JYU DISSERTATIONS 659

Doris Hernández Barros

Neuromagnetic studies of attention in children and youth

Role of exercise and impact on cognitive competence

UNIVERSITY OF JYVÄSKYLÄ
FACULTY OF EDUCATION AND PSYCHOLOGY

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ABSTRACT

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Attention has a complex relationship with internal and external influences during brain development when the brain changes considerably. This dissertation studies attention from two different perspectives: how it is affected by our activities and how it modulates other cognitive functions. More specifically, it explores the associations of physical activity (PA) and aerobic fitness (AF) with the brain bases of anticipatory and cross-modal attention in 13–17-year-old adolescents. In addition, attentional modulation of auditory processing of speech and non-speech sounds is examined in typically developed 9- to 10-year-old individuals and in children with developmental language disorder (DLD). The first study explores the links between PA and AF and the brain basis of anticipatory attention in adolescents. Results show that more active adolescents show greater interhemispheric asymmetry of brain alpha rhythm during anticipatory selective attention than less active participants, while physical fitness had no effect on activation asymmetry. There are divergent associations between PA, AF, and attention task performance for males and females. The second study explores the connection between PA and AF using neuromagnetic indicators of cross-modal visual and auditory attention in adolescents. Bilateral occipital visual areas were associated with the level of PA. The third study compares hemispheric balance during passive and active listening in children with DLD and typical language development. Children with language deficits showed less asymmetrical recruitment of the brain hemispheres than typically developing children when passively listening. During the active listening task, hemispheric involvement in children with atypical language development shifted toward a more typical pattern. The results of this thesis show that PA, but not AF, may influence the brain bases of visual attention during adolescence. In addition, the relevance of attention in auditory processing in typically and atypically developing children was indicated. Overall, attention is an important function during brain development that can be affected by experience and, in turn, modify other cognitive processes.

Keywords: attention, physical activity, aerobic fitness, brain development, magnetoencephalography.

TIIVISTELMÄ (ABSTRACT IN FINNISH)

Hernández Barros, Doris
Neuromagneettisia tutkimuksia lasten ja nuorten tarkkaavuudesta: Liikunnan vaikutus tarkkaavuudelle ja tarkkaavuuden merkitys kognitiivisille taidoille
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Tarkkaavuus on monella tavoin yhteydessä elimistömme sisäisiin ja ulkoisiin tekijöihin aivojen kehityksen aikana, jolloin aivot muovautuvat voimakkaasti. Tässä väitöskirjassa tutkitaan tarkkaavuutta kahdesta eri näkökulmasta: millä tavoin oma toimintamme vaikuttaa tarkkaavuuteen ja toisaalta miten tarkkaavuus moduloi muita kognitiivisia toimintoja. Tarkemmin sanottuna väitöskirjassa tutkitaan fyysisen aktiivisuuden ja aerobisen kunnon yhteyksiä ennakoivan tarkkaavuuden ja modaliteettien välisen tarkkaavuuden suuntaamisen aivoperustaan 13-17-vuotiailla nuorilla. Lisäksi väitöskirjassa tutkitaan millä tavoin tarkkaavuus vaikuttaa puheäänteiden ja ei-kielellisten äänteiden käsittelyyn aivoissa tyypillisesti kehittyneillä 9-10-vuotiailla lapsilla sekä lapsilla, joilla on kehityksellinen kielihäiriö. Ensimmäisessä tutkimuksessa selvitetään fyysisen aktiivisuuden ja aerobisen kunnon yhteyttä ennakoivan tarkkaavaisuuden aivoperustaan nuorilla. Tulokset osoittavat, että ennakoivan valikoivan tarkkaavaisuuden aikana fyysisesti aktiivisemmilla nuorilla oli voimakkaampi epäsymmetria aivojen alpha-taajuisessa rytmisessä toiminnassa kuin vähemmän aktiivisilla nuorilla. Fyysisen aktiivisuuden ja aerobisen kunnon yhteys kognitiiviseen toimintaan on miehillä ja naisilla erilainen. Toisessa tutkimuksessa selvitetään fyysisen aktiivisuuden ja aerobisen kunnon yhteyttä näön- ja kuulonvaraisen tarkkaavuuden jakamisen neuromagneettisiin indikaattoreihin nuorilla. Aivojen takaraivolohkojen näköaivokuoren toiminta, mutta ei ohimolohkojen kuuloaivkuoren toiminta, oli yhteydessä fyysisen aktiivisuuden määrään. Ohimolohkot (vasemmassa aivopuoliskossa) aktivoituivat tehtävässä vain rajatusti johtuen aivojen kehityksen vaiheesta. Kolmannessa tutkimuksessa tarkastellaan toiminnallista tasapainoa aivopuoliskojen välillä passiivisen ja aktiivisen kuuntelun aikana lapsilla, joilla on kehityksellinen kielihäiriö, ja lapsilla, joilla on tyypillinen kielellinen kehitys. Lapsilla, joilla on kehityksellinen kielihäiriö, aivopuoliskojen toiminta oli passiivisen kuuntelun aikana vähemmän epäsymmetristä kuin tyypillisesti kehittyvillä lapsilla. Aktiivisen kuuntelun aikana epätyypillisesti kehittyvien lasten aivopuoliskojen välinen jakauma muistutti tyypillisesti kehittyviä. Tutkielman tulokset osoittavat, että fyysinen aktiivisuus, mutta ei aerobinen kunto, voi vaikuttaa tarkkaavuuden aivoperustaan. Lisäksi tarkkaavuudella on merkitystä kuulonvaraisen tiedon käsittelyn aivoperustaan tyypillisesti ja epätyypillisesti kehittyvillä lapsilla. Kaiken kaikkiaan tarkkaavuudella on aivojen kehityksen aikana merkittävä rooli, johon kokemus voi vaikuttaa ja joka puolestaan vaikuttaa muihin kognitiivisiin toimintoihin.

Asiasanat: tarkkaavaisuus, liikunta, aerobinen kunto, aivojen kehitys, magnetoenkefalografia.

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LIST OF ORIGINAL PUBLICATIONS

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Considering the instructions and comments provided by the coauthors, the author of this thesis formulated the research questions, collected the MEG data for the first two studies, analyzed all the data, and wrote and reviewed the manuscripts.

FIGURES

TABLES

LIST OF ABBREVIATIONS

AF aerobic fitness
ANOVA analysis of variance
APOE ε4 ε4 allele of the apolipoprotein E
BDNF Brain-derived Neurotrophic factor
CC Corpus callosum
CRAE Central retinal arteriolar diameter
CRVE central retinal venular diameter
DLD Developmental Language Disorder
ECD Equivalent Current Dipole
ECG Electrocardiogram
ED Estimated difference
DSM-V Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EEG Electroencephalography
EOG Electrooculogram
ERP Event-related potential
FEF Frontal eye field
fMRI functional magnetic resonance imaging
Hz Hertz
IFG Inferior frontal gyrus
IFJ Inferior Frontal Junction
IGF-1 Insulin-like growth factor 1
IPS Intraparietal sulcus
km/h Kilometers per hour
LMM linear mixed model
MEG magnetoencephalography
MFG Middle frontal gyrus
MI Modulation Index
min minutes
Modlow moderate-to-low
MRI magnetic resonance imaging
MRT mean RT for correct responses
ms milliseconds
MVPA Moderate-to-vigorous physical activity
ns non-significant
PA physical activity
Pc proportion of correct responses
PSD Power spectral density
rANOVA repeated measures analysis of variance
ROI Region of interest
RT reaction time
RTI Reaction time task
s seconds
SD Standard deviation

SE Standard error
SEM Standard error of the mean
SMG supramarginal gyrus
SPL Superior Parietal Lobe
SSS Signal space separation method
SSR Steady-state response
TD typical development
TFR Time-frequency representation
TPJ Temporo-parietal junction
tSSS Spatiotemporal signal space separation method
TW time-window
val66met replacement of a valine for a methionine at codon 66 of BDNF
VEGF Vascular endothelial growth factor
VFC Ventral frontal cortex
VO_2 max maximum oxygen uptake
VRT variance of RT for correct responses

CONTENTS

ORIGINAL PAPERS

1 INTRODUCTION

The limitations of our sensory systems plus the richness of our environment create perceptual competition that is addressed in the brain through prioritization. This selection of relevant information (and therefore suppression of irrelevant input) is achieved through attention and guides our adaptive behavior. The complex and multidirectional interrelationship of attention with the functional state of our body makes it a labile factor that is affected by and, at the same time, can influence other cognitive functions. This is especially important in brain developmental stages, as attention undergoes a rather long-term maturation from childhood to adolescence (Davidson et al., 2006; Luna, 2009) and then expands in adulthood (Hoyer et al., 2021; Wetzel et al., 2006).

Because humans are very immature at birth, our brain's development is greatly influenced by the interplay of genetic and environmental factors, thus increasing our successful adaptation. During the first two decades of life, our brain undergoes significant changes, such as myelination and synaptic pruning, contributing to the optimization of neural connections and, therefore, to learning and adaptation. From birth to adulthood, several neural structures underlying attentional control (such as in the frontal and parietal regions) show protracted structural development (Gogtay et al., 2004; Tsujimoto, 2008). Attentional control seems to be acquired by young children early in their development. However, during adolescence, more subtle changes, such as speedy responses, enhanced efficiency of attention, and suppression of irrelevant information occur until adult-level processes are reached in the third decade of life (Ridderinkhof & van der Stelt, 2000).

During brain development, external influences can enhance or divert the course of attention. Indeed, longitudinal studies suggest that regular engagement in physical activity (PA; also known as chronic PA) and aerobic fitness (AF) capacity seem to modulate attention and inhibition in children and adolescents (Álvarez-Bueno et al., 2017; Singh et al., 2019). The results are clearer in children, showing comprehensible positive effects on attention and inhibition (de Greef et al., 2018). Studies performed with adolescents have yielded inconsistent results (Álvarez-Bueno et al., 2017; Herting & Chu, 2017). Based on increased accuracy scores (Hogan et al., 2013), reductions in reaction times (RTs) (Huang et al., 2015), or both (Westfall et al., 2018), it is assumed that exercise influences attention and inhibition in adolescents. In both cases, children and adolescents, it is not yet clear whether these associations are PA- or AF-related, or both. Thus, our knowledge about PA and AF's specific association with the underlying brain processes of attention/inhibition during adolescence is still incomplete.

Attentional control impacts other cognitive functions and their brain bases. This is particularly important in the case of neurodevelopmental disorders, the behavioral manifestations of which involve deviations in recruiting sensory areas, such as dyslexia (Wright & Conlon, 2009), or more complex cognitive functions, such as language in developmental language disorder (DLD) (van Bijnen et al., 2019). How attention can alter the course of these disorders is not fully known. Specifically, the modulatory effect of attention on the recruitment of auditory cortices during acoustic stimulation in children with DLD is not yet clear.

Methodologically, attentional control is usually studied by employing simple stimuli. However, tasks of this sort hardly represent what occurs in real-life situations, in which relevant and irrelevant information is not deliberately separated. This suggests the need for mirroring real-life conditions or using more naturalistic stimulation in attention studies, such as in anticipatory or cross-modal attention. Utilizing more real-life-like tasks is also beneficial for understanding the connections between the possible influences our bodily functions (PA and AF) can deploy on the brain's basis of attention. The critical associations of experience with attentional modulation of brain hemispheric involvement during development can also be established using this methodology.

This doctoral thesis aims to study attentional modulations of the brain bases of cognitive processing during important stages of brain development, namely childhood and adolescence. More specifically, the associations of PA and AF on the brain bases of anticipatory and cross-modal attention in adolescents are explored. Furthermore, based on the potential benefits of attention to understanding language development, another aim of this thesis is to test the effect of attentional modulation when speech and non-speech are auditorily processed by children with DLD.

1.1 Selective attention

In our interactions with a continuously changing environment, we constantly seek mechanisms that allow us to adapt successfully. To do so, we need to process a huge amount of information as quickly as possible. Selecting relevant information is vital for determining adequate behavior. Because our sensory systems have a limited capacity, we need a mechanism, such as attention, that allows us to prioritize the relevant information from our environment at the expense of ignoring irrelevant information. Attention guides our perception and behavior through two mechanisms. Top-down attentional control (or goal-driven attention) is oriented to particular locations or objects, based on internal goals or expectations. A bottom-up mechanism (or stimulus-driven attention) orients our attention to external, salient, and behaviorally relevant stimuli to detect new objects or events, thus providing an additional independent contribution to attention function.

Core brain regions supporting attentional orientation include parietal and frontal brain areas (Kastner et al., 1999; Nobre et al., 1997). It has been proposed that parietal and frontal areas are organized in two anatomical and functional interdependent networks: the dorsal and ventral frontoparietal networks (Corbetta & Shulman, 2002; Corbetta et al., 2008). The dorsal frontoparietal network enables goal-driven attention and links our intentions to suitable motor responses. Core regions of the dorsal frontoparietal network—such as the dorsal parietal cortex, particularly the intraparietal sulcus (IPS), superior parietal lobe (SPL), and dorsal frontal cortex along the precentral sulcus, near or at the frontal eye field (FEF)—have been associated with top-down control mechanisms (Bundesen, 1990; Desimone & Duncan, 1995). The ventral frontoparietal network supports bottom-up mechanisms, especially when the stimulus is unattended. Core regions of the ventral network include the temporoparietal junction (TPJ) and the ventral frontal cortex (VFC), including parts of the middle frontal gyrus (MFG), the inferior frontal gyrus (IFG), the frontal operculum, and the anterior insula (Bundesen, 1990; Desimone & Duncan, 1995).

Even though dorsal and ventral attentional networks are usually studied and presented as two separate networks, there is mounting evidence that attentional control is an emergent property of their dynamic interaction rather than being strictly linked to the activity of just one of them. The dorsal and ventral frontoparietal networks seem to interact to resolve which information will be prioritized and, therefore, to regulate behavior (Chica et al., 2013). Several regions, such as the inferior frontal junction (IFJ) (He et al., 2007) and the MFG (Fox et al., 2006), have been proposed to work as the interconnection between the dorsal and ventral frontoparietal networks. This idea is reinforced by the structure of the white matter fibers (Chica et al., 2013) connecting MFG to the dorsal parietal cortex (He et al., 2007).

Knowledge about these two networks has been derived mainly from visual attention studies, partly due to the challenges of studying audition with functional magnetic resonance imaging (fMRI). Recent studies have confirmed that auditory attention relies on frontoparietal attentional networks but includes some other areas, such as the supramarginal gyrus (SMG) (Bareham et al., 2018; Pando-Naude et al., 2021) and the lateral frontal cortex (Braga et al., 2013).

Visual and auditory studies have suggested that highly specialized perceptual areas should also be included within the core regions of top-down attentional control (Chica et al., 2013; Pando-Naude et al., 2021). Special interest has been devoted to knowledge about the mechanisms used by frontoparietal areas to influence the functioning of perceptual systems and their ultimate effects on behavior. The neural manifestations of the top-down orientation of attention can be noticed in the modulation of perceptual areas of the brain. Using fMRI, several studies have shown that the magnitude of neural activity in occipital visual areas enhances with increased top-down attentional control (Brefczinski & DeYoe, 1999; Gandhi et al., 1999; Kastner et al., 1999; Tootell et al., 1998;). Specifically, activation of parietal and frontal areas (especially IPS and FEF) leads to changes in the visual cortex (Bressler et al., 2008; Kastner et al., 1999; Serences et al., 2004). Similarly, the FEF in the frontal area is functionally connected to the right auditory cortex during auditory attention tasks (Müller & Weisz, 2012).

Other studies have shown top-down attentional control-related dynamic changes in perceptual processing. This modulation is produced by modifications of the oscillatory activity in the visual and auditory cortex. Modulations of theta (Kerlin et al., 2010; Plöchl et al., 2021), beta (Veniero et al., 2021), and alpha (Capilla et al., 2014; Capotosto et al., 2009; Kerlin et al., 2010; Lobier et al., 2018; van Diepen et al., 2015) rhythms seem to be involved in the mechanisms that top-down control uses to regulate visual and auditory processing.

During the attentional selection of information, the inhibitory control of irrelevant information also requires top-down modulation while suppressing reactive responses. Immature synaptic pruning and myelination may hinder the top-down modulation of behavior, such as the capability of cortical regions to impact subcortical, sensory, and motor regions. This would particularly affect the long-range connections and distributed circuits linking the frontal areas with the parietal and subcortical regions, which are known to underlie executive functions (Goldman-Rakic, 1988). Thus, how the interaction between attention and inhibition is achieved in the brain, especially during adolescence when mechanisms such as synaptic pruning, myelination, and neural circuitry are still under development, constitutes an important topic of study.

1.1.1 Anticipatory attention

During selective attention, we simultaneously focus on relevant inputs and inhibit irrelevant information according to our goals or expectations. Traditionally, attention to significant inputs and inhibition of irrelevant information have been studied separately. If these functions are studied in isolation, capturing their balance and interaction is impossible. An alternative approach to address this challenge is to investigate anticipatory attention. Anticipation is a property that the human brain uses to quickly allocate attentional resources. During top-down attentional control, anticipation reflects a preparatory stage that facilitates upcoming information processing (Brunia, 1999). To achieve this purpose, the brain works in two parallel and synchronized ways. One is by activating the brain areas responsible for processing the prioritized information and, at the same time, by inhibiting the brain areas in charge of processing irrelevant stimuli.

Both mechanisms of anticipatory attention can change the excitability of visual and auditory perception, resulting in the specific selection of relevant information and the suppression of distracters. Tasks measuring anticipatory aspects of attention usually require both focusing on the relevant information and inhibiting distracters for performing successfully. Brain areas and processes related to anticipatory attention have been studied using a paradigm in which a signal reveals the occurrence of the next target in either hemifield. The relative involvement of each brain hemisphere can index the two-fold anticipatory process (Jensen & Mazaheri, 2010; Klimesh et al., 2007). Similarly, the interhemispheric balance of brain dynamics seems to reflect the interaction between inhibition and attentional focusing (Jensen & Mazaheri, 2010).

Neuronal oscillations indicate rhythmic variations of neuronal excitability and are believed to be included in a wide variety of brain processes, including sensory processing (Buzsaki & Draguhn, 2004; Lakatos et al., 2005), neuronal interactions between areas (Fries, 2005), and control of input processing at the cognitive level (Canolty et al., 2006). Indeed, parieto-occipital recorded alpha oscillations, brain rhythm oscillations between 8 and 12 Hertz (Hz), seem to be particularly related to the control of visual (Vollebregt et al., 2015), auditory (Deng et al., 2020), and somatosensory (Haegens et al., 2011) anticipatory goal-driven attention. Increments in alpha peaks have been related to cognitive control (Haegens et al., 2014). In contrast, alpha decreases are interpreted as suppression of information processing (Klimesch et al., 2007). Therefore, alpha power variations are considered a gating mechanism of the brain to control the engagement of left and right brain areas during anticipatory attention (Jensen & Mazaheri, 2010). Interestingly, it is not yet clear whether lateralization of alpha oscillations is a cause or a consequence of spatial attention (Peylo et al., 2021).

1.1.2 Cross-modal attention

Besides anticipatory attention, another means of assessing the focusing of attention/inhibition component of selective attention is by using more naturalistic tasks, such as those involving cross-modal processing. In real-life situations, we receive information through all our senses that is integrated to create a unique percept to provide a proper response; for a review, see Kayser and Logothetis (2007). This is particularly important in social and cognitive contexts, such as emotional (Davies-Thompson et al., 2019) or language (Tian et al., 2022) processing. When information arises from several sensory systems at the same time, cross-modal attention sometimes leads to the integration of information; for a review, see Calvert and Thesen (2004). However, when it is required by goal-driven attention, the information arising from one modality is addressed while the information from other modalities is ignored.

In the latter situation, top-down attentional control directs the recruitment of primary sensory cortical regions and their cross-modal interplay by enhancing or diminishing the firing rate of their neurons. Primary sensory cortices are the first to receive external input. They are anatomically distant, but cellular-level studies performed using young mice have reported the existence of multimodal interaction at their level of processing (Ibrahim et al., 2016; Iurilli et al., 2012; Teichert & Bolz, 2017). The fast changes in cross-modal processing evidenced by animal studies suggest the existence of neuroplastic changes.

Cellular recordings in animal studies have provided valuable information about cross-modal processing in the brain (Teichert & Bolz, 2018). However, less is known about the precise mechanisms of cross-modal functioning in the human brain at the systemic level and their ultimate effects on behavior. The sensitivity of cross-modal sensory processing to plastic changes during brain development and to external contexts suggests the need for a better understanding of the underlying dynamically adaptive neuronal mechanisms. This implies that it is not only important to know about the interrelation of attention with visual or auditory cortices, but it is also necessary to expand the knowledge regarding their multimodal interrelationship.

Understanding the effects and mechanisms underlying top-down modulation of cross-modal processing in the brain extends our knowledge of how we perceive our environment.

1.2 Typical brain development in childhood and adolescence

Human brain development undergoes significant changes during childhood and adolescence. Throughout childhood, several processes, such as synaptic pruning and myelination, occur (Caviness et al., 1996). These mechanisms contribute to optimizing brain cell connections to achieve the fast learning required during this period.

At around 10 years of age, adolescence begins, defined by pubertal increases in sexual hormones (Spear, 2000), which also impact neurodevelopment (McEwen, 2001). Adolescence is behaviorally distinguished by increased novelty-seeking, including enhanced risk-taking behaviors (Chambers et al., 2003), greater peer influence, and peaking emotionality. All these seem to be supported by neurobiological changes, such as increased synaptic pruning and myelination. These neurobiological mechanisms might be relevant to prefrontal areas and their connections with frontal and subcortical areas (Webb et al., 2001).

From the first two years of life until adolescence, the used synaptic connections remain, but the unused ones are removed or pruned (Rauschecker & Marler, 1987). This mechanism allows the brain to better adapt to the individual's environment. Synaptic pruning enhances the computational capability and speed of information processing in regional circuitries.

Increased myelination is another brain mechanism that starts during childhood and matures significantly throughout adolescence (Huttenlocher & Dabholkar, 1997; Yakovlev & Lecours, 1967). It significantly increases the rate of neuronal communication (Drobyshevsky et al., 2005), allowing for distant region interaction. Increased myelination also enhances the efficiency of information processing, thus granting the configuration of more distributed circuitry essential for achieving complex behavior (Goldman-Rakic et al., 1993).

Taken together, synaptic pruning and myelination constitute the most prominent neurodevelopmental changes in children's and adolescents' brains. Even though myelination levels are approaching adult levels, the lack of complete myelination in this period underlies some limitations in connectivity (Oldham et al., 2022). Before reaching the adult level of circuitry distribution, adolescents continue to show immaturities that restrict both their computational performance (due to synaptic pruning) and processing velocity compared to adults (based on still immature myelination). Incomplete enhancements in regional circuitry and long-range connectivity in the adolescent brain support the maturation of executive behavior control.

Executive functions benefit from neurodevelopmental changes in adolescence. For instance, inhibition seems to be present starting in early childhood (Bell & Fox, 1992; Diamond & Goldman-Rakic, 1989), but in adolescence, the rates of correct inhibitory responses seem to increase (Luna et al., 2004; Wise et al., 1975). Speed of processing also seems to be shortened in RT tasks following adolescent brain maturation (Hale, 1990; Kail, 1993).

In summary, neural development through adolescence is distinguished by the fine-tuning of existing processes. Neurodevelopment impacting cognition increases quickly during childhood, changes into specialization in adolescence, until reaching stabilization and widely distributed circuitry in adulthood.

1.2.1 Atypical brain development

Brain development can follow a negative path leading to compromised cognitive functions. Internal or external interference with the developmental process may lead to a wide spectrum of functional consequences. Biological factors (genetic, hormonal), environmental influences (such as lack of stimulation or malnutrition), or a combination of both are considered to underlie atypical brain development that results in behavioral manifestations in affective or cognitive functioning (Boardman & Counsell, 2020; Frith, 2001).

Language is a cognitive function that can be negatively affected during brain development. However, due to the same principle, language development can be improved through positive influences, thus changing the direction of functional brain plasticity. Children with DLD (formerly known as specific language impairment) demonstrate language abilities below the expected level for their age despite having adequate non-verbal skills, normal hearing, and the absence of any medical condition (neurological damage, hearing loss, or genetic syndrome) that could explain the deficit (DSM-5-TR, APA, 2022). DLD is diagnosed during childhood and has an estimated prevalence of 7% at the time of entry to school (Norbury et al., 2016). DLD affects a wide range of receptive and expressive language skills (Bishop et al., 2016), with a lifelong prognosis affecting all aspects of social inclusion (Law, 2011).

The etiology of DLD is believed to be complex, resulting from a combination of genetic influences and environmental factors (Bishop, 2006). Structural or functional anomalies that could result in DLD are not yet known (Mayes et al., 2015), although the most accepted theory claims that DLD might be associated with failed cerebral lateralization of language (Bishop, 1990). This theory is one of the theoretical principles that underlies school interventions for children and adolescents with DLD (Tarviainen et al., 2021).

Investigating both typical and atypical development would provide crucial insight that is not otherwise available at the more stable adult level. This resulting knowledge could be of help in finding the best support for optimal brain development.

1.3 Factors influencing neuroplasticity during brain development

Neuroplasticity denotes the ability of the brain to alter its function or structure in regard to experience. It is crucial for both learning and functional recovery after injury. Brain development, as a form of neuroplasticity, is influenced by the interaction of environmental and biological factors. The literature seems to agree that biological factors determine a time frame within which environmental influences can have an effect (Luna, 2009).

External factors mostly coming from the environment can also significantly influence neuroplasticity. On the macro level, neuroplastic modifications occur after long-term stimulation, such as functional reorganizations that seem to be induced by synaptic potentiations (Trojan & Pokorny, 1999). According to the stimulus characteristics and the developmental stage, neuroplastic adaptation at both levels may include functional compensatory transformations or permanent reorganization.

1.4 PA and AF effects on neuroplasticity

An active lifestyle has been shown to correlate with some cognitive functions in humans (Álvarez-Bueno et al., 2017). PA and AF also seem to interact with underlying brain mechanisms, as evidenced in mice. Long-term engagement in PA has been proposed to stimulate metabolism, significantly affecting neuroplasticity. The mechanism behind this interaction in animal studies seems to be the increment of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) (Gomez-Pinilla et al., 2008), vascular endothelial growth factor (VEGF) (Carro et al., 2001), and insulin-like growth factor 1 (IGF-1) (Nieto-Estevez, et al., 2016), into the central nervous system. These modifications have been further linked with cellular structural changes such as enhanced neurogenesis (Brown et al., 2003), increased synaptic plasticity (Ocallaghan et al., 2007; van Praag et al., 1999), enhanced dendritic density (Redila & Christie, 2006; Stranahan et al., 2007), and angiogenesis (Carro et al., 2001; van Praag et al., 2005). Although these effects have been demonstrated only in mice, and without a clear connection to cognitive functions, similar effects have also been explored in humans (El-Sayes et al., 2019).

Interestingly, in humans, IGF-1 and VEGF seem to be modified by long-term exercise in young but not older individuals (El-Sayes et al., 2019), while BDNF seems to be modifiable by regular PA throughout the whole lifespan. Because of the structural changes in the brain induced by molecular and cellular modifications, macro-structural and functional changes in the human brain have been reported. Gray matter variations have been reported in association with higher AF (Herting & Nagel, 2012; Herting et al., 2016; Ruotsalainen et al., 2019). Structural modifications induced by AF also include enhanced white matter microstructure (Ruotsalainen et al., 2020, 2021) in the corpus callosum (CC) (Johnson et al., 2012; Verkooijen et al., 2017).

Exercise-induced changes in brain function (reported as mediated by previously mentioned cellular and metabolic changes) have been found, such as increased hippocampal activation (Wagner et al., 2017) and increased neural connectivity (Voss et al., 2013). Findings also indicate that regular exercise increases transcallosal inhibition (Lulic et al., 2017; McGregor et al., 2013).

1.4.1 PA and AF associations with attention/inhibitory control in the adolescent brain

Although most studies have used child or adult samples, some investigations have examined adolescents. Most of the studies involving adolescents have used structural rather than functional neuroimaging methods. The focus has been on AF more so than PA, and sometimes they are used as analogous concepts. The results of magnetic resonance imaging (MRI) studies have indicated associations of greater AF with white matter properties and with distinct cortical and subcortical structural connectivity patterns in adolescents (Herting & Nagel, 2012; Herting et al., 2014, 2016; Ruotsalainen et al., 2020).

When task-related brain activity is assessed, fMRI reveals links between AF and enhanced cognitive functions such as memory (Herting & Nagel, 2013). AF associations with changes in activation of certain brain areas, such as the frontal lobes and hippocampus in adolescents, have been established (Herting & Nagel, 2012; Herting et al., 2016; Ross et al., 2015). Some MRI/fMRI studies have also linked PA with more efficient cognitive processing in adolescents (Brooks et al., 2021; Chaddock-Heyman et al., 2018; Ruotsalainen et al., 2021).

Most functional neurocognitive studies conducted using adolescent samples have used electroencephalography (EEG) so far. Their sparseness and diversity of measures, research questions, and tasks make it challenging to draw conclusions. Attention and inhibitory control are among the most studied cognitive functions. Table 1 summarizes the studies linking PA or AF with functional neurocognitive measures of attention and inhibition in adolescents. The specific involvement of PA and AF in attentional and inhibitory control during adolescence is not yet clear. Attention has been reported to be linked to PA (Ludyga et al., 2018) and AF (Hogan et al., 2015), while inhibitory control also seems to be associated with PA (Ludyga et al., 2018, 2019, 2022) and AF (Hogan et al., 2013; Stroth et al., 2009). Research on the functional neural bases underlying the association of PA and AF with attention and inhibition in adolescents is limited and inconsistent. Specifically, the macro-level neural mechanisms underlying this relationship have yet to be determined.

TABLE 1 Studies on the underlying functional bases of the link between PA and AF with attention/inhibition

Reference	Age	Sample	Task	PA/AF Measure	Brain Measure	Results
Hogan et al., 2013	13–14 y	*n* = 30 11 females 19 males	Modified Eriksen flanker task including Go/NoGo conditions	AF: continuous-graded maximal exercise test	EEG/oscillations: coherence in the delta, theta, alpha, beta, and gamma range	AF associated with lower alpha, upper alpha, and beta coherence for NoGo trials, which was linked to changes in inhibition
Hogan et al., 2015	13–14 y	*n* = 30 11 females 19 males	modified Eriksen flanker task including Go/NoGo conditions	AF: continuous-graded maximal exercise test	EEG entropy	AF associated with lower entropy post-stimulus in the left frontal hemisphere, indicating more efficient allocation of cognitive resources to the task demands
Ludyga et al., 2018	12–15 y	*n* = 36: 13 females 23 males	Stroop	PA: 20 min of aerobic and coordinative exercise per school day over a period of 8 weeks	EEG/event-related potential (ERP): P300	High PA linked to greater P300 amplitude; this was most pronounced for the parieto-occipital region associated with decreases in incompatible RT on the Stroop task
Ludyga et al., 2019	12–15 y	*n* = 36 13 females 23 males	Stroop	PA: 20-min aerobic and coordinative exercise session on each school day over a period of 8 weeks	Retinal microcirculation: central retinal arteriolar (CRAE) and venular diameters (CRVE)	High PA linked to higher CRAE; the increase was associated with a decrease of RT in trials demanding inhibitory control
Ludyga et al., 2022	9–14 y	*n* = 184 (Sex balance not specified)	Stroop Color−Word or Go/NoGo task	PA: participation in open and closed skill sports	EEG/ERP: N200, N450, and P300	Association between open-skill sports and greater amplitude of N200 and N450; time spent in open-skill sports was related to better inhibitory control
Stroth et al., 2009	13–14 y	*n* = 35: 13 females 22 males	Eriksen flanker task	AF: graded fitness test	EEG/ERP: CNV, N200, and P300	High AF linked to enhanced inhibition (higher CNV and decrease N2 amplitudes)

In studies performed with structural or functional brain measures, the associations with PA or AF have been investigated separately. Hence, it is unclear whether the association of attention/inhibition with physical exercise is due to the amount of movement over time (PA), the capacity acquired by the body because of PA (AF), or both. Therefore, it is crucial to develop more research on this topic, especially in adolescence, to fill this research gap. Anticipatory and cross-modal attention tasks, together with the use of magnetoencephalography (MEG), with excellent temporal resolution and good spatial resolution, could especially help to investigate how attention impacts the recruitment of relevant areas in the brain during the adolescent stage of brain development.

1.5 Aims of the research

This thesis focused on attention as a neurocognitive function with relevance for understanding individual differences during child and adolescent development. Neural underpinnings of attention were clarified both as a labile target process affected by external influences, namely PA and AF, and, in turn, as itself modulating perceptual functions in typical vs. atypical cognitive development. In the three studies, MEG was used to measure the neuromagnetic indicators of brain processing during cognitive performance.

Study I aims to clarify the specific contributions of PA and AF to the underlying brain processes of attention and inhibition during adolescence. Alpha oscillations were recorded using MEG during a Posner cueing paradigm in which the participants had to detect a target anticipated by a preceding cue. We focused on the cue-induced modulation of alpha power in the ipsilateral and contralateral hemispheres. Based on the task demands, it was hypothesized that higher levels of PA or AF would show greater interhemispheric contrast (stronger modulation) of the alpha band, reflecting more efficient attentional and inhibitory processes in the brain.

Study II explores the link between PA and AF with the neuromagnetic indicators of cross-modal visual and auditory attention in typically developing adolescents. Specifically, we examined 1) the cortical bases, specifically the role of sensory cortices, of task-relevant cross-modal switching of attention and 2) the link of PA and AF with cross-modal (visual and auditory) attention in the adolescent brain. We expect that the dynamic ongoing activation of visual and auditory cortices will engage successfully to reflect the levels of attention required by the cross-modal attention task. Based on the findings of **Study I**, we hypothesized that PA would show a more direct link with the neural engagement of visual and auditory cortices in adolescents than AF.

In **Study III,** MEG was used to measure the interhemispheric asymmetry during attended and non-attended auditory processing in children with DLD across time. The neural activation derived from the MEG recordings in the left and right hemispheres of children with DLD and typically developing children were compared during the active and passive listening of speech and non-speech sounds. Specifically, we tested the hypothesis that 1) children with DLD show abnormal interhemispheric asymmetry during the auditory processing of speech and non-speech sounds and 2) attention modulates interhemispheric asymmetry. To provide a novel understanding of the neural basis of auditory processing deficits in DLD, we further tested 3) whether the presumed abnormal interhemispheric asymmetry and the attentional modulatory effect occurred during early sensory processing or in the later stages of auditory processing.

2 METHODS

2.1 Participants

In **Studies I** and **II**, participants were recruited from the Finnish Schools on the Move Program (Joensuu et al., 2018; Syväoja et al., 2019). Sixty-three adolescents volunteered to participate in **Study I**. Participants with neurological disorders, major medical conditions, or those using medication that influences the central nervous system were excluded. All participants had normal or corrected to normal vision and audition. Handedness was measured by the Edinburgh Handedness Inventory. Participants' stages of puberty were self-reported using the Tanner Scale (Marshall & Tanner, 1969, 1970). Four participants were excluded from the final sample, two of them because of the low quality of MEG data and two due to very few responses in one condition of the MEG task. Thus, 59 adolescents (12.8–17.00-year-old, 37 females, Table 2) were included in the final analysis. Fifty-seven participants were right-handed and two were left-handed.

