spatial filter for source modeling for each of the three effects in the control children. The spatial filter with regional sources derived from the control group data was used to obtain the strength of the source activity for each stimulus condition in AP and RD groups, i.e., the scalp data of AP and RD groups were "projected" into the sources derived using the control group data. The time window of interest for the N1 period of the target stimulus was between 140 and 200 ms, and the time window for the P3 period of the target stimulus was between 480 and 700 ms.

Source-Level Analysis Statistics

Residual variance was examined in BESA Research 6.1 to determine the goodness of fit of the regional source model for the neuronal data in each condition and each group (see **Supplementary Table 2**). T-tests for the residual variance were calculated using SPSS version 24 to confirm that there was no difference between conditions and groups. There was no significant group difference between any groups (control vs. AP; control vs. RD; AP vs. RD) with respect to the residual variance. The activity in each source was initially compared against zero using a *t*-test to determine if a signal was present in

the source. The source activity of the left anterior temporal lobe in the alerting and orienting networks did not show a significant difference from zero. This source was therefore excluded from further analysis. Source-level statistics were calculated using a 2 (conditions) × 3 (groups) repeated measures ANOVAs in SPSS version 24. Statistical analyses considered cued-target conditions and congruency target conditions as within-subjects factors. Between-subjects factors included the control, AP, and RD groups. For the source level statistics, N1 (140–200 ms) and P3 (480–700 ms) cued-target stimulus periods were selected from the source waveforms associated with the locations of the neuronal sources. The repeated measures ANOVA with trials as covariates, and group and condition as factors for neuronal source were checked to confirm that the number of trials did not affect the interaction between the groups. To correct for the multiple comparisons regarding RT and neuronal sources, we adjusted the alpha level using the false discovery rate method with $q = 0.05$ (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001, 2005). After correction, the p-Values smaller than or equal to the corrected alpha value (0.0120) were considered significant.

RESULTS

Behavioral Tests

Reaction time performance on the ANT was first examined to verify the existence of alerting, orienting, and inhibition effects, as well as possible differences between the groups. The repeated measures ANOVA (see **Table 2**) indicated significant main effects for the condition for alerting (non-cued vs. double-cued target stimuli), orienting (center-cued vs. spatially cued target stimuli), and inhibition (incongruent vs. congruent target stimuli) sub-processes and main effects of group with respect to RT performance. For alerting, the main effect of condition indicated a decrease in RT on double-cued target stimuli relative to non-cued target stimuli. For orienting, the main effect of condition indicated a decrease in RT on spatially cued target stimuli relative to center-cued target stimuli. For inhibition, the main effect of condition indicated an increase in RT on an incongruent target relative to a congruent target. No significant interactions between conditions and groups were found. The main effect of group was significant across the alerting, orienting, and inhibition conditions, indicating that the overall reaction time in children with RD was longer than that for control children and children with AP.

Within-group *post hoc* t-tests on RT performance (**Supplementary Table 3**) showed significant differences between all conditions (Alerting: non-cued vs. double-cued target stimuli, Orienting: center-cued vs. spatially cued target stimuli, Inhibition: incongruent vs. congruent target stimuli). Between-group *post hoc* t-tests on RT performance for each condition showed no significant differences after the alpha value correction (**Supplementary Table 4**).

Event-Related Field Potentials

Figure 3 shows the grand-averaged ERPs of control, AP, and RD children at electrodes located at bilateral occipital and fronto-central sites. From the onset of the target stimulus, related N1 (140–200 ms) and P3 (480–700 ms) waveforms for these three groups showed similar patterns without observable significant differences between groups. On the other hand, there was a significant difference between conditions within each group for the alerting and orienting effect in the time window from 140 ms to 200 ms. the inhibition effect showed a significant difference between conditions within each group in the time window from 480 to 700 ms.

Neuronal Sources of ERPs

Figures 4, **5** show the grand-averaged source waveforms for all conditions between groups. The group main effect (**Figure 6**) was significant and showed a difference in the left occipital lobe for the alerting (double-cued vs. non-cued target stimuli) and orienting network (spatially cued vs. center-cued target stimuli).

Figure 6 and **Table 3** show comparisons of control children and children with AP. The alerting network showed a significant main effect of condition in the left and right anterior temporal lobes and in the left and right occipital lobes. Increased activity resulting from the double-cued target stimulus as compared to a non-cued target stimulus was also observed. The interaction effect between condition and group was significant in the left occipital lobe, with the AP children having a larger alerting effect compared to the control children. The main effect of group was significant in the left occipital lobe of children with AP, as they exhibited larger responses than those of children in the control group.

The orienting network showed a significant main effect of condition in the right occipital lobe with increased activity to the spatially cued target stimulus compared to the center-cued target

TABLE 2 | Repeated measures ANOVA test statistics for reaction time performances between controls ($N = 77$), children with attentional problems ($N = 15$), and children with reading difficulties ($N = 23$).

		Alerting (no cue vs. double cue)			Orienting (center cue vs. spatial cue)			Inhibition (incongruent vs. congruent)		
	df	*F*	*P*	η^2_p	*F*	*P*	η^2_p	*F*	*P*	η^2_p
Main effect of condition	1	189.995	0.000	0.625	80.097	0.000	0.417	520.692	0.000	0.823
Condition × group interaction	2	1.603	0.206	0.028	3.291	0.041	0.056	2.244	0.111	0.039
Main effect of group	118	5.720	0.004	0.093	6.529	0.002	0.104	6.738	0.002	0.107

df, denotes degree of freedom; η^2_p, partial eta-squared. The FDR corrected alpha value is 0.012.

