KU Leuven
Biomedical Sciences Group
Faculty of Medicine
Department of Neurosciences

KU LEUVEN
DOCTORAL SCHOOL
BIOMEDICAL SCIENCES

AUDITORY TEMPORAL PROCESSING IN PRE-READERS AT RISK FOR DYSLEXIA

NEUROPHYSIOLOGICAL MARKERS AND PREVENTIVE INTERVENTION

Shauni VAN HERCK

Jury:

Supervisor:	Prof. Dr. Jan Wouters
Co-supervisor:	Prof. Dr. Pol Ghesquière
	Prof. Dr. Maaike Vandermosten
Chair examining committee:	Prof. Dr. Karel Talavera (KU Leuven, BE)
Chair public defence:	Prof. Dr. Astrid Van Wieringen (KU Leuven, BE)
Jury members:	Prof. Dr. Patrick Dupont (KU Leuven, BE)
	Prof. Dr. Bert De Smedt (KU Leuven, BE)
	Prof. Dr. Marie Lallier (BCBL, ES)
	Prof. Dr. Axelle Calcus (ULB, BE)

Dissertation presented in partial fulfilment of the requirements for the degree of Doctor in Biomedical Sciences

2023

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Abstract

Literacy contributes considerably to an individual's educational and professional outcomes. Even though learning to read initially requires a great amount of effort, the majority of people eventually attains fluent reading skills. Nonetheless, approximately 7% of the population continues to experience severe difficulties with reading and/or spelling and is diagnosed with developmental dyslexia. Research highlights the importance of early identification and preventive intervention to promote reading and related skills. Yet, this stands in sharp contrast to clinical practice where interventions are typically only provided after years of reading difficulties. Additionally, dyslexia interventions largely target phonological skills. Although the phonological deficit theory, which assigns dyslexia to underlying difficulties with phonological processing, has received a lot of support, a large body of research suggests that at least in a subgroup of individuals with dyslexia, these difficulties might be caused by an underlying deficit in auditory temporal processing. More specifically, it is proposed that an atypical processing of slow-rate dynamic information in speech, such as amplitude rise times, and an atypical neural synchronization to the speech signal, impede speech perception and consequently the quality of phonological representations. In this respect, interventions would benefit from addressing auditory temporal processing difficulties, by for example enhancing the speech envelope.

The current doctoral research had two overarching aims. The first aim was to identify the neurophysiological markers underlying the auditory temporal processing deficit in dyslexia. Part of this first aim was to investigate acoustic stimuli with an increased potential to uncover these neurophysiological markers in a pediatric population. The second aim was to investigate the impact of a preventive intervention on auditory temporal processing. To evaluate auditory temporal processing, we measured (1) auditory steady-state responses (ASSRs) to syllable and phoneme rate modulations using both regular sinusoidal amplitude modulated stimuli and pulsatile stimuli with shortened rise times, and (2) rise time sensitivity. We evaluated auditory temporal processing before, immediately after, and approximately one year after a 12-week preventive home-based intervention in pre-readers at cognitive risk for dyslexia who received a phonics-based training, either with or without auditory enhanced speech training, or engaged in active control training. Reading and spelling data collected at the start of third grade allowed to redefine all children as either typically reading children or children with dyslexia.

In the first study (Chapter 2), we examined the suitability of the pulsatile stimuli in a typically reading population of pre-reading to beginning reading children. We found that pulsatile stimuli greatly enhanced neural synchronization to syllable rate modulations, thereby considerably increasing data acquisition efficiency. Furthermore, the pulsatile stimuli also elicited a different hemispheric specialization at syllable rate. In our second study (Chapter 3), we demonstrated an atypical hemispheric specialization in children with dyslexia, even before the onset of formal reading instruction. This indicates a potential causal mechanism and supports the hypothesis that atypical neural synchronization is related to the development of dyslexia. We found no evidence for an atypical neural processing of rise times. Additionally, the phonics-based and enhanced speech intervention did not impact neural synchronization to either syllable or phoneme rate modulations. In the last study (Chapter 4), we showed that the enhanced speech intervention did improve rise time sensitivity. Therefore, it seems that the enhanced speech intervention directly trained rise time sensitivity, but did not yield transfer effects to indirectly trained neural synchronization. The phonics-based training did not improve rise time sensitivity.