Fifty-four teens volunteered to participate in **Study II** (also included in **Study I**). Three participants were excluded due to the low quality of the MEG data. All subjects (*n* = 51, 17 males and 34 females, Table 2) had normal or corrected to normal vision and hearing. Fifty participants were right-handed and one was left-handed.

TABLE 2 Demographic information for **Studies I**, **II**, and **III**

STUDY	GROUP	*N* (FEMALES)	AGE (MONTHS)	PUBERTY STAGE	MVPA (MIN/DAY)	AF (MINS)
I	high PA	17 (9)	171.93 ± 6.7	3.09 ± 0.9	**77.73 ± 13.4*** **	**7.02 ± 1.9* **
	modlow PA	36 (25)	176.35 ± 12.3	3.54 ± 1	**39.34 ± 10.4*** **	**5.29 ± 1.9* **
	high AF	20 (10)	177.39 ± 11.4	3.26 ± 0.9	58.32 ± 21.4	**7.70 ± 1.3*** **
	modlow AF	30 (20)	173.44 ± 9.7	- 3.60 ± 1	45.50 ± 19.9	**4.21 ± 1.4*** **
II	high PA	14 (9)	171.93 ± 6.7	3.09 ± 0.8	**77.73 ± 13.4*** **	**7.02 ± 1.9* **
	modlow PA	31 (22)	176.35 ± 12.3	3.54 ± 0.9	**39.34 ± 10.4*** **	**5.29 ± 1.9* **
	high AF	18 (11)	177.39 ± 11.4	3.25 ± 0.9	58.32 ± 21.4	**7.70 ± 1.3*** **
	modlow AF	25 (16)	173.44 ± 9.7	3.60 ± 0.8	45.50 ± 19.9	**4.21 ± 1.4*** **
III	DLD	9 (3)	113.25 ± 5.5			
	TD	9 (3)	113.50 ± 3.3			

In **Study III**, 18 participants (9–10-year-old children, Table 2) volunteered after all children from the special education district of one municipality in the city of Vantaa were invited to participate in the study. Of them, nine (six male) were children with DLD, and the rest were children with typically developed (TD) language skills matched for gender and age. The children with DLD were diagnosed at Helsinki University Central Hospital prior to school entry.

The study was conducted according to the ethical principles stated in the Declaration of Helsinki and the respective local Ethical Committees (the Central Finland Healthcare District Ethical Committee for **Studies I** and **II,** and the Ethics Committee of the Hospital District of Helsinki and Uusimaa for **Study III**), which accepted the studies. Prior to participation, each participant or their legal guardians signed written informed consent. All the participants were compensated for participating in the studies.

2.2 PA and AF measures

The shuttle-run test (Léger et al., 1988) was used in **Studies I** and **II** to measure AF, a measure extensively utilized to estimate a person's maximum oxygen uptake (VO_2 max). Adolescents were requested to run in the middle of two lines divided by 20 meters. An audio indicator showed when the running speed should be accelerated. The AF level of the participants was estimated using the time consumed to not reach the final lines for two consecutive acoustic signals. The speed at the first and second levels was 8.0 and 9.0 kilometers per hour (km/h), respectively. After that, the speed was increased by 0.5 km/h per level. The duration of each level was one minute.

Participants were classified by their level of AF into two groups. The third tercile (66%) of the number of minutes each participant lasted until leaving the test was used as a cutoff point to divide the sample into high or moderate-low

PA groups (modlow). Before dividing the sample, the data were standardized by sex and age.

PA was objectively measured in **Studies I** and **II** using triaxial ActiGraph (Pensacola, FL, USA) GT3X+ and wGT3X+ accelerometers carried by the adolescents for seven consecutive days. Participants were instructed to wear the accelerometers on their right hips during waking hours, excluding water-related activities. A valid measurement day comprised a minimum of 10 h of data. Activity counts were recorded in 15-second periods. Time periods of at least 30 min of consecutive null counts were considered non-use time. A customized Visual Basic macro for Excel was used to reduce the data. The moderate-to-vigorous PA (MVPA) index was then calculated as the weighted average value of MVPA per day ([average MVPA min/day weekdays × 5 + average MVPA min/day weekends×2] / 7). Data were gathered at a sampling frequency of 60 Hz and filtered.

Accelerometer-based MVPA was used to divide the sample into groups according to their regular PA level (Table 2). The third tertile (66%) of the MVPA index was employed as a cutoff point to split the sample into high or modlow PA groups.

PA was determined for 48 adolescents in **Study I** and 45 participants in **Study II**. AF was assessed for 46 adolescents in **Study I** and 43 participants in **Study II**. In **Studies I** and **II**, eight participants' (one male and seven female) AF values are missing because of school absence on the test day. In **Studies I** and **II**, six participants' (three male and three female) PA values are missing due to not having enough valid measurement days (two weekdays and one weekend day). In both studies, all adolescents had at least one measure of PA or AF.

2.3 Cognitive assessment

2.3.1 MEG tasks

In **Study I,** anticipatory selective attention capacity was measured using a visuospatial covert attention task (Figure 1) created from a modified Posner paradigm (Posner, 1980; Vollebregt et al., 2015). A visual cue (a fish looking to the right or left) anticipated the appearance of a target (one of the sharks on either side opened its mouth wider than the other). Participants were asked to "save" the fish from being eaten by the shark by indicating (by pressing, as quickly as possible, the button at the left or the right), which shark (left or right) opened its mouth wider. The probability of validly cued targets (the gaze of the fish was directed toward the same side as the targeted shark) was 75%. The probability of invalidly cued trials (the gaze of the fish was directed toward the other side as the targeted shark) was 25%. The task was performed in four blocks of 100 trials each. Between blocks, subjects had small rests (1–2 minutes) and started the following block when they reported being ready for it. The task lasted approximately 20 minutes.

The associated MEG and behavioral data from this task were further analyzed. Behaviorally, mean RT, accuracy for validly cued and invalidly uncued targets, and cueing effect indexes (for RT and accuracy: the difference between RT and the number of correct responses for validly cued and invalidly uncued targets) were used in subsequent analyses.

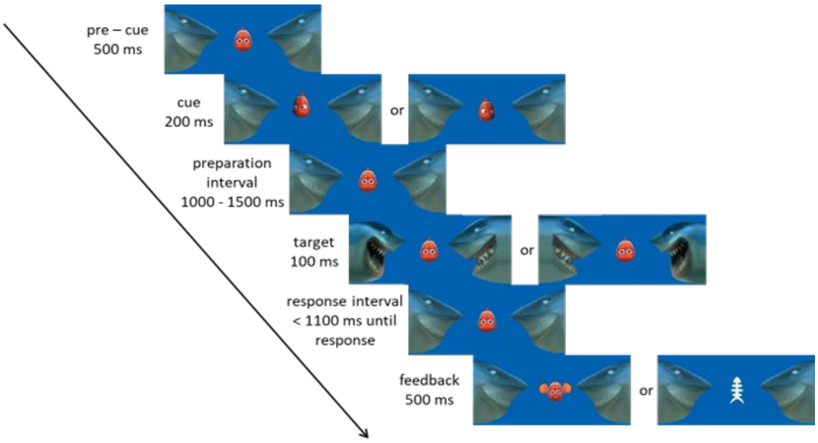

FIGURE 1 The paradigm for **Study I**; from Hernández et al. (2021)

The behavioral variables were inspected to identify outliers. The typical values (Z scores) that exceeded 2.5 standard deviations (SDs) were considered outliers and were not included in subsequent analyses.

In **Study II,** sensory cortices engagement was assessed using the cross-modal attention task (Figure 2). Adolescents received continuous and simultaneous visual and auditory stimuli. The visual stimulus was visual noise, in which the luminance value of each pixel varied randomly between 0 and 255 at a frequency of 15 Hz, functioning as the “tagging frequency” for the visual modality (adapted from Parkkonen et al. (2008)). The auditory stimulus was white noise modulated at 40 Hz operating as the “tagging frequency” for the auditory modality (adapted from Lamminmäki et al. (2014)). This procedure created a specific tagging frequency to be detected from the brain activity in each modality. An active task was utilized to direct participants’ attention to one modality or the other. The visual target was a 40 × 40 pixel square whose luminance was randomly varied between 0 and 255, appearing in the left or right hemifield. The auditory target was a 40-Hz single tone that was played either in the left or right ear. Adolescents were asked to report on which side (left or right) the target appeared (visual or auditory stimuli, depending on the block) and to ignore the non-signaled stimulus modality.

The task consisted of 36 separate blocks. The duration of each block was approximately 36.5 s. In each block, there were both auditory and visual target stimuli, and a visual or auditory cue at the beginning of each block indicated which modality to pay attention to (nine blocks for visual stimuli and nine for auditory stimuli in a counterbalanced order). The signal indicating a focus on the visual modality was a white screen displayed for a few seconds. The signal to focus on the auditory modality was a tone with a frequency of 440 Hz. Each block contained eight randomly selected stimuli (four visual and four auditory) with four seconds of interstimulus interval. Left and right stimuli had the same probability of occurrence.

After 18 blocks were administered, there was a pause during which participants could rest for a few (1–2) mins. When participants expressed that they were ready to continue, the other 18 blocks were administered. The total duration of the task was approximately 22 mins.

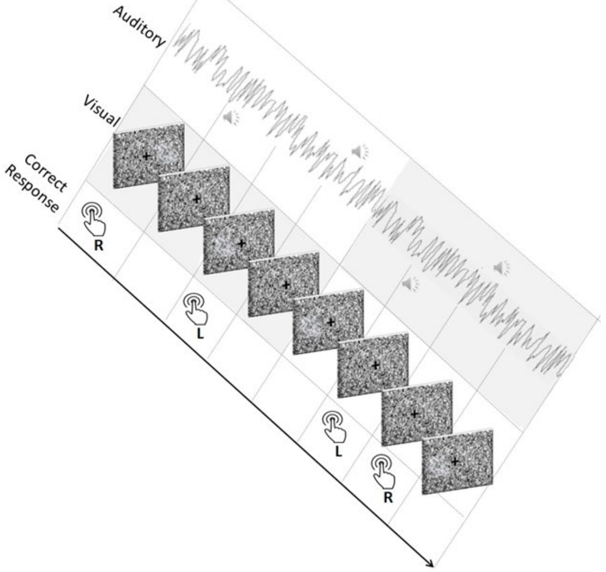

FIGURE 2 The paradigm for **Study II**; from Hernández et al. (2023)

In **Study III,** attentional involvement during passive and active listening was measured using the passive and active listening tasks (Figure 3). Participants were asked to listen to the speech (Finnish vowel /a/) and non-speech (sinewave and complex tones) sounds in single sessions. In the passive condition, children watched silent cartoons and were asked to ignore the sounds. During the active condition, participants were asked to press a button when they heard the same stimulus twice in a row.

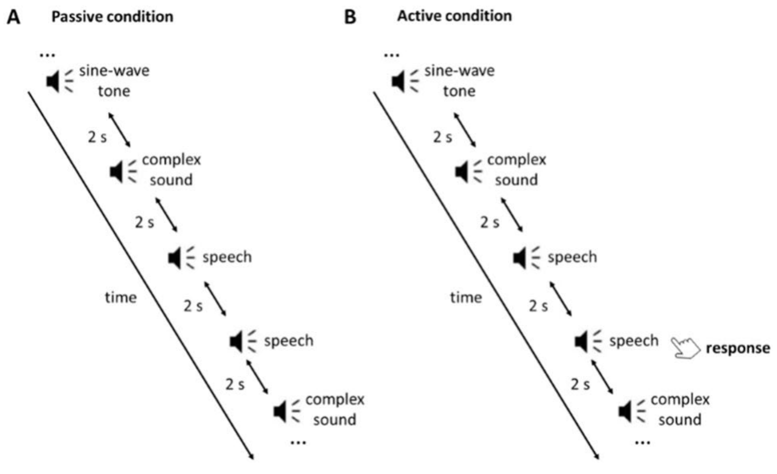

FIGURE 3 The paradigm for **Study III**; from Hernández et al. (2022)

2.3.2 Additional behavioral tasks (Study II)

In **Study II**, adolescents' behavioral abilities were measured in addition to the MEG recordings. Attentional speed was assessed using the reaction time task (RTI) from the Cambridge Automated Neuropsychological Test Battery, Cambridge Cognition Ltd., 2006). The RTI task measured the RTs and, specifically, the velocity of response toward an unexpected target. During the unexpected condition, a yellow dot appeared in any of five circles on the screen. The adolescents were instructed to withhold their responses until they saw the yellow dot. When it appeared, they had to tap, as quickly as possible, the correct circle on the screen where the target appeared. Participants performed practice trials until they understood the task. Scores were based on their RTs (in milliseconds, ms) and motion time (in ms).

Participants' inhibitory control capabilities were evaluated by means of a modified Eriksen flanking task (Eriksen & Eriksen, 1974). For each trial, the target (central arrow) was surrounded by nontarget stimuli (flanker arrows). In the compatible condition, adolescents had to report the orientation of the target (left or right) as fast as possible. In the incompatible condition, adolescents had to respond as quickly as possible to the opposite orientation of the target (right button for the left target orientation and left button for the right target direction). In both conditions, congruent (target directed in the same direction as nontargets) and incongruent (target directed in the opposite direction as nontargets) trials were included. All targets had the same probability of occurrence. Accuracy (in percentages) and RTs (in ms) were recorded separately for congruent and incongruent trials in each condition.

In the Flanker and RTI tests, the variables concerning accuracy were withdrawn from the final analysis due to reaching ceiling effects.

2.4 MEG data acquisition

The neuromagnetic activity associated with the visuospatial covert attention paradigm (**Study I**), and the cross-modal attention task (**Study II**) was recorded using an Elekta Neuromag Triux system (MEGIN Oy, Helsinki, Finland). The brain functioning indicators of the passive and active auditory discrimination task (**Study III**) were recorded with a 306-channel Elekta Neuromag™ Neuromagnetometer (Elekta Oy, Helsinki, Finland). In **Studies I** and **II**, five head-position indicator coils were attached to the participants' heads in five locations (three on the frontal part of the head and one behind each ear). In **Study III**, four head-position indicator coils were attached to the children's scalps. In all the studies, the coils' positions were recorded using a 3D digitizer relative to three anatomical landmarks (nasion and pre-auricular points). Before starting the recordings, the position of the participants' heads with respect to the helmet was measured, and their position was continuously monitored throughout the recordings (Uutela et al., 2001). Other points all around the head were also digitized.

Electrooculograms (EOG), with two electrodes placed above and below the right eye for vertical movements and two electrodes attached to the outer edge of both eyes for horizontal movements, were used to monitor eye movements. In **Study III**, heart activity was measured using electrocardiogram (ECG) recordings.

The behavioral responses were collected using two response pads (right and left) placed on a table mounted on the chair and positioned on the subjects' legs for **Studies I** and **II**. The tasks were projected onto a panel situated one meter from the subjects' eyes. For **Study III**, one MEG-compatible button was used to collect the responses.

In **Studies I** and **II,** recorded MEG signals were bandpass filtered at 0.03–330 Hz and sampled at 1,000 Hz. The raw data were preprocessed using MaxFilter TM 2.2 software (MEGIN Oy, Helsinki, Finland). To eliminate external interferences arising during the measurement, the signal space separation (SSS) method (Taulu et al., 2004) was used. The signal space-time separation (tSSS) method (Taulu & Simola, 2006) replaced the SSS in the case of adolescents wearing some other internal magnetic source or braces. MaxFilter TM 2.2 software was used to correct for possible head movements during the measurements. The rest of the preprocessing was performed using Meggie (CIBR, Jyväskylä, Finland; Heinilä & Parviainen, 2022), a graphical user interface for MNE Python (Gramfort et al., 2014). During preprocessing, epochs contaminated by eye movements (measured with EOG) or cardiac artifacts (measured by an MEG channel) were removed from the analysis. In addition, the data were visually scrutinized to eliminate epochs that were contaminated with other types of artifacts.

In **Study III**, MEG signals were bandpass filtered at 0.1–200 Hz and sampled at 600 Hz. To compensate for possible head movements and to eliminate artifacts due to external interferences arising during the measurement, the raw data were preprocessed using the tSSS method (Taulu & Simola, 2006) and Maxfilter software (MEGIN Oy, Helsinki, Finland). The initial head location was taken as the target position for motion compensation. Epochs containing eye movements were discarded. Artifacts caused by cardiac signals were suppressed by averaging the MEG signal with respect to the heartbeat, using principal component analysis according to Uusitalo and Ilmoniemi (1997). After this, the data were visually inspected to eliminate the remaining artifact-contaminated epochs. The number of artifact-contaminated epochs removed was less than 2.5% of the total number of epochs.

2.5 MEG measures

2.5.1 Oscillatory activity (Study I)

In **Study I**, artifact-free MEG signals from gradiometers were analyzed using MNE Python (Gramfort et al., 2014). Time-frequency representations (TFRs) were calculated in a frequency range of 2–30 Hz, for a period ranging from -0.2 to 1.4 s, with a frequency resolution of 2 Hz. A Morlet wavelet transformation (Morlet et al., 1982) was used with the number of cycles equal to half of each frequency value. For each channel, a modulation index (MI) was calculated using the following equation:

$$MI = (freq\_left\ cued\ trials - freq\_right\ cued\ trials) / \tfrac{1}{2} * (freq\_left\ cued\ trials + freq\_right\ cued\ trials)$$

MIs were used to assess the alpha band (8–12 Hz) modulation on the visuospatial covert attention task. The whole-head TFRs were averaged together for all adolescents. Three MEG channels in the occipital regions (where increased left alpha and decreased right alpha could be clearly identified) were chosen (Figure 4) and averaged.

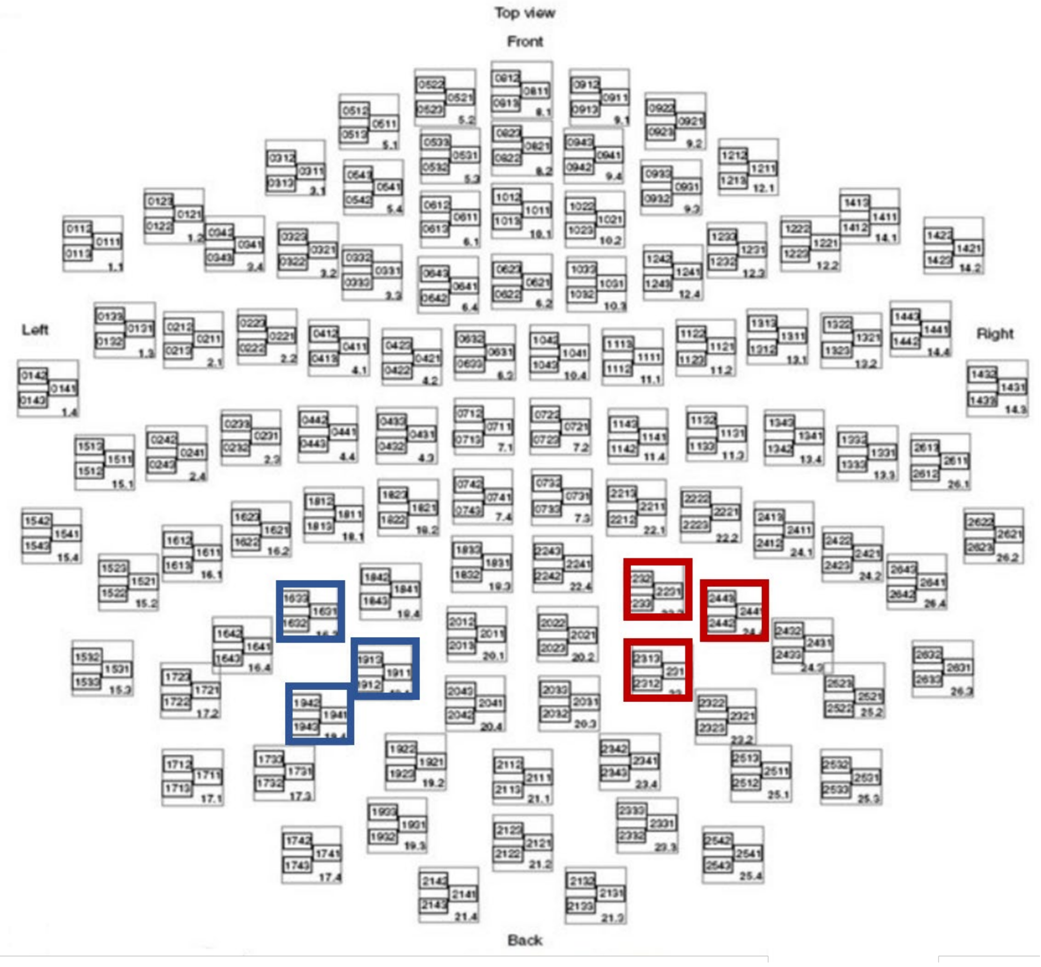

FIGURE 4 Localization of the channels chosen for the calculation of the alpha MI in the right (red circle) and left (blue square) hemispheres in **Study I**; from Hernández et al. (2021).

The interhemispheric asymmetry of alpha MI during the task was calculated as the difference between the alpha MI from the left minus right hemispheres. The whole time window (TW, 0–1,200 ms) of alpha MI in the right and left hemispheres and the interhemispheric asymmetry was divided into three TWs (0–400 ms, 401–800 ms, 801–1,200 ms) for the subsequent stage of statistical analysis.

2.5.2 Frequency tagged steady-state evoked responses (Study II)

In **Study II**, artifact-free data analysis from planar gradiometers was conducted using Matlab (Mathworks Inc., 2020). Frequency spectra were calculated using Welch's method (Hanning window and fast Fourier transform; size 8,192 samples, 50% overlapping windows, frequency resolution 0.1221 Hz). Three regions of interest (ROIs) comprising 16 gradiometers (eight pairs), each situated over the bilateral temporal cortex and the middle occipital cortex, were chosen and utilized to calculate averages for each ROI. The visual and auditory frequency tagged responses were identified based on their peak frequency and amplitude. The visual tag-related signal was recognized as the highest peak between 14 Hz and 16 Hz in the occipital ROI. The auditory responses (right and left) were recognized as the biggest peak between 39 Hz and 41 Hz in each temporal ROI. The amplitude values for each ROI (at 15 Hz for bilateral occipital and at 40 Hz for left and right temporal ROIs) were used for further analysis. The data were inspected to identify outliers. Typical values (Z scores) that surpassed 2.5 SD were treated as outliers and were replaced with the closest non-atypical value.

The amplitude of the tag-related signals in the attended vs. unattended condition in each ROI were contrasted. The effect of attention was determined for both modalities. In the visual modality, the attention effect was calculated as the normalized difference between the attended and the unattended conditions for the amplitudes at 15 Hz in the occipital ROI. In the auditory modality, the attention effect was calculated as the normalized difference between the attended and unattended conditions for the amplitudes at 40 Hz in both the right and the left temporal ROIs. Normalization was performed by subtracting the unattended value from the attended value and dividing the result by the value obtained in the attended condition. The attention effects in each ROI were utilized for correlation analysis with the behavioral outcomes from the cross-modal attention task.

2.5.3 Evoked neural activity (Study III)

In **Study III**, the artifact-free epochs for intervals from 200 ms before the stimulus onset (pre-stimulus baseline) until 800 ms after it were averaged. The active neural populations were modeled using equivalent current dipoles (ECD; Hämäläinen et al., 1993) with XFit software (Elekta Oy, Helsinki, Finland). Structural MRI images were not accessible; therefore, an average sphere model for a group of children of the same age group previously measured was used. The 22 sensors chosen were the same for all participants.

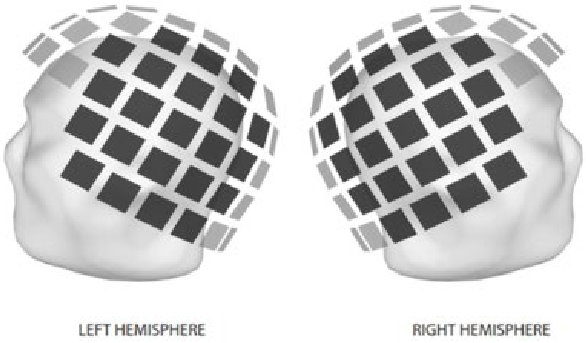

FIGURE 5 Sensors included in the ECD model for each hemisphere in **Study III**; from Hernández et al. (2022).

In each hemisphere, an ECD was fitted within the TW of the robust evoked response around 100 ms, relying on the maximally dipolar topography and the maximum magnetic field strength. The posterior-inferior current flow of the N100 response was checked in all source models. Several candidate ECDs were fitted, and the one with the highest goodness-of-fit value was chosen. The consequent ECDs were compared based on numerical goodness-of-fit values and on a visual match between measured and estimated signals. The goodness-of-fit value was prioritized when choosing the final model.

Source modeling was executed individually. For each child, ECDs were determined separately first for each stimulus. The locations and orientations of two ECDs, one for each hemisphere, were kept fixed, while their amplitudes were allowed to vary to better account for the signals recorded by all sensors during the entire averaging interval. The magnetic field topographies of the different sound types were comparable, and the same ECD successfully explained the activation of all sound types (Figure 6). The active and passive conditions showed equivalent spatial characteristics of activation. Hence, the same ECDs (identified in the active condition for speech, separately for the left and right hemispheres) were used for the passive and active conditions. The ECDs identified in the active condition explained reasonably well the responses registered in the passive condition for both TWs (Figure 6B).

Two TWs were defined for subsequent analysis. The first TW was established at 90–180 ms (N100 m) after stimulus onset. The peak amplitude during this early TW was collected independently for each stimulus type. The second TW comprised the sustained brain activation between 185 and 600 ms after stimulus onset for each stimulus type. The average amplitude value within this later TW was used in the analysis and was collected separately for each stimulus type.

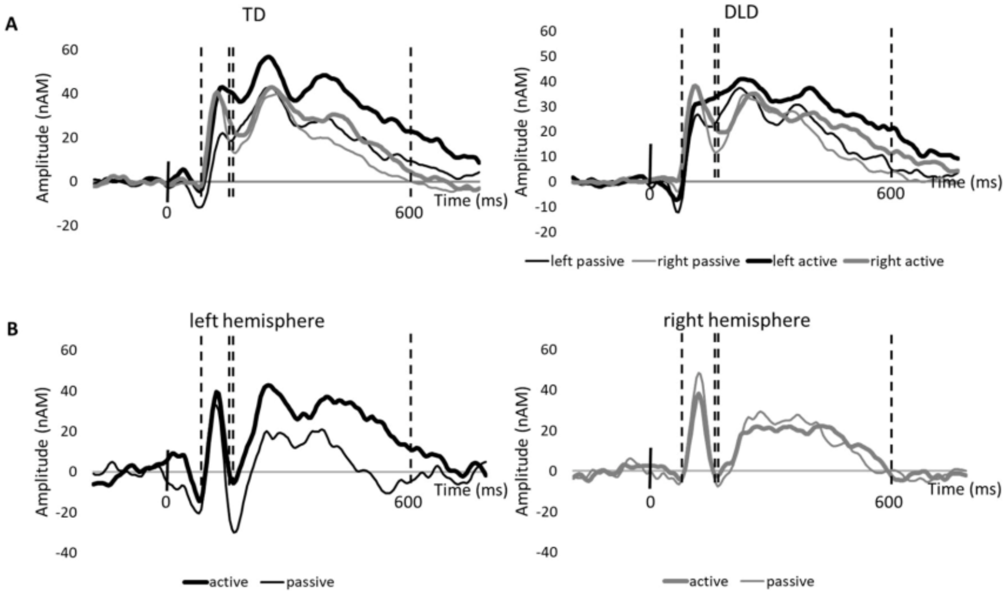

FIGURE 6 Temporal course of dipolar source activation in **Study III**. Early (90–80 ms) and late (185–600 ms) time windows are represented by dashed vertical lines. The three sound types were averaged altogether. (A) Grand-average waveforms of the ECDs located in the left (black) and right (gray) hemispheres in the passive (thin) and active (thick) conditions for the TD and DLD groups. (B) Mean waveforms for passive (thin) and active (thick) listening in the left and right hemispheres of a TD participant; from Hernández et al. (2022).

2.6 Behavioral performance analysis

In **Study I**, behavioral responses to the MEG task (visuospatial covert attention task) were gathered and evaluated. Incorrect responses (< 2.5% of the data) and RT below or above 2.5 SDs from the mean in each condition for each participant (< 2.5% of the data) were treated as outliers and were discarded from subsequent analyses. RTs under 250 ms were removed from the analysis. Average RTs for cued and uncued targets were calculated individually for each adolescent. A cueing effect index was calculated for the RTs as the difference between the RTs of invalidly cued minus validly cued targets. Accuracy was defined as the percentage of correct responses. The cueing effect index for accuracy was defined as the difference between the number of correct responses for the validly cued minus the invalidly cued targets.

In addition, using the EZ model (Wagenmakers et al., 2007), three new variables (drift rate, boundary separation, and non-decision time) were individually calculated for each adolescent. Drift rate is an index for the signal-to-noise ratio of the information processing system used to measure the participant's capability or the task's complexity (Wagenmakers et al., 2007). The boundary separation index is the mechanism of the speed-accuracy trade-off and the response strategy. The non-decision time index is the time before a decision is made, usually assumed to be included in the RT measure (Luce, 1986). Drift rate, boundary separation, and non-decision time were calculated regarding three parameters: the mean RT for correct responses (MRT), the variance of RT for correct responses (VRT), and the proportion of correct responses (Pc).

In **Study II**, behavioral responses with an RT of less than 250 ms (less than 2% of the trials) were discarded from the subsequent analysis. The accuracy for each modality was defined as the percentage of correct responses (in auditory attended and visual attended subtasks). Misses (ignored targets in the attended condition) in the visual and auditory subtasks reflected failed top-down attentional control and were understood as inattention errors. False alarms (answers to unattended stimuli) in the visual and auditory subtasks indicated failure of inhibitory control.

2.7 Statistical analysis

2.7.1 Repeated measures ANOVA (Studies I and II)

In **Study I**, two repeated measures ANOVAs (rANOVA) were conducted on the MI of alpha power, one for each between-subjects factor (PA and AF groups). Within-subjects factors were hemisphere (left, right) and TWs (1st, 2nd, 3rd). To clarify the more exhaustive differences revealed by the rANOVA tests, further follow-up tests with rANOVA for each TW (for AF and PA groups as between-subjects factors) were performed.

In **Study II**, two rANOVAs on the recruitment of visual and auditory cortices (strength of steady-state responses, SSRs), one for each between-subjects factor (PA and AF groups), were conducted. Within-subjects factors were ROI (occipital, left temporal, and right temporal) and strength of SSRs in terms of task demands (attended, unattended). Post-hoc comparisons examined the differences in estimated marginal means with Bonferroni correction for multiple comparisons.

2.7.2 Mediation analysis (Study I)

In **Study I**, a mediation analysis was conducted to test whether alpha oscillatory dynamics mediate the link between PA or AF and cognition. All the possible models in which alpha could mediate the association of attention or inhibition with PA or PA levels were tested. The resultant combinations were analyzed using MPlus software with a 1,000-sample bootstrap. Full information maximum likelihood, accounting for missing values at random, and including all available data were utilized. A bootstrap confidence interval was employed in the mediation analysis. Additionally, a moderation analysis was completed on the mediating effect, employing sex as a moderating variable to establish whether sex affected the potential mediation effects.

2.7.3 Correlation analysis (Studies I and II)

In **Study I**, to determine the link between brain, cognitive (behavioral), and PA/AF measures, we used bivariate Pearson correlation coefficients. In **Study II**, to test the associations between the attention measures (behavioral) of the cross-modal attention task (and additional behavioral tests) at the visual and auditory ROIs, bivariate Spearman correlation coefficients with false discovery rate corrections were used.

2.7.4 Linear mixed models (Study III)

In **Study III**, a linear mixed model (LMM) was used (Brown & Prescott, 2015; Magezi, 2015) to test the possible differences between the DLD and TD groups by using R (R Core Team, 2019).

One model per TW was calculated using the fixed effects of hemisphere, sound type, group, attentional condition, and the random effects of participants. The dependent variable for the first TW was the maximum amplitude. For the second TW, the dependent variable was the averaged amplitude. The two dependent variables were modeled individually by the candidate covariates: hemisphere (right/left, right as baseline), sound type (speech/sine/complex, speech as baseline), group (DLD/TD, DLD as baseline), and attention (passive/active, passive as baseline). The final models were computed using a restricted maximum likelihood method, thus reducing the biases of estimated variances. The contrasts were formulated in terms of the final model and examined using t-tests or z-tests.

3 OVERVIEW OF THE RESULTS OF ORIGINAL STUDIES

3.1 Study I: PA and AF show different associations with brain processes underlying anticipatory selective visuospatial attention in adolescents

Study I evaluated the influence of PA and AF on the neural oscillatory measures underlying anticipatory attention in adolescents. The rANOVA analysis revealed that the late (3^{rd} TW: 801–1,200 ms) interhemispheric alpha asymmetry during anticipatory attention was larger in the high than in the modlow PA group (hemisphere × PA group interaction 3^{rd} TW ($F_{(1,51)} = 4.268$ $p = 0.04$); Figure 7). However, no differences were observed between the high and modlow AF groups.

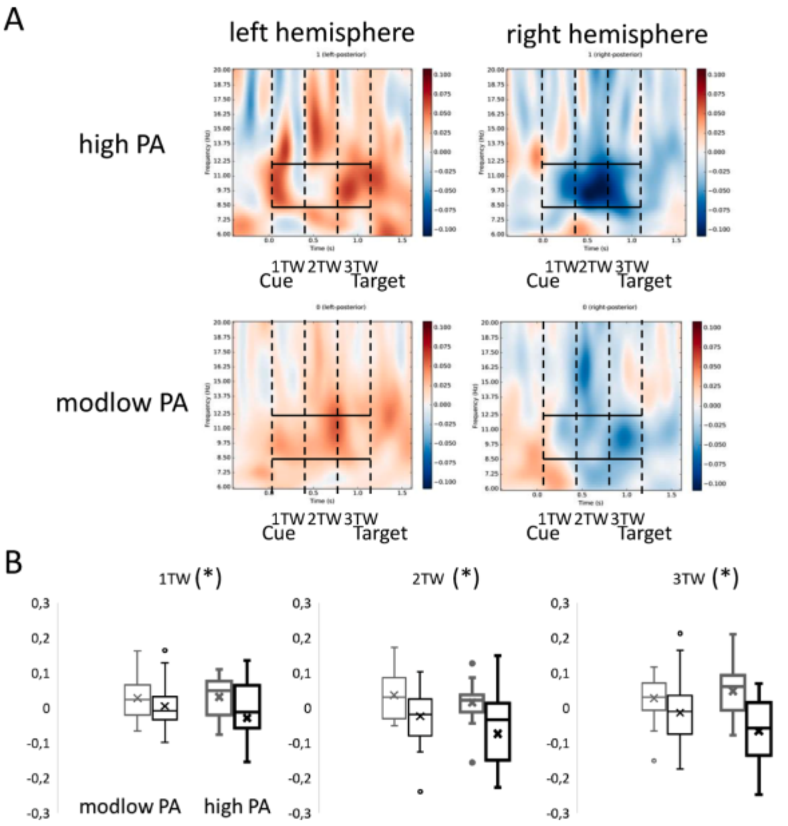

FIGURE 7 Alpha power modulation regarding the spatial cue for the PA groups in **Study I**. (A) TFRs of the alpha power MI in the right and left hemispheres for the two PA groups. (B) Boxplots indicating the right (black) and left (gray) hemispheres in each TW for the PA groups; from Hernández et al. (2021).