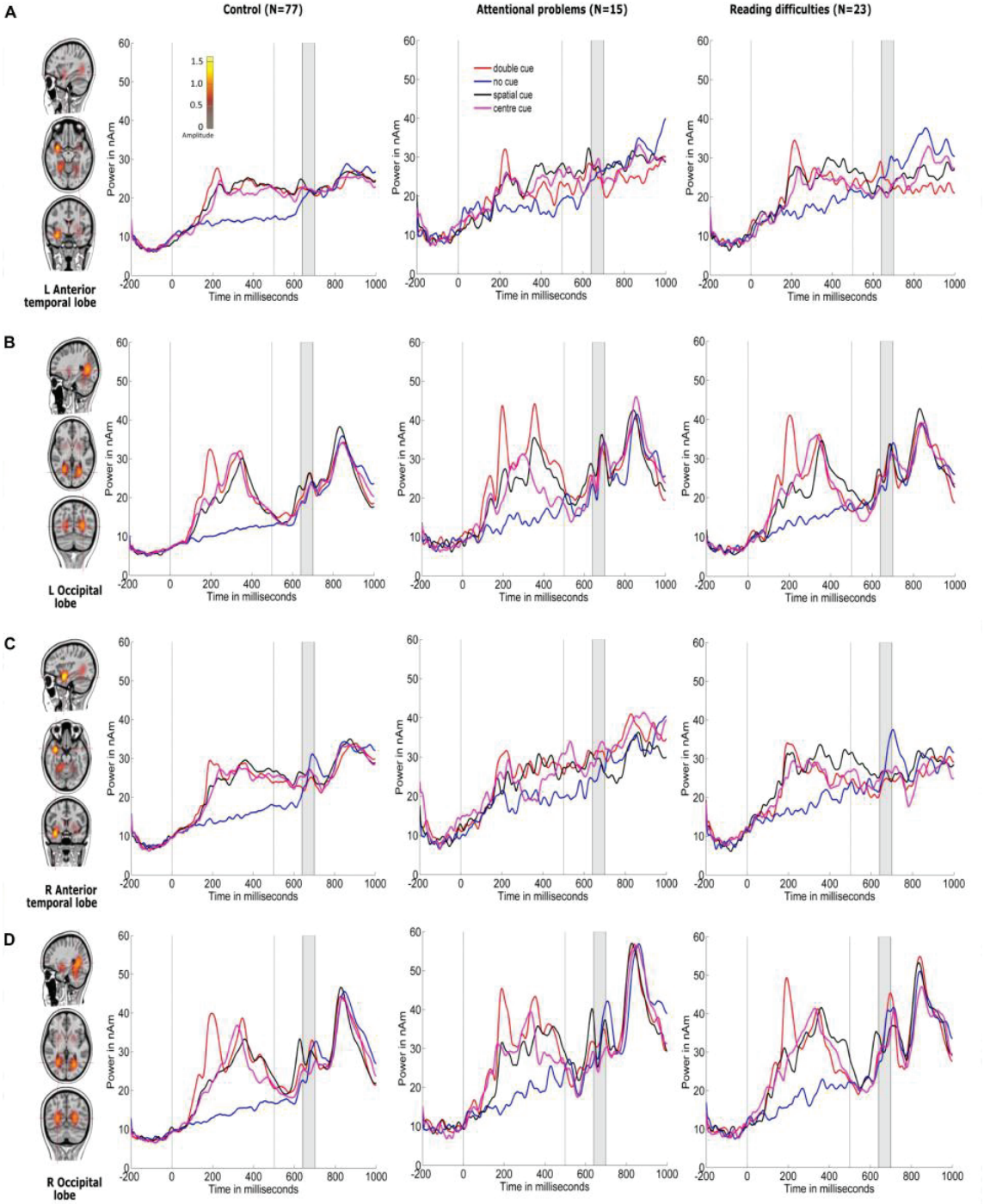

FIGURE 4 | Source locations of grand-averaged ERPs collapsed across all conditions (congruent and incongruent target stimuli, including non-cued, double-cued, center-cued, and spatially cued target stimuli) over time points of the N1 period of the target stimulus (140–200 ms) using CLARA in control children. CLARA was used as a model to derive the source waveforms for control children (N = 77), children with attentional problems (N = 15), and children with reading difficulties (N = 23). Grand-averaged source waveforms were extracted for double-cued (red), non-cued (blue), spatially cued (black), and center-cued (magenta) target stimuli using regional sources at the foci revealed by CLARA (shown on the right side of each source). Cue onset is at 0 ms and target stimulus onset is at 500 ms. Brain activations were localized in the **(A)** left anterior temporal lobe, **(B)** left occipital lobe, **(C)** right anterior temporal lobe, and **(D)** right occipital lobe. The color bar denotes source amplitude. The shaded gray area denotes the source analysis time window.