In sum, the current research contributes to our understanding of the neurophysiological mechanisms underlying the development of dyslexia and

the development of preventive interventions. Our results showed evidence of an auditory temporal processing deficit present already in pre-readers and therefore potentially causally related to dyslexia. Additionally, our findings highlight the importance of auditory trainings in dyslexia. The enhanced speech training is certainly promising, but can still be improved. We believe that the present work represents a vital step towards a better understanding of dyslexia and the development of more effective interventions.

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Abbreviations and acronyms

A	Amplification
AC	Active Control
ACNE	Active Control and No Envelope Enhancement intervention group
ADHD	Attention Deficit Hyperactivity Disorder
AM	Amplitude Modulated
ANF	Auditory Nerve Fiber
ANOVA	Analysis of Variance
ASD	Autism Spectrum Disorder
ASSR	Auditory Steady-State Response
AST	Assymetric Sampling in Time
CDS	Child-directed speech
COVID-19	Coronavirus Disease 2019
CT	Computed Tomography
CI	Confidence Interval
dB SPL	Decibel Sound Pressure Level
dBpeSPL	Decibel Peak Equivalent Sound Pressure Level
DC	Direct Current
DR	children with dyslexia
DTI	Diffusion Tensor Imaging
E	Envelope

EE	Envelope Enhancement
EEG	Electroencephalography
EMM	Estimated Marginal Means
f	Frequency
F0	Fundamental frequency
FFT	Fast Fourier Transform
fMRI	Functional Magnetic Resonance Imaging
GG	GraphoGame
GG-FL	GraphoGame Flemish
GGEE	GraphoGame and Envelope Enhancement intervention group
GGNE	GraphoGame and No Envelope Enhancement intervention group
Hz	Hertz
FFW	Fast ForWord
FI	Fletcher Index
Hz	Hertz
IQ	Intelligence Quotient
IQR	Interquartile range
kHz	kilohertz
LH	Left Hemisphere
LIST	Leuven Intelligibility Sentence Test
LK	Letter Knowledge
M	Mean
Mdn	Median
MEG	Magnetoencephalography
MRI	Magnetic Resonance Imaging
ms	milliseconds
mV	milliVolt
N	Number
NE	No Envelope Enhancement
p	Peak
PA	Phonological Awareness
pc	percentile
PET	Positron Emission Tomography
PULS	Pulsatile
RAN	Rapid Automatized Naming
RAPD	Rapid Auditory Processing Deficit

RH	Right Hemisphere
s	Signal
RTD	Rise Time Discrimination
SAM	Sinusoidal Amplitude Modulated
SD	Standard Deviation
SES	Socio-Economic Status
SWN	Speech-Weighted Noise
t	time
T0	Test phase at the middle of kindergarten
T1	Test phase at the end of kindergarten
T2	Test phase at the end of first grade
TEMPEST	Temporal Envelope Speech Tracking
TFS	Temporal Fine Structure
TR	Typically Reading children
TSF	Temporal Sampling Framework
VSTM	Verbal short-term memory
WN	White Noise

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All was well.

Harry Potter and the Deathly Hallows

Preface

Literacy is a prerequisite in order to fulfil nearly any role in our society. It is deeply ingrained in our culture, and mastering it is essential to function properly at both the social and the professional level. Communicating with friends and family, pursuing a career, and many other important aspects of our daily lives would be nearly impossible without being proficient at reading and writing. Hence, it is not hard to imagine that struggling with these skills places a great burden on one's life, with far-reaching emotional, behavioral and social consequences.