The exploratory mediation analysis showed that late anticipatory interhemispheric asymmetry mediates the link between PA levels and drift rate in the MEG task (the indirect effect was significant: ab estimate = -0.107, bias-corrected bootstrap confidence interval = [-0.306; 0.000]) but direct and total effects were not (direct: c′ estimate = 0.104, p = 0.458; total: c estimate = -0.003, p = 0.983; Figure 8). This mediation was not moderated by sex, as revealed by the moderation in the mediator analysis (d4 estimate = -0.103, p = 0.798, bias-corrected bootstrap confidence interval = [-1.144; 0.503]).

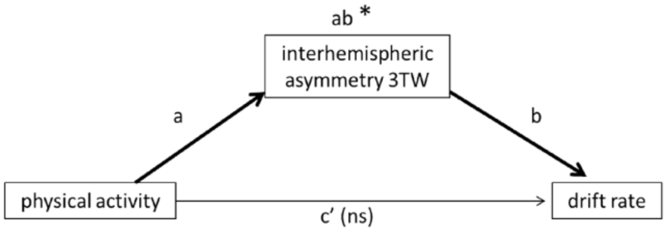

FIGURE 8 Mediation path evaluated for **Study I** on the role of interhemispheric asymmetry of alpha MI for the third TW in mediating (indirect effect shown with darker arrows) the link between PA and drift rate; from Hernández et al. (2021).

The correlation analysis revealed that PA and AF were strongly associated ($r = 0.524$, $p < 0.001$) in the whole sample (Figure 9A). When the sample was divided by sexes, a higher PA level was linked to a higher difference between RTs for invalidly cued minus validly cued targets ($r = 0.485$, $p = 0.035$, Figure 9B). Additionally, higher AF was associated with a higher drift rate in females ($r = 0.580$, $p = 0.001$, Figure 9C).

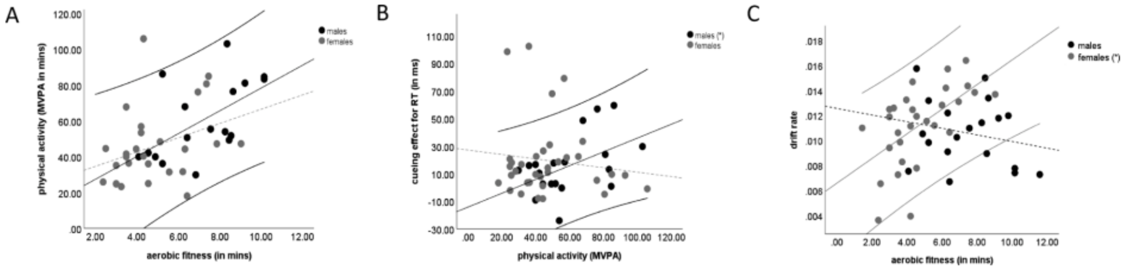

FIGURE 9 Linked measures for **Study I** for males (black) and females (gray). (A) The maximum time during AF test (min) plotted against moderate-to-vigorous PA (MVPA) (min/day). (B) Cueing effect for RTs from the visuospatial covert attention task plotted against MVPA. (C) Drift rate plotted against AF; from Hernández et al. (2021).

3.2 Study II: Spectral signatures of cross-modal attentional control in the adolescent brain and its link with PA and AF

Study II aimed to investigate the neural mechanisms underlying the possible effects that high levels of regular PA/AF might have over cross-modal attentional control in adolescents. The recruitment of visual and auditory sensory cortices during continuous and simultaneous visual (15 Hz) and auditory (40 Hz) stimulation was examined with SSRs at these specific frequencies. The link between PA or AF and cross-modal attention/inhibition in the brain was also explored.

All participants showed SSRs in the bilateral occipital ROIs, but only some of them showed SSRs in the left and right temporal ROIs. The adolescents with auditory frequency tag driven SSRs in the left temporal ROI were older (178.29 ± 10.37 months) than participants without those responses (169.22 ± 8.63 months) ($F_{(1, 53)} = 11.59$, $p = 0.001$, Figure 10).

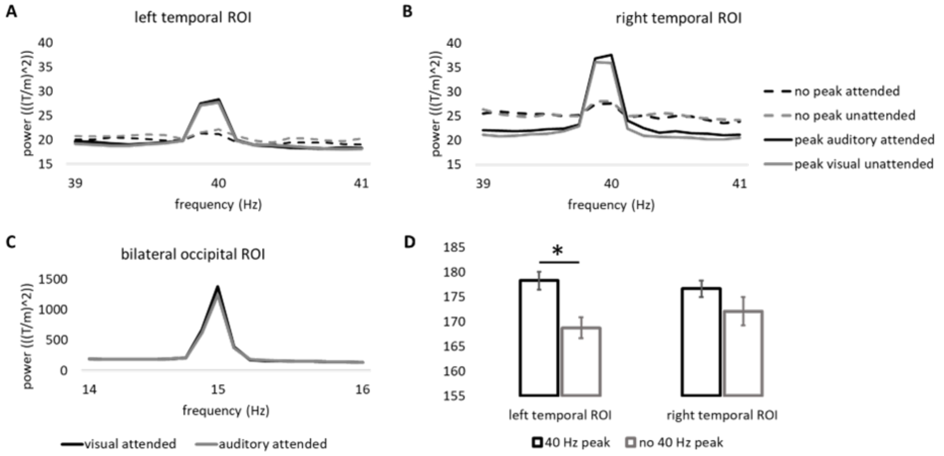

FIGURE 10 Power spectral density (PSD) of the engagement in the visual and auditory cortexes of participants with and without responses in **Study II**. (A) PSD of participants with (solid lines) and without (dashed lines) the auditory SSR peak for the attended (black) and unattended (gray) conditions in the left temporal area. (B) PSD of participants with (solid lines) and without (dashed lines) the auditory SSR peak based on attention requirements in the right temporal ROI. (C) PSD of participants with the visual SSR peak for the attended (black) and unattended (gray) conditions in the visual modality in bilateral occipital areas. (D) Bar representation of the age differences (months) of participants with (black) and without (gray) auditory SSR in the left and right temporal ROIs; from Hernández et al. (2023).

The rANOVAs analyses revealed that the participants in the high PA group showed larger visual frequency tag-driven SSRs in the bilateral occipital areas when attention was focused on both visual and auditory stimulation ($F_{(1, 43)} = 4.95$, $p = 0.03$; Figure 11) than the participants in the modlow PA group. No significant effects were found between the two groups of AF ($p = 0.60$).

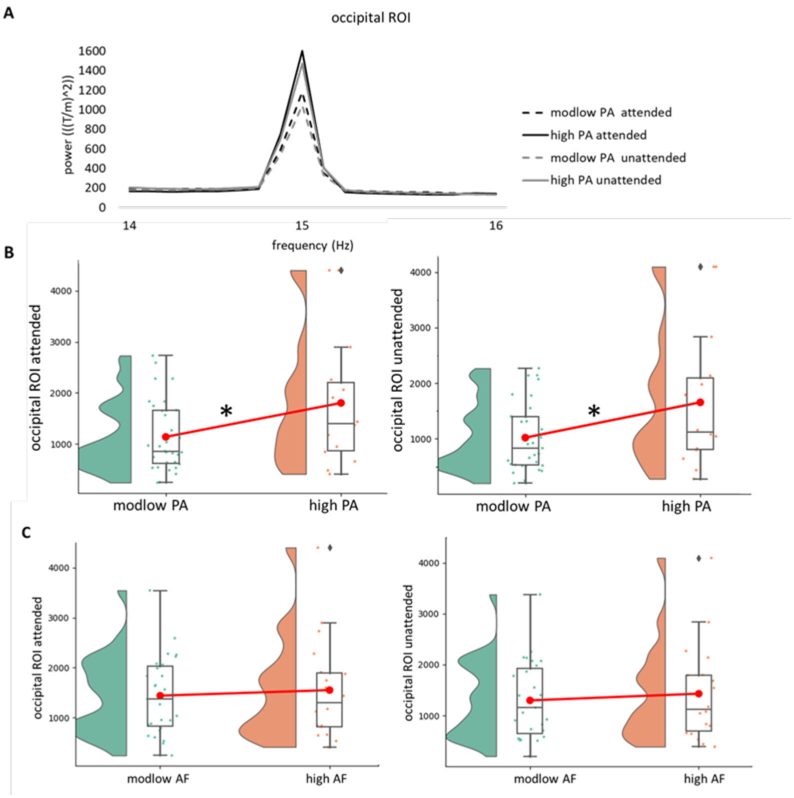

FIGURE 11 SSRs' modulations in the bilateral occipital ROI for the PA groups in **Study II**. (A) Spectra of the visual SSRs for the modlow (dashed lines) and high PA (solid lines) groups in the attended visual (black) and unattended auditory (gray) conditions. (B) Distributions and differences of the attended and unattended responses in the occipital ROI for the modlow (green) and high (orange) PA groups. (C) Distributions and differences of the responses in the occipital ROI for the modlow (green) and high (orange) AF groups; from Hernández et al. (2023).

Behaviorally, the performance in the cross-modal attention task of participants in the higher PA and AF groups did not differ from that of participants in the modlow PA and AF groups. Similar results were obtained in the additional behavioral tests (RTI and Flanker tests).

3.3 Study III: Attentional modulation of interhemispheric (a)symmetry in children with DLD

The aim of **Study III** was to compare the hemispheric balance of activation during passive and active listening between groups of children with DLD and those with typical language development. The stimuli were speech and non-speech sounds. The activation produced by the sounds was traced in the left and right supratemporal areas in two TWs.

The LMM analysis revealed that in the first TW (90–180 ms), the amplitude between the left and right hemispheres did not differ in the passive or active conditions for either group (Figure 12A, B). In the second TW (185–600 ms), the LMM analysis showed different patterns of interhemispheric asymmetry between the two groups (Figure 5A). The TD group showed higher mean amplitude in the left hemisphere than in the right hemisphere in both attentional conditions (passive condition: estimated difference (ED) = 8.81, standard error (SE) = 4.08; $t_{(188)}$ = 2.160, p = 0.03; active condition: ED = 14.18, SE = 4.01; $t_{(188)}$ = 3.54, p < 0.001). The DLD group did not show a difference in amplitude between hemispheres in the passive condition (ED = 2.17, SE = 4.01; $t_{(188)}$ = 0.54, p = 0.59). However, in the active condition, the left hemisphere tended to show a higher mean amplitude than the right hemisphere, with a p-value close to significance (ED = 7.54, SE = 4.01; $t_{(188)}$ = 1.88, p = 0.06) (Figure 12C, D).

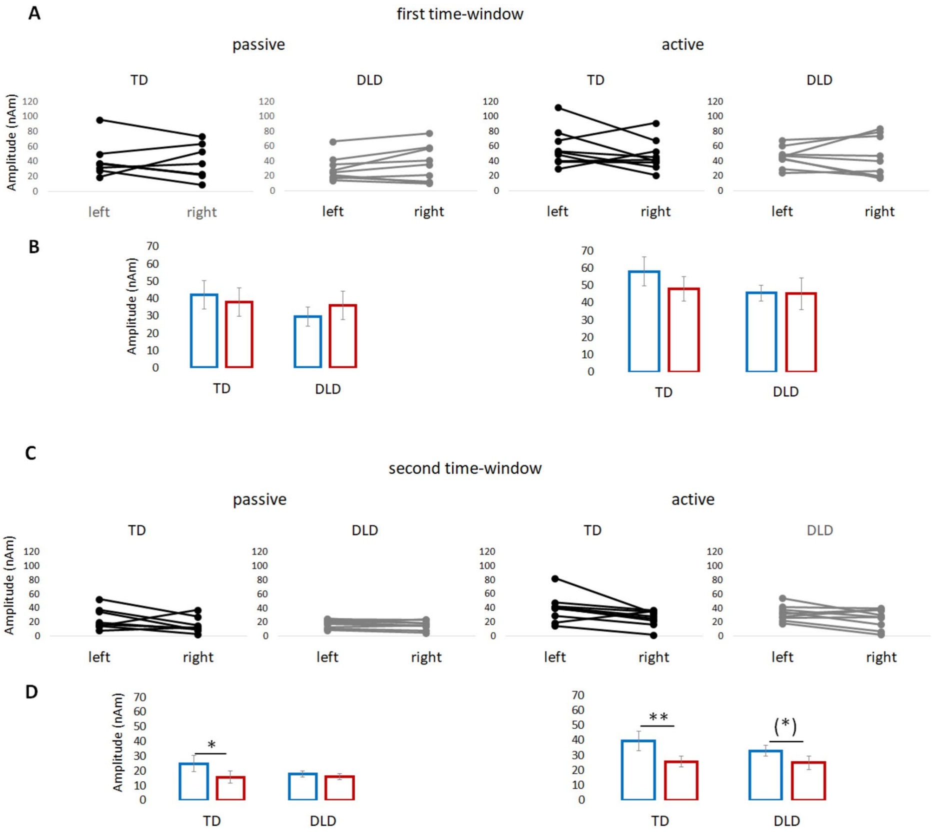

FIGURE 12 Main results for **Study III**. (A) Individual strengths of activation between hemispheres per condition in the first TW of children with DLD (gray) and children with TD (black). (B) Mean activations between the left (blue) and right (red) hemispheres regarding passive and active conditions in the first TW for children with DLD and children with TD. (C) Individual strengths of activation per condition between hemispheres in the second TW for children with DLD (gray) and children with TD (black). (D) Mean activations between the left (blue) and right (red) hemispheres regarding active and passive conditions in the second TW for children with DLD and children with TD. Whiskers symbolize the standard error of the mean (Hernández et al., 2022).

4 DISCUSSION

4.1 Study I: PA and AF show different associations with brain processes underlying anticipatory selective visuospatial attention in adolescents

The findings of **Study I** showed larger interhemispheric alpha asymmetry during anticipatory selective attention in participants with greater PA than in those with low levels, but there was no difference between the participants with high and low levels of AF. This finding suggests the association of enhanced PA with increased effective interhemispheric communication. This finding is in line with previous studies indicating links between regular exercise and the corpus callosum microstructure (Chaddock-Heyman et al., 2018 Cristi-Montero et al., 2022; Lulic et al., 2017; McGregor et al., 2013; Ruotsalainen et al., 2020). However, the direct interconnection of exercise, structural microstructure, brain function mechanisms, and the mechanisms' expression in behavior are still largely unknown.

Despite the close relationship between physical activity and aerobic fitness, only physical activity is related to brain function and behavior. This suggests that it is not the shared variance between PA and AF (highlighted by the strong correlation), but some unique features of PA unrelated to fitness that render it beneficial to attentional performance, likely by triggering more strongly asymmetric hemispheric involvement. The nature of the physical activity variance that is not shared with aerobic fitness remains to be elucidated. The unique features of physical activity relevant for **Study I** support the theoretical differences between the concepts and suggest that future studies should avoid treating physical activity and aerobic fitness as similar measures.

The results of **Study I** also showed the mediating role of interhemispheric alpha asymmetry in occipital areas on the link between physical activity and the behavioral manifestations of anticipatory attention (especially processing speed). This indicates that for adolescents with a higher level of physical activity, the anticipatory attentional recruitment of visual areas is stronger than for adolescents with lower levels of physical activity. Indeed, in adolescence, synaptic pruning and myelination facilitate speed and efficiency of information processing for long connections and distributed circuitries (Luna, 2009). Thus, it is possible that these mechanisms are underlying factors of the physical activity-related effects for the adolescent brain shown in **Study I**.

We explored the association between behavioral performance in the visuospatial covert attention task and physical activity/aerobic fitness. Significant associations were found only when the sample was divided by sex. Results revealed that more physically active males showed greater reliance on the cue. This suggests that males are more likely to respond quickly at the cost of having more errors. On the other hand, fitter females demonstrated more efficient processing of information (indicated by greater accuracy and shorter reaction times). These findings further support the notion that physical activity and aerobic fitness are best understood as related but different concepts. In addition, the sex differences in anticipatory attentional performance shown in **Study I** is consistent with the interpretation (from previous studies) of hormonal modulation of cognitive processing during adolescence. It is then plausible that the faster and more accurate responses in more physically fit females may be related to the hormonal increase in myelination and thus faster nerve conduction that is achieved in adolescence (Paus, 2010). Taken together, these results suggest that neurodevelopment in adolescence may not be uniform across sexes, thus showing qualitatively different developmental processing in males and females.

The late alpha interhemispheric asymmetry modulatory effect on the relationship between physical activity levels and more efficient information processing (drift rate) was independent of sex. However, this result (and the above findings on behavioral performance) should be taken with caution, as it might be that the sample size (mostly when dividing the sample into groups based on sexes in addition to the physical activity groups) was too small for the emergence of significant results.

4.2 Study II: Spectral signatures of cross-modal attentional control in the adolescent brain and its link with PA and AF

The results of **Study II** revealed that the tagging frequencies of simultaneous visual and auditory stimulation are linked with variations in the neural activity of visual and auditory cortical areas, respectively. The strength of these signals varied in accordance with top-down attentional control, as attending the visual or auditory stream was required by task demands. This suggests that top-down control can be exerted over sensory processing in adolescence. However, only visual areas showed the expected pattern of SSRs based on task demands in all the participants.

Auditory areas showed the expected pattern of greater attended than unattended SSRs in only a portion of the participants. An association with participants' age was found specifically for the left temporal cortex, suggesting a maturational effect. These findings imply that bilateral occipital areas might be fully developed in adolescence, but this is not the case for temporal areas, especially in the left hemisphere. This interpretation aligns with previous studies showing that some areas of the temporal lobe (posterior superior temporal gyrus) exhibit equally protracted development to the frontal cortex (Gogtay et al., 2004). All this somewhat contradicts the preliminary belief that the development of cognition in adolescence is driven mainly by the single prolonged maturation of the prefrontal areas, showing that the left temporal cortex may still be undergoing maturational changes in adolescence.

Only bilateral occipital and no temporal cortices were associated with physical activity. This supports the findings of **Study I,** which revealed a physical activity modulation of occipital areas functioning in anticipatory selective attention. All these findings suggest that physical activity is especially associated with visual areas. However, this may be a consequence of brain developmental limitations during adolescence. Some areas do not show an effect due to immaturity, yet it is possible to notice the effect later in life. Further studies are needed to clarify the potential visual advantage of physical activity in the adolescent brain or modulation of the visual area due to limited regional involvement because of brain immaturity during adolescence.

Physical activity and aerobic fitness linked with interhemispheric asymmetry could not be tested in the occipital areas because of MEG spatial resolution limitations and in the temporal areas due to the described maturational effect. In our sample, only auditory processing in the immature left temporal cortex related to the inhibition of irrelevant information in the auditory subtask. This suggests that the right temporal cortex may be responsible for another type of processing, presumably the focusing of attention. To accomplish this, some transfer of information between hemispheres may be necessary, which has been proposed to occur through the corpus callosum in neurotypical individuals. (Josse et al., 2008). Whether this interhemispheric communication (hypothetically mediated by the corpus callosum) is modulated by physical activity or aerobic fitness needs to be elucidated with adults.

4.3 Study III: Attentional modulation of interhemispheric (a)symmetry in children with DLD

The results of **Study III** showed a lack of interhemispheric asymmetry for passive listening in children with DLD. According to the results for children with typical development, this kind of processing seems to be asymmetric. The right auditory cortex of children with DLD showed comparable functioning to those of the typically developing individuals, while the left auditory cortex showed a possible functional suppression. This likely reduces the use of analytic language skills in children with DLD. Indeed, some studies have reported larger hemispheric asymmetry being related to better task performance, such as in reading (Chiarello et al., 2009), verbal IQ (Everts et al., 2009), or dichotic listening (Hirnstein et al., 2014). Recent literature concludes that, in neurodevelopmental disorders such as autism, interhemispheric asymmetry is more clinically relevant than either right or left hemisphere dominance (Leisman et al., 2022).

When speech and non-speech sounds were actively processed, the balance of auditory cortices in children with DLD was like the hemispheric asymmetry shown by typically developed children. This might suggest the usefulness of improving top-down attentional control as an additional treatment goal in DLD (probably via interhemispheric asymmetry).

In this study, LMM was used to try to solve the problem of small samples, which are often avoided in research practice. Preventing studies in which it is not possible to find sufficiently large samples is neither efficient (from a methods point of view) nor fair to patients suffering from rare diseases, who would remain unstudied. In this way, we tried to address difficult aspects of the research, such as small sample sizes.

4.4 Methodological considerations and limitations

A major limitation of **Studies I** and **II** resides in their sample size, restricting the extent of our interpretations. More specifically, there were more participants in the modlow PA and AF groups than in the high PA and AF groups. There were also more females than males in our sample. This was the reason why, in **Study I**, biological sex differences in the behavioral data were explored, but the sample size was not sufficient to test them using the brain data. Another limitation lies in the cross-sectional type of these studies, which did not allow us to determine causal inferences from the links found for PA or AF.

In **Studies I** and **II**, PA was measured objectively, while AF was indirectly measured. This could have resulted in discrepancies in how PA and AF relate to the phenomenon studied. As more structural studies using the same sample (Ruotsalainen et al., 2019, 2020, 2021) showed more likely associations of structural changes in the brain linked more to AF than to PA, an advantage of the objectively measured PA or the indirectly measured AF seems to be unlikely in our sample.

In **Studies I** and **II**, the association of behavioral variables with brain data or PA/AF measures was limited by the ceiling effects reached in some of the variables of behavioral performance. This motivated the exclusion of these variables from further analysis. To avoid this limitation in future studies, we recommend the use of tasks with adjustable levels of complexity. This kind of task might reveal a more realistic link between PA/AF levels and demanding cognitive processing.

In **Study I**, the results of the mediator analysis provided new knowledge about the brain processes that might mediate the impact of PA on cognition, although (based on the limited sample size) this should be taken with caution. The absence of a direct effect in the mediation model (direct influence of PA over drift rate) might be caused by the small sample size, particularly in the high PA and AF groups. Therefore, it is possible that the power was sufficient to detect the indirect effect but insufficient to detect the direct and total effects.

The aims of **Study II** were also limited by the lack of 40 Hz tag-driven SSRs observed in the left and right temporal areas of the participants. As temporal cortices did not show the SSRs reliably, an effect of attention in the auditory cortices could not be seen, presumably due to auditory areas not showing the same level of maturation as the visual cortices. The methodological approach used in **Study II** focused on visual and auditory cortices. Thus, the possibility that other brain areas might contribute to the top-down control of multisensory integration cannot be ruled out.

The interhemispheric asymmetry in the occipital regions was investigated in **Study I,** but this was not possible in **Study II**. Due to the spatial resolution limitations of MEG, reliable measurement of large contiguous visual areas cannot be guaranteed.

The main limitations of **Study III** also derive from the small sample size, which could limit the statistical power if we had used more typical statistical analysis, such as ANOVA. This limitation was mainly remedied using the LMM approach, which allowed us to overcome the likely high group variances and to constrain the potential influence of outliers. In addition, this statistical test enabled us to extend the results to a similar population of children with DLD.

As another limitation of **Study III**, the active condition in the current study simply required processing the incoming sound to detect immediate repetitions. This was done to prevent sound type-specific effects but results that concern more complex attentional demands cannot be inferred from this study.

The variability of neural auditory processing suggests that it is important to address individual-level dynamics in the auditory cortex. In **Study III**, the vast within-group discrepancy in the amplitude values, particularly in the first TW, confounds the interpretation of group results for this TW. Especially with small sample sizes, it is relevant to consider the individual-level data alongside statistical testing.

4.5 General discussion

This doctoral thesis aimed to study the brain functional bases of typical attentional/inhibitory processing in adolescence and their link with physical activity and aerobic fitness. This purpose was achieved by focusing on anticipatory attention in **Study I** and cross-modal attention in **Study II**. In addition, the attentional role of the atypical processing of sounds in children with DLD was studied in **Study III**. Results showed physical activity-related functional modulations in occipital areas for anticipatory and cross-modal attention processing in adolescents according to **Studies I** and **II**. In **Study III,** attentional modulation toward a more typical functioning of auditory cortices was observed for children with DLD.

Together, the results of **Studies I** and **II** and previous findings from our research group (Ruotsalainen et al., 2019, 2020, 2021) suggest that physical activity and aerobic fitness induce structural and functional modifications in the brain via different mechanisms. By summing up these studies, we provide some new knowledge of the brain functions that might underlie the effect of physical activity on attention during brain development, especially in adolescence. **Studies I and II** suggest that physical activity is more associated with functional modifications in the brain supporting improved attentional function than aerobic fitness. In contrast, Ruotsalainen et al.'s (2019, 2020, 2021) studies showed that aerobic fitness is more related to structural changes in the adolescent brain than physical activity. Our results highlight the more important association of active behavior than predisposed capacity on the functional basis of cognitive performance in youth. In turn, these results support previous interpretations indicating that genetics might impose limits on our capabilities, but whether these capabilities are modified depends on our behavior and the influence of the environment.

Indeed, neuroplasticity induced by exercise seems to be limited by some genetic polymorphisms, such as val66met, the replacement of a valine for a methionine at codon 66 of the BDNF (Lemos et al., 2016), or APOE ε4, ε4 allelle of the apolipoprotein E (Adeosun et al., 2014). Carriers of these genetic characteristics fail to show exercise-induced improvements in cognitive tasks as compared to noncarriers (Egan et al., 2003; Flory et al., 2000). Thus, the level of promotion of neuroplasticity might be constrained by individual genetic information. More research is needed to disentangle genetics and more specific environmental impacts on brain structure and function during brain developmental stages.

The main results from **Studies I** and **II** suggest physical activity-related changes to brain function involving specifically occipital areas in adolescents. A possible explanation for this could be related to the sensitivity of visual areas to motion (Kiorpes & Movshon, 2004). However, it is not clear whether the functioning of bilateral occipital areas might be especially sensitive to the brain changes that physical activity-related metabolic modifications exert in the body. Another explanation would be that due to the immaturity of other brain areas at the time, only the more developed occipital regions are able to show this effect. Thus, what might be the potential mechanisms underlying physical activity association with functional bases of attention in adolescents?

Findings from **Study I** add new understanding to the role of lateralization and cerebral asymmetries in neurotypical attentional control. More uneven (but synchronized) hemispheric attentional processing seems to be associated with greater levels of physical activity, and interhemispheric asymmetry seems to reach the highest levels of cognitive, motor, and sensory processing in adulthood (Güntürkün et al., 2020). **Study I** adds to this knowledge by showing that some level of asymmetry is present in adolescence, which seems to be influenced by physical activity. However, brain maturation might limit the appearance of auditory functional asymmetry in adolescence, according to **Study II**.

Effective functional interhemispheric asymmetry needs to be supported by structural and functional left-right communication. The corpus callosum is a critical brain structure for interhemispheric interaction (Hinkley et al., 2016). Numerous studies have investigated the impact of physical activity/aerobic fitness on brain structure and function in youth but have paid little attention to interhemispheric asymmetry and the corpus callosum as associated structures. However, white matter pathways of the corpus callosum have shown links with physical activity in children (Chaddock-Heyman et al., 2018) and adolescents (Cristi-Montero et al., 2022; Ruotsalainen et al., 2020). In the study conducted by Ruotsalainen et al. (2020), white matter structure in the corpus callosum showed a moderator effect on the link between physical activity and working memory performance in adolescents. This effect was only obtained for less structurally compact fibers (low levels of fractional anisotropy), which occur in developmental brain stages. These findings, together with results from **Studies I** and **II,** suggest that physical activity-related structural changes in the corpus callosum might affect physical activity-enhanced functional hemispheric asymmetries during brain development. Future studies combining MRI/fMRI and MEG/EEG might help in clarifying the link between structural and functional-related changes in the adolescent brain associated with physical activity and aerobic fitness.

Evidence indicates that functional interhemispheric asymmetry is a dynamic phenomenon that is modifiable by varying endogenous and environmental factors (Güntürkün & Ocklenburg, 2017; Ramírez-Sánchez et al., 2021). Thus, experience (such as physical activity) could interact with pre-determined genetic mechanisms to create more asymmetric functional processing. This interface could underlie the varying associations found for physical activity and aerobic fitness with brain function in youth, as aerobic fitness has been associated with genetic influences (Schutte et al., 2016). This reinforces the idea of physical activity/aerobic fitness modulation of the corpus callosum during brain development, based on the reported associations of physical activity and aerobic fitness with corpus callosum (Chaddock-Heyman et al., 2018 Cristi-Montero et al., 2022; Ruotsalainen et al., 2020). This may be applicable for dealing with pathologies of the lateralized human brain, such as depression (Zheng et al., 2022), strokes (Park et al., 2021), or degenerative diseases (Lubben et al., 2021). Future studies are needed to clarify the role of the corpus callosum (and other white matter structures) on the link between physical activity and functional asymmetries during childhood and adolescence and their ultimate effects on cognition.

While hemispheric functional asymmetries might be an advantage in the optimization of cognitive functions, they can also be considered a potential vulnerability when the brain region is damaged. This might be an underlying mechanism in some neurodevelopmental disorders, in which deviations of the typical maturational patterns of asymmetries are disrupted, as in the case of DLD, as has been shown in **Study III** of this dissertation.

Research indicates that moderate-to-vigorous physical activity facilitates long-range interhemispheric connections (through modifications in white matter structures such as the corpus callosum) and further enhances attentional performance. The corpus callosum has been suggested to support functional brain specialization, such as language processing (Josse et al., 2008). The loss of functional specialization might be related to verbal deficits (Hinkley et al., 2016). Interestingly, the gain in the mechanism might be related to increased attentional performance, which in turn seems to be positively related to greater levels of moderate-to-vigorous physical activity, according to **Study I**. This gain mechanism would increase the possibility of using physical activity as a tool to change brain development in a positive direction across the lifespan.

Study III showed that attention modulates the contribution of the brain hemispheres during auditory processing in children with DLD. These results also open important questions regarding the relevance of "paying attention" to treating DLD. The use of general factors to support rehabilitation instead of focusing only on the dysfunctional part of the disorder might help to overcome the deficit. Perhaps children with DLD need to actively use their compensatory mechanisms, which makes them get tired more easily, leading to atypical behavioral manifestations. This might create a new line of treatment for DLD. By employing approaches that promote the improvement of attentional capacity in developmental stages of life, auditory processing could be enhanced, and therefore, the behavioral expressions of the disorder could be improved.

This approach could open the door for using non-pharmacological treatments, such as those including physical activity-induced neuroplasticity, as it has been described to benefit executive functions in youth (Ludyga et al., 2021). Further research is needed to determine if this is really the case and if the suggested rehabilitation approach leads to more typical auditory processing. In the case of being useful, there is still an opportunity for effective interventions in the next decade of life for children with DLD. Thus, as suggested before (section 4.3), working on reaching typical interhemispheric asymmetry in children and adolescents by involving physical activity can become a useful tool for clinical and educational programs.

In contrast to earlier studies addressing physical activity or aerobic fitness-related brain processing in selective attention, **Studies I** and **II** include adolescents, largely underrepresented in research focusing on physical activity/aerobic fitness modulations of brain function during development. Our results expand the knowledge collected so far, mainly in children, into adolescence and add to the discussion about age-related changes in brain functions underlying attention across the lifespan. We confirmed previous developmental studies showing a progressive improvement of cognitive processing, but incomplete relative to the adult level, during adolescence by showing incomplete maturation that might be resolved later during adulthood (**Study II**). Altogether, the findings of **Studies I** and **II** emphasize the benefit of including adolescents when examining physical activity/aerobic fitness links with attention and inhibition in youth, as it seems that the changes from childhood to adulthood are not unidirectional.

In conclusion, **Studies I** and **II** on the brain functional bases of attention/inhibition and their association with physical activity and aerobic fitness in adolescents provide a comprehensive view of the potential neural mechanisms involved in the attentional advantage associated with exercise during brain development. In addition, findings from **Study III** suggest the relevance of cognitive central functions such as attention in the auditory processing of sounds in typically and atypically developed children. The findings of this thesis show that attention is a significant cognitive function during brain development that can be affected by experience and, in turn, can modify other cognitive processes.

4.6 Future directions

From the integration of these three studies, new questions arise that cannot be addressed without further research. For instance, we conclude that physical activity is associated with functional changes in the adolescent brain, while previous literature (Ruotsalainen et al., 2019, 2020, 2021) suggests that aerobic fitness is linked to microstructural changes in gray and white matter in the same age group. Indeed, structural hemispheric asymmetry is assumed to direct functional asymmetry of the human brain (Hutsler & Galuske, 2003), but experimental support for this hypothesis remains scarce. Future studies combining both structural and functional methods in youth are especially needed to investigate the interconnection of structural and functional level exercise-induced neuroplastic changes in the brains of children and adolescents.

A plausible physical activity-related functional enhancement of brain bases of attentional control in children with DLD could lead to a more typical imbalance of hemispheric activations, resulting in improvements in the behavioral manifestations of the deficit. Future longitudinal studies exploring these effects could have important clinical and educational implications. To achieve this goal, the maximization of the positive influence of exercise on health and disease should be sought. Further investigations are needed to continue exploring the underlying principles and mechanisms that mediate exercise-induced cognitive processing during the brain development stages. For this purpose, it would be beneficial to compare children's and adolescents' brain mechanisms with those of adults.

The three studies in this thesis were based on developmental changes and their physiological bases at the group level. In future studies, it would be useful to focus on subject-specific developmental trajectories to properly track individual developmental differences.

YHTEENVETO (SUMMARY)

Neuromagneettisia tutkimuksia lasten ja nuorten tarkkaavuudesta: Liikunnan vaikutus tarkkaavuudelle ja tarkkaavuuden merkitys kognitiivisille taidoille.