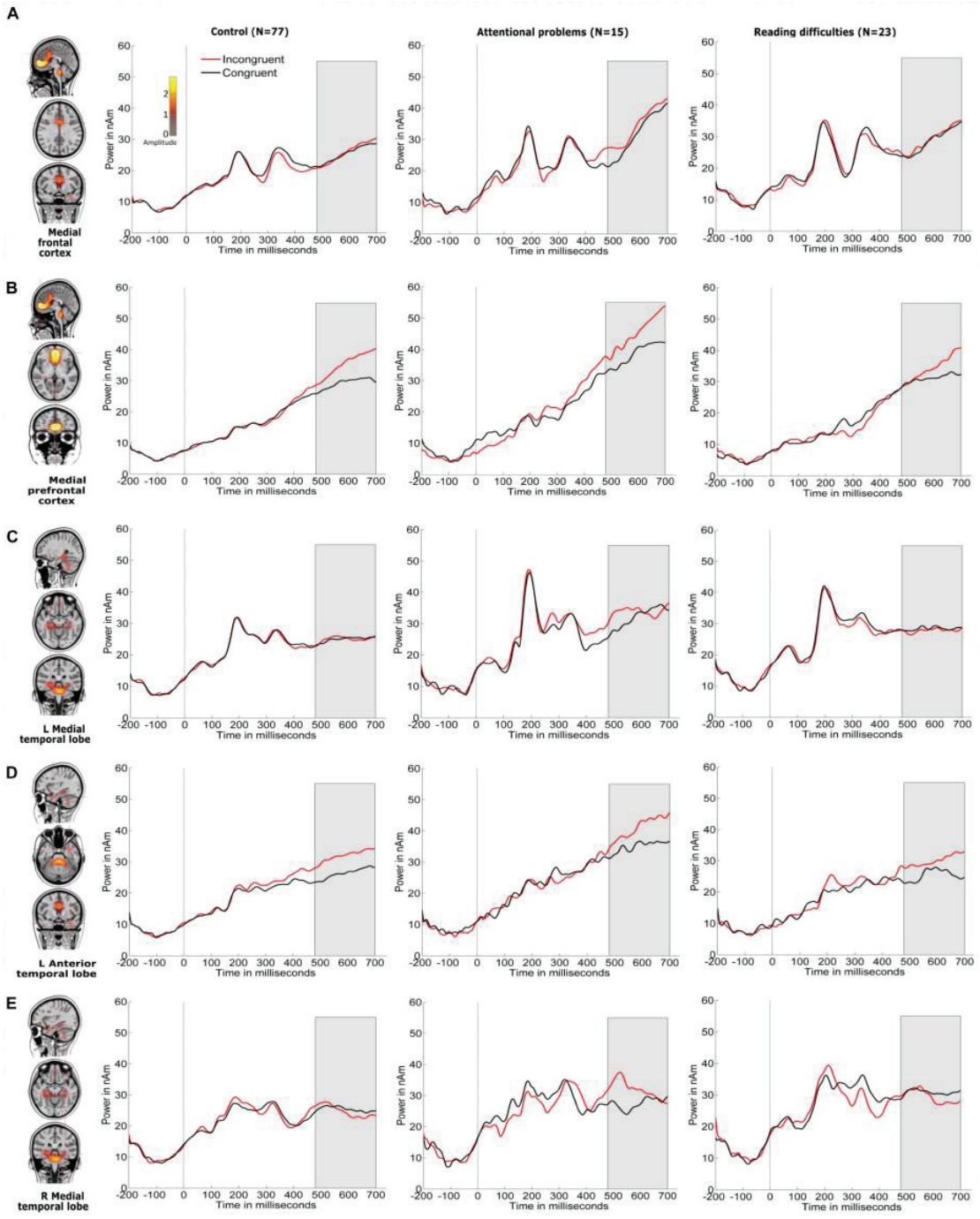

FIGURE 5 | Source locations of grand-averaged ERPs collapsed across all conditions (congruent and incongruent target stimuli, which include non-cued, double-cued, center-cued, and spatially cued target stimuli) over time points of the P3 period of the target stimulus (480–700 ms) using CLARA in control children. CLARA was used as a model to derive the source waveforms for control children (N = 77), children with attentional problems (N = 15), and children with reading difficulties (N = 23). Grand-averaged source waveforms were calculated for incongruent (red) and congruent (black) target stimuli and extracted using regional sources at the foci, as revealed by CLARA (these are shown on the right side of each source). Target stimulus onset is at 0 ms. Brain activations were localized in the **(A)** medial frontal cortex, **(B)** medial prefrontal cortex, **(C)** left medial temporal lobe, **(D)** left anterior temporal lobe, and **(E)** right medial temporal lobe. The color bar denotes source amplitude. The shaded gray area denotes the source analysis time window.