Reading acquisition is a complex cognitive task that requires formal instruction. With sufficient instruction, most children attain fluent reading and spelling skills. Nevertheless, a number of children experience considerable difficulties with reading and/or spelling and eventually receive the diagnosis of developmental dyslexia. Reading and related skills in children with dyslexia can be promoted by targeted interventions. However, in practice, interventions are often provided untimely. Ideally, interventions should be provided in the early stages of reading difficulty, or preferably even preventively. To implement preventive and effective interventions, a thorough understanding of the mechanisms underlying dyslexia is imperative.

Over the decades, a substantial amount of research has aimed to uncover the mechanisms underlying the development of dyslexia. At present, the

phonological processing deficit is widely agreed upon as the core deficit in dyslexia. Yet, the underlying (neural) dysfunctions are still uncertain. More recent research efforts have pointed to an underlying (neural) auditory temporal processing deficit. Despite evidence in support of this theory, results are often conflicting. Furthermore, studies conducted to investigate neural auditory temporal processing difficulties often include stimuli that are inadequate to tap into the specific underlying mechanisms.

In conclusion, dyslexia research is largely focused on uncovering the mechanisms underlying the development of dyslexia as well as the development of (preventive) interventions with the overarching aim of reducing the impact of reading failure, or even preventing it altogether. The present doctoral research aims to contribute to this overarching goal by addressing two aims. The first aim is to elucidate the neural mechanisms underlying auditory temporal processing difficulties in dyslexia. To this end, we first examine a set of stimuli that might contribute to uncovering these neural mechanisms. The second aim is to investigate the impact of a preventive intervention on (neural) auditory temporal processing.

In the next chapter, we provide the theoretical and methodological background of the present doctoral research, along with an overview of our research objectives. The main emphasis is on acoustical and neural aspects of auditory temporal processing in the context of dyslexia research and interventions targeting these deficits.

Chapter 1

General Introduction

1.1 Typical reading acquisition

The vast majority of people rely on their reading skills on a daily basis. With sufficient practice, these skills seem to come so naturally that we tend to forget the years of education and practice required to reach this level of proficiency. Indeed, reading acquisition is a highly complex cognitive task that requires explicit formal instruction and practice (Rastle et al., 2021), unlike the acquisition of spoken language.

A main challenge for beginning readers is mapping a series of visual symbols onto (the meaning of) speech. In alphabetic writing systems, such as Dutch and English, reading acquisition starts with teaching the child about how written symbols (i.e. graphemes or letters) map onto corresponding speech sounds (i.e. phonemes), referred to as the alphabetic principle (Castles et al., 2018). Mastering grapheme-to-phoneme conversion rules enables the child to translate visual symbols into speech, which allows for subsequent access to their meaning. This initial decoding reading strategy is referred to as the

sublexical or indirect reading strategy (Coltheart et al., 2001), or phonological recoding (Share, 1995), and lays the foundation for successful reading acquisition (Ziegler & Goswami, 2005).

While the sublexical reading strategy is predominantly used in the beginning stages of reading development, a more automated lexical reading strategy comes into play with experience (Coltheart et al., 2001; Jackson & Coltheart, 2013). With increasing reading experience, a direct association is formed between written and spoken word forms, allowing for rapid and direct access to spoken words and their meaning. Although proficient readers mainly rely on the lexical reading strategy, the sublexical reading strategy is still used for reading novel words and non-words (Ziegler et al., 2008).

1.1.1 Phonological processing

Considering that reading acquisition essentially relies on mapping visual symbols onto already existing knowledge of speech sounds, the foundations for reading develop implicitly at the level of spoken language. More specifically, phonological processing lays the foundation for reading acquisition.