Aivojen tarkkaavuustoimintojen avulla luokittelemme saapuvan tiedon merkitykselliseksi tai merkityksettömäksi. Tällä hetkellä ymmärretään kuitenkin puutteellisesti, miten aivojen toiminta mahdollistaa huomion suuntaamisen olennaiseen tietoon ja toisaalta epäolennaisen tiedon huomioimatta jättämisen tavoitteellisen tehtävän aikana. Ennakoiva ja eri aistinkanavien välillä tapahtuva tarkkaavuuden suuntaaminen ovat esimerkki tehtävistä, jotka edellyttävät sekä tarkkaavuuden kohdistamista että tiedon inhiboimista tarkoituksenmukaisella tavalla. Tämä on erityisen tärkeää aivojen kehityksen aikana. Kehityksen aikana myös monenlaiset kokemukset vaikuttavat herkästi tarkkaavaisuuteen ja sen aivoperustaan. Toisaalta tarkkaavuus myös vaikuttaa herkästi muihin kognitiivisiin toimintoihin. Tässä väitöskirjassa tutkittiin tarkkaavaisuutta näistä kahdesta näkökulmasta: miten oma toimintamme vaikuttaa tarkkaavuuden aivoperustaan ja miten tarkkaavuus moduloi muuta kognitiivista prosessointia. Tämän väitöskirjan ensimmäisenä tavoitteena (tutkimus I) selvitettiin fyysiseen aktiivisuuden ja aerobisen kunnon yhteyttä ennakoivan tarkkaavuuden taustalla olevaan aivotoimintaan nuoruusiässä. Tutkimuksessa hyödynnettiin aivojen rytmisessä toiminnassa erottuvia alfaoskillaatioita. Toisena tavoitteena (tutkimus II) oli selvittää aistitiedon käsittelyyn liittyvän sensorisen aivokuoren roolia tarkkaavuuden kohdentamista vaativassa tehtävässä nuoruusiässä, ja fyysisen aktivaation sekä aerobisen kunnon yhteyttä tähän aivoaktivaatioon. Tämä toteutettiin käyttämällä kuulonvaraisia ja näönvaraisia jatkuvia ärsykkeitä, joita oli moduloitu tietyllä taajuudella mahdollistamaan sensorisen aivokuoren aktivaation seuraaminen. Kolmas tavoite (tutkimus III) oli selvittää missä määrin tarkkaavuus vaikuttaa kuuloaivokuoren aivovasteisiin puheäänille ja ei-kielellisille äänille lapsilla, joilla on kielellinen kehityshäiriö. Tähän käytettiin kuuloaivokuoren herätevasteita. Tutkimus I osoitti, että ennakoivan tarkkaavuuden aikana esiintyvä aivopuoliskojen välinen tyypillinen epäsymmetria rytmisessä toiminnassa oli suurempi paljon liikkuvien ryhmässä verrattuna vähän liikkuvien ryhmään. Korkean ja matalan aerobisen kunnon ryhmien välillä ei ollut eroa. Aivopuoliskojen välinen epäsymmetria takaraivolohkossa välitti fyysisen aktiivisuuden ja tehtäväsuoriutumisen välistä yhteyttä, erityisesti ennakoivan tarkkaavuustehtävän käsittelynopeuden osalta. Toisin sanoen, että paljon liikkuvien ryhmään kuuluvilla nuorilla näköaivokuoren alueiden rekrytointi ennakoivan tarkkaavuuden aikana oli voimakkaampaa kuin vähemmän liikkuvien ryhmään kuuluvilla nuorilla. Käyttäytymisen kannalta merkittäviä yhteyksiä havaittiin vain, kun otos jaettiin sukupuolen mukaan. Paljon liikkuvien miesten kohdalla ennakoivalla vihjeellä oli voimakkaampi vaikutus: he reagoivat todennäköisemmin nopeasti, vaikka virheitä tulisi enemmän. Toisaalta hyväkuntoisemmilla naisilla tiedonkäsittelyn tehokkuus oli parempaa, sekä tarkkuuden että reaktioajan osalta. Tutkimus II osoitti, että näönvaraisen ja kuulonvaraisen aivotoiminnan vahvuus

kullakin sensorisella aivokuorella vaihteli tarkkaavuuden kohteen mukaisesti, kun tehtävän vaatimukset edellyttivät joko näönvaraisen tai kuulonvaraisen aistivirran huomioimista. Tämä vaihtelu oli odotetun mukaista visuaalisilla aivokuoren alueilla, mutta oli toimi vain osittain kuuloaivokuoren alueilla. Tämä liittyi luultavasti lasten ikään ja erityisesti vasemman kuuloaivokuoren kypsymättömyyteen tarkastellussa koehenkilöjoukossa. Aivotoiminnan voimakkuus takaraivolohkon visuaalisilla alueilla oli yhteydessä suurempaan fyysisen aktiivisuuden määrään. Tutkimus III osoitti symmetrisempää aivopuoliskojen välistä aktivaatiota passiivisen kuuntelun aikana lapsilla, joilla oli kielellinen kehityshäiriö, verrattuna tyypillisesti kehittyneiden lasten kontrolliryhmään. Kehityksellisestä kielihäiriöstä kärsivillä lapsilla oikean kuuloaivokuoren toiminta vastasi kontrollilapsia, kun taas vasemman kuuloaivokuoren toiminta vaikutti vaimentuneen. Kun ääniä käsiteltiin aktiivisesti, kielellisestä kehityshäiriöstä kärsivien lasten kuuloaivokuorten välinen tasapaino muistutti tyypillisesti kehittyneiden lasten aivotoiminnan tasapainoa. Kaiken kaikkiaan tämän väitöskirjan tulokset viittaavat siihen, että tarkkaavuuden suuntaamisen taustalla oleva aivotoiminta on yhteydessä liikunnan määrään mutta ei aerobiseen kuntoon nuoruusiässä. Passiiviseen kuunteluun verrattuna tarkkaavuuden suuntaaminen aktiivisesti tehtävään vaikutti aivopuoliskojen väliseen tasapainoon kuulonvaraisen tiedonkäsittelyn aikana lapsilla, joilla on kehityksellinen kielihäiriö. Kaiken kaikkiaan tulokset viittaavat siihen, että oman elimistömme toiminta voi vaikuttaa kognitiivisiin toimintoihin muovaamalla tarkkaavuuden aivomekanismeja aivojen kehityksen aikana.

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ORIGINAL PUBLICATIONS

I

PA AND AF SHOW DIFFERENT ASSOCIATIONS WITH BRAIN PROCESSES UNDERLYING ANTICIPATORY SELECTIVE VISUOSPATIAL ATTENTION IN ADOLESCENTS

by

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Physical activity and aerobic fitness show different associations with brain processes underlying anticipatory selective visuospatial attention in adolescents

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ABSTRACT

Current knowledge about the underlying brain processes of exercise-related benefits on executive functions and the specific contributions of physical activity and aerobic fitness during adolescence is inconclusive. We explored whether and how physical activity and aerobic fitness are associated with the oscillatory dynamics underlying anticipatory spatial attention. We studied whether the link between physical exercise level and cognitive control in adolescents is mediated by task-related oscillatory activity. Magnetoencephalographic alpha oscillations during a modified Posner's cueing paradigm were measured in 59 adolescents (37 females and 22 males, 12–17 years). Accelerometer-measured physical activity and aerobic fitness (20-m shuttle run test) were used to divide the sample into higher- and lower-performing groups. The interhemispheric alpha asymmetry during selective attention was larger in the high than in the low physical activity group, but there was no difference between the high and low aerobic fitness groups. Exploratory mediation analysis suggested that anticipatory interhemispheric asymmetry mediates the association between physical activity status and drift rate in the selective attention task. Higher physical activity was related to increased cue-induced asymmetry, which in turn was associated with less efficient processing of information. Behaviorally, more physically active males showed stronger dependence on the cue, while more fit females showed more efficient processing of information. Our findings suggest that physical activity may be associated with a neural marker of anticipatory attention in adolescents. These findings might help to explain the varying results regarding the association of physical activity and aerobic fitness with attention and inhibition in adolescents.

1. Introduction

Regular physical activity (PA) and aerobic fitness (AF) have been shown to benefit cognitive functions, specifically executive control (Hillman et al., 2008; Smith et al., 2010). These cognitive benefits have been suggested to arise from the influence of PA and/or AF on brain structure and function. Despite an increasing number of studies clarifying the brain correlates of physical activity and fitness, there are still many gaps in the understanding of the specific association between performance measures of the body and the neurocognitive basis of executive functions. At the molecular, cellular, and circuit levels, regular PA has been suggested to be an important metabolic activator, significantly increasing the levels of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) (Gomez-Pinilla et al., 2008) or vascular-endothelial growth factor (Carro et al., 2001). These changes are further associated with increased neurogenesis (Brown et al., 2003), enhanced synaptic plasticity (Ocallaghan et al., 2007; van Praag et al., 1999), enhanced spine density (Redila and Christie, 2006; Stranahan et al., 2007), and angiogenesis (Carro et al., 2001; van Praag et al., 2005). However, these effects have been almost exclusively shown in mice, and without a direct link to cognitive functions. During recent years, the link between physical performance and the brain has been

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increasingly approached also in humans, yet the neural mechanisms underlying the cognitive consequences of higher regular PA and higher AF are still unclear. In the current study, we aim to investigate whether PA or AF associates with modifications in brain functions underlying cognition in adolescents.

Among different cognitive functions, PA and AF have been most often associated with improvements in measures of attention and/or inhibition (de Greeff et al., 2018; Muiños and Ballesteros, 2018). The evidence is clearer for children (Syväoja et al., 2014; Crova et al., 2014; van der Niet et al., 2014; Singh et al., 2019) and older adults (Colcombe and Kramer, 2003; Muiños and Ballesteros, 2018) than for adolescents and young adult populations. This might be related to the developmental changes taking place at this age range especially in cognitive control. Some studies do exist in adolescents, but the results are mixed. Performance in attention tasks is shown to be linked mainly with higher PA (Vanhelst et al., 2016; Booth et al., 2013) and for AF there are both positive (Hogan et al., 2015) and negative findings (Stroth et al., 2009). Tasks requiring inhibition, on the other hand, seem to be associated with higher levels of AF (Huang et al., 2015; Stroth et al., 2009; Westfall et al., 2018; Shigeta et al., 2021), with some exceptions (Tee et al., 2018), but not with PA (Pindus et al., 2015). Thus, although there seems to be general agreement regarding the positive association between physical performance measures and attention/inhibition skills, the more fine-grained interdependencies are not clear. Most of the research so far focus on the outcome measures, (i.e. reaction time or accuracy) and studies attention and inhibition separately. An alternative way would be to focus on the ongoing cognitive process using a task that requires the subject to simultaneously focus on the relevant information while inhibiting the irrelevant information. A kind of task requiring the engagement of both, attention and inhibition could be the one focusing on the anticipatory phases of attention allocation.

Anticipation is a key function of the human brain, which allows an individual to make use of external information to allocate attentional resources in a manner that is relevant for the behavioral goals. It thus reflects a preparatory stage of top-down control of behavior to ease upcoming information processing (Brunia, 1999). Anticipatory selection control in the brain can be shown to operate in two concurrent ways: (1) by selectively pre-activating the brain areas in charge of processing the relevant stimuli and (2) by inhibiting those brain areas intended to process what was determined to be irrelevant. When using a paradigm in which a visual cue implies the forthcoming target to emerge in either hemifield, this two-fold anticipatory process seems to be indexed by interhemispheric modulation (i.e., uneven involvement of the brain hemispheres) of alpha rhythm in the brain (Jensen and Mazaheri, 2010).

Alpha rhythm (at around 10 Hz), a widely studied brain oscillation, has been suggested to be especially important for directing neuronal resources during tasks that require attention to or inhibition of incoming information (Jensen and Mazaheri, 2010; Jensen et al., 2002; Bonnefond and Jensen, 2013; Klimesch, 1999, 2012; Klimesch et al., 2007). Increased alpha activity is considered to reflect system-level inhibition in the brain, while suppression of alpha activity is considered to indicate a release from inhibition or allocation of attention to relevant aspects of a task (Klimesch, 2012). Anticipatory attention is usually studied by using a covert attention task such as the Posner's cueing paradigm. In this task, a cue directs the participant's attention towards the left or right visual hemifield prior to the presentation of a target. The power of alpha activity, measured from the visual areas of the brain immediately after the cue, allows the study of the neural resources allocated to the attended and unattended visual hemifields. A cue-induced decrease in alpha power in the contralateral hemifield (in reference to the cued hemifield) indicates the preparatory engagement of neuronal resources to code information in the attended location. On the other hand, a cue-induced increase of alpha power in the ipsilateral hemisphere implies preparatory inhibition of brain areas involved in coding information of the irrelevant spatial location. This interhemispheric modulation of alpha rhythm during a visuospatial attention task in response to a cue has been indexed by the modulation index (MI) (Vollebregt et al., 2015, 2016). Magnetoencephalography (MEG) seems to be the most suitable tool to reliably record activity in the brain hemispheres because it offers excellent temporal resolution and high spatial resolution. By focusing on oscillatory alpha activity, MEG can be used to index the allocation of attention and inhibition of irrelevant information during ongoing task performance.

The visuospatial covert attention paradigm has been successfully used to reveal the neural mechanisms underlying anticipatory visual attention in general (Jensen and Mazaheri, 2010; Vollebregt et al., 2015) and changed attentional capacity in cases of attention deficit disorder (Vollebregt et al., 2016). MEG, and especially alpha oscillations, has also shown sensitivity to individual variation with relevance to cognitive performance (Haegens et al., 2014) and thus may show sensitivity also to the variance due to physical performance measures. Similarly, brain oscillations (Chaire et al., 2020; Luque-Casado et al., 2020; Wang et al., 2015), especially alpha rhythm (Chaire et al., 2020), have proven to reflect the influence of PA and AF in the brain. Relevant to the present study, Wang et al. (2015) assessed the relationship between AF and neural oscillations (theta and beta rhythms) during visuospatial attention using the Posner's cueing paradigm. Although they did not explore the effects of PA on anticipatory attention, the authors showed an association between physical performance measures (i.e., AF) and enhanced attentional control in young adults. Thus, the visuospatial covert attention paradigm seems to be a sensitive enough measure to demonstrate changes in the brain's attentional resources related to variance in the level of PA or AF in adolescents.

Adolescence is a particularly interesting period from the perspective of physical activity and aerobic fitness, as the whole body is undergoing significant maturational changes. Importantly, there are multiple factors, both biological and psychological, that are likely to contribute to the specific influence of higher AF (Huang et al., 2015; Hogan et al., 2013, 2015; Marchetti et al., 2015; Stroth et al., 2009; Westfall et al., 2018) or higher level of PA (Booth et al., 2013; Tee et al., 2018; Vanhelst et al., 2016) on cognition during adolescence. During this stage, it is important to be also aware of the possible sex-related differences. Indeed, Colcombe and Kramer's (2003) review of the enhancing effects of AF in older adults found that studies in which more than 50% of participants were women reported greater cognitive benefits of AF than studies enrolling mostly men, indicating that hormonal or other biological sex-related differences may influence the AF-related effects on the brain. Sex-related differences may influence the link between PA or AF and cognition also in other stages of life. This effect could be especially pronounced during adolescence, since it has been suggested to be a sensitive period for pubertal hormone-dependent brain organization (Sisk and Zehr, 2005). For this reason, biological sex is a variable that needs to be controlled for when exploring the link between PA or AF and cognition in adolescents.

To better understand the effect of physical performance-related changes in body metabolism on brain functioning, it is important to consider the specific characteristics of PA and AF. Even though PA and AF are closely related, they are different concepts and are measured distinctively. PA is related to energy expenditure resulting from any body movement (Caspersen et al., 1985), and it is usually measured by quantifying the amount of movement done in a certain period of time. On the other hand, AF is conceived as an achieved condition, and it is usually directly measured by obtaining the maximal oxygen uptake (VO_2 max) during maximal effort tasks. Based on their differences, PA and AF may have also different associations with brain function and structure as well as cognition. Very few studies have investigated the effect of both PA and AF on cognition in the same individuals (but see Haapala et al., 2014; Iuliano et al., 2015; Ruotsalainen et al., 2020a).

Using magnetic resonance imaging (MRI) our group reported associations of AF, but not accelerometer-measured PA, with grey matter volume (Ruotsalainen et al., 2019) and white matter integrity (Ruotsalainen et al., 2020a) in adolescents' brains, indicating that the level of

PA alone is not directly associated with structural modifications in the brain. In contrast, Ruotsalainen et al. (2020b) found that accelerometer-measured PA, but not AF, was related to resting state (BOLD) functional connectivity in adolescents. As PA and AF are influenced by different variables (for example, genes have a clearer influence on AF than on PA [Bouchard et al., 2011; Ross et al., 2019]), we infer that PA and AF might influence brain structure and function in different ways. Therefore, they might have a different impact on cognition: if the same genes influence fitness and some brain structural properties, then fitness is associated with the cognitive functions that are supported by these brain structures. PA, on the other hand, partly reflects fitness-unrelated aspects, which do not need to be associated with the same brain areas. Indeed, PA can influence physiological aspects that are directly linked with body activity (and biological factors caused by this activity, i.e., the accumulated effects of acute ongoing exercise). Also, PA could influence the areas that are directly linked to the activity itself, such as motor areas or visuomotor control. Thus, PA may influence cognition by modulating the dynamics of functional connections rather than structural properties in the brain.

As stated above, the most often reported benefits of PA and AF for cognition are evident in tasks requiring attention and/or inhibition. Behaviorally, some studies report an increase in accuracy scores (Hogan et al., 2013), while others have found reductions in reaction time (RT) (Huang et al., 2015) or both in adolescents (Westfall et al., 2018). A new analysis approach (the “EZ diffusion model”) has been suggested for better quantifying these measures (Wagenmakers et al., 2007). In addition to typical task performance measures (accuracy and RT), the EZ model combines typical behavioral outcomes based on accuracy and RT to measure dissociable underlying processes used to solve the task (drift rate, boundary separation, and non-decision time). “Drift rate” has been defined as an index for the signal-to-noise ratio of the information processing system that can be used to quantify the subject’s ability or the task’s difficulty (Wagenmakers et al., 2007). “Boundary separation” is considered a mechanism of the speed-accuracy trade-off and response strategy. “Non-decision time” refers to the temporal period before a decision, which is usually assumed to be included in the RT measure (Luce, 1986). Earlier studies have related improvements in drift rate and boundary separation to higher AF in adolescents (Westfall et al., 2018), but the brain processes associated with these improvements have not been elucidated.

Altogether, the cellular-level findings in animal studies, along with the evidenced improvement of attention and inhibition throughout the lifespan, suggest that PA and AF influence the underlying mechanisms supporting executive functions in the brain. The micro-level changes (such as neurogenesis, changes in synaptic strength and, intracortical connections) induced by PA and AF directly associate with those brain properties that are suggested to contribute to the electrophysiological activity, such as oscillatory activity (Shors et al., 2012), and hence the cognitive functions that are supported by this oscillatory activity. Alpha oscillations are considered to ‘route’ the information processing in the brain depending on attentional demands. Thus, we hypothesize that the influence of PA and AF on brain functions can be demonstrated in the alpha oscillations underlying anticipatory attention and inhibition in adolescents. More specifically, we assume that the higher levels of PA and AF could be reflected as stronger anticipatory modulation of alpha asymmetry. Based on the reported differences in how PA and AF influence brain structure and function, and their different theoretical and methodological definitions, we further assume they might relate to anticipatory alpha asymmetry in different ways. Thus, we aim to clarify the specific contributions of PA and AF on the underlying brain processes of attention and inhibition during adolescence.

To test our hypotheses, we recorded alpha oscillations using MEG during a Posner cueing paradigm in which the participants had to detect a target from two stimuli located in the right or left hemifields. The location of the target was anticipated by a preceding cue. We focused on the cue-induced modulation of alpha power in the ipsilateral and contralateral hemispheres. According to the alpha modulation hypothesis (Jensen and Mazaheri, 2010), a lower value of alpha in the visual areas of the contralateral hemisphere, and a higher value of alpha in the visual areas of the ipsilateral hemisphere, in reference to the cue, would indicate a better allocation of resources for attention and inhibition, respectively. Therefore, an increased interhemispheric asymmetry (difference of alpha values between contralateral and ipsilateral hemispheres) would indicate an improvement in the allocation of attentional resources. Based on the task demands, we hypothesized that higher levels of PA or AF would show bigger interhemispheric contrast (stronger modulation) of the alpha band, reflecting more efficient attentional and inhibitory processes in the brain. The behavioral performance in terms of attention and inhibitory control was measured in order to test the exploratory hypothesis that anticipatory alpha oscillations mediate the link between PA or AF and behavioral scores of attention/inhibitory control. The possible influence of sex in the associations of PA or AF with anticipatory selective attention was examined for the behavioral outcomes and controlled for in the brain data analysis.

2. Results

2.1. Demographic information, physical activity and aerobic fitness

Table 1 summarizes the demographic information for the two groups based on PA and AF. Demographic information is also given separately to males and females. Statistically significant differences between PA groups and sexes (independent-samples t-tests) are denoted.

Males showed higher levels of MVPA (moderate to vigorous PA, as measured by the accelerometer on a daily basis) than females (males: 59.60 ± 20.66 min/day; females: 46.98 ± 21.4 6 min/day) (t[51] = 2.083, p = 0.042) (see Table 1). Males also showed higher levels of AF (minutes until exhaustion in maximal shuttle run test) (males: 7.53 ±

Table 1

Demographic information and statistical differences for the groups based on physical activity (PA), aerobic fitness (AF) and sex.

	Sex		PA		AF	
	Males	Females	High	Modlow	High	Modlow
Age (years) ± SD (n)	14.34 ± 1.4 (22)	13.98 ± 0.9 (37)	13.66 ± 0.7 (17)	14.23 ± 1.2 (36)	14.31 ± 1.0 (20)	13.97 ± 1.2 (30)
Pubertal stage 1 (n)	3.43 ± 1 (21)	3.66 ± 0.8 (32)	3.27 ± 0.8 (15)	3.56 ± 0.9 (32)	3.20 ± 0.7 (20) *	3.83 ± 0.9 (29) *
Pubertal stage 2 (n)	3.14 ± 1.2 (21)	3.28 ± 0.9 (32)	3.00 ± 0.9 (15)	3.28 ± 1.0 (32)	3.00 ± 1.0 (20)	3.41 ± 1.0 (29)
Weight, kg (n)	55.88 ± 14.2 (22)	54.84 ± 7.6 (36)	51.45 ± 10.8 (17)	56.58 ± 10.2 (35)	51.09 ± 9.0 (20)*	57.36 ± 10.4 (30)*
Height, cm (n)	167.54 ± 12.9 (22)*	161.15 ± 6.4 (36)*	159.76 ± 9.2 (17)*	165.17 ± 8.9 (35)*	162.94 ± 9.7 (20)	164.37 ± 10.1 (30)
Body mass index (n)	19.60 ± 2.6 (22)*	21.11 ± 2.8 (36) *	19.98 ± 2.6 (17)	20.64 ± 2.5 (35)	19.14 ± 2.0 (20)*	21.18 ± 3.0 (30) *
MVPA, min/day (n)	59.60 ± 20.6 (19)*	46.98 ± 21.4 (34)*	78.11 ± 14.7 (17)***	38.94 ± 10.1 (36)***	61.79 ± 23.8 (17)*	45.01 ± 19.1 (27)*
AF, mins (n)	7.53 ± 2.1 (20) ***	4.69 ± 1.8 (30) ***	7.07 ± 2.2 (13) **	5.18 ± 1.9 (31) **	8.07 ± 1.6 (20) ***	4.33 ± 1.5 (30) ***

* p-value under 0.05.
** p-value under 0.01.
*** p-value under 0.001.
SD: standard deviation; MPVA: moderate to vigorous PA; modlow: moderate-to-low.

2.12 min; females: 4.69 ± 1.84 min) (t[48] = 5.024, $p < 0.001$) (see Table 1).

PA and AF showed a clear association ($r = 0.524$, $p < 0.001$) in the whole sample (see Fig. 1A and Experimental Procedures in Section 4.2 for details about the subject groups). When females and males were analyzed separately, this association was significant for males ($r = 0.577$, $p = 0.015$) but not for females.

2.2. Associations between physical activity, aerobic fitness and the neural and behavioral correlates of attention/inhibition skills

MEG measurements were performed during the visuospatial covert attention task, in which a cue (a small fish, valid in 75% of the cases) was presented before two possible targets (two sharks on each side of the screen). Participants were instructed to answer as fast as possible which shark (located in the left or right hemifield) opened its mouth more to eat the small fish (see Fig. 2A). The task requirements, and the underlying oscillatory dynamics in the left and right hemispheres (based on extensive literature [Jensen and Mazaheri, 2010; Bonnefond and Jensen, 2013; Vollebregt et al., 2015]), are schematically illustrated in Fig. 2B. From this task, RT, cueing effect for RT, cueing effect for accuracy, and EZ model variables (drift rate, boundary separation, and non-decision time) were included in statistical analysis for behavioral effects. Further, the level of alpha power and its interhemispheric balance were used in the statistical analysis for the neural effects. Finally, the correlation between behavioral and brain measures was also examined.

2.2.1. Physical activity vs. Behavioral performance in visuospatial covert attention task

The visuospatial covert attention task measures did not correlate with PA levels. When this correlation was examined separately for males and females, the cueing effect for RT (reaction time for uncued minus reaction time for cued targets) correlated with PA levels (MVPA, see Experimental Procedures, Section 4.2) in males ($r = 0.485$, $p = 0.035$). This result shows that the higher the PA level, the higher the difference between RTs for uncued minus cued targets (see Fig. 1B). No significant correlations were observed for females.

2.2.1.1. Aerobic fitness vs. Behavioral performance in visuospatial covert attention task. The visuospatial covert attention task measures did not correlate with AF levels. In the separate analysis for males and females, significant correlations were found between drift rate and AF levels for females ($r = 0.580$, $p = 0.001$). This result shows that higher AF was associated with a higher drift rate (see Fig. 1C). No significant correlations between EZ-model variables and AF were found for males.

2.3. Physical activity and aerobic fitness vs. Brain measures

The temporal variation of the spectral power at the alpha band in each hemisphere was measured in cued (i.e. cue to the left hemifield for the left hemisphere target and cue to the right hemifield in the right hemisphere target) and uncued (i.e. cue to the left hemifield for the right hemisphere target and cue to the right hemifield for the left hemisphere target) conditions. To examine the modulation of alpha oscillations in response to the cue, left cued vs. right uncued and left uncued vs. right cued conditions were contrasted. Modulation indexes (MI) for each hemisphere were calculated as the power from left cued trials minus right cued trials normalized by their mean (Vollebregt et al., 2015). Average time–frequency representations (TFRs) over selected occipital MEG sensors in each hemisphere (see Fig. 3B) were obtained. MI for left and right hemispheres were used to test the existence of alpha modulation (i.e. increase vs. decrease in response to the cue) and differences between groups. Three different time-windows were selected *a priori* and used for further analysis (0–400 ms [ms], 401–800 ms and 801–1,200 ms post-cue). To test differences in brain measures (left increase and right decrease of alpha MI in the three time-windows) repeated measures ANOVA (rANOVA) analysis was performed separately for PA and AF groups.

The presence of post-cue alpha modulation was verified. As the MI was calculated by subtracting the right cued from the left cued conditions (divided by their sum), and the alpha increases ipsilaterally to the attended hemifield, MI was expected to be positive in the left hemisphere and negative in the right hemisphere (see Fig. 2B). Fig. 3A illustrates the cue-induced modulation of spectral power in left and right hemispheres (time–frequency representation) for AF groups. In the same way, Fig. 4A show the time–frequency representation obtained for PA groups. Both rANOVAs showed a clear main effect of hemisphere (AF as between subjects factor: hemisphere $F_{(1,48)} = 19.114p < 0.001$; PA as between subjects factor: hemisphere $F_{(1,51)} = 17.246p < 0.001$) in alpha power reflecting the expected pattern between hemispheres (left > right).

When AF was used as between subjects factor no significant interaction or between subjects effect were found for AF. A significant interaction of hemisphere × time-window was found (hemisphere × TW $F_{(2,96)} = 8.339p < 0.001$). A main effect of time-window was close to significance (TW: $F_{(1.543,\ 74.071)} = 3.306p = 0.054$). A follow-up test (separately for each time-window), conducted in order to clarify the more detailed differences, revealed a clear main effect of hemisphere in alpha power in the second (hemisphere: $F_{(1,48)} = 20.962p < 0.001$) and third (hemisphere: $F_{(1,48)} = 17.104p < 0.001$) time – windows reflecting the left > right alpha modulation. The direction of the differences between hemispheres can be seen in Fig. 3C.

When PA was used as a between subjects factor, there was a tendency

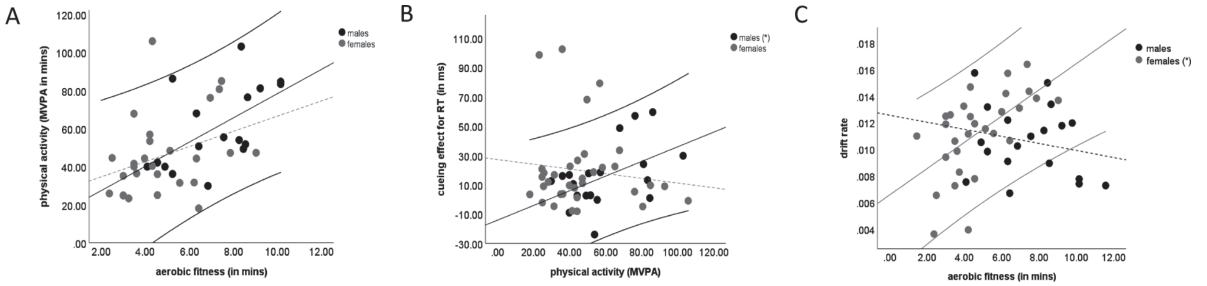

Fig. 1. Associations of studied variables. Black dots represent males and grey dots represent females. The solid central line represents the linear trend line and the two external lines represent the 95% confidence interval for the significant sex group. The dotted central line represents the linear trend line for the non-significant sex group. (A) Aerobic fitness (maximum time during maximal shuttle run test, min) plotted against physical activity (MVPA, moderate to vigorous physical activity, min/day) for males and females. Solid trend line and confidence interval for males, dotted trend line for females. (B) Cueing effect for reaction times from visuospatial covert attention task plotted against physical activity for males and females. Solid trend line and confidence interval for males, dotted trend line for females. (C) Drift rate from visuospatial covert attention task plotted against aerobic fitness for males and females. Solid trend line and confidence interval for females, dotted trend line for males.

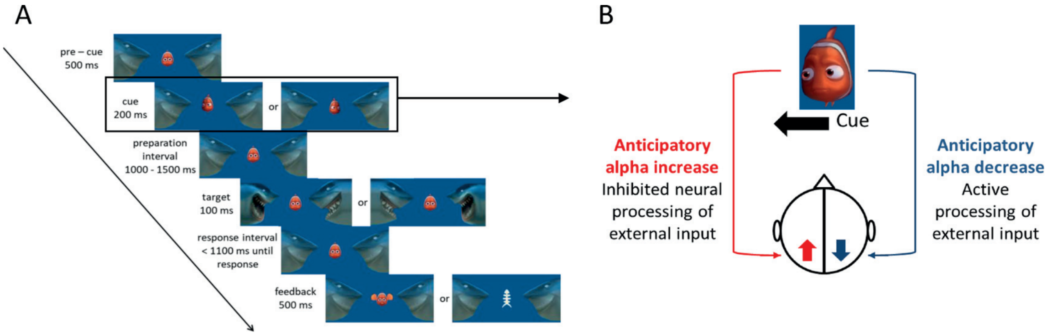

Fig. 2. Schematic representation of Posner's modified visuospatial covert attention task. (A) The progress of the task: a visual cue (fish looking either left or right) was followed by a target (one shark opens its mouth more than the other). Participants should detect the target as soon as possible by pressing the left or right button. (B) Illustration of the alpha modulation hypothesis (Jensen and Mazaheri, 2010) and the expected change in alpha power during the visuospatial covert attention task in the two hemispheres.

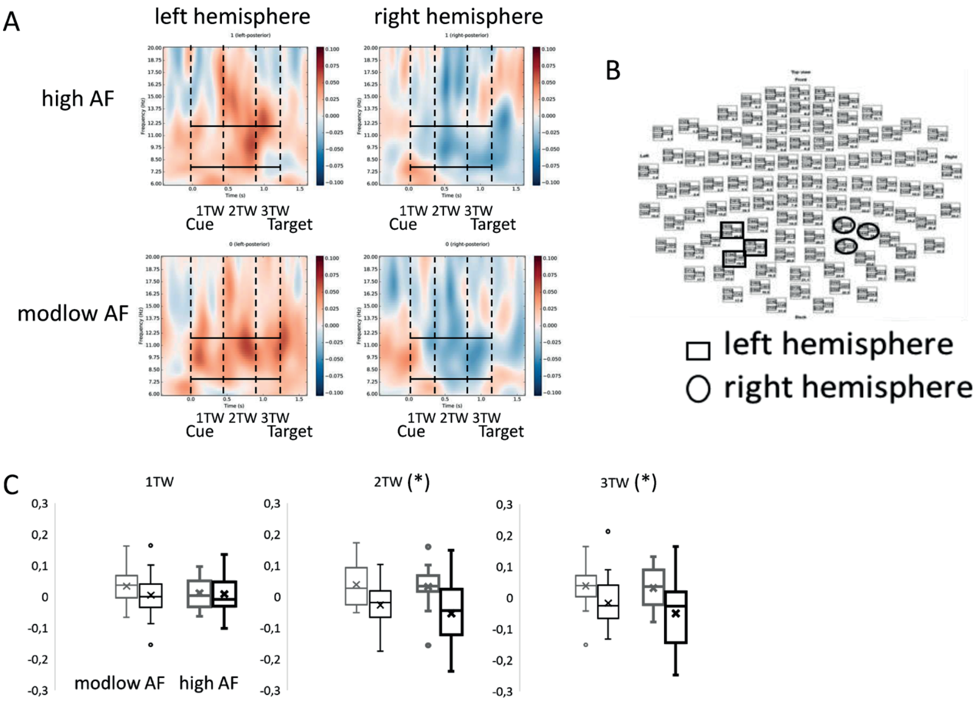

Fig. 3. Modulation of alpha power in response to the spatial cue for AF groups. (A) Time-frequency representations of the alpha power modulation index in the left and right hemispheres for moderate to low (modlow) and high aerobic fitness (AF) groups. Dotted lines delimit the three *a priori* selected time-windows. The first dotted line corresponds with the onset of the cue and the last dotted line corresponds with the onset of the target. Solid horizontal lines delimit the alpha rhythm frequency range (8–12 Hz). (B) Location of selected channels for calculating the alpha modulation index in the left and right hemispheres (square for the left hemisphere and circle for the right hemisphere. (C) Boxplot representation of left (in grey) and right (in black) hemispheres in each time-windows for modlow (light color) and high (dark color) AF groups.

towards significant main effect for group (TW: $F_{(1,\ 51)} = 3.544p = 0.065$). Moreover, also the effect of time-window (TW: $F_{(1.727,\ 88.099)} = 2.983p = 0.063$) and hemisphere × time-window interaction (hemisphere × TW: $F_{(1.728,\ 88.152)} = 2.474p = 0.098$) showed small p-values, however not reaching the 0.05 level of significance. To perform similar analysis as for AF groups, and to test our hypotheses on group differences, we further tested the effect of hemisphere and group in each time-window. The follow up test revealed a main effect of hemisphere in the three TWs (1TW: $F_{(1,\ 51)} = 4.831p = 0.033$; 2TW: $F_{(1,\ 51)} = 14.838p < 0.001$; 3TW: $F_{(1,\ 51)} = 19.580p < 0.001$) and a hemisphere × PA group interaction for the third TW (hemisphere × TW: $F_{(1,\ 51)} = 4.268p = 0.044$). Also, a main effect of PA group in the second time-window ($F_{(1,51)} = 4.468p = 0.039$) was found, probably reflecting the way alpha MI is calculated. The direction of the differences between hemispheres can be seen in Fig. 4B.

2.4. Associations between MEG measures and cognition

To test the correlation between the brain activation and behavioral performance, interhemispheric asymmetry (the difference between left – right hemisphere alpha MIs) was calculated as a single variable indexing the observed difference between hemispheres.

The interhemispheric asymmetry during the third time-window showed a significant correlation with drift rate. A bigger interhemispheric asymmetry during the third time-window was associated with lower drift rate values ($r = -0.359$, $p = 0.006$) (see Fig. 5B). No significant correlations were identified between the interhemispheric asymmetry during the third time-window and other behavioral measures from the visuospatial attention task.