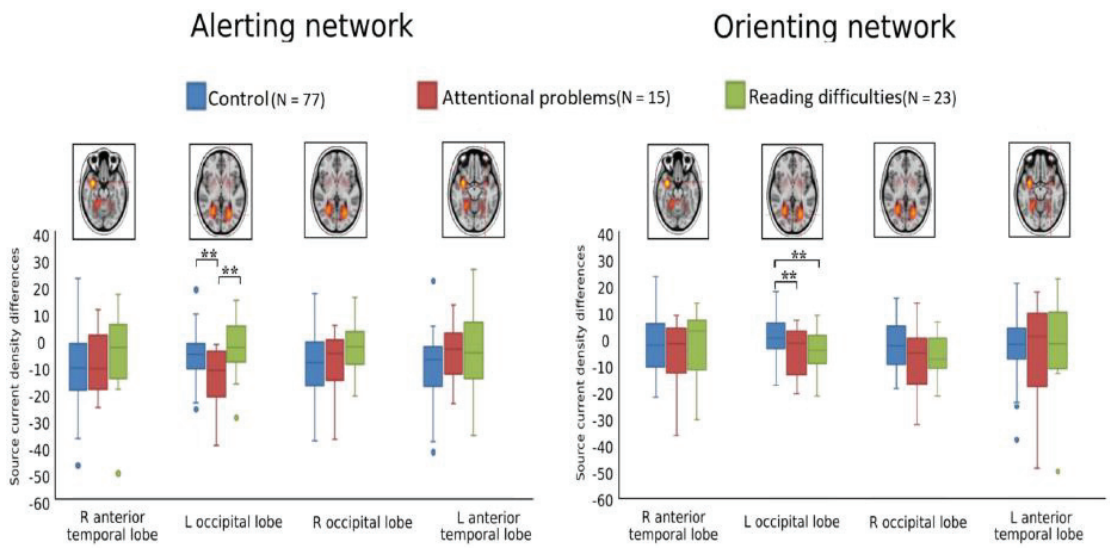

FIGURE 6 | Boxplots of alerting (double-cued vs. non-cued target stimuli) and orienting (spatially cued vs. center-cued target stimuli) for source strength for control (blue, $N = 77$), attentional problems (red, $N = 15$), and reading difficulties (green, $N = 23$) groups; $^{**}p < 0.005$. The FDR corrected alpha value is 0.012.

stimulus. The interaction effect between condition and group in the left occipital lobe showed a significantly larger orienting effect in children with AP than in control children.

Figure 6 and **Table 4** compare control children and children with RD. The alerting network showed a significant main effect for condition in the left and right anterior temporal lobes and in the left and right occipital lobes. There was also increased activity in response to the double-cued target stimulus compared to a non-cued target stimulus. The main effect of group was significant in the left occipital lobe with control children having larger responses than children with RD.

The orienting network showed a significant main effect for condition in the right occipital lobe. There was increased activity to the spatially cued target stimulus compared to a center-cued target stimulus. The interaction effect between condition and group in the left occipital lobe showed a significantly larger orienting effect in children with RD than in control children. The main effect of group was significant in the left occipital lobe with the control children having smaller responses than children with RD.

The inhibition network showed the main effect for group was significant in the right medial temporal lobe with children with RD showing a smaller response than children in the control group.

Figure 6 and **Table 5** show comparisons of children with AP and children with RD. The alerting network showed a significant main effect for condition in the left and right anterior temporal lobes and the left and right occipital lobes. There was increased activity to the double-cued target stimulus compared to a non-cued target stimulus. The interaction effect between condition and group was significantly larger in the left occipital lobe of children with AP having a larger alerting effect than in children with RD.

The orienting network showed a significant main effect of condition in the left and right occipital lobes with increased activity to the spatially cued target stimulus compared to the center-cued target stimulus.

The condition by group interactions for the repeated measures ANOVAs with trial numbers as covariates are significant. Alerting: $F(2,110) = 6.685$, $p = 0.002$, $\eta_p^2 = 0.108$. Orienting: $F(2,110) = 6.865$, $p = 0.002$, $\eta_p^2 = 0.111$.

DISCUSSION

We examined the reaction time performance, event-related potentials (ERP), and neuronal source activations of attentional sub-processes related to alerting, orienting, and inhibition using the attention network test (ANT) in typically developing 12−13-year-old children, as compared to those with attentional problems (AP) and those with reading difficulties (RD). Our results on reaction times (RT) showed that there were no significant differences in the reaction time performance for the alerting, orienting, and inhibition effects between any of the groups, although children with RD had slower RTs in general. The ERP sensor-level analyses did not reveal statistically significant differences in the target-related N1 or P3 between groups. However, neuronal source activity did show group differences (see **Table 6**). Children with AP showed a larger alerting effect (double-cued vs. non-cued target stimuli) in the left occipital lobe compared to control children and children with RD. Children in the control group showed a smaller orienting effect (spatially cued vs. center-cued target stimuli) in the left occipital lobe compared to children with AP and children with RD. No group differences

TABLE 3 | Repeated measures ANOVA test statistics for alerting, orienting, and inhibition sources between control (*N* = 77) and attentional problems (*N* = 15) children.

Control (*N* = 77) vs. AP (*N* = 15)															
Alerting (double cue vs. no cue)	**R anterior temporal lobe**				**L occipital lobe**			**R occipital lobe**			**L anterior temporal lobe**				
	df	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**		
Main effect of condition	1	20.538	0.000	0.186	47.541	0.000	0.346	22.256	0.000	0.198	18.105	0.000	0.167		
Condition × group interaction	1	0.006	0.941	0.000	9.802	0.002	0.098	0.001	0.972	0.000	2.375	0.127	0.026		
Main effect of group	90	1.119	0.293	0.012	18.413	0.000	0.170	5.634	0.020	0.059	0.020	0.888	0.000		
Orienting (spatial cue vs. center cue)	**R anterior temporal lobe**				**L occipital lobe**			**R occipital lobe**			**L anterior temporal lobe**				
	df	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**		
Main effect of condition	1	0.009	0.926	0.000	1.776	0.186	0.019	11.748	0.001	0.115	0.813	0.370	0.009		
Condition × group interaction	1	0.656	0.420	0.007	7.044	0.009	0.076	2.080	0.153	0.023	0.013	0.909	0.000		
Main effect of group	90	0.004	0.834	0.000	5.418	0.022	0.057	2.763	0.100	0.030	1.080	0.301	0.012		
Inhibition (incongruent vs. congruent)	**Medial prefrontal cortex**				**Medial frontal cortex**			**L anterior temporal lobe**			**R medial temporal lobe**			**L medial temporal lobe**	
	df	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**
Main effect of condition	1	1.920	0.169	0.021	0.012	0.914	0.000	0.455	0.502	0.005	1.107	0.296	0.012	3.060	0.084	0.033
Condition × group interaction	1	0.662	0.418	0.007	5.006	0.028	0.053	0.579	0.451	0.006	1.363	0.246	0.015	4.697	0.033	0.050
Main effect of group	90	1.093	0.299	0.012	1.883	0.173	0.021	1.432	0.235	0.016	5.313	0.023	0.056	3.363	0.070	0.036