Phonological abilities are generally divided into three sub-components: phonological awareness, rapid automatized naming and verbal short-term memory (Wagner & Torgesen, 1987). Firstly, phonological awareness (PA) refers to the ability to perceive, identify and manipulate the sounds of spoken words and is one of the strongest predictors of reading skills across languages (Castles & Coltheart, 2004; Melby-Lervåg et al., 2012; Puolakanaho et al., 2007; Ziegler & Goswami, 2005). Notably, in children, phonological awareness develops in a hierarchical fashion from larger (i.e. stressed syllables and syllables) to smaller phonological units (i.e. onset-rime and phonemes), forming a so-called linguistic hierarchy (Goswami, 2019b). Whereas awareness of the larger phonological units is considered to be present in preliterate children, phoneme awareness only develops as a consequence of formal reading acquisition (Goswami & Bryant, 2016). The quality of the phonological representations at any of the above linguistic levels is decisive for reading acquisition (Ziegler & Goswami, 2005). Secondly, rapid automatized naming (RAN) is another strong predictor of reading ability (Kirby et al., 2008; Norton & Wolf, 2012). RAN is the ability

to retrieve phonological representations from long-term memory (Torgesen et al., 1997). Even though RAN is related to both reading accuracy and fluency, it is most strongly associated with the latter (Araújo et al., 2015; Moll et al., 2014). Lastly, verbal short-term memory (VSTM) is the ability to temporarily store verbal information in memory. VSTM is a direct predictor of reading ability that is specifically relevant in the first stages of reading development, by supporting grapheme-to-phoneme decoding (Cunningham et al., 2021; Wagner & Torgesen, 1987).

Despite the established predictive values of phonological awareness, rapid automatized naming and verbal short-term memory to reading ability, this subdivision of phonological abilities as introduced by Wagner and Torgesen (1987) has been heavily debated. To begin with, it has been disputed whether RAN and VSTM are actually subskills of phonological processing (Savage et al., 2007; Vandewalle et al., 2010). Additionally, not all three components exert an equal impact on reading ability. While PA and RAN are independent predictors of reading ability, there is less support for the predictive value of VSTM (Caravolas et al., 2012; Hulme & Snowling, 2013). Additionally, the impact of these phonological skills on reading ability is largely influenced by orthographic transparency and the stage of reading development (Brizzolara et al., 2006; Vaessen & Blomert, 2010; Ziegler et al., 2010).

A robust predictor of reading that was not included in the subdivision of Wagner and Torgesen (1987) is letter knowledge (LK). Letter-sound knowledge is a fundamental prerequisite for reading in alphabetic languages and is predictive of later reading ability even in preliterate children (Caravolas et al., 2012; Clayton et al., 2020; Hulme & Snowling, 2013; Schatschneider et al., 2004).

Taken together, the strongest predictors of reading ability are phonological awareness, rapid automatized naming and letter knowledge (Caravolas et al., 2012; Clayton et al., 2020; Hulme & Snowling, 2013; Schatschneider et al., 2004). A common denominator of these skills is that they all rely to some extent on the availability and the quality of phonological representations. Phonological representations are in essence representations of the phonological structure of speech, and therefore require an accurate perception of the acoustic structure of the speech signal (Goswami, 2019a).

1.2 Auditory temporal processing

In order to understand how the perception of the acoustic structure of the speech signal contributes to phonological processing skills and ultimately to reading, we will describe the auditory system (**1.2.1**), the acoustic structure of speech (**1.2.2**), and neural auditory temporal processing (**1.2.3**) in the following section.