2.5. Brain oscillatory dynamics as mediators between physical activity or aerobic fitness and cognition

The possible mediator role of brain oscillatory measures in the

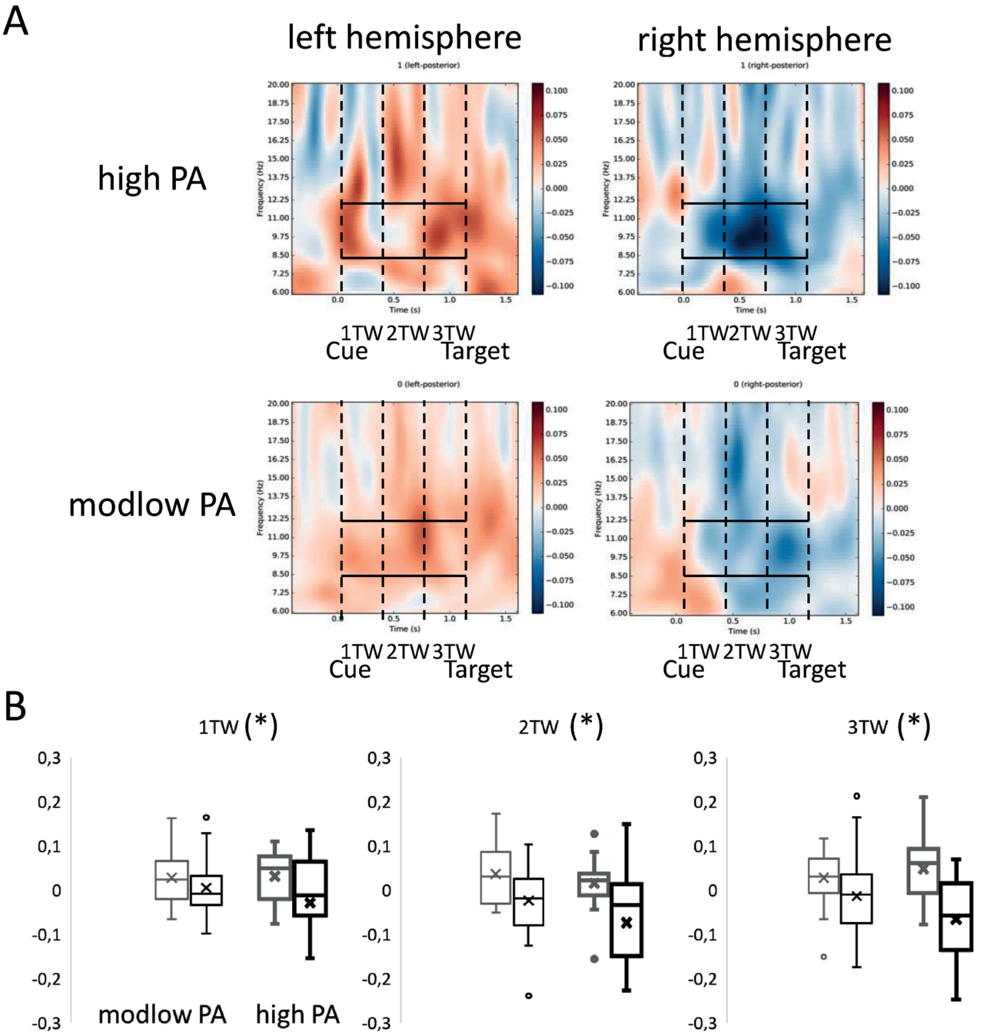

Fig. 4. Modulation of alpha power in response to the spatial cue. (A) Time-frequency representations of the alpha power modulation index in the left and right hemispheres for moderate-to-low (modlow) and high physical activity (PA) groups. Dotted lines delimit the three *a priori* selected time-windows. The first dotted line corresponds with the onset of the cue and the last dotted line corresponds with the onset of the target. Solid horizontal lines delimit the alpha rhythm frequency range (8–12 Hz). (B) Boxplot representation of left (in grey) and right (in black) hemispheres in each time-windows for modlow (light color) and high (dark color) PA groups.

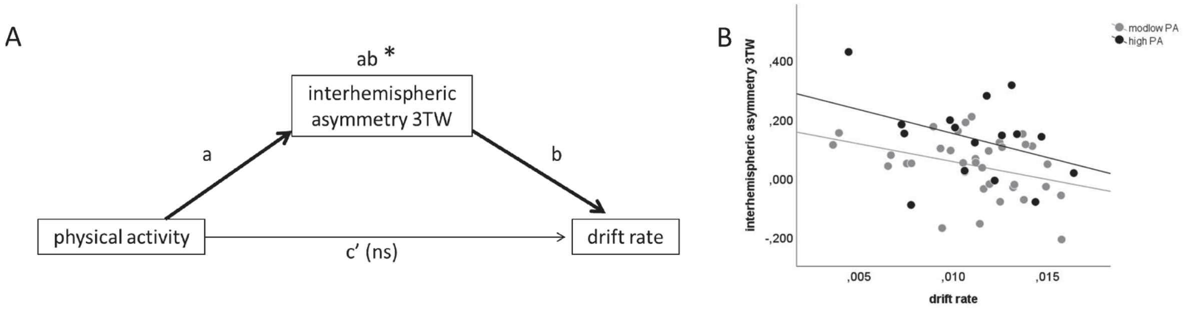

Fig. 5. Schematic illustration of the mediation model. (A) Mediation path examined about the role of interhemispheric asymmetry of alpha modulation index during the third time-window in mediating the relationship between physical activity and drift rate from the visuospatial covert attention task. Darker arrows indicate a significant path (only an indirect effect). (B) Interhemispheric asymmetry during the third time-window plotted against drift rate for both physical activity groups. Black dots and trend line correspond to high physical activity group and grey color dots and trend line correspond to moderate-to-low (modlow) physical activity group.

relationship between PA or AF and cognition was tested. A mediator analysis was used to test the underlying assumption that task-related modulation of oscillatory power mediates the influence of PA or AF on performance in visuospatial covert attention task. First, significant correlations between brain measures, PA or AF groups and cognitive variables were tested. Of the brain measures, only the interhemispheric asymmetry of alpha power during the third time-window fulfilled this assumption correlating with PA groups (but not AF groups) and cognitive variables (only drift rate). The resultant combination was tested with a mediator model using MPlus software by means of a bootstrap of 1,000 samples. Mediation was tested by determining whether the confidence interval for the indirect effect contained zero (Fritz and

MacKinnon, 2007). The intervals not including zero were considered significant.

The mediation model was built with PA groups as the independent variable, drift rate as the dependent variable and interhemispheric asymmetry during the third time-window as the mediator. Indirect effect was significant (ab estimate = – 0.107, bias-corrected bootstrap confidence interval = [−0.306; 0.000]) but direct and total effects were not (direct: c' estimate = 0.104, p = 0.458; total: c estimate = – 0.003, p = 0.983) (see Fig. 5A). In this model, the relationship between independent (PA groups) and dependent (drift rate) variables was not significant, but this relationship was increased in magnitude when late interhemispheric asymmetry was included as a mediator. As the mediated effect and the direct effect have opposite signs, the model indicates substantial mediation (MacKinnon, 2008). The results of this model thus suggest that the late interhemispheric asymmetry of alpha power mediates the association between PA levels and drift rate in the visuospatial covert attention task across the whole sample.

To determine if sex influenced the above mediation effect, a moderation in the mediator effect analysis was performed. The results showed no significant difference in indirect effects between males and females (d4 estimate = −0.103, p = 0.798, bias-corrected bootstrap confidence interval = [−1.144; 0.503]). The results of this model suggest that sex does not moderate the indirect or total effects of late interhemispheric asymmetry of alpha power in the association between PA levels and drift rate.

3. Discussion

This study evaluated the influence of PA and AF on brain oscillatory measures underlying anticipatory attention allocation within the same sample of adolescents. As expected, even though the levels of PA and AF were strongly correlated, they showed specific associations with cognitive performance and underlying brain measures. Adolescents, especially males, with higher levels of PA showed stronger utilization of the cue in anticipating their response, reflected as a bigger cueing effect (RT difference between uncued vs. cued targets) in reaction time. In line with these behavioral findings, the group with higher PA level showed stronger cue-induced interhemispheric alpha asymmetry during the stage of attention allocation in a modified Posner's cueing task, in which attention (vs. inhibition) is selectively directed to one of the visual hemifields. The exploratory mediation analysis suggested that this interhemispheric alpha asymmetry mediated the association between PA status and drift rate, a measure of information processing speed, calculated as an individual performance measure in the Posner's cueing task. Larger cue-induced asymmetry was associated with slower overall information processing at the behavioral level, in an analysis integrating valid and invalid spatial cues. Although males and females showed a differential association between PA and AF and cognition, this mediator effect was not influenced by sex.

Males with a higher level of PA indicated stronger cue-based anticipation, as the bigger difference in reaction times between cued and uncued trials, suggesting a greater reliance on the cue. It is important to note that this bigger difference could be determined from a gain of valid cueing or by a cost of invalid cueing. As paying attention to the cue is what makes the targets valid or invalid, both, a gain of valid cueing and cost of invalid cueing, could be considered as cueing effect. The result of a stronger reliance on the cue for higher physically active males is partly in line with an earlier study showing a complex association between attentional control and PA measures especially in males (Booth et al., 2013). By measuring selective attention, sustained attention, and attentional control/switch, Booth and colleagues found that higher total volume of PA (mostly including light intensity activity) predicted poorer performance on the attention tasks, while higher MVPA was associated with better executive function performance in adolescent males. In contrast, Vanhelst et al. (2016) reported a positive effect of PA on attention capacity in adolescents independent of sex. Differences between our results and earlier findings might be related to the way the attentional tests were administered (computerized vs. paper and pencil), and to the way cueing was used in the experiments. In our study, we used a rather high ratio of cued/uncued trials (75/25%) which may emphasize attentional shifting over efficient attention control for optimal performance. It seems important to acknowledge the specific task requirements to make correct interpretations of the behavioral benefits by PA. In sum, there is some evidence for an association between higher levels of PA and more dependence on the cue in adolescents, more clearly in males than in females. The possible sex difference indicated by our findings needs to be confirmed by further studies, as we had a fairly small number of participants (especially when both sex and physical activity groups were separately analyzed).

Interestingly, we demonstrated a modest but significant difference at the brain level, related to the cue-based allocation of attentional resources. The significant hemisphere × PA group interaction indicated a larger difference between the ipsilateral increase and contralateral decrease of alpha oscillations in the two hemispheres in the high PA group. This effect appeared at around 800 ms after the cue onset, right before the target. This means that for adolescents with a higher level of PA, the cue-based engagement of visual attentional resources (anticipatory inhibition/preparation of the brain processes corresponding to the uncued/cued hemifield, respectively) is stronger than for individuals with lower levels of PA. This result can be interpreted according to Banich (1998), who suggested that, depending on task demands, the interaction between the brain hemispheres, rather than the specific processes accomplished by each hemisphere separately, can influence selective attentional functioning. Therefore, PA seems to be related to a stronger reliance on cues for engaging anticipatory attentional control, reflected in both behavioral measures (reaction time difference between uncued vs. cued targets) and brain measures (anticipatory interhemispheric asymmetry of alpha oscillations).

The effect of PA was not observed in the overall performance in the selective attention task. It was seen instead in the strategy of performing the task, perhaps reflecting prioritization of anticipatory focusing of attentional resources over adaptive shifting of attention. Indeed, the overall behavioral outcome did not differ, but only the reliance on the cue. In fact, as evidenced by the subsequent mediation analysis, the strong interhemispheric asymmetry was linked with less efficient attentional processing, as measured by the drift rate variable (reflecting the speed of information processing), when a single measure of drift rate was calculated, integrating cued and uncued targets. Our results would thus suggest that rather than focusing on the absolute benefit of PA on cognitive functions, it would be useful to examine the influence of PA on the more specific mechanisms of information processing in the brain. Indeed, it might be that by specifically influencing part of the neurocognitive resources underlying attentional control, PA may appear beneficial for executive functions in some tasks but not in others. Thus, differential effects across tasks could depend on the specific neurocognitive requirements of a given task. This interpretation of our data would help to explain the discrepant findings concerning the effects of PA on executive functions in youth (Alvarez-Bueno et al., 2017; Esteban-Cornejo et al., 2015).

What could then be the underlying mechanisms by which PA contributes to the neural bases of attention? Our experimental manipulation focused on the attentional control that requires communication between the left and right visual areas. The dynamic interaction between hemispheres, modulating the processing capacity of the brain, is proposed to occur via the main pathway connecting the cerebral hemispheres, the corpus callosum (Banich, 1998; Qin et al., 2016). A recent study by our group (Ruotsalainen et al., 2020a) investigated the link between both PA and AF with the white matter connections in adolescents using MRI and fractional anisotropy (assessing microstructural changes in the brain's white matter). The main results in this study showed that only the level of AF (and not PA) was related to white matter properties. However, it was also described that the level of fractional anisotropy in the body of the corpus callosum could moderate the relationship between PA and working memory. Specifically, high levels of PA were positively related to working memory only when the fractional anisotropy level was low (which could signify e.g. earlier stages of corpus callosum maturation). The authors suggest that specific tracts of white matter (such as corpus callosum) could moderate the relationship between both PA and AF with cognition in adolescents. This reasoning is in line with the general notion that the responsiveness of the brain networks to external influences (including physical activity), i.e. brain plasticity, is not stable but varies across development.

Interestingly, it has been suggested by some studies, that the changes in white matter fractional anisotropy are associated with variations in alpha oscillatory activity in corresponding areas (Jann et al., 2012; Valdés-Hernández et al., 2010). It may thus be, that white matter properties, representing the structural skeleton for neuronal communication, bring about the physical activity (and fitness) -related influences into oscillatory dynamics and attention allocation. When both of these measures show also developmental differences, it would be critical to acknowledge the maturational state (and consequently, the level of plasticity) of the brain to explain the possible effects of PA and AF over cognitive performance. Further research is warranted to clarify the role of interhemispheric interaction via the corpus callosum in the influence of PA and AF on executive functions (such as attentional control/inhibition and working memory).

Our exploratory mediation analysis indicated that the interaction (or, more specifically, the degree of imbalance) between the hemispheres (interhemispheric asymmetry) during attention allocation seemed to mediate the relationship between physical activity levels and performance in a visuospatial selective attention task. PA increased the imbalance between the ipsi- and contralateral hemispheres according to the selective attention task requirements. However, this increment in interhemispheric asymmetry did not improve the efficiency in the selective attention task (as measured by drift rate). This unexpected result could be partly explained by a strategy of choice emphasizing the processing of the cue. Adolescents with higher PA could be prioritizing the anticipation for upcoming information, as was hinted also by the stronger behavioral cueing effect. Similar results were obtained in a longitudinal study measuring the association of preadolescent children's motor competencies with working memory maintenance and neurophysiological measures of task preparation (Ludyga et al., 2020). Ludyga et al., (2020) described a more effective utilization of the cue-relevant information by an increase in the cue-P300 amplitude during the task preparation stage in a Stenberg paradigm (used to assess working memory capacity) in children with higher motor competencies, thus in line with our findings. The authors suggest that children with high motor competencies exhibited a more proactive control strategy allowing active maintenance of task goals.

It seems that the differences in strategy between children with low and high accelerometer-measured motor competencies can also be observed in adolescents when solving a selective attention task. However, this strategy could have a cognitive cost leading to a worse global efficiency in the selective attention task, especially when the proportion of uncued targets in the task is rather high. The cost-benefit effect of relying on the cue could also arise due to shared neural resources between selective attention and working memory (For a review see Gazzaley and Nobre, 2012). PA has been associated with increased working memory capacity in children and adults (Alvarez-Bueno et al., 2017; Kamijo et al., 2011; Ludyga et al., 2020). In a task requiring both, working memory (holding the side of the target in memory) and possible attentional switching, the strategy relying on working memory may limit the resources for adaptive attentional switching (Luna et al., 2020).

In line with earlier studies in youth, PA and AF were found to be strongly correlated (Butte et al., 2007; Gutin et al., 2005; Ruotsalainen et al., 2019). Nevertheless, they showed different associations with executive control and its underlying brain processes. While AF was shown to be associated with brain structural measures more strongly than PA (Ruotsalainen et al., 2019, 2020b), the opposite was true for functional measures, i.e. brain oscillatory dynamics underlying anticipatory attention allocation: We did not find any relationship between AF and alpha oscillations. This result aligns with earlier findings obtained with a very similar paradigm to ours. Wang et al., (2015) performed a similar study in young adults measuring oscillatory brain activity during the performance in Posner's visuospatial covert attention paradigm. Even though they aimed to measure a broader band of brain rhythms including theta and beta oscillations in addition to alpha oscillations (and, topographically, they focused on broader scalp areas: midline frontal to posterior regions), they also found that fitness levels did not modulate alpha recruitment in response to a cue. Thus, we replicated this Wang et al. (2015) result, and expand it to concern also earlier life stages, namely adolescence.

Although brain functional measures did not associate with AF, there was an indication of a correlation between behavioral measures and AF. Higher AF was related to higher drift rate values in the visuospatial attention task, but only in females. Drift rate was calculated as part of the EZ diffusion model for two-choice RT tasks (Wagenmakers et al., 2007) and was based on the variance of reaction times for correct decisions and the proportion of correct decisions. The drift rate has been interpreted as an index of processing speed in decision tasks (Wagenmakers et al., 2007). Previous studies have also reported the association between fitness and behavioral performance in attention/inhibition in adolescents (Cadenas-Sanchez et al., 2017; Huang et al., 2015; Marchetti et al, 2015; Westfall et al., 2018). Therefore, although the anticipatory gating of relevant information, reflected as asymmetric alpha oscillations in visual areas, was not specifically influenced by AF, AF seems to be related to selective attention/inhibition processing.

The tendency to observe PA vs. AF -related influences in males vs. females, respectively, cannot be fully scrutinized based on our moderate sample size but evokes interesting questions about the role of sex differences. In our data, the AF level in females seemed to be associated with more efficient attentional/inhibitory processing (drift rate) in the visuospatial attention task. On the other hand, PA level in males seemed to be associated with the clearer benefit of cued over uncued targets (presumably reflecting a choice of strategy). The latter result concerning sex-specific benefits of PA was already discussed above and shown to receive some support from earlier findings (Booth et al., 2013). The selective advantage of AF for females' cognition/executive functions has also been reported before for older adult populations (Baker et al., 2010; Barha et al., 2017; Colcombe and Kramer, 2003; van Uffelen et al., 2008). Our minor finding support and expands those previous studies by showing a sex-dependent positive effect of AF over selective attention/inhibition also earlier in life. There are some potential underlying explanations for the observed female-specific advantage of fitness for executive functions. Based on a study exploring the association between circulating BDNF levels and cognitive functioning, it has been hypothesized that the brain-derived neurotrophic factor (BDNF) is more closely related to cognition in women compared to men (Komulainen et al., 2008). Moreover, some studies have suggested that increased feminine hormone, estradiol, might be related to greater BDNF expression in the cortex and hippocampus of females of different species (Scharfman et al., 2003; Singh et al., 1995; Sohrabji et al., 1995). While BDNF is one of the mechanisms by which physical performance is thought to contribute to cognition, these differences may underlie also the differential effects between the sexes. However, more studies are needed to investigate the differences in PA and AF in the two sexes and the possible mediator role of sex hormones in the relationship between AF-related increments of BDNF and cognition.

It is important to note that we cannot rule out the effect of peer group influence, personality, and preferences in free-time activities, that are likely to influence PA more than AF (Palmer-Keenan and Bair, 2019; Sevil et al., 2018), which thus impacts the interpretation of our results, and especially the possible sex differences. In line with earlier studies (Booth et al., 2013; Tomkinson et al., 2018; Woll et al., 2011), PA levels were higher in males than in females. It may be that higher levels of activity in boys at this age also reflect engagement to regular, goal-directed training, which could be generalized as higher competitiveness also in other contexts. This could influence the choice of strategy in the visuospatial attention task. In the same way, underlying genetic factors could influence the association between AF and attentional processing in females.

Our results also raise the probable developmental perspective in the study of the underlying brain mechanisms in the association between PA or AF and attention/inhibition. Benefits from PA have been reported mostly for young adults (Hillman et al., 2006; Kamijo et al., 2011; Kamijo and Takeda, 2009). Evidence of benefits from PA on attention/inhibition is weaker in other age groups. However, AF seems to benefit selective attention and inhibition, especially during childhood (Chaddock et al., 2011; Pontifex et al., 2011; Voss et al., 2011) and older adulthood (Colcombe et al., 2004; Prakash et al., 2011). Perhaps this age-dependent variation in observed interlinks between physical performance measures (AF vs. PA) and neurocognitive functions reflects also the overall changes in the strength of genetic contribution, more strongly reflected in the AF, on these functions. Altogether, the current evidence suggests a U-shaped relationship between PA and selective attention/inhibition across the lifespan. Further work is required to establish whether this is the case or whether this reflects only an insufficient number of studies tackling regular PA engagement across the lifespan.

A major limitation of this study resides in its small sample size, which limits the strength of our interpretations. Another limitation lies in the cross-sectional nature of this study, which prevents us from making causal inferences from the associations found for PA or AF. The results of our mediator analysis provide valuable insights for understanding brain processes that might mediate the effects of PA on cognition, although they should be interpreted with caution. The absence of a direct effect in our mediation model (direct influence of PA over drift rate) could be a result of the reduced sample size. It may thus be that there was sufficient power to detect the indirect effect, but insufficient power to detect the direct and total effects. Longitudinal studies would be needed for a better understanding of the neural level mediators of the cognitive benefits of PA and AF during different phases of life. Finally, this study measured only PA and AF effects over selective attention and inhibitory control processes in the visual modality. Testing these effects in different modalities or cross-modal interactions should also be considered in future research.

In conclusion, our results showed that higher levels of PA, but not AF, were related to improved anticipatory brain processes underlying allocation of attention in the adolescent brain. However, the anticipatory interhemispheric asymmetry was related to reduced overall performance in the visuospatial attention task, thus suggesting a choice of strategy prioritizing the cue processing. Behaviorally, female and male adolescents showed dissociable effects of PA and AF on anticipatory selective attention/inhibitory control.

4. Experimental procedures

4.1. Participants

Sixty-three adolescents were recruited to participate from among the participants of a larger study related to the Finnish Schools on the Move Program (Joensuu et al., 2018; Syväoja et al., 2019) measuring the behavioral effects of PA and AF on cognition. The potential subjects were informed about the study and voluntarily manifested their interest to participate. All subjects were native Finnish speakers and came from the Central Finland area ($n = 54$) or the South Finland area ($n = 9$). Sixty participants were classified as right-handed and three as left-handed by the Edinburgh Handedness Inventory. From the initial 63 participants, four were excluded from further analysis due to low quality of MEG data ($n = 2$) or very few responses in the uncued condition during the visuospatial covert attention task ($n = 2$). Finally, the analysis was done with a total of 59 participants (22 males and 37 females) with age ranges from 12.8 to 17.0 years old (14.11 ± 1.07 years).

All participants were volunteers, and they as well as their legal guardians signed informed consent before the beginning of the study in agreement with prior approval of the Central Finland Healthcare District Ethical Committee. Participation in this study was compensated with a €30 gift card. The sample did not include participants with neurological disorders, major medical conditions or those using medication that influences the central nervous system. All participants had normal or corrected to normal vision.

Self-reports about the participants' stages of puberty with the Tanner Scale (Marshall and Tanner, 1969, 1970) were used to measure the pubertal development in our sample. All the participants reported being between categories 2 and 5 for pubertal stage 1 and between 1 and 5 for pubertal stage 2. For demographic information and statistical differences for the groups based on AF, PA or sex, see Table 1.

4.2. Measures of physical activity and aerobic fitness

AF was estimated with the shuttle run test (Leger et al., 1988; Joensuu et al., 2018), a measure widely used to estimate a person's maximum oxygen uptake ($\underline{VO_2max}$). Participants were instructed to run between two lines with a separation of 20 m. Speed should have accelerated every time they heard an audio signal. The time participants spent before failing to reach the end lines in two consecutive tones indicated their level of AF. The speed in the first and second levels was 8.0 and 9.0 km/h, respectively. Afterward, speed increased by 0.5 km/h per level. The duration of each level was one minute. The number of minutes that each participant lasted until exhaustion and abandoning the test (normalized by gender and age) was used to measure the participant's AF level. To differentiate them by their level of AF into high or moderate-to-low (modlow) AF groups, the distribution of minutes until exhaustion was divided into three equal parts. Participants in the highest tertile (cutoff point tagging 66% of the distribution) were considered as being part of the high AF group. In the same way, participants in the two lowest tertiles were allocated to the modlow AF group.

PA was measured with accelerometers, specifically triaxial ActiGraph (Pensacola, FL, USA) GT3X + and wGT3X + monitors, which the participants wore during seven consecutive days (Joensuu et al., 2018). They were instructed to wear it on their right hip during waking hours except for water-related activities. A valid measurement day consisted of at least 10 h of data. Data were collected in raw 30 Hz acceleration, standardly filtered and converted into 15 s epoch counts. Periods of at least 30 min of consecutive zero counts were considered as non-wear time. A customized Visual Basic macro for Excel software was used for data reduction. A cut-off point of ≥ 2296 cpm (Evenson et al., 2008) was used to define moderate to vigorous intensity PA (MVPA, min/day). MVPA was calculated as a weighted mean value of MVPA per day ([average MVPA min/day of weekdays $\times$ 5 + average MVPA min/day of weekend $\times$ 2] /7). To differentiate participants by their PA level into the high or modlow PA groups, the distribution of MVPA (min/day) was divided into three equal parts. Participants in the highest tertile (cutoff point tagging 66% of the distribution) were placed into the high PA group. In the same way, participants in the two lowest tertiles were allocated to the modlow PA group.

PA was measured in a total of 53 participants and AF was measured in a total of 50 participants. School absence on the day of the test was the reason for missing AF values (2 males and 7 females), while an insufficient number of valid measurement days (two weekdays and one weekend day) was the reason for missing data of regular PA measurements (3 males and 3 females). All subjects had at least one measure of PA or AF.

4.3. Stimuli and task

We used a visuospatial covert attention paradigm from Vollebregt et al. (2015) based on a modified Posner's cueing paradigm (Posner, 1980). The task of the participants was to save a fish from being eaten by a shark. A schematic representation of the sequence of phases displayed in the task is shown in Fig. 2A. The first phase was the pre-cue period (500 ms), when the subjects were presented with a fish in the middle of the screen as a fixation point and two sharks on both sides of the screen. Next, a cue was presented during 200 ms consisting of the fish's eyes looking to the left or the right shark. The cue indicated the side of the screen where the target would appear. The target (both sharks opened their mouths but one more than the other) was presented after 100 ms. The probability of validly cued targets (the gaze of the fish was directed towards the same side as the targeted shark) was 75%. Afterward, participants had a preparation interval varying in time (1,000–1,500 ms) to avoid the subject's prediction of the target's occurrence. The duration of the response interval following the target presentation was determined by the subject's response with a maximum time of 1100 ms. Subjects had to report (by using their index finger in a MEG-compatible response pad) the side corresponding to the shark that opened its mouth more. Afterward, the feedback (a happy fish for correct responses or a fishbone for errors) was presented. During the whole task, subjects were instructed to continuously watch the fish's eyes (fixation point). Instructions with standardized guidelines were given to the subjects in advance, and before starting the measurements, the instructions were repeated in a short video (4 s of duration). To ensure that the participants learned the instructions correctly, a practice session was performed with 100 trials and the same amount of right and left targets. During the practice, the task was the same, only the probability of validly cued targets was modified (80%) to reinforce learning the cue. Subjects were reminded about fixating on the small fish's eyes at the beginning of the task and in every break between blocks.

The visuospatial covert attention task was programmed and controlled using Presentation software (Neurobehavioral Systems, Albany, CA) and consisted of four blocks of 100 trials each. Each block contained 75 cued targets and 25 uncued ones. Between blocks, subjects could rest and after some minutes they decided when to start the following block. Left and right cues had the same probability of occurrence. The total duration of the task was approximately 20 min.

4.4. MEG recordings and analysis

The brain activity related to the visuospatial covert attention paradigm was recorded using an Elekta Neuromag Triux system (Elekta Neuromag, Helsinki, Finland) for the subjects living in Central Finland. The recordings for the subjects from Southern Finland were performed in Aalto Brain Centre's MEG core using Elekta Neuromag™ (Elekta Neuromag, Helsinki, Finland). The MEG devices in the two institutes are essentially the same. During the subject's preparation, five head-position indicator coils were attached to their heads (three in the front and two behind both ears). Coil locations were determined using a 3-D digitizer in reference to three anatomical landmarks (nasion and preauricular points). At the beginning of the recording, their position with respect to the helmet was measured and continuously tracked during the whole measurement (Uutela et al., 2001) to correct for head movement during the analysis stage. With the use of the electrooculogram (EOG), vertical (two electrodes located at the external canthi of both eyes) and horizontal (two electrodes above and below the right eye) eye movements were monitored. During the measurements, the subjects were seated comfortably inside a magnetically shielded room and were instructed to avoid movements of the head and the eyes. Two response pads (left and right) were positioned on a table attached to the chair and located over the subject's legs. The task was projected on a panel located 1 m from the subject's eyes.

The MEG signals were band-pass filtered at 0.03–330 Hz and sampled at 1000 Hz. The raw data were pre-processed using Maxfilter™ 2.2 software (Elekta Neuromag, Helsinki, Finland). A signal space separation method (SSS) (Taulu et al., 2003), removing external interference emerging during the measurement, was used in most of the subject's recordings. SSS was replaced by the spatiotemporal signal space separation method (tSSS) (Taulu and Simola, 2006) (also included in Maxfilter 2.2 software) for the analysis of data from participants wearing braces or other internal magnetic sources. Head movements occurring during the measurement were also corrected by using Maxfilter 2.2 software. The rest of the analysis was performed with MNE-Python software (Gramfort et al., 2014). The analysis was performed with the brain activity recorded from the gradiometers. The time–frequency representations (TFRs) were calculated in a frequency range of 2–30 Hz and for a time period ranging from −0.2 to 1.4 s in reference to the onset of the cue. The frequency resolution used was 2 Hz. A Morlet wavelet transformation (Morlet et al., 1982) was used for this purpose with the number of cycles equal to half of each frequency value. For each channel, a modulation index (MI) was calculated with the following equation:

MI = (freq_left cued trials – freq_right cued trials)/½ * (freq_left cued trials + freq_right cued trials)

The resulting MIs were used to evaluate the visuospatial covert attention task-based modulation in the alpha band (8–12 Hz). Whole head TFRs were averaged together for the whole sample of 59 participants. Averages of three MEG channels in occipital regions where alpha increased (left) and alpha decreased (right) could be clearly identified were selected. The location of the left (contralateral) and right (ipsilateral) selections of MEG channels for the occipital region used for further analysis is shown in Fig. 3B. The difference between the alpha MI from the left minus right hemispheres was used to calculate the interhemispheric asymmetry of alpha MI during the task. Because there are not references from previous studies to infer where (in time) the PA or AF –related effects could appear, we chose to use an exploratory approach. The whole time-window available (0–1200 ms) of alpha MI in the left and right hemispheres and interhemispheric asymmetry, was divided in three equal and smaller time-windows (0–400 ms, 401–800 ms, 801–1,200 ms).

MEG and behavioral data were analyzed in a blinded manner towards the group assignment to obtain an unbiased assessment of neurophysiological or cognitive outcomes.

4.5. Behavioral performance analysis

During the MEG measurement, behavioral responses from the visuospatial covert attention task were collected and analyzed. Incorrect responses (<2.5% of the data) and reaction times below or above 2.5 standard deviations from the mean in each condition for each participant (<2.5% of the data) were considered as outliers and excluded from further analysis. Reaction times under 250 ms were considered too short to reflect selective attention processing and were removed from the analysis. There was no difference in the number of cued and uncued targets from the visuospatial covert attention task used for further analysis for the whole sample divided by sex, the two groups based on AF and for the two groups based on PA.

Average reaction times for cued and uncued targets were calculated separately for each subject. A cueing effect index for RT was calculated as the difference between the reaction times for uncued minus cued targets. Accuracy was calculated as the percentage of correct responses. The cueing effect index for accuracy was calculated as the difference between the number of correct responses for cued minus uncued targets. Accordingly, average reaction times, accuracy for cued and uncued targets and the cueing effect indexes were used in further analysis.

In addition to typical task performance measures (accuracy and RT), the EZ model was used to analyze the results from the visuospatial covert attention task. Three new variables (drift rate, boundary separation and non-decision time) were calculated for each participant according to

Wagenmakers et al. (2007). Drift rate, boundary separation, and non-decision time are determined from three parameters: the mean RT for correct responses (MRT), the variance of RT for correct responses (VRT), and the proportion of correct responses (Pc), as in the EZ model (for more details and R code see Wagenmakers et al. 2007).

4.6. Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 24.0 (Armonk, NY: IBM Corp.). Variables resulting from behavioral measures were assessed for normality. Only variables showing normal distribution were included in the statistical analysis. Resulting variables from the visuospatial covert attention task used for further analysis were: RT for cued and uncued targets, cueing effect for RT, drift rate, boundary separation and non-decision time. All brain measures were included in future analyses.

We conducted two rANOVAs on the MI of alpha power, one for each between-subjects factor (PA and AF groups). Within-subjects factors were hemisphere (left, right) and time-windows (1st, 2nd, 3rd). In the first version of the models used, sex and puberty (1 and 2) were included as covariates. However, the model showed that none of the covariates were significant predictors. Because of this, biological sex and puberty as covariates were removed as covariates from the final models. Subsequent follow-up tests with rANOVA (separately for each time-window), were conducted for AF and PA groups as between-subjects factors to clarify the more detailed differences revealed by the primary analysis of variance tests.

Bivariate Pearson correlation coefficients were used to describe the associations between relevant brain data (interhemispheric asymmetry of alpha MI during the third time-window), the cognitive measure (visuospatial covert attention task) and PA or AF variables (MVPA and minutes until exhaustion in the shuttle run test).

Because sex is a variable that needs to be controlled for when exploring the link between PA or AF and cognition in adolescents, the existence of a sex effect in the behavioral performance was tested. Unfortunately, we could not do the same with the brain data because of the low signal to noise ratio, which could compromise the reliability of the potential results.

To test our hypothesis on whether oscillatory dynamics at the alpha band mediates the effect of PA or AF on cognition, a mediator analysis was performed by using MPlus software version 8.0 (Muthén and Muthén, 1998–2017). Before the analysis, we tested whether the assumptions for using the mediator model (normality and significant correlations between the three variables included in each model [independent variable, dependent variable, and moderator]) were met. Combinations with significant correlations of the mediator with independent and dependent variables were also included in the analysis. All possible models where alpha modulatory activity could mediate cognition improvements due to PA or AF levels were tested. The resultant combination was tested with a mediator model using MPlus software using a bootstrap of 1000 samples. Full information of maximum likelihood (FIML), which accounts for missing values at random (MAR) and includes all available data, was used.

In the mediation analysis, the bootstrap confidence interval was used, as it makes no assumption about the shape of the sampling distribution of the indirect effect (*ab*; Hayes and Rockwood, 2017). In bootstrapping, the indirect effect is estimated by randomly resampling cases from the dataset and estimating the model and resulting indirect effect in the bootstrap sample (Hayes and Rockwood, 2017; Preacher and Hayes, 2004). An empirical representation of the sampling distribution of the indirect effect is built by repeating this process 1,000 times. By using various percentiles of the bootstrap distribution, a confidence interval for the *ab* is constructed. Mediation is tested by determining whether the 95% confidence interval contains zero (Fritz and MacKinnon, 2007). If the interval is above or below zero, this supports mediation, and if the interval includes zero, it does not provide evidence of mediation. As recommended by Mackinnon (2008), the bias-corrected and accelerated bootstrap confidence intervals for the indirect effect were estimated using 1,000 bootstrap samples.