AP, Children with attentional problems; L, left; R, Right; df, denotes degrees of freedom; η^2p, partial eta-squared. The FDR corrected alpha value is 0.012.

TABLE 4 | Repeated measures ANOVA test statistics for alerting, orienting, and inhibition sources between control (*N* = 77) and reading difficulties children (*N* = 23).

Control (*N* = 77) vs. RD (*N* = 23)															
Alerting (double cue vs. no cue)	**R anterior temporal lobe**				**L occipital lobe**			**R occipital lobe**			**L anterior temporal lobe**				
	df	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**		
Main effect of condition	1	14.043	0.000	0.125	8.105	0.005	0.076	15.222	0.000	0.134	17.684	0.000	0.153		
Condition × group interaction	1	2.112	0.149	0.021	2.337	0.130	0.023	2.811	0.097	0.028	4.638	0.034	0.045		
Main effect of group	98	0.571	0.452	0.006	8.129	0.005	0.077	1.498	0.224	0.015	2.757	0.100	0.027		
Orienting (spatial cue vs. center cue)	**R anterior temporal lobe**				**L occipital lobe**			**R occipital lobe**			**L anterior temporal lobe**				
	df	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**		
Main effect of condition	1	5.473	0.021	0.053	1.954	0.165	0.020	12.234	0.001	0.111	2.774	0.099	0.028		
Condition × group interaction	1	1.578	0.212	0.016	8.345	0.005	0.078	2.266	0.135	0.023	0.645	0.424	0.007		
Main effect of group	98	0.242	0.624	0.002	6.720	0.011	0.064	2.821	0.096	0.028	1.315	0.254	0.013		
Inhibition (incongruent vs. congruent)	**Medial prefrontal cortex**				**Medial frontal cortex**			**L anterior temporal lobe**			**R medial temporal lobe**			**L medial temporal lobe**	
	df	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**
Main effect of condition	1	0.073	0.787	0.001	1.558	0.215	0.016	1.900	0.171	0.019	4.604	0.034	0.045	0.844	0.361	0.009
Condition × group interaction	1	0.942	0.334	0.010	1.124	0.292	0.011	0.098	0.755	0.001	4.018	0.048	0.039	0.212	0.647	0.002
Main effect of group	98	0.018	0.893	0.000	3.824	0.053	0.038	0.007	0.933	0.000	6.563	0.012	0.063	5.454	0.022	0.053

RD, Children with reading difficulties; L, left; R, Right; df, denotes degrees of freedom; η^2p, partial eta-squared. The FDR corrected alpha value is 0.012.

TABLE 5 | Repeated measures ANOVA test statistics for alerting, orienting, and inhibition sources between attentional problems (N = 15) and reading difficulties (N = 23) children.

AP (N = 15) vs. RD (N = 23)																
Alerting (double cue vs. no cue)	**R anterior temporal lobe**				**L occipital lobe**				**R occipital lobe**				**L anterior temporal lobe**			
	df	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**		***F***	***P***	**η^2p**		***F***	***P***	**η^2p**	
Main effect of condition	1	7.255	0.011	0.168	15.343	0.000	0.299		8.652	0.006	0.194		2.880	0.098	0.074	
Condition × group interaction	1	1.013	0.231	0.027	9.741	0.004	0.213		1.643	0.208	0.044		0.098	0.757	0.003	
Main effect of group	36	0.097	0.757	0.003	2.905	0.097	0.075		1.831	0.184	0.048		1.487	0.231	0.040	
Orienting (spatial cue vs. center cue)	**R anterior temporal lobe**				**L occipital lobe**				**R occipital lobe**				**L anterior temporal lobe**			
	df	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**		***F***	***P***	**η^2p**		***F***	***P***	**η^2p**	
Main effect of condition	1	0.785	0.381	0.021	7.674	0.009	0.176		9.117	0.005	0.203		0.799	0.377	0.022	
Condition × group interaction	1	2.086	0.157	0.055	0.004	0.947	0.000		0.001	0.972	0.000		0.114	0.737	0.003	
Main effect of group	36	0.035	0.853	0.001	0.037	0.848	0.001		0.036	0.851	0.001		0.003	0.954	0.000	
Inhibition (incongruent vs. congruent)	**Medial prefrontal cortex**				**Medial frontal cortex**				**L anterior temporal lobe**				**R medial temporal lobe**			**L medial temporal lobe**
	df	***F***	***P***	**η^2p**	***F***	***P***	**η^2p**		***F***	***P***	**η^2p**		***F***	***P***	**η^2p**	***F*** ***P*** **η^2p**
Main effect of condition	1	0.262	0.612	0.007	0.653	0.424	0.018		0.148	0.703	0.004		0.235	0.631	0.006	0.912 0.346 0.025
Condition × group interaction	1	1.921	0.174	0.051	0.878	0.355	0.024		0.214	0.647	0.006		5.404	0.026	0.131	3.452 0.071 0.087
Main effect of group	36	0.873	0.356	0.024	0.135	0.716	0.004		1.098	0.302	0.030		0.002	0.962	0.000	0.025 0.874 0.001