1.2.1 The auditory system

The auditory system refers to all structures that a sound wave encounters in between arriving to the ear and its neural processing in the auditory cortex and contains two subsystems: the peripheral and the central auditory system. The peripheral auditory system comprises the outer, the middle and the inner ear. Sound waves enter the outer ear, where they hit the pinna and are consequently transmitted through the ear canal to the tympanic membrane in the middle ear. The airborne vibrations in the tympanic membrane are converted to mechanical vibrations in the ossicles in the middle ear (i.e. the malleus, the incus and the stapes), and eventually, through the oval window, to liquid-borne vibrations of the basilar membrane in the cochlea in the inner ear. The basilar membrane has a tonotopic organization, meaning that the region of the basilar membrane that vibrates differs depending on the frequency of the stimulus. Higher frequencies vibrate near the basis of the basilar membrane, while lower frequencies vibrate near the end of the basilar membrane (von Békésy, 1960). As a consequence, the stereocilia of the hair cells on the organ of Corti will bend. This process converts the vibrations into electrical energy that is processed in the central auditory system.

The central auditory system (see **Figure 1.1**) further transmits the sounds from the ear to the brain starting with the auditory nerve that connects to the cochlear nuclei in the brainstem. From here on, a contralateral and ipsilateral pathway ascend to the superior olivary complex. Fibers then ascend to the midbrain inferior colliculus, the medial geniculate body in the thalamus and finally left and right auditory cortices (Gelfand, 2018).

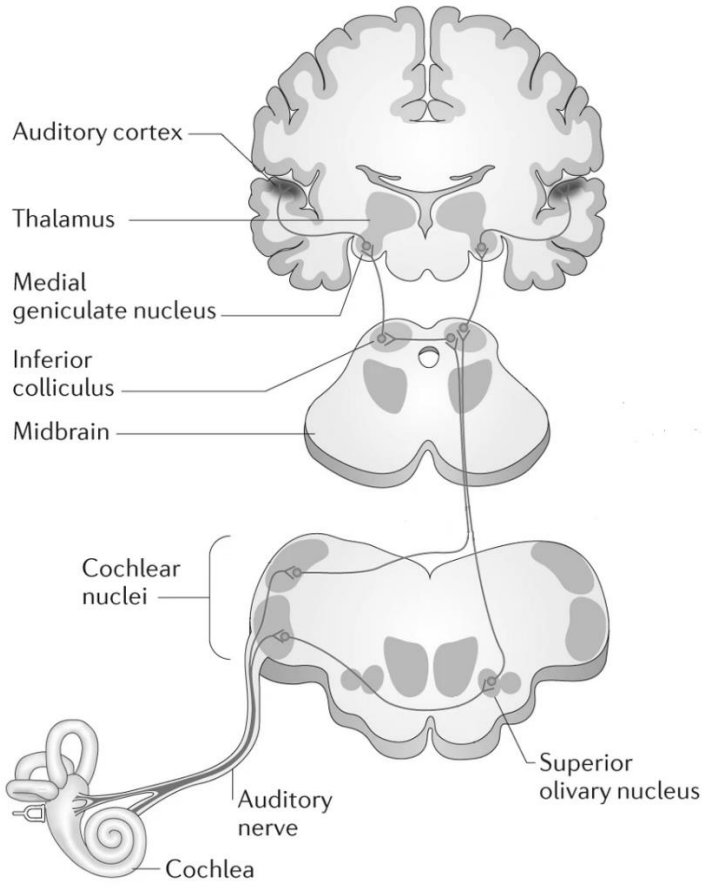


Figure 1.1: The central auditory system. Figure adapted from Javitt & Sweet (2015).

1.2.2 The speech signal

Speech can be described as a highly complex signal that varies in amplitude and frequency over different timescales. Based on these multiple timescales, three main temporal features have been characterized: periodicity, fine structure, and envelope (Rosen, 1992). The periodicity of the speech signal contains modulation rates between 50 and 500 Hz. The periodicity reflects the fundamental frequency (F0), and results from the vocal fold vibrations during voiced speech. The temporal fine structure (TFS) refers to the rapid temporal changes of the sound pressure waveform at rates between 600 and 10000 Hz. The envelope of speech contains slow temporal modulations in the overall amplitude of the speech signal between 2 and 50 Hz (Rosen, 1992).