CRediT authorship contribution statement

Doris Hernández: Investigation, Formal analysis, Writing - original draft, Visualization. **Erkka Heinilä:** Software, Formal analysis. **Joona Muotka:** Formal analysis. **Ilona Ruotsalainen:** Project administration, Investigation, Writing - review & editing. **Hanna-Maija Lapinkero:** Project administration, Investigation. **Heidi Syväoja:** Funding acquisition, Investigation, Writing - review & editing. **Tuija H. Tammelin:** Funding acquisition, Investigation, Writing - review & editing. **Tiina Parviainen:** Funding acquisition, Conceptualization, Supervision, Methodology, Formal analysis, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brainres.2021.147392.

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II

SPECTRAL SIGNATURES OF CROSS-MODAL ATTENTIONAL CONTROL IN THE ADOLESCENT BRAIN AND THEIR LINK WITH PA AND AF LEVELS

by

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Spectral signatures of cross-modal attentional control in the adolescent brain and their link with physical activity and aerobic fitness levels

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Highlights

- Visual and auditory cortices' engagement differs in cross-modal processing in adolescence.
- Adolescents with responses in the left temporal cortex are older than those without responses.
- Physical activity, but not aerobic fitness, is associated with visual engagement benefits in the adolescent brain.

Abstract

Top–down attentional control seems to increase and suppress the activity of sensory cortices for relevant stimuli and to suppress activity for irrelevant ones. Higher physical activity (PA) and aerobic fitness (AF) levels have been associated with improved attention, but most studies have focused on unimodal tasks (e.g., visual stimuli only). The impact of higher PA or AF levels on the ability of developing brains to focus on certain stimuli while ignoring distractions remains unknown. The aim of this study was to examine the neural processes in visual and auditory sensory cortices during a cross-modal attention–allocation task using magnetoencephalography in 13–16-year-old adolescents (*n* = 51). During continuous and simultaneous visual (15 Hz) and auditory (40 Hz) noise-tagging stimulation, participants attended to either visual or auditory targets appearing on their left or right sides. High and low PA groups were formed based on seven-day accelerometer measurements, and high and low AF groups were determined based on the 20-m shuttle-run test. Steady-state (evoked) responses to the visual stimulus were observed in all the adolescents in the primary visual cortex, but some did not show responses in the primary auditory cortices to the auditory stimulus. The adolescents with auditory-tag-driven signals in the left temporal cortex were older than those who did not show responses. Visual cortices showed enhanced visual-tag-related activity with attention, but there was no cross-modal effect, perhaps due to the developmental effect observed in the temporal areas. The visual-tag-related responses in the occipital cortex were enhanced in the higher-PA group, irrespective of task demands. In summary, sensory cortices are unequally involved in cross-modal attention in the adolescent brain. This involvement seems to be enhanced by attention. Higher PA seems to be associated with a specific visual engagement benefit in the adolescent brain.

Keywords: cross-modal attention, steady-state responses, physical activity, aerobic fitness, visual cortex, auditory cortex

1. Introduction

We are confronted with huge amounts of sensory information in our daily lives. Attention is the cognitive capacity that allows us to focus on the relevant aspects of that information, while the irrelevant content is ignored. Our capacity for attention can be controlled or guided by goals or task requirements, namely top–down cognitive control or executive control (Diamond, 2013). Cognitive control is a key skill needed for any other cognitive competence (so-called central function). Top–down influence seems to enhance the activity in sensory cortices for items that are relevant and suppress activity for items irrelevant to task goals (Gazzaley & Nobre, 2012). Cognitive control develops rather late in children and adolescents (Davidson et al., 2006; Luna, 2009) and is therefore likely to be prone to different endogenous or external influences. Indeed, cognitive control of attention can be modulated by several factors such as emotions in a threatening situation (Dennis & Chen, 2007), other cognitive functions such as working memory resources (Myers et al., 2017), or the environment such as in the case of bilingual language switching in their native language or second language environment (Zhang et al., 2021). The different brain mechanisms and factors that might contribute to enhancing the capacity for attentional control remain to be fully understood.

Usually, unimodal paradigms (i.e., requiring the processing of only one sensory modality) have been used in the study of attention. Unimodal tasks are easy to use in lab settings, but they do not represent real-life situations well, which weakens their validity. A way forward to overcome this limitation would be to use cross-modal attention paradigms, where attention needs to be switched between two modalities (e.g., visual and auditory). Attention often occurs simultaneously through multiple sensory modalities, such as visual, auditory, and/or tactile. While each sensory cortex is designed to process a specific type of information, there seems to be considerable overlap in their representations between them (Karim et al., 2021; Rapp & Hendel, 2003). There is growing evidence suggesting that the processing of stimuli in one modality can be enhanced (Dematte et al., 2006; Zhao et al., 2021) or diminished (Geangu et al., 2021; Robinson et al., 2020) by the simultaneous presentation of stimuli in different modalities. Therefore, besides the well-established cortical areas that are suggested to provide "central attentional control" (i.e., prefrontal areas, cingulate gyrus, and posterior parietal cortex [Lepsien & Nobre, 2006]), it is possible that attentional demands in cross-modal tasks also modulate the sensory processing of information (Lage-Castellanos et al., 2022; van Atteveldt et al., 2014).

Interestingly, it seems that attention is one of the cognitive functions that is also influenced by changes in body physiology, namely by physical activity/exercise. The positive effects of physical activity/exercise on academic achievement (Alvarez-Bueno et al., 2017) have been speculated to stem from effects in cognitive functions, specifically attention/inhibition (Becker et al., 2014; Hillman et al., 2009). Physical exercise generates metabolic changes in the body that have been suggested to give rise to long-term modifications in the brain, both functionally and structurally (Cotman et al., 2007). Physical activity has also been linked to some effects on cognition, especially attention (Singh et al., 2019; Syväoja et al., 2014) and inhibitory control (Alvarez-Bueno et al., 2017; Wu et al., 2022). However, the “full pathway” of how the metabolic changes in the brain induced by higher involvement in regular physical activity can be linked to the observed changes in cognition has not been clearly shown. One confusing factor in the earlier literature is that physical activity (PA) and aerobic fitness (AF) used to be treated as comparable concepts. PA is a measure of the amount of movement done over time (Caspersen et al., 1985), while AF is considered a body condition people have or achieve because of physical activity, and they might well have different associations with brain structure and function.

To better understand the specific associations that either PA or AF levels have with brain structure and function, the same group of subjects needs to be used for both comparisons. Supporting the divergent role of PA vs. AF for the brain, earlier studies have indicated that AF is associated more strongly with brain structural measures than PA (Ruotsalainen et al., 2019, 2020), but PA might influence brain functional properties, which underlie cognition in adolescents (Hernández et al., 2021; Ruotsalainen et al., 2021).

In the domain of attention, we showed that a higher level of PA was associated with stronger modulation of brain oscillations underlying attentional control in adolescents, but AF did not show the same relationship (Hernández et al., 2021). Participants with higher levels of PA showed more reliance on spatial cues (either intentionally or implicitly) than adolescents with lower PA in a selective visual attention task. This association was mediated by the related interhemispheric asymmetry of alpha cortical oscillations. To move closer to real-life task settings, it is important to test whether similar PA-related brain functional modifications underlie cross-modal attentional capacities.

Some behavioral studies testing the associations of PA and AF with multisensory integration have used cross-modal task requirements. They showed that higher levels of acute and regular PA were associated with improvements in multisensory (visual–auditory) integration tasks in children (O’Brien et al., 2021) and older adults (Mahoney et al., 2015; Merriman et al., 2015; O’Brien et al., 2017). Interestingly, this is in line with the idea that at the time of maturational/aging-related modifications in the synaptic connections in the brain, it may be beneficial to engage in physical exercise to improve or maintain functional capacity.

To explore the possible role of PA and AF levels on cross-modal attention at the neural level in adolescents, we used a cross-modal attention paradigm with simultaneous recording of the neuromagnetic activity of the whole brain. The neural steady-state responses (SSRs) in the visual and auditory cortices during a cross-modal attention task provide a useful paradigm for separating the activation engaged in visual and auditory stimulation during attended or unattended conditions. The engagement of sensory cortices in task performance can be reliably followed by using a cross-modal attention paradigm, where each sensory cortex is probed by a continuous signal that contains a specific tag frequency. In the case of an audio–visual cross-modal attention paradigm, simultaneously presented continuous auditory and visual signals are amplitude modulated with a unique frequency. The modality-specific responses can later be extracted from the neural signal and contrasted between attended and unattended conditions. Due to its good spatial resolution, magnetoencephalography (MEG) allows for the extraction of modality-specific functional markers of attention allocation in the visual and auditory cortical areas.

First, we studied the cortical basis, specifically the role of sensory cortices, for task-relevant (attended) vs. task-irrelevant (unattended) information processing during cross-modal attention tasks. Second, we studied the associations between these attention effects at the visual and auditory sensory cortices and the behavioral measures of top–down attentional and inhibitory control. Finally, we explored the link between PA and/or AF levels with sensory cortex engagement, as well as behavioral performance measures, in this cross-modal (visual and auditory) attention task in the adolescent brain. We expected that the ongoing activation of visual and auditory cortices would modulate engagement in a task-specific manner and would reflect the level of attention required by the cross-modal attention task. Based on previous findings (Hernández et al., 2021; Ruotsalainen et al., 2020, 2021) suggesting a stronger role of PA than AF for functional brain measures, we also hypothesized that PA level would specifically show an association with the efficiency of neural engagement of sensory cortices to task-relevant signals (hence, difference between attended vs. unattended condition). To test our hypotheses, the attended and unattended cortical SSRs in each sensory cortex were contrasted between groups with high vs. low PA/AF in typically developed adolescents. An indicator of the efficiency of task-related attention (contrasting cortical entrainment of SSRs during attended vs. unattended conditions in each sensory cortex) was correlated with behavioral performance.

2. Methods

2.1. Participants

Participants were recruited from the sample of a larger study measuring the behavioral associations of AF/regular PA with cognition (Finnish Schools on the Move Program, Joensuu et al., 2018; Syväoja et al., 2019). All participants without neurological disorders, use of medication that influenced the central nervous system, or major medical conditions were invited to participate. Of these, 54 adolescents volunteered to participate in the study. Three participants were excluded from further analysis due to the low quality of the MEG data. All subjects (*n* = 51, 17 males and 34 females) were Finnish native speakers. Adolescents, as well as their legal guardians, signed informed consent forms at the beginning of the study. All subjects had normal or corrected to normal vision and hearing. The study was approved by the Central Finland Healthcare District Ethical Committee to be conducted in accordance with the Declaration of Helsinki.

Handedness was assessed using the Edinburgh Handedness Inventory, and all participants were classified as right-handed. Self-reports about their stage of puberty with the Tanner Scale (Marshall & Tanner 1969; 1970) were used to measure the pubertal development in our sample.

Participants were divided into two groups by their level of AF, estimated using the shuttle-run test (Léger et al., 1988), where the participants ran between two lines at an increasing speed (see Section 2.2 for details). The number of minutes that the participant lasted until exhaustion was taken as the measure of AF, and the third tertile (66%) was used as a cut-off point to divide the sample into high or moderate-to-low (modlow) AF groups once the data were normalized by gender and age.

Participants were also divided into two groups based on their PA levels, estimated by accelerometer data that were recorded during seven consecutive days (see the next paragraph for more details). The third tertile (66%) of moderate-to-vigorous PA (MVPA, see Section 2.2 for details) was used as a cutoff point to divide the sample into high or modlow PA groups. Table 1 summarizes the demographic information and statistical differences for the final sample, divided into two groups based on AF/PA measures.

Table 1. Demographic information (mean ± SD) and statistical differences for the groups based on physical activity and aerobic fitness.

	Physical activity		**Aerobic fitness**	
	high	modlow	high	modlow
Age (months)	171.93 ± 6.7	176.35 ± 12.3	177.39 ± 11.4	173.44 ± 9.7
Pubertal stage	3.09 ± 0.8	3.54 ± 0.9	3.25 ± 0.9	3.60 ± 0.8
Physical activity (MV, min/day)	**77.73 ± 13.4**	**39.34 ± 10.4*****	58.32 ± 21.4	45.50 ± 19.9
Aerobic fitness (20-m shuttle run test, min)	**7.02 ± 1.9**	**5.29 ± 1.9***	**7.70 ± 1.3**	**4.21 ± 1.4*****

* $p < 0.05$

*** $p < 0.001$

SD: standard deviation; modlow: moderate-to-low; MV: moderate-to-vigorous

2.2. PA/AF measures

AF was measured using a maximal shuttle-run test (Leger et al., 1988), a measure widely used to estimate a person's maximum oxygen uptake (VO_2max). The test was performed as described by Nupponen et al. (1999) and specified for the present data collection by Joensuu et al. (2018). Participants were instructed to run between two lines separated by 20 m. An audio signal indicated that the speed should be accelerated. The speeds at the first and second levels were 8.0 and 9.0 km/h, respectively. After the second level, the speed increased by 0.5 km/h per level. The duration of each level was one minute. The participants' level of AF was indicated by the time they spent until they failed to reach the end lines in two consecutive tones.

PA was measured using triaxial accelerometers (ActiGraph, Pensacola, FL, USA; models GT3X + and wGT3X+). Accelerometers were worn by the participants for seven consecutive days. Participants were instructed to wear the accelerometer on their right hips during waking hours, except for water-related activities. The data were collected at a sampling frequency of 60 Hz and were standardly filtered. A valid measurement day consisted of at least 10 h of data. Activity counts were collected in 15-s epochs. Periods of at least 30 min of consecutive zero counts were considered non-wear time. A customized Visual Basic macro for Excel software was used for data reduction. Moderate-to-vigorous physical activity (MVPA) was calculated as a weighted-mean value of MVPA per day ([average MVPA min/day of weekdays × 5 + average MVPA min/day of weekend × 2] / 7).

PA was measured in 45 participants, and AF was measured in 43 participants. For eight participants (one male and seven females), AF values were missing due to absence on the day of the test, while for six participants (three males and three females), PA values were missing due to an insufficient number of valid measurement days (two weekdays and one weekend day). All participants had at least one measure of PA or AF.

2.3. Stimuli and procedure in MEG measurements

The cross-modal attention task (see Fig. 1) was programmed and controlled using PsychoPy software (Peirce et al., 2019). The participants were presented with continuous and simultaneous visual and auditory stimulation to produce frequency-tagged brain activity in each modality. The visual stimulus was varying visual noise, for which the luminance value of each pixel varied randomly between 0 and 255 at a frequency of 15 Hz, serving as the “tagging frequency” for the visual modality (adapted from Parkkonen et al., 2008). The auditory stimulus was a white noise stimulus that was amplitude-modulated at 40 Hz, serving as the “tagging frequency” for the auditory modality (adapted from Lamminmäki et al., 2014). An active task was used to guide the participants’ attention to one modality or another. The visual target was a square of 40 × 40 pixels for which the luminance value of each pixel varied randomly between 0 and 255, which appeared either in the left or right hemifield. The auditory target was a simple tone of 40 Hz delivered to either the left or right ear. The stimulation was divided into 36 separate blocks.

The duration of each block was approximately 36.5 seconds. Both auditory and visual target stimuli were present in each block, and a visual or auditory cue at the beginning of each block indicated which modality should be attended (nine blocks for visual and nine for auditory stimuli in a counterbalanced order). The cue indicating focusing on the visual modality was a white screen shown for a few seconds. The cue indicating focusing on the auditory modality was a tone with a frequency of 440 Hz. Each block contained eight randomly selected stimuli (four visual and four auditory) with interstimulus intervals of 4 s. Left and right stimuli had the same probability of occurrence.

After 18 blocks were administered, there was a break during which the participants could rest for some minutes. When the participants reported being ready to continue, the other 18 blocks were presented. Participants were instructed to report on which side (left or right) the target (visual or auditory stimuli, depending on the block) appeared by using MEG compatible response pads, and to ignore the stimulation modality not signaled at the beginning of each block. The total duration of the task was approximately 22 minutes.

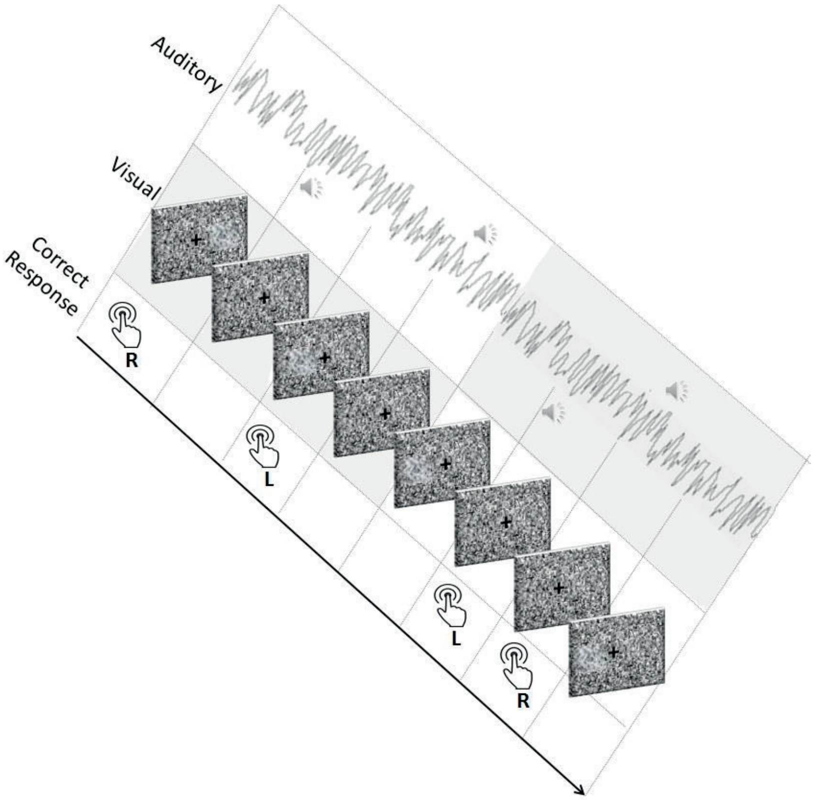

Fig. 1. Schematic illustration of the progress of the cross-modal attention task. Dynamically varying noise at different frequencies for the visual and auditory modalities was embedded with left vs. right hemifield targets in each modality. At the beginning of each block, visual or auditory cues signaled whether attention should be directed toward visual or auditory modalities (attended modality shaded in gray color). Participants needed to indicate whether the target appeared on the left or right by pressing the corresponding button.

To ensure that the participants had learned the instructions correctly, a practice session was performed prior to the real measurements. The practice lasted until the researchers considered that the adolescents had understood the task requirements. The participants understood the task only after each participant correctly identified at least two visual and two auditory targets on each side.

2.4. MEG recordings and analysis

Brain activity related to the cross-modal attention task was recorded using an Elekta Neuromag Triux system (MEGIN Oy, Helsinki, Finland). During the subjects' preparation, five head-position indicator coils were attached to their heads in different locations (three on the frontal part of the head and one behind each ear). Coil's locations were registered using a 3-D digitizer in relation to three anatomical landmarks (nasion and pre-auricular points). At the beginning of the recording, the participants' position with respect to the helmet was measured and continuously tracked during the whole measurement (Uutela et al., 2001). Additional points located all around the head were also digitized. Eye movements were monitored using electro-oculograms (EOG), with two electrodes attached to the external canthi of both eyes for horizontal movements and two electrodes attached above and below the right eye for vertical movements. After the preparation period, the subjects were seated comfortably inside a magnetically shielded room and were instructed to avoid movement of the head and eyes. Two response pads (left and right) were positioned on a table attached to the chair and located over the subject's legs. The task was projected onto a panel located one meter from the subject's eyes.

MEG signals were band-pass filtered to 0.03–330 Hz and sampled at 1,000 Hz. The raw data were pre-processed using Maxfilter^{TM} 2.2 software (MEGIN Oy, Helsinki, Finland). The signal space separation method (SSS) (Taulu et al., 2004) was used to remove the external interference emerging during the measurement. SSS was replaced by the spatiotemporal signal space separation method (tSSS) (Taulu & Simola, 2006) (also included in Maxfilter 2.2 software) for the analysis of data from participants wearing braces or other internal magnetic sources. Possible head movements occurring during the measurement with respect to the initial head position were also corrected using Maxfilter^{TM} 2.2 software. The rest of the pre-processing was performed with Meggie (CIBR, Jyväskylä, Finland; Heinilä & Parviainen, 2022), a graphical user interface for MNE-Python (Gramfort et al., 2014). With the use of this software, epochs contaminated with eye movements (as measured with EOG) or cardiac artifacts (measured by an MEG channel) were removed from the analysis. Additionally, the data were visually inspected to exclude epochs contaminated by other kinds of artifacts.

The rest of the analysis was performed using Matlab (Mathworks Inc., 2020b). Analysis was performed with the brain activity recorded by planar gradiometers. Frequency spectra were computed with Welch's method (Hanning window and FFT size 8,192 samples, 50% overlapping windows, frequency resolution 0.1221 Hz). Three ROIs consisting of 16 gradiometers (eight pairs), each located over the bilateral temporal cortex and the middle occipital cortex, were determined and used to compute the areal averages of the MEG signals. Identification of the visual and auditory frequency-tagged responses was performed based on peak frequency and amplitude. The visual tag-related signal was identified as the highest peak between 14 Hz and 16 Hz in the occipital areal average (peak always at 15.015 Hz). The auditory responses (left and right) were identified as the biggest peak between 39 Hz and 41 Hz in the bilateral temporal areal averages. The amplitude values for each ROI (at 15 Hz for bilateral occipital and at ca. 40 Hz for left and right temporal ROIs) were used for further analysis. The six resulting variables (visually attended and auditory attended in bilateral occipital, left temporal, and right temporal areas) and their individual variations were inspected to identify outliers. Typical values (Z-scores) that exceeded 2.5 standard deviations were considered outliers and were substituted with the closest non-atypical value.

In addition to contrasting the amplitude of the tag-related signals in the attended vs. unattended condition in each cortical ROI, we calculated the attention effects directly for both modalities. In the visual modality, the effect of attention was calculated as the normalized difference between the amplitudes at 15 Hz for the attended and unattended conditions in the occipital ROI. In the auditory modality, the effect of attention was calculated as the normalized difference between the amplitudes at 40 Hz for the attended and unattended conditions in both the left and right temporal ROIs. In both cases, normalization was done by subtracting the unattended value from the attended value and dividing the outcome by the value from the attended condition. The attention effects in each ROI were used for correlation analysis with the behavioral results from the cross-modal attention task.

2.5. Behavioral performance analysis

During the recordings, behavioral responses to the cross-modal attention task (the MEG task) were collected and further analyzed. Responses with a response time of less than 250 ms (less than 2% of the trials) were removed from further analysis for being considered too short to reflect attentional processing. From the remaining valid trials, the accuracy for each modality was calculated as the percentage of correct responses (in auditory attended and visual attended subtasks). Misses (ignored targets in the attended condition) in the visual and auditory subtasks were considered as indexing failed top–down attentional control and interpreted as inattention errors. False alarms (answers to unattended stimuli) in the visual and auditory subtasks were considered an indexing failure of inhibitory control.

Participants' behavioral skills were also measured outside MEG recordings. Speed of attention was assessed with the reaction time (RTI) task, which is a subtest in the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition Ltd., 2006). The RTI task measures reaction time (RT) and, specifically, the speed of response toward an unpredictable target. During the unpredictable condition, a yellow spot appeared in any of the five circles on the screen. Participants were instructed to retain their answers until they saw the yellow spot. Only then should they have touched, as fast as possible, the correct circle on the screen where the target had appeared. The subjects performed rehearsal trials until they understood the task and, afterward, 15 task trials. Scores were based on their RT (ms) and in-movement time (ms).

The participants' inhibitory control skills were assessed using a modified Eriksen Flanker task (Eriksen & Eriksen, 1974). In each trial, the target (central arrow) was flanked by non-target stimuli (surrounding arrows). During the compatible condition, participants needed to report as fast as possible the target's direction (left or right). During the incompatible condition, participants needed to report as fast as possible the opposite direction of the target (left button for the right direction of the target and right button for the left direction of the target). In both conditions, congruent trials (the target pointing in the same direction as the non-targets) and incongruent trials (the target pointing in the opposite direction to the non-targets) were included with the same probability of appearance. Accuracy (in percentages) and RT (in ms) were recorded separately for congruent and incongruent trials for each condition.

In the two additional behavioral tasks (Flanker and RTI), the variables regarding accuracy were removed from the final analysis due to reaching ceiling effects (more than 50% of the participants' accuracy values were near the upper limit of the task range).

The resulting variables used for further analysis per task were as follows: (1) MEG task: Cross-modal attention task (misses for visual and auditory subtasks; false alarms for visual and auditory subtasks); (2) Flanker task (RT for compatible and incompatible conditions; error rates for incongruent trials); and (3) RTI task (RT for five-choice condition, movement time for five-choice condition). All the resulting behavioral variables were inspected to identify outliers. The values (Z scores) that exceeded 2.5 standard deviations were considered outliers (atypical) and were changed to the closest non-atypical values.

2.6. Statistical analysis

Statistical analysis was performed with SPSS (IBM SPSS Statistics for Windows, Version 26.0; IBM Corp., Armonk, NY, USA). To answer our research questions on the effect of attention and possible interaction with PA/AF in the engagement of sensory cortices, we conducted two repeated measures analyses of variance (rANOVA) on the neural engagement of visual and auditory cortices (strength of SSRs), one for each between-subjects factor (PA and AF groups). Within-subjects' factors were ROI (occipital, left temporal, and right temporal) and power of SSRs based on task requirements (attended, unattended). Post-hoc comparisons tested the differences in estimated marginal means with Bonferroni correction for multiple comparisons.

Bivariate Spearman correlation coefficients with false discovery rate (FDR) corrections were used to test the associations between the attention effects (calculated as the normalized difference between attended and unattended conditions) at the visual and auditory sensory cortices and the behavioral performance of the cross-modal attention task (misses and false alarms in the visual and auditory subtasks).

One-way ANOVA was used to test differences between the high vs. low PA and AF groups in the behavioral (MEG) task and additional behavioral tasks.

3. Results

3.1. General spectral results

The existence of neural entrainment in the occipital and (left and right) temporal ROIs was confirmed for each participant. Figure 2 shows the power spectral density (PSD), evidencing a peak at around 40 Hz for the left and right temporal ROIs and at 15 Hz for the occipital ROIs. All participants showed 15-Hz SSRs (peak) in bilateral occipital ROIs (see Fig. 2C). However, only 35/51 participants showed 40-Hz SSRs in the left temporal ROI, and 36/51 participants showed 40-Hz SSRs in the right temporal ROI (see Fig. 2A, B). For comparison, the grand average PSD was plotted for individuals who showed responses, contrasted with those individuals who did not show responses.

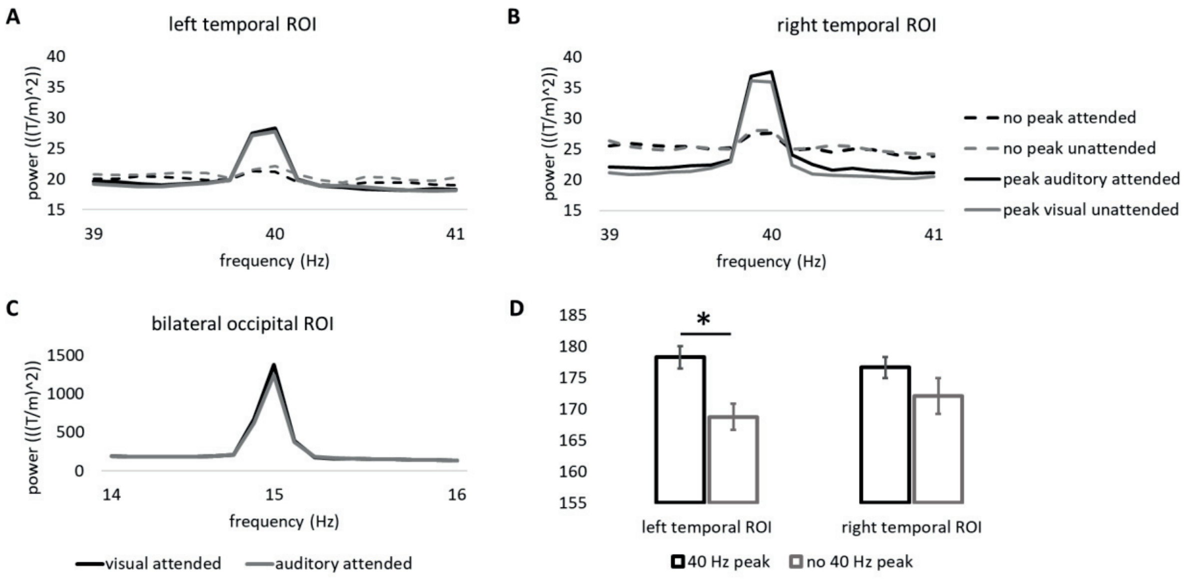

Fig. 2. PSD showing neural engagement in visual and auditory primary sensory cortices for participants with and without tag-related responses. (A) PSD of the participants with (solid lines) and without (dashed lines) the 40-Hz peak for the attended (black) and unattended (gray) conditions in the left temporal area. (B) PSD of the

participants with (solid lines) and without (dashed lines) the 40-Hz peak for the attended (black) and unattended (gray) conditions in the right temporal area. (C) PSD of the participants with the 15-Hz peak for the attended (black line) and unattended (gray line) conditions in the visual modality in the bilateral occipital areas. (D) Bar representation of the differences in age (months) for the participants with (black color) and without (gray color) 40-Hz SSRs in the left and right temporal ROIs.

To investigate whether the likelihood of SSRs at the individual level could indicate a state of maturation, we further tested the existence of age differences between participants with and without responses in both left and right temporal cortices with one-way ANOVA. Participants with 40-Hz SSRs in the left temporal ROI were older (178.28 ± 10.36 months) than participants without 40-Hz SSRs (168.75 ± 8.31 months) ($F_{(1,\ 50)} = 10.44$, $p = 0.002$). However, in the right temporal ROI, the age of participants with 40-Hz SSRs (176.64 ± 10.32) did not significantly differ from the age of participants without 40-Hz SSRs (172.07 ± 11.13, $F_{(1,\ 50)} = 1.98$, $p = 0.165$; see Fig. 2D).

3.2. Effects of attention on sensory cortices and their interaction with PA/AF in the brain

Both rANOVAs (PA and AF as between-subjects factor) showed the main effect of attention (PA as between-subjects factor: $F_{(2,\ 1.000)} = 36.79$, $p < 0.001$; AF as between-subjects factor (: $F_{(1,\ 1.000)} = 29.95$, $p < 0.001$). Both rANOVAs also showed a significant interaction of ROI x attention (PA as between-subjects factor: $F_{(2,\ 1.006)} = 37.29$, $p < 0.001$); AF as between-subjects factor: $F_{(2,\ 1.004)} = 29.51$, $p < 0.001$). Post-hoc comparisons showed that in the occipital ROI, the power of the 15-Hz SSRs was higher in the attended (1470.12 ± 149.03) condition than in the unattended (1338.48 ± 138.61) condition ($p < 0.001$). In the left temporal ROI, no differences were found between the attended (23.96 ± 1.51) and unattended (24.82 ± 1.77) conditions ($p = 0.31$). In the right temporal ROI, no differences were found between the attended (30.68 ± 2.32) and unattended (31.21 ± 2.68) conditions ($p = 0.68$).

Both rANOVAs showed a main effect of ROI (PA as between-subjects factor: $F_{(2,\ 1.000)} = 92.47$, $p < 0.001$; AF as between-subjects factor: $F_{(2,\ 1.000)} = 105.07$, $p < 0.001$) in SSR engagement, indicating stronger amplitudes for occipital than for left and right temporal areas. A between-subjects effect of group was found for PA ($F_{(1,\ 43)} = 4.95$, $p = 0.03$), but not for AF ($p = 0.60$). When PA was used as the between-subjects factor, a significant interaction between ROI × PA was found ($F_{(2,\ 1.000)} = 5.24$, $p = 0.03$). Post-hoc comparisons showed that the strength at the 15-Hz SSRs in the occipital ROI was higher ($p = 0.03$) for the participants in the high PA group (1729.73 ± 238.22) than for the participants in the modlow PA group (1078.87 ± 160.09) (see Fig. 3). No group differences were found for the left ($p = 0.20$) or right (*p* = 0.34) temporal ROIs. When AF was used as a between-subjects factor, no significant interaction of ROI x AF was found (*p* = 0.60).

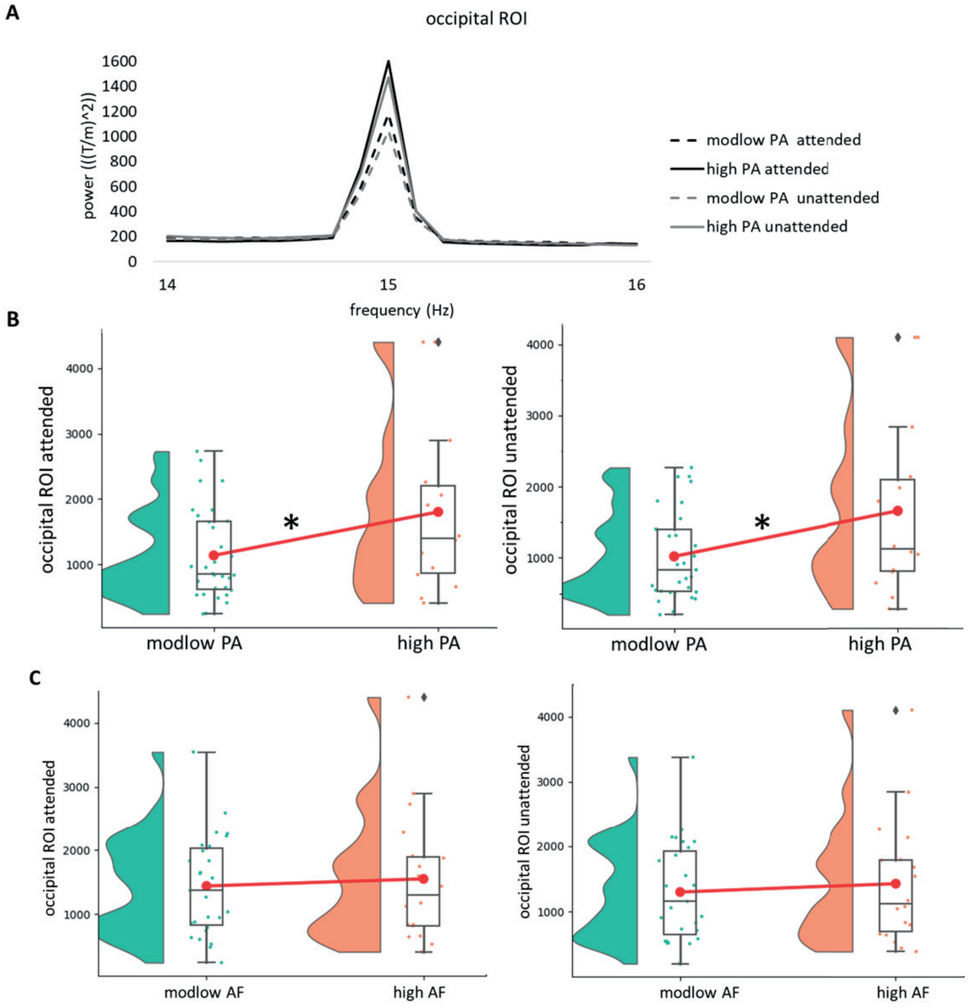

Fig. 3. Modulation of SSRs in the bilateral occipital ROI for the PA groups. (A) Spectra representing the 15 Hz SSRs for the modlow (dashed lines) and high PA (solid lines) groups in the visual attended (black) and auditory attended (gray) conditions. (B) Raincloud plots showing the distributions and differences in the strength of the responses (attended and unattended) in the bilateral occipital ROI for the modlow (green) and high (orange) PA groups. (C) Raincloud plots showing the distributions and differences in the strength of responses (attended and unattended) in the bilateral occipital ROI for the modlow (green) and high (orange) AF groups.