AP, Children with attentional problems; RD, Children with reading difficulties; L, left; R, Right; df, denotes degrees of freedom; η^2p, partial eta-squared. The FDR corrected alpha value is 0.012.

TABLE 6 | Summary of neuronal source results related to alerting (non-cued vs. double-cued target stimuli), orienting (center-cued vs. spatially cued target stimuli), and inhibition (incongruent vs. congruent target stimuli) sub-processes of the attention network.

Sub-processes	**Neuronal source**	**Group × condition effect**	**Direction of group difference**
Alerting Source: DC vs. NC	L occipital lobe	C ≠ AP AP ≠ RD C = RD	C < AP RD < AP
Orienting Source: SC vs. CC	L occipital lobe	C ≠ AP C ≠ RD AP = RD	C < AP C < RD

C, control children; AP, children with attentional problems and RD, children with reading difficulties; L, left; R, right; not equal (≠), interaction effect; equal (=), no interaction effect; NC, non-cued target stimuli; DC, double-cued target stimuli; CC, center-cued target stimuli; SC, spatially cued target stimuli.

were found for the neuronal sources related to the inhibition effect.

A meta-analysis as well as individual studies on children and adults with ADHD examining reaction times for the alerting effect (non-cued vs. double-cued target stimuli) and orienting effect (center-cued vs. spatially cued target stimuli) found no differences between control and ADHD groups in that regard (Berger and Posner, 2000; Huang-Pollock and Nigg, 2003; Adólfsdóttir et al., 2008; Kratz et al., 2011; Fabio and Urso, 2014). In line with these studies, our results on RT for alerting and orienting effect showed no group differences between controls and children with AP.

Previous studies on dyslexics (Bednarek et al., 2004; Goldfarb and Shaul, 2013) showed that there was a significant difference in the inhibition effect (incongruent target vs. congruent target) compared to a control group. In contrast with these studies, our results on RT for inhibition effects showed no group differences.

When examining brain activity using ERPs at the sensor level, a comparison of target-related N1 and P3 measures between control, AP, and RD groups did not show group differences in any of the three attention networks (alerting, orienting, or inhibition). To our knowledge, there have been no previous findings on target-related N1 amplitude modulation associated with alerting and orienting effects in children or adults with attentional or reading problems within the same study. There seem to be differences between the groups in the pre-stimulus (before target onset) time window. Future studies on N1- alerting and orienting effects during the pre-stimulus period could therefore reveal further processing differences between the groups.

In our investigation, children with AP did not differ from control and RD children with respect to P3 amplitude for the inhibition effect. This is in contrast to earlier studies, which found group differences in P3 in adults (Kratz et al., 2011; Hasler et al., 2016). Both of these studies showed a lower amplitude of P3 in the ADHD group compared to the control group, suggesting an ineffective attentional allocation to stimulus processing and evaluation. An adult study on lateralized ANT (the target being an arrow up or down and presented to the left or right of the fixation cross) supports our finding in the RD group that inhibition of irrelevant information measured by the P3 ERP

component to the target (NoGo P3) is preserved in dyslexia (Mahé et al., 2014).

However, as described above, our RT results do not show group differences in alerting, orienting, and inhibition effects. It is possible that the scalp-level ERP may not be able to capture the differences in these attentional processes. One reason for this could be the use of cluster-based permutation statistics, which could yield results that are more conservative compared to some earlier studies (Maris and Oostenveld, 2007; Pernet et al., 2015). A statistically more sensitive method might have been the use of ANOVA for the selected set of electrodes, but this has the drawback of arbitrary channel selection not being the best representation of the actual brain responses. Therefore, we examined source-level information to disentangle the neural sources in the AP and RD groups utilizing the source model derived from the control group data (Santhana Gopalan et al., 2019).

The N1-related sources for the target stimulus were localized in the left and right occipital lobes and the left and right anterior temporal lobes between 140 ms and 200 ms. However, the left anterior temporal lobe did not show any alerting or orienting effect differing from zero and was therefore excluded from further analysis and interpretation. P3-related sources for the target stimulus were localized in the medial prefrontal cortex, medial frontal cortex, left anterior temporal lobe, and left and right medial temporal lobes.