The speech envelope in particular is crucial for speech intelligibility. Studies have indeed demonstrated that a degradation of the speech signal only has very little impact on overall speech intelligibility, as long as the temporal envelope information is retained (Drullman et al., 1994; Shannon et al., 1995). Furthermore, the speech envelope conveys information about the phonological units embedded in the linguistic hierarchy. More specifically, the amplitude modulation rates in the speech envelope coincide with the rates at which key phonological units occur in speech, namely stressed syllables or prosodic information at rates below 2 Hz, syllables at rates around 4 Hz, and phonemes at rates between around 12 and 30 Hz (Greenberg et al., 2003; Leong & Goswami, 2014).

A temporal cue that is critical to perceive the amplitude modulation rates in speech is the amplitude rise time (see **Figure 1.2**). Rise times indicate the rate of amplitude change (from minimal to maximal amplitude) in the speech envelope and are most prominent at the onset of syllables. When producing a syllable, the amplitude rises and reaches its peak as the vowel within the syllable is produced (Greenberg, 2006). Rise times thus function as auditory edges and convey important acoustic cues for the segmentation of the speech signal into phonological units. This is further supported by the core role attributed to rise times in the neural encoding of the speech signal (Goswami, 2018, 2022; Lallier et al., 2018).

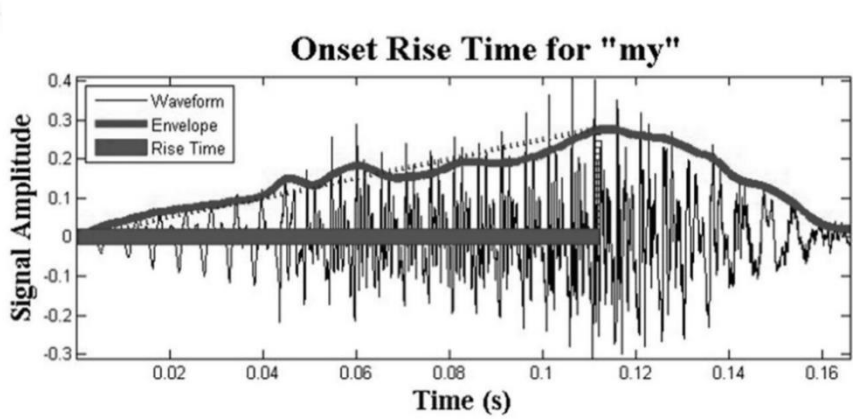


Figure 1.2: Example of rise time for the English word "my". Figure adapted from Goswami & Leong (2013).

1.2.3 Neural auditory temporal processing

Speech perception in essence relies on the neural encoding of the speech signal. Hence, it is important to understand the neural mechanisms underlying auditory temporal processing and speech perception.

It is generally agreed upon that neural auditory processing is supported by oscillatory activity in the brain (Ghitza & Greenberg, 2009; Giraud & Poeppel, 2012b; Peelle & Davis, 2012; Riecke et al., 2018). Neural oscillations can typically be classified into five frequency bands that are intrinsically present in the brain, delta (< 4 Hz), theta (4 – 8 Hz), alpha (8 – 13 Hz), beta (13 – 30 Hz) and gamma (> 30 Hz) (Buzsáki & Draguhn, 2004). This oscillatory activity results from the shifting of populations of neurons between high excitability (sending an electrical pulse) and low excitability (recovering from sending an electrical pulse). It has been hypothesized that the efficiency of information processing is determined by the phase at which information arrives in the brain. Information arriving at high excitability periods is processed more efficiently compared to information arriving at low excitability periods (Peelle & Davis, 2012).