3.3. Associations between brain measures and behavioral performance measures

A higher attention effect (i.e., increased amplitude for attended vs. unattended, calculated as the ratio between attended–unattended/attended) in the left temporal ROI was associated with more false alarms in the visual subtask (rho = 0.32, *p* = 0.02), although when FDR correction was applied, this correlation was not significant (*p* = 0.23). When the sample was divided by groups based on the presence of 40-Hz SSRs in the left temporal ROI, this correlation was significant for the group that did not show SSRs (rho = 0.54, *p* = 0.03) but not for the group that showed SSRs (*p* = 0.36) (see Fig. 4). No other significant correlations were observed for the cross-modal attention task with brain measures (attention effect occipital ROI vs. misses auditory p = 0.66, misses visual p = 0.47, false alarms auditory p = 0.66, false alarms visual p = 0.40; attention effect left temporal ROI vs. misses auditory p = 0.16, misses visual p = 0.99, false alarms auditory p = 0.29; attention effect right temporal ROI vs. misses auditory p = 0.74, misses visual p = 0.54, false alarms auditory p = 0.66, false alarms visual p = 0.36).

No significant correlations were found for RTI and Flanker tasks with brain measures (attention effect occipital ROI vs. RTI RT p = 0.14, RTI movement time p = 0.17, Flanker congruent RT p = 0.72, Flanker incongruent RT p = 0.90, Flanker incongruent false alarms p = 0.48; attention effect left temporal ROI vs. RTI RT p = 0.10, RTI movement time p = 0.49, Flanker congruent RT p = 0.59, Flanker incongruent RT p = 0.80, Flanker incongruent false alarms p = 0.49; attention effect right temporal ROI vs. RTI RT p = 0.06, RTI movement time p = 0.93, Flanker congruent RT p = 0.26, Flanker incongruent RT p = 0.38, Flanker incongruent false alarms p = 0.49).

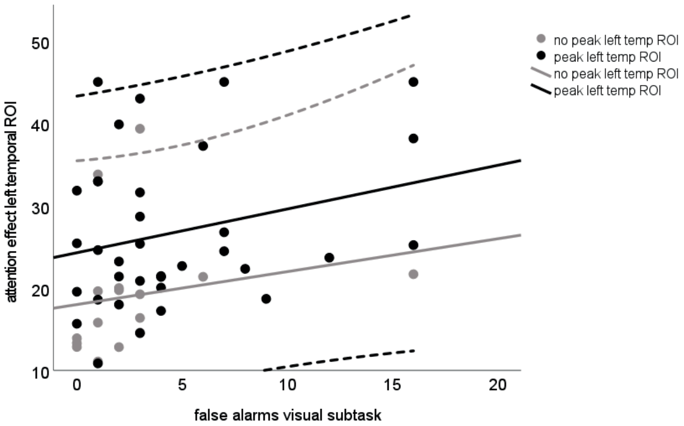

Fig. 4. Association between the attention effect in the left temporal ROI and the number of false alarms in the visual subtask. The black color represents the participants with 40 Hz SSRs in the left temporal ROI. Gray represents the adolescents without 40 Hz SSRs in the left temporal ROI. The solid central lines represent the linear trend line, and the two external dashed lines represent the 95% confidence interval.

3.4. Behavioral performance in cross-modal attention (MEG) task, RTI and Flanker tasks, and their association with physical activity and aerobic fitness.

The behavioral performance in the cross-modal attention task of participants in the high PA group did not differ from that of participants in the modlow PA group (misses visual subtask p = 0.91, misses auditory subtask p = 0.13, false alarms visual subtask p = 0.59, false alarms auditory subtask p = 0.28) (see Fig. 5A). Similar results were obtained for the additional behavioral tasks, RTI (mean five-choice RT p = 0.93, mean five-choice movement time p = 0.52), and Flanker tasks (RT compatible condition p = 0.94, RT incompatible condition p = 0.82, errors incongruent trials p = 0.41) across groups of PA (see Fig. 5B).

The behavioral performance in the cross-modal attention task of participants in the high AF group did not differ from that of participants in the modlow AF group (misses visual subtask p = 0.41, misses auditory subtask p = 0.24, false alarms visual subtask p = 0.79, false alarms auditory subtask p = 0.78) (see Fig. 5A). Similar results were obtained in the RTI test (mean five-choice RT p = 0.43, mean five-choice movement time p = 0.71). Adolescents in the high AF group made fewer errors (4.17 ± 2.12) in the incongruent trials of the Flanker task than those in the modlow AF group (6.72 ± 4.95) (t [1, 34.611] = 2.30, p = 0.03); see Fig. 2A. RTs in the compatible and incompatible conditions of the Flanker task did not differ across the AF groups (RT-compatible p = 0.89, RT-compatible p = 0.57) (see Fig. 5B).

There was a significant correlation between PA and AF (rho = 0.524, p < 0.001; see Fig. 5C).

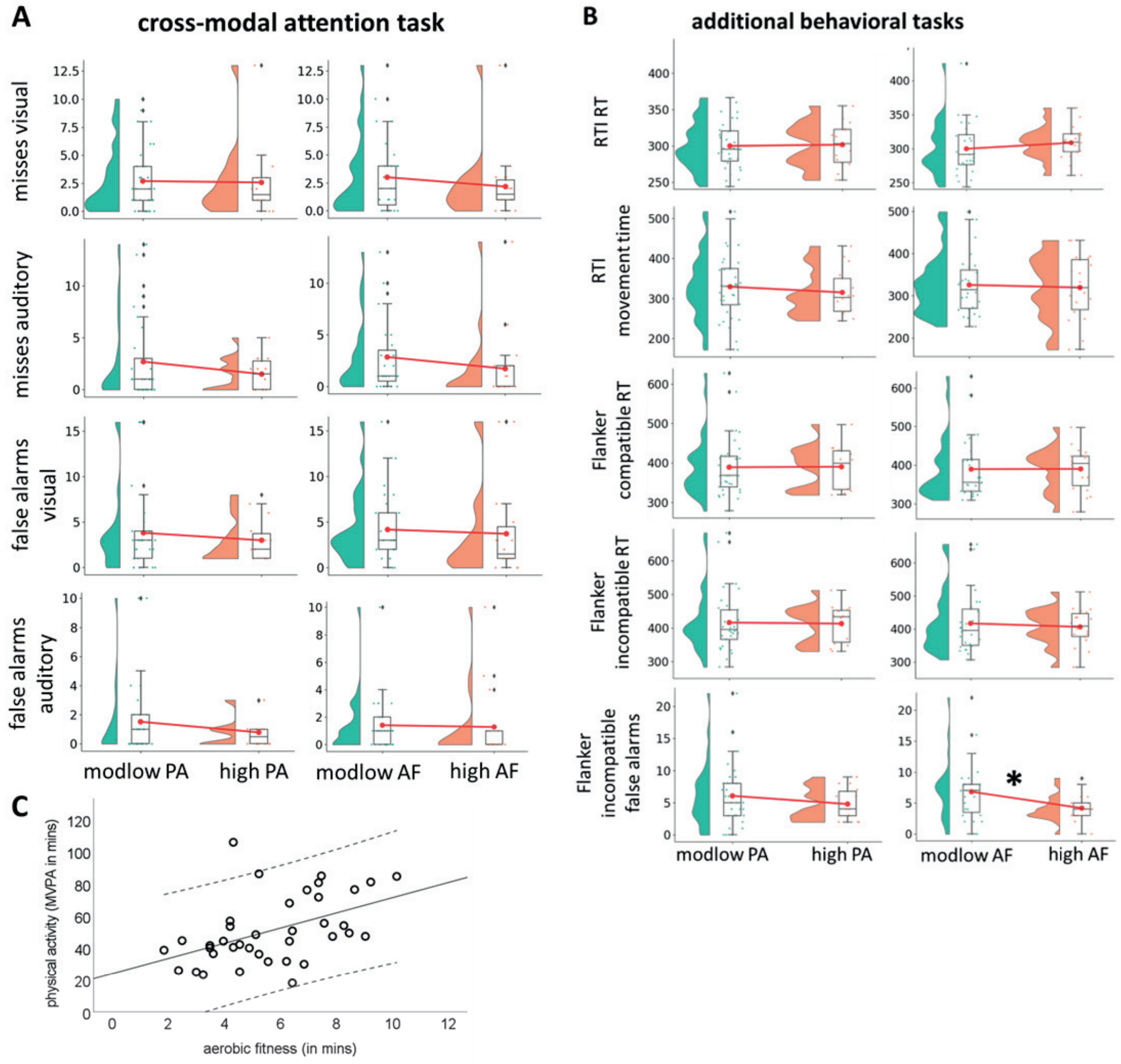

Fig. 5. Raincloud plots showing the distribution of variables for modlow (green) and high (orange) groups of physical activity and aerobic fitness (solid red line connects the groups' mean value) in (A) the cross-modal attention task and (B) the additional behavioral tasks (RTI and Flanker). (C) Scatterplot showing the association between physical activity and aerobic fitness.

3. Discussion

We explored the neuromagnetic indicators of cross-modal attention, namely frequency-tagged SSRs in visual (occipital) and auditory (temporal) cortices during audiovisual task performance, and their link with behavioral performance. Second, we clarified that the level of PA, but not AF, is associated with the brain basis of cross-modal attention, especially in visual areas, in typically developing adolescents.

Contrary to our expectations, we found divergent engagement of visual versus auditory sensory cortices during the cross-modal attention task. Bilateral occipital cortices showed clear SSRs for visual stimulation at 15 Hz in all participants. This general engagement of visual areas suggests that the primary visual cortical areas follow dynamic changes in sensory stimulation with the presented temporal frequency. However, the expected SSRs for auditory stimulation at 40 Hz in the bilateral temporal cortices were only observed in 35 out of 51 participants for the left temporal cortex, and 37 participants in the right temporal cortex.

The less systematic response of auditory areas could be explained by the developmental stage of the adolescent brain. During brain development, synaptic pruning (an experience-dependent loss of synaptic connections) occurs at separate times in different cortical areas. The visual cortex has been suggested to reach maturity during childhood by about 7 years of age (Huttenlocher, 1990), while the auditory cortices mature later during adolescence (Gogtay et al., 2004; Ponton et al., 2000) by about 12 years of age (Huttenlocher & Dabholkar, 1997). Indeed, earlier neuromagnetic studies clearly show immature auditory responses in children at the age of 7 years (Parviainen et al., 2019) that persist at least until the age of 13 (Sussman et al., 2008; van Bijnen et al., 2022). For the cortical circuits to be able to generate SSRs for external acoustic information, especially at the high frequency range of 40 Hz, the synaptic connections need to have reached the needed temporal precision. It is exactly the temporal processing properties that have been suggested to demonstrate a protracted developmental trajectory in cortical circuits (Ponton et al., 2000).

Another possible explanation is that the different tagging frequencies between the cortices (15 Hz for occipital ROI and 40 Hz for left and right temporal ROIs) could underlie these effects. Indeed, it may be that cortical engagement is more pronounced at lower frequencies in any sensory processing (Albouy et al., 2022; Otero et al., 2022). Particularly in auditory areas, the importance of lower frequencies for language processing in the brain has been highlighted (Haegens & Golumbic, 2018), specifically for processing words (Kolozsvári et al., 2021) and sentences (Kolozsvári et al., 2021; Molinaro & Lizarazu, 2018). However, the frequencies used in the current study were chosen based on earlier literature that showed an increase in the entrainment of oscillatory activity in the human auditory cortex triggered by about 40 Hz stimulation frequencies (Lamminmäki et al., 2014; Ross et al., 2005), as in the case of auditory steady-state responses (ASSRs). Even though ASSRs are known to be generated in the brainstem by using animal models, the generators of 40-Hz ASSRs have also been localized in the primary auditory cortex (Li et al., 2018).

In line with the maturational hypothesis, the adolescents with 40 Hz SSRs were older than those who did not show SSRs, but only for the left temporal area. Our findings are in line with those studies suggesting that the maturation of the right hemisphere auditory cortex might precede the maturation of the left hemisphere (Edgar et al., 2016; Herdman, 2011; Ono et al., 2020; Parviainen et al., 2011, 2019). More studies with longitudinal follow-up measurements would be needed to reveal possible maturational differences in engagement across hemispheres in adolescents. In general, our findings provide evidence of a developmental effect on the already known asymmetric organization of the auditory primary cortices at the level of sensory processing (Hernández et al., 2022; Parviainen et al., 2005; Poeppel, 2003).

We expected that SSRs in both visual and auditory sensory cortices would show increased amplitude in the attended condition compared to the unattended condition. This hypothesis was confirmed for the visual cortex, where the effect of attention was observed. In this regard, the results are in line with those studies showing attention-induced changes in sensory cortices in unimodal (Fiebelkorn et al., 2018) and multimodal tasks (Plöchl et al., 2022). In sum, our findings partially support the idea of modulation of neural activity in the sensory cortices exerted by top–down attentional control, as that modulation was only found for the visual cortex in our study.

No effect of attention was observed in the auditory cortices of the SSRs. This can be linked with the developmental effects found in auditory cortices (i.e., the 40 Hz stimulation did not lead to observable responses in ca. 30% of the subjects). If the cortical circuits fail to show SSRs with the (bottom–up) representation of high-frequency acoustic modulation in the sound, it may also be that the connections with the areas providing top–down modulation to the sensory circuits are not yet fully in function. Perhaps the expected attentional modulation can be seen later in the lifespan. Future studies comparing adolescents and adults are needed to disentangle the developmental influence from other neuronal mechanisms that might be underlying the cross-modal induced changes in sensory cortices.

As expected, based on earlier literature, only PA, but not AF, showed an association with cortical processes during the cross-modal attention task. Our results showed higher neural engagement of bilateral occipital cortices during attended and unattended conditions for participants with high PA than for those with moderate to low PA, while no effects for AF were found. One possible contributing factor is that the above-mentioned maturational effects are involved in the increased neural engagement of bilateral occipital cortices for adolescents with higher levels of PA. During adolescence, synaptic connections that do not participate in behaviorally meaningful functional networks and neural coding are pruned. This is especially true for occipital areas (Rauschecker & Marler, 1987). It may be that individuals with higher levels of PA are more exposed to visual material in general, and thus, visual areas are more strongly functionally coupled with sensory input during the first two decades of life. This, however, seems to be a purely sensory/automatic process, as there was no difference between the attended and unattended conditions. In general, our results support the idea that PA might be related to functional changes in the brains of adolescents more strongly than AF, as suggested by previous studies from our research group (Hernández et al., 2021; Ruotsalainen et al., 2020; 2021). More developmental studies approaching this issue comparing adolescents with children and adults are needed to confirm the contribution of maturational changes to this effect.

Higher-fit participants showed fewer errors in the additional Flanker task. This finding supports previous studies reporting better inhibitory skills associated with higher AF in adolescents (Huang et al., 2015; Shigeta et al., 2021; Stroth et al., 2009; Westfall et al., 2018). However, AF (as well as errors in the Flanker task) were not linked to the neuromagnetic signatures of cross-modal attention in the visual and auditory cortices. This suggests that AF might be involved with inhibitory control processes in adolescents, but this effect does not seem to be related to their brain processing of cross-modal attention in sensory cortices to the extent that we probed it with the SSRs.

PA was not associated with any behavioral effect with measures from Flanker, RTI, or cross-modal tasks. Adolescents with moderate to low PA performed the cross-modal attention task equally well as did the participants with high PA. This suggests that group differences in bilateral occipital activation patterns are not linked with performance differences, but rather reflect enhanced reactivity of the visual cortex during cross-modal task. Previously, structural changes in occipital regions have been associated with high PA levels, especially in older populations (Dawe et al., 2021; Erickson et al., 2010) and midlife adults (Tarumi et al., 2021). These changes were related to either increased cortical thickness due to gray matter volume (Erickson et al., 2010) or white matter properties (Dawe et al., 2021). Functional studies have also found links between higher PA levels and occipital brain areas related to pre-attentional processing (Pesonen et al., 2019) in adults. In adolescents and children, this kind of finding is rarer. However, in line with our results, Ludyga et al. (2018) reported a PA-related amplitude increase of visual P300 in parieto-occipital regions for 12- to 15-year-old adolescents. This amplitude increase was associated with better inhibitory control skills. Altogether, these findings suggest that PA might start influencing occipital areas around adolescence and that these changes remain during adulthood.

Thus, we provide evidence suggesting that visual and auditory cortices, as they have been studied here (by using SSRs in visual and auditory cortices), do not necessarily operate in a mutually exclusive way. This means that they may be part of a common neural network involved in cross-modal attention that, due to maturational reasons, seems to be led by bilateral occipital areas in adolescence.

As a controversial result, the 40-Hz SSRs in the left temporal ROI were linked with the cognitive performance level in the cross-modal attention task. Interestingly, this association was specifically driven by the participants without a recognizable peak at the 40 Hz frequency band. The increased baseline amplitude at 40 Hz (but not the SSRs) correlates positively with the failure to inhibit unattended stimuli (i.e., increment of false alarm responses; in other words, responses to stimuli in the unattended [visual] stream). This suggests that the level of engagement of the left auditory cortex during audiovisual cross-modal attention tasks might reflect the efficiency of inhibitory mechanisms in the brain. It might be that the lack of maturation in the left temporal cortex SSRs at 40 Hz during adolescence is behaviorally expressed as deficient inhibitory control during cross-modal processing, but this was not tested in our study. These results are consistent with previous studies showing a link between increased activation in temporal areas and high load inhibitory processing in typically developed adolescents (McAlonan et al., 2009; Woolley et al., 2008). Perhaps, at the early stages of development, a compensatory strategy of the still immature left temporal cortex to deal with cross-modal attention is to increase 40 Hz responses to relevant (auditory) information at the expense of not successfully inhibiting responses to irrelevant stimuli.

A possible neurophysiological explanation for this effect could be related to the role of gamma band oscillations in the brain. Despite the 40 Hz SSRs in our study, gamma band oscillations and 40 Hz ASSRs are distinct phenomena; they might share some properties because they all oscillate at a similar frequency. Cognitive gamma oscillations (40–120 Hz) have been previously identified as supporting attention/inhibitory processing (Fries et al., 2001), and inhibitory GABAergic interneurons seem to be part of their key circuitry (Wang & Buzsáki, 1996). Indeed, auditory 40 Hz ASSRs/gamma oscillations have been associated with inhibitory control abnormalities in disorders such as autism (Seymour et al., 2020) and schizophrenia (Metzner et al., 2022). This also suggests that the auditory 40 Hz SSRs in the left temporal cortex in the present study, and its age effects in adolescents, could reflect the developmental stage of inhibitory processes in these cortical networks.

There are some limitations to this study. First, due to the lack of 40 Hz SSRs observed for a group of adolescents in the left and right temporal areas, the effect of attention was not equally reliably approachable for the auditory than for the visual domain. Another limitation of this study is related to the relatively small sample size. When treated as one group, the associations of PA/AF levels were approachable with the present sample, but the individual variance in the strength of the responses weakened further comparisons. With a larger sample, it would have been possible to split the sample based on the presence of SSRs in the auditory cortices.

In future studies, it would be important to investigate these processes in a small age range while ensuring a large enough sample size, given the strong variation of the auditory cortex signaling shown within our sample. Finally, we focused our methodological approach on attentional effects at the sensory level of processing in the visual and auditory cortices, which is a new approach, especially in developmental brain stages. Naturally, other brain areas are known to contribute to the top–down control of cross-modal attention, and our results must be seen as complementing the existing literature that so far has contributed more to uncovering the role of the "higher level" association areas.

5. Conclusion

The brain network underlying audiovisual cross-modal attention processing in the adolescent brain shows unequal involvement of visual and auditory sensory cortices. All of the adolescents showed the expected tag-driven signals in the primary visual cortex, while primary auditory cortices showed partial involvement in the cross-modal task, with more immature involvement of the left auditory cortex. These findings suggest that there are developmental differences between auditory and visual sensory cortices in temporal precision during adolescence. The visual sensory cortex showed enhanced tag-related activity with attention. The steady-state responses in the occipital cortex were enhanced in adolescents with higher physical activity but not with higher aerobic fitness, irrespective of task demands.

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III

ATTENTIONAL MODULATION OF INTERHEMISPHERIC (A)SYMMETRY IN CHILDREN WITH DLD

by

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Attentional modulation of interhemispheric (a)symmetry in children with developmental language disorder

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The nature of auditory processing problems in children with developmental language disorder (DLD) is still poorly understood. Much research has been devoted to determining the extent to which DLD is associated with general auditory versus language-specific dysfunction. However, less emphasis has been given to the role of different task conditions in these dysfunctions. We explored whether children with DLD demonstrate atypical interhemispheric asymmetry during the auditory processing of speech and non-speech sounds and whether this interhemispheric balance is modulated by attention. Magnetoencephalography was used to record auditory evoked fields in 18 children (9 to 10 years old), 9 with DLD and 9 with language typical development, during active or passive listening to speech and non-speech sounds. A linear mixed model analysis revealed a bilateral effect of attention in both groups. Participants with DLD demonstrated atypical interhemispheric asymmetry, specifically in the later (185–600 ms) time window but only during the passive listening condition. During the active task, the DLD group did not differ from the typically developed children in terms of hemispheric balance of activation. Our results support the idea of an altered interhemispheric balance in passive auditory response properties in DLD. We further suggest that an active task condition, or top–down attention, can help to regain leftward lateralization, particularly in a later stage of activation. Our study highlights the highly dynamic and interhemispheric nature of auditory processing, which may contribute to the variability in reports of auditory language processing deficits in DLD.

Developmental language disorder (DLD), also known as specific language impairment (SLI), has been linked to the abnormal processing of auditory information[1,2]. The main deficit in children with DLD has been suggested to be related to the processing of speech sounds[3–6], with influences at different levels such as vowels[5], syllables[3,4,6], words[7,8], and longer narratives[9,10]. However, others claim that impairment arises at a more basic level of auditory processing, such as the processing of non-speech sounds[11] or all kinds of sounds, including speech and non-speech, which would expand the deficit to a more generalized auditory processing impairment[2]. Given the dynamically varying and task-specific nature of auditory language processing, it is likely that multiple factors, which may vary across experiments, contribute to the specific expression of the deficit at the neural level. In the current study, instead of approaching the deficit in DLD based on the types of sounds, we take a more general approach, focusing on the role of attention (namely, active versus passive task conditions) to the auditory processing of different (speech, non-speech) sound types.

In the study of auditory and language perception in DLD, little consideration has been devoted to the so-called central functions that may modulate language perception and higher cognitive processes during language acquisition and that can have a major impact on the appearance of the functional deficit. Indeed, some evidence suggests that attention and its selectivity may be involved in the perceptual problems observed in DLD[5,9,10,12]. With the use of event-related potentials (ERPs), children with DLD have shown a different pattern of activation

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during attention toward speech sounds compared with typically developing children. When they were asked to attend to tones embedded in speech sounds, both groups of children showed an equivalent level of involuntary attention to the speech sounds in the active task condition. However, in the passive task, children with DLD allocated delayed and less emphasized neural resources to processing speech sounds than did typically developing children[5]. Using behavioral tasks, Niemi et al.[9] showed difficulties in modifying the ear advantage through focused attention to the left ear in children with DLD. Even though attention has shown a modulatory influence on auditory processing in children with DLD, its contribution is still not clear, as some studies have also found no effects of attention in children with DLD[13,14].

The earlier results also reveal another important source of discrepancy in previous studies of DLD, namely the question about the hemispheric lateralization of the deficit. The literature has shown diverse patterns of impaired hemispheric involvement in auditory processing in children with DLD. The deficit is suggested to be left dominant[8,9,11,15–17], right dominant[18,19], or bilateral[20]. Thus, it is unclear to what extent the problems in DLD should be approached as hemisphere-specific or interhemispheric interaction problems. Based on the complexity of language processing, a correct balance between the brain hemispheres, more than the specific involvement of each of them, is likely to be required[21], and there may also be developmental differences in lateralization in typical development[22,23]. Structurally, atypical interhemispheric asymmetry has been observed in children with DLD. Using structural MRI, Plante et al.[24] showed larger right than left perisylvian areas in children with DLD than in control children.

Approaching the main deficit of DLD as interhemispheric asymmetry rather than a specific hemispheric problem could help to better understand the behavioral manifestations of the disorder. Indeed, by considering both brain hemispheres and their interaction, some discrepancies in the literature regarding hemispheric deficits in DLD could be explained [see, e.g.,[8,9,11,15–20]].

Due to the interhemispheric connections and functional lateralization of auditory perception, the question of interhemispheric asymmetry and its attentional modulation is closely intertwined with the nature of auditory processing deficit. In general, leftward lateralization is typically reported for processing speech sounds[25,26], but as stated above, the picture is less clear with respect to the lateralization of the deficit in DLD, both for speech and for nonspeech sounds. Importantly, regarding the nature of the auditory processing deficit, it is not clear what the role of attention (i.e., active versus passive listening conditions) is in abnormal lateralization or interhemispheric balance in DLD. To clarify this in the present study, we tested the effect of attentional modulation on the auditory processing of speech and non-speech sounds in the two hemispheres of children with DLD.

With time-sensitive imaging techniques, such as electroencephalography (EEG) and magnetoencephalography (MEG), it is possible to track the sequence of neural processing from early sensory cortices to later perceptual activation and beyond. MEG also allows us to reliably examine the interhemispheric balance in activation. Some studies have reported abnormal auditory activation in DLD during the first stages of auditory processing, occurring within 100 ms post-stimulation[2,4,5,10,18], generally identified as reflecting essentially sensory processing of information. In this time window, the deficits described are related to delayed[18] and weaker[2,4,5,10] auditory perceptual processing in children with DLD. Other studies allocate the deficit to a later time window, 200–600 ms after stimulus presentation[6,8,11,17,27], comprising pre-lexical, phonological, and lexical-semantic processes. The deficits identified in this later time window were related to the short-term maintenance of linguistic activation that underlies spoken word recognition[6,8], frequency discrimination[11,27], or the passive processing of tones[17]. The later time window is of particular interest for typical and atypical development because it shows a response type to purely passive stimulation, which is unique to the child's brain[22,28–30]. It is noteworthy that most of the aforementioned studies were performed with EEG, where the fairly low spatial resolution does not allow us to reliably approach the hemispheric difference in activation[2,5,6,10,11,27], or with MRI/fMRI, with limited temporal resolution for following the different stages of processing[15,20,24].

Here, we used MEG to clarify interhemispheric asymmetry during attended and non-attended auditory processing in DLD across time. The neural activation derived from the MEG recordings in the left and right hemispheres of children with DLD and typically developing children was compared during the active and passive listening of speech and non-speech sounds. Specifically, we tested the hypothesis that (1) children with DLD show abnormal interhemispheric asymmetry during the auditory processing of speech and non-speech sounds. Furthermore, based on earlier findings[5,9,10,12], we hypothesized that (2) attention modulates interhemispheric asymmetry. We anticipated that the difference in the (interhemispheric) pattern of activation between children with DLD and children with typical language development would be smaller during active listening than during passive listening [cf.[5]]. To provide a novel understanding of the neural basis of auditory processing deficits in DLD, we further tested 3) whether the presumed abnormal interhemispheric asymmetry and the attentional modulatory effect occurred during early sensory processing or later stages of auditory processing. Particularly interesting in this respect is the prolonged activation evidenced predominantly in children[22].

Results

First time window (90–180 ms).

Modeling. The model was built to test our research questions concerning (1) the abnormal interhemispheric (a)symmetry in DLD during the auditory processing of speech and nonspeech sounds and (2) the attentional modulation of this interhemispheric (a)symmetry. Using the backward method, all pairwise interactions were tested with a likelihood ratio test after testing that the three-wise interaction was not needed ($chi^2 = 0.006$, $p = 0.936$, $df = 1$). In the reference model, we had a random intercept and a random slope for the hemisphere. The pairwise interaction group * attention was first removed ($chi^2 = 0.097$, $p = 0.755$, $df = 1$). The interactions between hemisphere * attention ($chi^2 = 4.319$, $p = 0.038$, $df = 1$) and hemisphere * group ($chi^2 = 1.474$, $p = 0.225$, $df = 1$)

	Est. value (SE)	*df*	t-value	*p*-value
Intercept	35.83 (7.60)	188	4.713	0.000
Hemisphere[a]	− 6.92 (6.21)	188	− 1.115	0.266
Group[b]	2.12 (10.62)	16	0.199	0.845
Attention[c]	9.58 (2.45)	188	3.917	0.000
Hemisphere × group	9.89 (8.47)	188	1.168	0.244
Hemisphere × attention	7.18 (3.45)	188	2.080	0.039

Table 1. Fixed effects of the model for the first time window: estimated difference (standard error [SE]), degrees of freedom, t-value, and *p*-value. [a]Baseline for hemisphere: right, [b]baseline for group: DLD, and [c] baseline for attention: passive.

	Lower	Est	Upper
Intercept	15.22	21.93	31.60
Hemisphere	10.85	16.40	24.79
Cor (int,hemi)	− 0.81	− 0.53	− 0.04
Residual	11.135	12.37	13.75

Table 2. Approximate 95% confidence intervals for the standard deviations of a random intercept, a random slope for hemisphere, and the correlation between the random intercept and the random slope, and for the standard deviation of a residual.

were then tested separately and included in the model to directly test our research questions. Besides a random intercept, a random slope for the hemisphere ($\text{chi}^2 = 38.154$, $p < 0.001$, $df = 2$) and their covariance ($\text{chi}^2 = 4.360$, $p = 0.037$, $df = 1$) were required.

We also tested whether a random slope for attention with covariances was needed in the random part (besides the hemisphere) ($\text{chi}^2 = 3.240$, $p = 0.357$, $df = 3$), and we did not include it in the final model. As we had a random slope for the hemisphere, no different variances for groups ($\text{chi}^2 = 0.447$, $p = 0.504$, $df = 1$) were needed. We additionally pre-studied the models, including sound and a random intercept, and found that the pairwise interactions could be removed from the model in the following order: sound type * group ($\text{chi}^2 = 0.078$, $p = 0.962$, $df = 2$), group * attention ($\text{chi}^2 = 0.077$, $p = 0.782$, $df = 1$), sound type * attention ($\text{chi}^2 = 0.944$, $p = 0.624$, $df = 2$), and hemisphere * sound type ($\text{chi}^2 = 1.295$, $p = 0.523$, $df = 2$), leaving only sound in the model ($\text{chi}^2 = 22.127$, $p < 0.001$, $df = 2$). To have more power to study a random part and our pre-specified research questions, we continued modeling without sound and resulted with a model with the main effects group, attention, and hemisphere, two interactions (hemisphere * attention and hemisphere * group), and a random part with the intercept, the slope for the hemisphere, and their covariance.

The final model obtained from the mixed-model approach for the first time window (90–180 ms) is presented in Table 1, showing the estimates, standard errors, their ratios (t-values), and their *p*-values. The estimates and confidence intervals for the standard deviations of the random intercept, the random slope along with their correlation, and the residual are shown in Table 2. All the assumptions (linearity, variance structure, and normality) for the model were sufficiently fulfilled.

Interhemispheric asymmetry and effects of attention. Figure 1A shows the individual amplitude values for the first time window separately for the TD group and the DLD group. The average amplitude values of responses from the data per group and condition for the first time window are depicted in Fig. 1B. The results outlined above are based on the fitted random intercept model, and they describe the differences in the raw average values well (Fig. 1B).

Attention showed a clear main effect, with generally higher amplitudes in the active condition than in the passive condition (ED = 9.58, SE = 2.45, t(188) = 3.917, $p = 0.001$). There was also a significant interaction between attention and hemisphere (ED = 7.18, SE = 3.45, t(188) = 2.080, $p = 0.039$).

Consequently, we further tested hemispheric balance under different attentional conditions, separately in the DLD and TD groups, to directly evaluate our hypothesis on the divergent hemispheric asymmetry of activation in DLD versus TD. In the TD group, the amplitude in the left versus right hemispheres did not differ in the passive (ED = 2.97, SE = 6.30; t(188) = 0.471, $p = 0.638$) or active conditions (ED = 10.15, SE = 6.21; t(188) = 1.635, $p = 0.104$). In the DLD group, there was also no difference between the left and right hemispheres, whether in the passive (ED = − 6.92, SE = 6.21; t(188) = − 1.115, $p = 0.266$) or active conditions (ED = 0.25, SE = 6.21; t(188) = 0.041 $p = 0.967$). Figure 3 shows the grand average waveforms for both groups (children with DLD and TD) for the left and right hemispheres during the active and passive conditions.

Second time window (185–600 ms).