There is evidence for structural and functional changes in the left occipital lobe (lingual gyrus) in the ADHD group compared to typically developing children (Dickstein et al., 2006; Xia et al., 2014; Lei et al., 2015). Furthermore, in an adult study, it was shown that shifting of attention from the cue to the target stimulus activates the occipital lobe (Corbetta et al., 1998). Our results in children with AP showed an increased neuronal response in the left occipital lobe for the alerting effect (double-cued vs. non-cued target stimuli) compared to control children. This could be interpreted as an atypical attentional visual process for the target stimulus based on warning cue information. Attentional disengagement and voluntary orienting have been considered important aspects of top-down attentional control processes related to selective sensory and motor processing (Hopfinger et al., 2000). It has been suggested that a network consisting of the occipital lobe, central, and parietal areas is involved in top-down attentional control, as evidenced by studies showing these areas to be active when following a cue to shift the spatial attention toward the target stimulus (Hopfinger and Ries, 2005; Corbetta et al., 2008; Zhao et al., 2017). Based on previous studies, children with AP who display larger orienting effect (center-cued vs. spatially cued target stimuli) than control group could be interpreted as having reduced top-down control (Corbetta et al., 2008; Zhao et al., 2017).

The neuronal source activation across both double-cued and non-cued target stimuli differed between children with AP and control children in the right occipital lobe and also between children with RD and control children in the left occipital lobe. This difference was not related to the alerting effect but instead to the target stimulus, regardless of which of the two cueing conditions was examined. This shows that children with AP and children with RD might have subtle differential processing atypicalities in the anticipation of a visual warning cue and in response preparation toward the target stimuli (Konrad et al., 2005, 2006; Xuan et al., 2016).

Our finding of the group difference between children with RD and controls for the alerting sub-processes in the left occipital lobe could be linked to structural and functional neuroimaging studies of dyslexia (Pugh et al., 2000; Démonet et al., 2004; Richlan, 2012; Xia et al., 2017). A recent review on developmental dyslexia has suggested that left posterior occipitotemporal dysfunction is a secondary deficit area in dyslexia, as it was assumed that phonological processing deficits reflected in the temporoparietal junction would lead to interference with the development of the left occipitotemporal cortex (Kronbichler and Kronbichler, 2018). Therefore, it is possible that atypical processing of visual information in the left occipital regions could be seen in children with RD, even for non-linguistic material.

With respect to the inhibition network, previous studies showed an abnormal activity pattern of the medial frontal region, including the anterior cingulate cortex (ACC) and parietal cortex compared to control groups (in children and adults) (Durston et al., 2003; Konrad et al., 2005, 2006). In contrast with the previous studies, our study showed no group differences in the neuronal sources related to the inhibition network. The non-correspondence between RT results and the neuronal source results may be due to that RT results represent the amount of differences in RT performance processes and that the processes assessed in this study could only respond to a few cognition attributes that mediate the task's performance (Wilkinson and Halligan, 2004; Konrad et al., 2005).

The overall strength of the neural response does not reveal possible top-down or bottom-up modulation of the neural responses. Future studies should examine whether the frontal and temporal cortices interact during the inhibition effect and whether this interaction could partly explain the group differences observed. Connectivity analyses could reveal the direction of the effect between the regions, providing clues on whether the differences in temporal cortex activity are caused by top-down modulation from the frontal areas or whether the temporal cortex findings are independent of the activity in the frontal areas.

Generally, EEG/ERP source imaging has limitations in terms of spatial accuracy, making exact comparisons to fMRI studies difficult (Grech et al., 2008; Costa et al., 2015). It is also possible that some neuronal sources related to the AP and RD groups were not revealed when using this spatial filter source model, which was designed based on the control group as prior information for the activity during an ANT test. To overcome this limitation, neuronal source imaging could be carried out at an individual subject level and mapped to a corresponding MRI. It is also important to note that in this study, the number of participants in the attentional problems and reading difficulties groups were considerably smaller than for the control group. This limits the generalizability of the results and warrants further studies to verify the current findings.

In summary, both children with AP and children with RD showed differential results in alerting and orienting networks

compared to control children with respect to the attention network task. Children with AP exhibited increased source activity in the left occipital lobe for the orienting effect. Furthermore, the children with RD showed different source activity in the left occipital lobe for the alerting and orienting networks. These results show how attentional processes differ across the attention network in children with AP and children with RD. This suggests different underlying mechanisms for attentional and reading problems. Overall, the results of reaction time performance and neuronal sources adds to the growing body of literature that has found the attention network to be a useful cognitive model for conceptualizing attentional problems and reading difficulties in children (Bednarek et al., 2004; Konrad et al., 2006; Booth et al., 2007; Mullane et al., 2011; Goldfarb and Shaul, 2013).

DATA AVAILABILITY STATEMENT

The analyzed data sets from this study are available from the research group upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the University of Jyväskylä, Finland. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

OL, KL, JH, and PL designed the experiment. Research assistants, PS, OL, and PL recruited the participants and collected the data. PS analyzed the data, wrote the main manuscript, and created all figures. All authors commented on and reviewed the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2020.00160/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

Supplementary Table 1. Summary of rejected trials in proportion and their standard deviation for control (N=77), attentional problems (N=15), and reading difficulties (N=23) groups.

Group	non-cued target stimuli	double-cued target stimuli	centre-cued target stimuli	spatially-cued target stimuli	congruent target stimuli	Incongruent target stimuli
Control	0.24 (0.131)	0.20 (0.114)	0.20 (0.110)	0.21 (0.116)	0.18 (0.102)	0.15 (0.085)
AP	0.29 (0.102)	0.27 (0.116)	0.25 (0.097)	0.29 (0.089)	0.23 (0.096)	0.20 0.083)
RD	0.32 (0.133)	0.29 (0.116)	0.25 (0.131)	0.27 (0.113)	0.23 (0.101)	0.21 (0.100)

Note: Control - control children; AP - children with attentional problems; RD - children with reading difficulties.

Supplementary Table 2. Mean (M) and standard deviation (SD) of residual variance for each condition and each group to determine the goodness of fit of the regional source model. No significant difference was found between any of the groups.

	Control		AP		RD	
	Mean	SD	Mean	SD	Mean	SD
no cue	13.005	6.438	12.196	6.143	14.575	7.455
double cue	11.412	5.731	10.636	5.707	13.107	7.687
center cue	11.919	6.124	10.058	6.126	12.011	5.622
spatial cue	11.357	5.498	8.817	4.280	11.517	5.652
Incongruent	15.512	7.594	14.533	7.064	16.778	8.388
Congruent	14.818	7.672	13.881	8.617	15.650	7.532

Note: Values are in percentage. Control - control children; AP - children with attentional problems; RD - children with reading difficulties.

Supplementary Table 3. Summary of the reaction time (RT) results, accuracy and statistics for control (N=77), attentional problems (N=15), and reading difficulties (N=23) groups. Also shown is the RT (mean and standard deviation in millisecond) of each non-cued and cued target stimulus condition of the ANT.

	Condition		M (ms)	SD (ms)	Accuracy M (SD)	Paired t-test for RT			
						M^a (ms)	SD^a (ms)	t-value	Cohen's D_z
Control group (N = 77) df (76)	Alerting	Non-cued	785	99	0.98 (0.02)	61.06	39.22	13.66***	1.61
		Double-cued	724	87	0.97 (0.03)				
	Orienting	Centre-cued	755	93	0.97 (0.04)	50.73	45.31	9.82***	1.11
		Spatially-cued	705	90	0.98 (0.02)				
	Inhibition	Incongruent	806	97	0.96 (0.05)	119.69	50.92	20.62***	2.35
		Congruent	686	84	0.99 (0.01)				
Attentional problems (N = 15) df (14)	Alerting	Non-cued	790	66	0.98 (0.02)	67.31	63.34	4.15**	1.06
		Double-cued	722	74	0.97 (0.02)				
	Orienting	Centre-cued	745	62	0.98 (0.03)	27.51	36.22	2.94*	0.76
		Spatially-cued	717	64	0.99 (0.02)				
	Inhibition	Incongruent	810	71	0.97 (0.02)	125.47	48.42	10.04***	2.59
		Congruent	684	60	0.99 (0.01)				
Reading difficulties (N = 23) df (22)	Alerting	Non-cued	872	141	0.97 (0.03)	79.40	40.97	9.29***	1.94
		Double-cued	793	133	0.96 (0.05)				
	Orienting	Centre-cued	847	139	0.97 (0.03)	66.82	54.17	5.92***	1.23
		Spatially-cued	780	149	0.97 (0.04)				
	Inhibition	Incongruent	900	140	0.94 (0.05)	144.17	39.81	17.37***	3.62
		Congruent	756	128	0.99 (0.01)				

Note: ***$p < 0.0005$, **$p < 0.005$, and *$p < 0.05$ (two-tailed). M and SD denotes the mean and stand deviation. M^a and SD^a denote the average difference and standard deviation of the difference between the RTs for two target stimuli, respectively. The t-values denote test statistics with degrees of freedom (df). Cohen's D_z denotes the effect size between RTs for different target stimuli.

Supplementary Table 4. A summary of independent sample t-tests between groups for reaction time effects.

	Control vs. AP			**Control vs. RD**			**AP vs. RD**		
Conditions	**t-value (df = 90)**	***p-value***	**Cohen's d**	**t-value (df = 98)**	***p*-value**	**Cohen's d**	**t-value (df = 36)**	***p*-value**	**Cohen's d**
Non-cued	-0.189	0.850	-0.053	-3.348	0.001	-0.796	-2.107	0.042	-0.699
double cue	0.049	0.961	0.014	-2.921	0.004	-0.694	-1.859	0.071	-0.617
alerting (NC – DC)	-0.505	0.615	-0.143	-1.948	0.054	-0.463	-0.716	0.478	-0.238
Center-cued	0.420	0.675	0.119	-3.659	0.001	-0.869	-2.668	0.011	-0.885
spatial-cued	-0.512	0.609	-0.145	-2.981	0.003	-0.708	-1.536	0.133	-0.510
orienting (CC – SC)	1.870	0.065	0.528	-1.427	0.157	-0.339	-2.468	0.018	-0.819
Incongruent	-0.147	0.883	-0.041	-3.647	0.001	-0.867	-2.297	0.027	-0.762
congruent	0.082	0.934	0.023	-3.067	0.002	-0.729	-2.015	0.051	-0.669
inhibition (INCON – CON)	-0.405	0.686	-0.114	-2.117	0.037	-0.503	-1.299	0.202	-0.431

Note: df denotes degrees of freedom. Cohen's d denotes the effect size between groups. NC: non-cued target stimuli, DC: double-cued target stimuli, CC: center-cued target stimuli, SC: spatially-cued target stimuli, CON: congruent target stimuli, and INCON: incongruent target stimuli. The FDR corrected alpha value is 0.0120.

III

TIME-FREQUENCY ANALYSIS OF ATTENTIONAL SUBPROCESSES IN TYPICALLY DEVELOPING CHILDREN

by

Praghajieeth Raajhen Santhana Gopalan, Otto Loberg, Jarmo A. Hämäläinen, & Paavo H.T. Leppänen

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