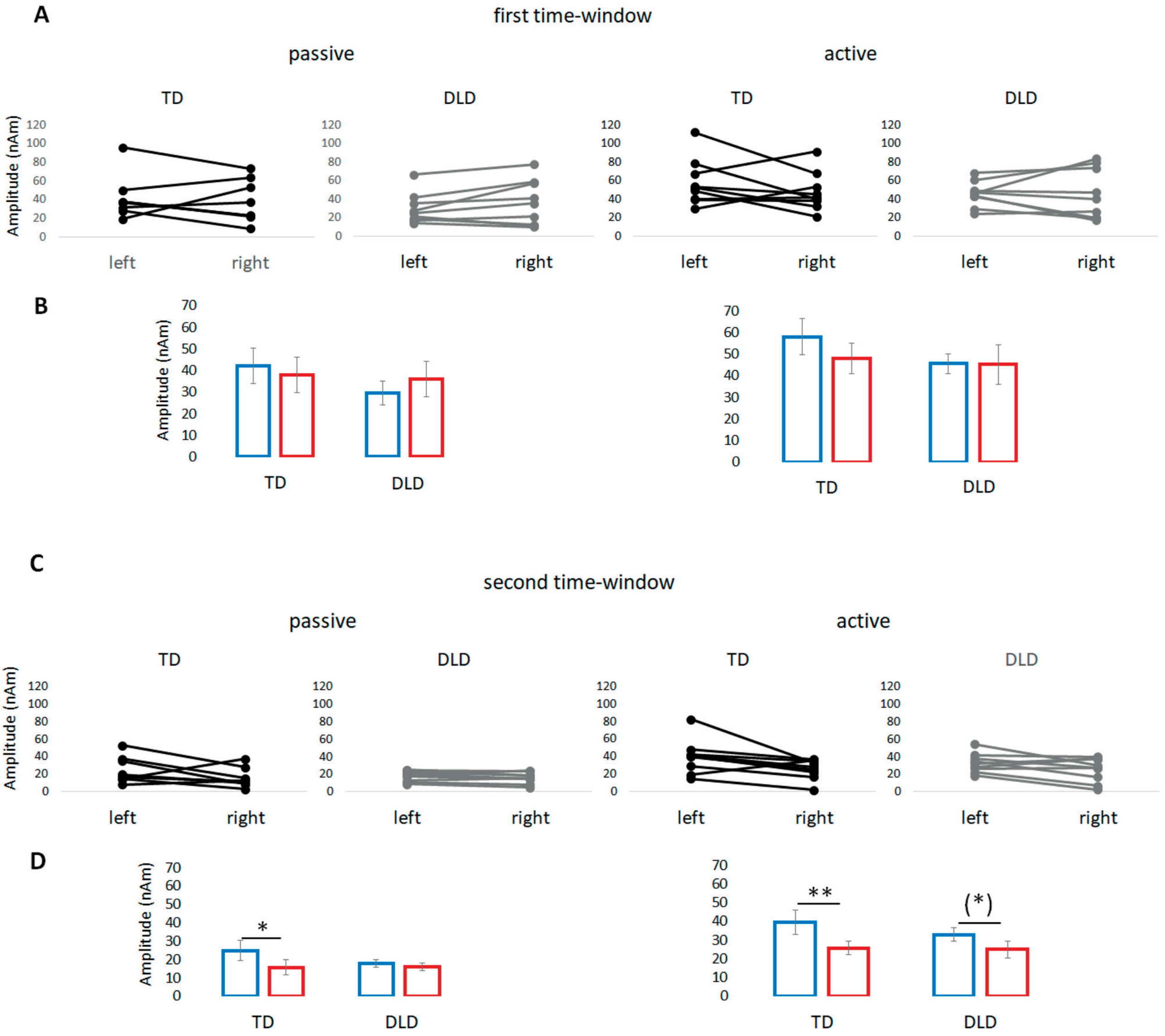

Figure 1. Main results in both time windows. (**A**) Comparison of the individual strength of activation between the left and right hemispheres in response to passive and active conditions in the first time window for children with DLD (gray) and children with TD (black). (**B**) Comparison of the averaged activation between the left (blue) and right (red) hemispheres in response to active and passive conditions in the first time window for children with DLD and children with TD. (**C**) Comparison of the individual strengths of activation between the left and right hemispheres in response to passive and active conditions in the second time window for children with DLD (gray) and children with TD (black). (**D**) Comparison of the averaged activation between the left (blue) and right (red) hemispheres in response to active and passive conditions in the second time window for children with DLD and children with TD. Whiskers represent the standard error of the mean (SEM).

Modeling. The model was built to test the possible group differences in hemispheric (a)symmetry during auditory processing of speech and non-speech sounds, as well as the attentional modulation of this interhemispheric asymmetry. As in the first time window, all the pairwise interactions were tested with a likelihood ratio test after testing and removing the three-wise interactions ($chi^2 = 0.103$, $p = 0.748$, $df = 1$). In the reference model, we had a random intercept and random slopes for the hemisphere and attention and their covariances. The covariates and their interactions to be tested were group, hemisphere, and attention. The pairwise interaction group * attention was removed ($chi^2 = 0.002$, $p = 0.968$, $df = 1$). At the next level, the pairwise interaction group * hemisphere was kept in the model ($chi^2 = 1.510$, $p = 0.219$, $df = 1$) to test our specific research questions. Moreover, we checked the random part of the previous model such that different variances for the groups were added. Besides attention, the hemisphere was required ($chi^2 = 25.274$, $p < 0.001$, $df = 3$), and besides the hemisphere, attention was needed ($chi^2 = 17.614$, $p < 0.001$, $df = 3$). The interaction between hemisphere and attention was not required ($chi^2 = 1.732$, $p = 0.279$, $df = 1$). Moreover, the off-diagonal terms in the covariance matrix for a random part were tested and not needed ($chi^2 = 2.392$, $p = 0.495$, $df = 3$). The difference in the variances in groups

	Est. value (SE)	*df*	t-value	*p*-value
Intercept	15.23 (3.09)	188	4.928	0.000
Hemisphere[a]	2.17 (4.01)	188	0.541	0.589
Group[b]	0.54 (4.32)	16	0.124	0.903
Attention[c]	9.87 (2.70)	188	3.662	0.000
Hemisphere × group	6.64 (5.42)	188	1.226	0.222
Hemisphere × attention	5.37 (2.48)	188	2.167	0.032

Table 3. Fixed effects of the model for the second time window: estimate (SE), degrees of freedom, t-value, and *p*-value. [a]Baseline for hemisphere: right, [b]baseline for group: DLD, and [c]baseline for attention: passive.

	Lower	Est	Upper
Intercept	5.11	7.97	12.43
Attention	5.49	8.61	13.50
Hemisphere	6.64	10.21	15.70
Residual	7.96	8.90	9.95

Table 4. Approximate 95% confidence intervals for the standard deviation of a random intercept, random slopes for attention and hemisphere, and a residual.

was not significant for the mixed model with two interaction terms at the population level and the random intercept and slopes for hemisphere and attention at the individual level ($chi^2 = 0.866$, $p = 0.352$, $df = 1$).

We also tested the pairwise interactions for sound and attention, hemisphere, and group with a random intercept: attention * group ($chi^2 = 0.003$, $p = 0.955$, $df = 1$), attention * sound type ($chi^2 = 1.071$, $p = 0.585$, $df = 2$), hemisphere * sound type ($chi^2 = 1.976$, $p = 0.374$, $df = 2$), and group * sound type ($chi^2 = 3.110$, $p = 0.211$, $df = 2$). After testing the pairwise interactions, we also tested the significance of the sound type ($chi^2 = 28.685$, $p < 0.001$, $df = 2$). Due to statistical power, the sound type was not included in the more precise model selection because it did not show any interactions.

The final model for the second time window (185–600 ms) is presented in Table 3, which shows the estimates, standard errors, their ratios (t-values), and their *p*-values. The estimates and confidence intervals for the standard deviations of the random intercept and random slopes, along with the residual, are shown in Table 4. All the assumptions for the model were fulfilled sufficiently well.

Interhemispheric asymmetry and effects of attention. Attention showed a clear effect with higher amplitudes in the active than passive listening condition (ED = 9.87, SE = 2.70, t(188) = 3.662, $p < 0.001$). There was also a significant interaction between attention and hemisphere (ED = 5.37, SE = 2.48, t(188) = 2.167, $p = 0.032$). We tested hemispheric balance in the two attentional conditions, keeping the groups separate to directly test our research questions. The results revealed different patterns of interhemispheric asymmetry in the two groups (see Fig. 1). For the TD group, both attentional conditions indicated a higher mean amplitude in the left hemisphere than in the right hemisphere (passive condition: ED = 8.81, SE = 4.08; t(188) = 2.160, $p = 0.032$; active condition: ED = 14.18, SE = 4.01; t(188) = 3.539, $p < 0.001$). For the DLD group, there was no difference in amplitude between hemispheres in the passive condition (ED = 2.17, SE = 4.01; t(188) = 0.541, $p = 0.589$). However, in the active condition, the left hemisphere showed a higher mean amplitude than the right hemisphere, with a *p*-value close to significance (ED = 7.54, SE = 4.01; t(188) = 1.882, $p = 0.061$).

Figure 1C shows the individual amplitude values for the second time window. The average amplitude values of the responses from the data per group and condition for the second time window are depicted in Fig. 1D. The results outlined above are based on the fitted random intercept model, and they describe the differences in the raw average values well (Fig. 1D).

Discussion

In this study, the hemispheric balance of auditory activation during active and passive listening was compared between groups of children with DLD and children with typical language development. Speech and non-speech sounds were used as stimuli, but sound type did not show any significant interaction with other factors, so it was not included in the final model. We followed the activation elicited by sounds in two separate time windows: early activation before 200 ms and long-lasting activation after 200 ms. Attention showed a clear effect on auditory activation over the entire time window and all sound types alike for both groups. The results revealed an atypical interhemispheric asymmetry of activation for the participants with DLD during passive listening, confirming our first hypothesis. More specifically, in the later prolonged activation, the DLD group demonstrated a relative decrease in the left compared to the right supratemporal area, independent of sound type. Interestingly, in the active condition, the interhemispheric balance shifted toward the direction observed in the TD group.

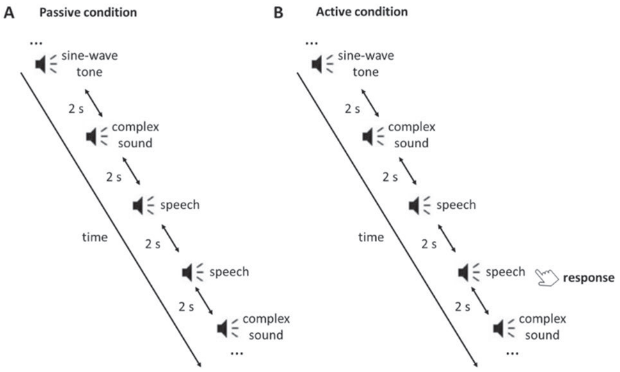

Figure 2. Schematic representation of passive and active conditions in the listening task for the passive (**A**) and active (**B**) conditions.

This finding supports our second hypothesis that attention modulates interhemispheric asymmetry in DLD. An active mode of perception thus seems to play a significant role in the neural-level dysfunctions observed in DLD.

The atypical hemispheric balance observed in the DLD group during passive listening was significant in the later sustained activation. The relative involvement of the left hemisphere was smaller in the DLD group, with symmetrical activation of the left and right hemispheres, than in the TD group, with stronger responses in the left than in the right hemisphere. The atypical pattern of interhemispheric asymmetry during auditory processing could be interpreted as reflecting a hard-coded dysfunction in the neural basis of auditory perceptual processing in DLD, as was evident in the passive condition. This result is in line with previous studies showing differences between children with DLD and typically developed children in passive listening tasks[2,5,17].

The hemispheric balance in the first time window did not indicate clear group differences. Shafer et al. (2007)[5] reported that children with DLD showed a leftward asymmetry of the scalp distribution of the maximum of the peak studied (negative difference, Nd, in the latency range of N1) during passive listening to speech sounds, while typically developed children showed a rightward asymmetry. The inconsistency between their study and our results could, in principle, arise from differences in methods. Shafer et al.[5] used EEG and topographic information of a fronto-central positivity and inferior-posterior negativity, generally considered to be consistent with sources in the left and right auditory cortices. We analyzed the MEG-derived waveforms of sources determined to be located directly in the auditory cortices.

However, it is also likely that the specific developmental stage has a major impact on activation at around 100 ms in children, and the age range of Shafer's sample is less restricted (8 to 10 years old) than the children included in our study (9 to 10 years old). Two overlapping activation types are reported in this time window, with strong interindividual variability in their appearance[22]. More specifically, an early peak denoted as P1/P1m shows clearly delayed latencies in children and appears at around 100 ms[31], overlapping in latency with the emerging N1/N1m response especially in younger individuals. Even in adults, these two responses show divergent hemispheric distributions[26]. Thus, depending on whether they are analyzed separately or not in a study, the results may vary greatly, which complicates the interpretations of activation (and comparison across studies) within this time window (90–180 ms) in children. In this case, a restricted age range (like in the case of our study), is desirable given how rapidly auditory encoding neural activity changes throughout childhood.

In the later stage of activation, at around 250 ms, the children with DLD showed a divergent hemispheric balance of activation compared to the children with TD when the stimuli were passively presented. The DLD group demonstrated bilaterally symmetric activation, while the TD group showed stronger responses in the left hemisphere compared to the right hemisphere. Therefore, the obligatory response properties of the auditory cortices seem to deviate in language-impaired children. The passive response properties in this time window were also altered in our earlier study of DLD[17], but the pattern was somewhat different. Although we used almost the same sample as van Bijnen et al. (2019)[17], in contrast to our results, they reported an increase, rather than a decrease, in left-hemisphere activation in children with DLD. This suggests that not only the cortical auditory response properties but also the cortical appearance of language-related dysfunctions are highly sensitive to differences in stimulation conditions (monaurally presented simple tones in van Bijnen et al. (2019)[17] versus binaurally presented mixture of speech, complex sounds, and tones in the current study).

It is also noteworthy that the activation evoked by all sound types in the present study (see Fig. 3) continues well after 600 ms, both for active and passive conditions, whereas the responses to the passive presentation of only simple sine-wave tones in van Bijnen et al. (2019; see Fig. 2 in that article) return to the baseline clearly earlier, by 500 ms at the latest. This salient difference in the persistence of activation in the perisylvian area, especially for the active condition, speaks to strongly contextual (and predictive) processing of sensory information.

Consequently, the expression of the deficit in DLD at the neural level may diverge across dissimilar experiments due to the dynamically varying and task-specific nature of auditory processing. This can be significantly pronounced when language processing is also involved. Indeed, the current results, together with van Bijnen et al. (2019)[17], are compatible with the idea that the functional division of labor between the hemispheres in automatic responsivity to auditory (language) information may be compromised in DLD, with an atypical balance toward the left hemisphere in processing nonlinguistic (sinewave) stimuli and an atypical balance toward

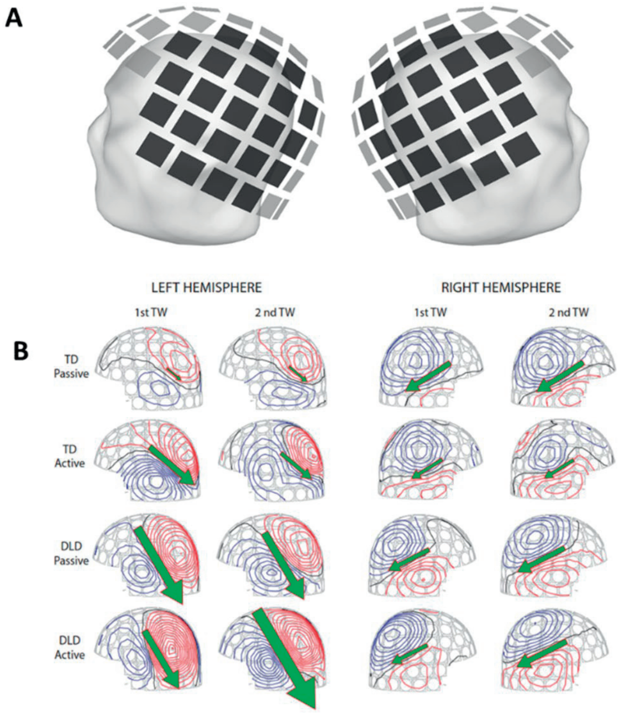

Figure 3. (**A**) Plot representing the 22 sensors included in the ECD model for each hemisphere. (**B**) Field distribution and ECD orientation (arrows) in the left and right hemispheres in both time windows of one subject in the TD group (above) and one subject in the DLD group (below) in active and passive conditions for speech sound.

the right hemisphere in processing linguistic stimuli. It is important to note, however, that we did not see an interaction between sound type (speech versus nonspeech) and group in the present study; therefore, there is no support for language specificity of the auditory deficit in DLD. Nonetheless, given the above reasoning on the sensitivity of auditory processing to various factors, this may also reflect the strong influence of context on processing (presence of speech stimuli).

Previous investigations examining the potential brain structures implicated in DLD have also reported differential patterns of atypical brain organization involving both brain hemispheres[20,24,32,33]. Badcock et al. (2012)[20] used MRI and fMRI to compare gray matter volumes and brain activation during the auditory processing of speech. The authors reported reduced gray matter volumes in the right caudate nucleus and increased gray matter volumes in the left inferior frontal cortex in children with DLD. Reduced gray matter volumes in children with DLD were also found bilaterally in the superior temporal cortex. Furthermore, during speech processing, they reported bilateral underactivation of the superior temporal cortex for children with DLD. Although the left and right hemispheres did not seem to differ in the latter area, the study demonstrated bilateral effects in children with DLD, in contrast to the one-hemisphere deficit often reported.

Similarly, Plante et al.[24] showed atypical structural rightward perisylvian asymmetries (the right area was larger than expected, whereas the left area was of expected size) in children with DLD, with a link to their language performance. To date, several structural brain asymmetries have been reported; however, their associations with functional measures and behavioral manifestations of the disorder need to be better elucidated. More studies are needed to clarify the specific functional and behavioral consequences of a structural atypical hemispheric balance in DLD. Notably, however, these existing results align with our findings on the importance of focusing on interhemispheric balance rather than hemisphere-specific effects in understanding auditory deficits in DLD.

Besides reflecting abnormal (structural) wiring, the deviations in interhemispheric balance in DLD during passive listening could also indicate bias in automatic preference for speech versus other sound types. It has been reported that children with typical development pay attention to speech even when they are instructed to ignore it[5,34]. Thus, the pattern showing a leftward bias for all sounds in children with typical development[2], also reported by the present study, could result from automatically emerging increased responsiveness of cortical processing toward speech sounds as a result of a developmental interplay between inherited and environmental factors. Consequently, the diminished responsiveness of the auditory cortex of children with DLD to speech could reflect atypical structural properties associated with the disorder, compromising the typical speech tuning of the cortex during development. Indeed, some studies suggest that developmental disorders of language, such as dyslexia, are associated with genetically regulated dysfunction at an early stage of development (migration)[35], although this view has also been critically evaluated[36].

The plausible diminished responsiveness of the auditory cortices in DLD might be suggesting that what is elicited by this type of task in children with DLD is a very delicate and small difference. This can be supported by the nature of the behavioral manifestations of DLD disorder. In the literature (and in our study) the auditory deficit in children with DLD are usually small ones. This is an important notion and might be suggesting paying attention to the small signs of developmental disorders to avoid leaving important signs unnoticed.

Interestingly, during active auditory processing, a deviant interhemispheric balance in children with DLD was not evident. Further, the DLD group did not differ from the TD group in the distribution of activation across the hemispheres and showed similar leftward lateralization. Thus, our results indicate that while passive response properties of the auditory cortices evidence an atypical left–right balance of activation, active engagement in the processing of the incoming auditory stream of sounds can modify the altered hemispheric balance.

In this study, we focused on the interhemispheric balance of brain activation during auditory processing, rather than on the specific involvement of each hemisphere in active and passive conditions. Such different approaches may explain the varying results regarding hemisphere-specific results in DLD. Our results are in line with the claims of Badcock et al.[20] and Plante et al.[24], who showed bilateral structural abnormalities in DLD. At the same time, our results do not disagree with studies showing either specifically left-hemisphere[8,9,11,15–17] or right-hemisphere[18,19] deficits in participants with DLD. Our present findings suggest that, for a better understanding of the deficit, it may be beneficial to focus on the relative involvement of both hemispheres. In general, when comparing conditions, relational measures across hemispheres may also be more reliable and informative due to the many (even structural) factors that may influence amplitude measures [cf.[37]].

The differential pattern of hemispheric balance across groups emerged at the later time window, which has earlier been indicated in the processing of phonetic and phonological information[38–40], and thus may also relate here to a rather abstract level of analysis. However, processing any auditory information, including passively presented simple tones, seems to evoke activation in this later time window, specifically in children[17,41]. Thus, it seems likely that both the automatic responsivity of the auditory cortex (the so-called obligatory, exogenous elements) and active task-driven processes (endogenous elements) can underlie the deviant pattern of activity in DLD.

Most studies attributed the effect of attention in participants with DLD to an underlying deficit in attentional processes[5,9,10,12]. Our results suggest that active task conditions may mitigate the atypical (passive) response characteristics to sounds in DLD and do not imply a causal role for attentional deficit, at least when simple passive versus active task conditions are considered. Indeed, it is important to note that the active condition in the present study was merely required to process the identity of the incoming sound signal to identify immediate repetitions. This was done to avoid sound type-specific effects. Naturally, we cannot infer that our results are related to more complex attentional demands and their possible role in the behavioral-level outcomes of DLD.

As attention seems to modulate the involvement of the brain hemispheres during the auditory processing of sounds in children with DLD, this might open a new line of rehabilitation for DLD disorder. Strengthening general factors (like attention) that support the processing of sounds rather than the dysfunctional part (language processing), may prove valuable in dealing with children with DLD. Thus, using approaches that contribute to improving attentional capacity during developmental stages of life, could enhance the auditory processing, and furthermore, the behavioral manifestations of the disorder.

Previous studies typically point to deficits in children with DLD either in the first[2,4,5,10] or the second[6,8,27] time window of auditory processing, as they were defined in the present study. Based on our findings, it seems relevant to acknowledge the dynamically varying nature of neuronal (auditory) processing for unbiased findings. For this, the temporal and spatial sensitivity of MEG offers an ideal means to approach even individual-level dynamics in the auditory cortex. However, the interindividual variance needs to be acknowledged when interpreting auditory-evoked responses. In our study, the large within-group variation in the amplitude values, especially in the first time window (cf. Figure 4A), aligns with earlier findings that allude to a strong impact of individual variability in the basic auditory response properties in children[22,42,43] and adults[44]. This complicates the interpretation of group differences for this early time window. Indeed, particularly with small sample sizes, it is important to acknowledge the individual-level data, along with statistical testing.

It is however important to consider the limitations of the present study, mostly due to the small sample size. We believe this limitation to be mostly accounted for using linear mixed model approach, which allowed us to overcome the likely high differences in group variances. Although the use of this statistical test legitimates to spread our results to the similar population of children with DLD, our results should be interpreted with caution and suggest the need for replication with bigger sample sizes.

Conclusion

This study showed an atypical interhemispheric balance during the auditory processing of speech and non-speech sounds in children with DLD, thus reinforcing the idea of approaching the deficit in DLD from the perspective of interhemispheric communication rather than as a hemisphere-specific dysfunction. Our findings further indicate the significance of the task requirements (active versus passive condition) for the appearance of auditory processing deficits in DLD. The abnormal interhemispheric asymmetry during passive auditory processing in children with DLD shifted toward the more typical left-lateralized response pattern in the active task condition. Further research is needed to elucidate the role of the task and the stimulation environment in determining hemisphere-specific engagement in different auditory conditions. Importantly, however, our findings evidence that the neural manifestation of top–down control seems to influence atypical brain reactivity to auditory input in DLD.

Methods

Participants. The participants of this study were selected from the cohort of a study aiming to investigate the etiology, linguistic development, and prognosis of DLD in the City of Vantaa, Finland[45,46]. As a result, all participants from the special education district of one municipality in the city of Vantaa were invited to participate in the study. Altogether, 18 participants volunteered. Nine of them were children with DLD (9–10 years old, six

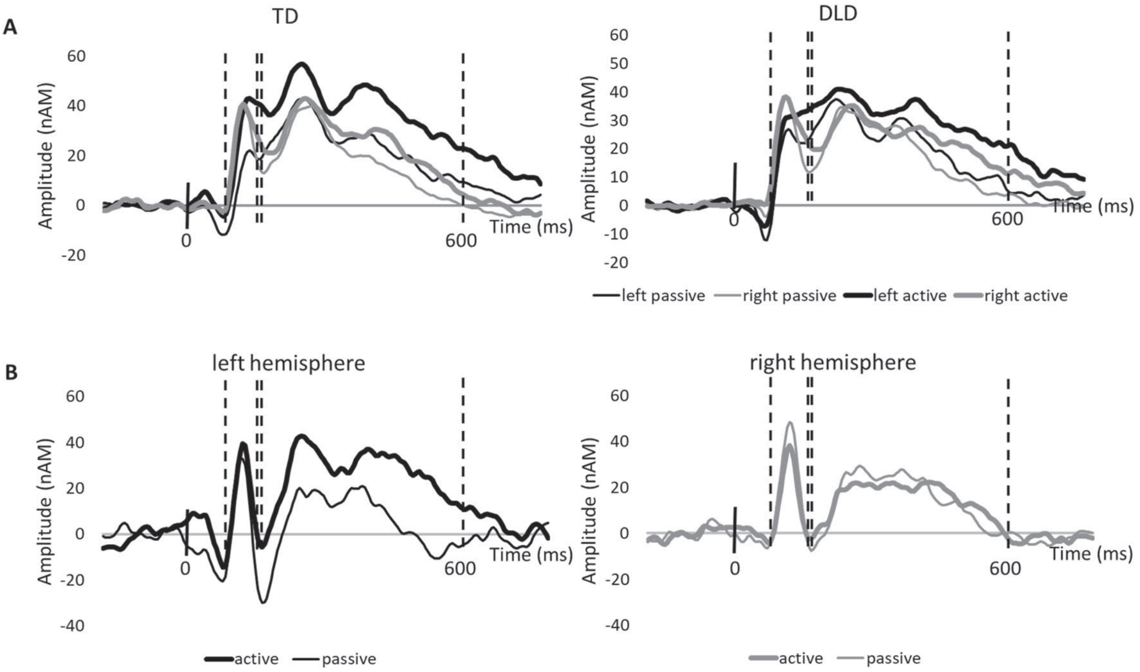

Figure 4. Time-course of activation of the dipolar sources. The early (90–180 ms) and late (185–600 ms) time windows are depicted with dashed vertical lines. (**A**) Grand-average waveforms of the ECDs located in the left (black lines) and right (gray lines) hemispheres separately for the TD and DLD groups. Responses to active and passive listening conditions averaged over the three sound types are plotted in thick and thin lines, respectively. (**B**) Average waveforms for active and passive listening in the left and right hemispheres of one TD participant.

males). The other nine were children with typically developed (TD) language skills matched for gender and age. All participants were reported to be right-handed and native Finnish speakers. Individual hearing thresholds were tested to be within normal limits. The children with DLD had been diagnosed at Helsinki University Central Hospital prior to school entry.

Before starting the measurements, all the participants and/or their legal guardians signed an informed consent form in agreement with the prior approval of the Ethics Committee of the Hospital District of Helsinki and Uusimaa. The study was conducted according to good research practices, in line with legal requirements, and the guidelines of the Finnish National Board on Research Integrity.

Stimuli and procedure. The stimuli were synthetic speech and non-speech sounds [cf.[47]]. Speech stimuli were utterances of the Finnish vowel /a/, created using a Klatt synthesizer[48] for Macintosh (Sensimetrics, Cambridge, MA, USA). During the speech sound, the fundamental frequency (F0) decreased steadily from 118 to 90 Hz, resembling a normal male voice. The formant frequencies F1, F2, and F3 were 700, 1130, and 2500 Hz, respectively, and the formant bandwidths were 90 Hz for F1, 100 Hz for F2, and 60 Hz for F3. The vowel envelope had 15-ms fade-in and fade-out periods.

Non-speech stimuli were complex and simple sounds constructed based on speech sounds using Sound Edit (Macromedia, San Francisco, CA, USA). A complex sound was formed by a combination of three sine-wave tones, with the frequencies taken from the formants of a speech sound. A simple non-speech sound was a sine-wave tone composed of the same value of F2 frequency as in a speech sound. The envelope of a non-speech sound was similar to a speech sound. Each stimulus had a duration of 150 ms.

During the measurement, the participants were seated comfortably inside a sound treated magnetically shielded room and were instructed to avoid excessive movement of the head and eyes. Stimuli were controlled with the program Presentation (Neurobehavioral Systems Inc., San Francisco, CA) running on a PC and were delivered binaurally through plastic tubes and earpieces at 65 dB (SPL) above hearing level. The participants were instructed to listen to the stimuli in passive and active modes in separate sessions. During the passive condition (Fig. 2A), they watched silent cartoons and were instructed to ignore the sounds. During the active condition (Fig. 2B), the participants were asked to press a button, with their dominant hand, when they heard the same stimulus twice in a consecutive manner.

During the MEG recordings, stimuli were randomly delivered to the participants until a maximum of 100 stimuli per category was reached. The stimulation was stopped before when participants gave signs of being tired. In the active condition, a similar average number of stimuli were presented for DLD group (speech: 50,66; complex sound: 49; sine-wave tone: 47,11) and TD group (speech: 52,22; complex sound: 51,88; sine-wave tone: 52,22). In the passive condition, also a similar average of stimuli was delivered to the participants with DLD (speech: 63,88; complex sound: 58,12; sine-wave tone: 60,12) and controls (speech: 64,12; complex sound: 56,37; sine-wave tone: 58,5) in each category. Stimuli were separated by an interstimulus interval of two seconds. The total duration of the task was approximately 20 min per condition.

MEG recordings and analysis. Magnetic brain responses were recorded using a 306-channel Elekta Neuromag™ Neuromagnetometer (Elekta Oy, Helsinki, Finland). Prior to the measurements, four head-position indicator coils were attached to the participants' scalps, and the coil locations were determined with a 3-D digitizer in relation to three anatomical landmarks (nasion and pre-auricular points). At the beginning of each measurement, an electric current was applied to the coils to enable the measurement of their locations with respect to the MEG helmet. The head position within the helmet was tracked continuously throughout all measurements. Horizontal and vertical eye movements were also monitored using EEG electrodes (electro-oculogram [EOG] and electrocardiogram [ECG]).

The MEG signals were band-pass filtered at 0.1–200 Hz and sampled at 600 Hz. The raw data were preprocessed using the spatiotemporal signal space separation method (tSSS)[49], included in Maxfilter software (Elekta, Neuromag), to compensate for possible head movements and to remove external interference emerging during the measurement. The initial head position was used as the destination head position for movement compensation. Epochs contaminated by eye movements (as measured with EOG) were rejected, and artifacts caused by cardiac signals (identified with the use of ECG) were suppressed by averaging the MEG signal with respect to heartbeat, using Principal Component Analysis (PCA) to identify the strongest components and removing the component(s) that captured the electromagnetic artifact produced by heartbeat[50]. Additionally, the data were visually inspected to exclude epochs contaminated by the remaining artifacts. The number of artifact-contaminated epochs eliminated were less than 2,5% of the total number of epochs. The artifact-free epochs were then averaged for intervals from 200 ms before stimulus onset (pre-stimulus baseline) until 800 ms after it.

The active neural populations were modeled using Equivalent Current Dipoles (ECD;[51]) with XFit software (Elekta Oy, Helsinki, Finland). Structural MR images were not available for these children. Therefore, an average sphere model for a group of children of the same age group who have been previously was used. For each participant, the center of the sphere was adjusted to the center of the head in the coordinates $x = -2.0$, $y = 3.4$, $z = 44.4$. The modeling was done by first selecting standard groups of 22 gradiometer sensors, one covering the left temporal area and the other covering the right temporal area (see Fig. 3A). The selected 22 sensors were the same across participants.

Separately in each hemisphere, an ECD was fitted within the time window of the robust evoked response at around 100 ms, based on the maximally dipolar topography and the maximum magnetic field strength. The well-known posterior-inferior current flow of the N100 response was confirmed in all the source models. Several candidate ECDs were fitted, and the one with the highest goodness-of-fit value was selected. The resulting ECDs were compared in terms of numeric goodness-of-fit value but also based on a visual match between measured and estimated signals. The goodness-of-fit value was the priority in choosing the final model, and in all cases, this also appeared to be the ECD with a good match between the measured and the estimated field pattern. Goodness-of-fit values were reasonable across all individuals (left hemisphere: on average 90.07, with minimum of 80 and maximum of 97.2; right hemisphere: on average 92.62, with minimum of 79.3 and maximum of 98).

Source modeling was performed separately for each participant. For every participant, ECDs were first determined separately for each stimulus. The locations and orientations of two ECDs, one for each hemisphere, were kept fixed, while their amplitudes were allowed to vary to best explain the signals recorded by all sensors over the entire averaging interval. The magnetic field topographies across sound types (speech, complex, and sine-wave tone) were comparable, and the same ECD successfully explained the activation for all sound types (see Fig. 4). Likewise, for most of the subjects, the active and passive conditions exhibited highly comparable spatial characteristics of activation. Therefore, to enable a reliable comparison of the strength of activation across experimental conditions, we used the same ECDs (identified in the active condition for speech, separately for left and right hemisphere) to extract the time course of activation for both active and passive conditions. As exemplified by Fig. 3B, the ECDs determined in the active condition accounted well the responses recorded in passive condition in both time-windows. For the early time-window the two-dipole model accounted for 73% of the measured data in the active condition, and 62% of the measured data in the passive condition. For the late time-window the two-dipole model accounted for 71% of the data in the active and 68% of the data in the passive condition.

Two-time windows of interest were defined for further analysis. These time windows were based on previous literature, where transient auditory activation was systematically observed within the initial 200 ms after the stimulus onset (N100m, [cf.[52,53]]), and a longer-lasting, developmentally specific response was reported after 200 ms (N250m, [cf.[22,29,47]]). The grand average time courses of the present data demonstrate robust and long-lasting activation throughout the first 600 ms (see Fig. 4A), and these activation components are clear, especially in the single-subject waveform (Fig. 4B). To quantify the strength of these activation components, the first time window was set to 90–180 ms (N100m) after the stimulus onset, and the maximum amplitude during this time window was collected separately for each stimulus type. The second time window comprised sustained brain activation at 185–600 ms after the stimulus onset. The mean amplitude value within this period was used in the analysis and collected separately for each stimulus type.

Statistical analysis. When comparing a well-defined and homogeneous group (such as a clinical group) with a more randomly selected control group, as is the case here, the control group's data may show more variability. Therefore, to consider both the correlations of repeated measurements within subjects and the possibly different variances between the DLD and TD groups, a linear mixed model (LMM) was used[54,55]. The LMM does not assume equal variances between groups; consequently, it is more suitable to handle the differences in variance between our groups.

Moreover, the 2 × 2 × 3 structure of the values for the brain responses in each individual (two attentional conditions per hemisphere for three types of sounds) leads to the non-independence of multiple responses from the same participant. In the LMM, this is considered using an individual-specific random intercept and slope (or slopes), leading to different baseline values and different regression coefficients at the individual level, respectively.

For the first time window, the test variable was the maximum amplitude within the time interval 90–180 ms post stimulation. For the second time window, the test variable was the mean amplitude from the interval of 185–600 ms after the stimulus onset. One model for each time window was computed using the fixed effects of hemisphere, sound type, group, attentional condition, and the random effects of a participant. The two variables (maximum and mean amplitude) were thus modeled separately by the candidate covariates: hemisphere (right/left, right as baseline), sound type (speech/sine/complex, speech as baseline), group (DLD/TD, DLD as baseline), and attention (passive/active, passive as baseline). The dependence between measurements can be modeled by adding a random intercept and slopes to a classical linear regression model at the individual level.

When selecting the model, a backward method was used, starting from the model with main effects, all pairwise interactions, a three-wise interaction, and a final random part. By testing the fixed effects, each model was estimated with a maximum likelihood (ML) method, and when testing random effects, a restricted maximum likelihood (REML) method was used. In the selection process, the nested models were compared using a likelihood ratio test and its *p*-value based on a chi^2 distribution. Moreover, the difference in the variances of the group (DLD/TD) was tested using a likelihood ratio test. The final model was calculated using an REML to reduce the biases of estimated variances in the model. Besides the estimated fixed coefficients, a set of contrasts was formulated based on the final model and tested using t-tests or z-tests.

The validity of each mixed model was evaluated using graphical tools. The linearity was evaluated with a scatterplot of fitted values versus responses and a scatterplot of fitted values versus residuals separately for each group. The normality of the random effects and residuals was checked separately for each group using qq plots. The analysis was performed using R[56] package nlme and its function lme.

Data availability

The dataset analyzed during the current study are not publicly available due to legal restrictions but are available from the corresponding author on reasonable request.

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Author contributions

T.P., P.H. and R.S. designed the research and performed the experiment. D.H., T.P. and T.T. analyzed the data. D.H. and T.P. wrote the main manuscript. D.H., T.P. and S.K. did the statistical analysis. All authors reviewed the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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