In the context of speech encoding this means that, to ensure optimal processing of relevant information in the speech signal, the ongoing neural oscillations reset their activity to the incoming auditory information so that important features in the speech signal will arrive at periods of high excitability. This is referred to as neural phase-locking or neural synchronization (Peelle & Davis, 2012) (see **Figure 1.3**). Notably, the frequency bands intrinsically present in the brain remarkably coincide with the amplitude modulation rates present in the speech envelope, which in their turn correspond to the production rates of key phonological units (see **Table 1.1**). As a result, neural oscillations subserve the parsing of the speech signal into phonological units at different grain sizes, by synchronizing their activity to the corresponding modulation rates in the speech envelope. Specifically, synchronization in the delta range (< 4 Hz) is related to processing stressed syllables or prosody, synchronization in the theta range (4-8 Hz) is linked to syllable-rate processing, and synchronization in the beta (13-30 Hz) and gamma (> 30 Hz) ranges is associated with phoneme rate processing (Ghitza, 2011; Ghitza & Greenberg, 2009; Meyer, 2018; Poeppel, 2003). Successful synchronization to these temporal modulations in the speech signal is highly correlated with speech perception and intelligibility

(Ghitza & Greenberg, 2009; Giraud & Poeppel, 2012a; Peelle & Davis, 2012). Fundamental for sustaining synchronization to the speech signal are amplitude rise times. Rise times enhance the precision of neural synchronization by triggering neural oscillations to reset their activity to the temporal modulations in the speech signal (Gross et al., 2013). More specifically, it is the sharpness of the rise times that facilitates neural synchronization (Doelling et al., 2014; Poeppel, 2014).

Table 1.1: Correspondence between phonological units, amplitude modulations and oscillatory rates

Phonological unit	AM rate	Oscillatory rate
Stressed syllable	~ 2 Hz	delta
Syllable	~ 4 Hz	theta
Phoneme	12 – 30 Hz	beta / low-gamma

Besides exhibiting a bottom-up synchronization to the speech signal, neural oscillations at lower frequencies additionally impact oscillations at higher frequencies in a top-down manner, thereby displaying a nested hierarchical structure (see **Figure 1.3**). Specifically, cross-frequency coupling between the delta and theta bands and between the theta and gamma bands has already been established (Giraud & Poeppel, 2012a; Gross et al., 2013; Meyer, 2018). Rise times are instrumental in establishing this nested hierarchy of oscillations by increasing cross-frequency coupling (Gross et al., 2013).

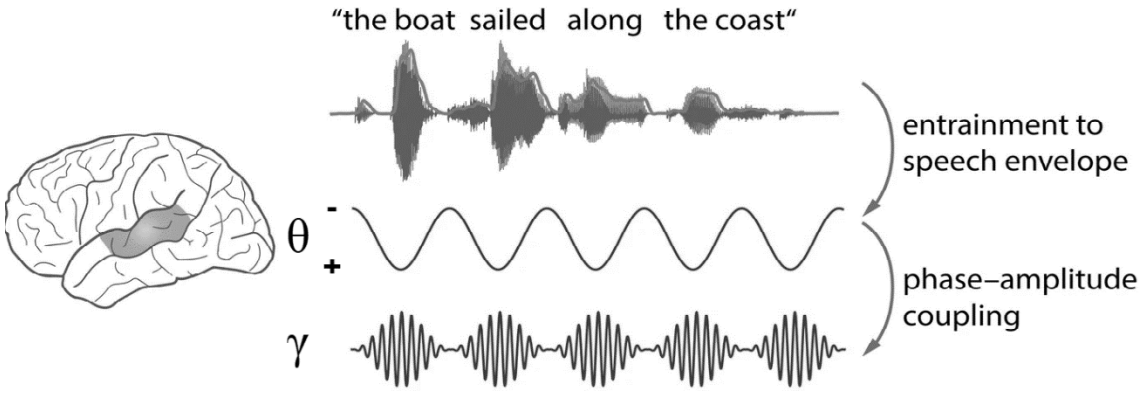


Figure 1.3: Neural synchronization to speech. Neural oscillations synchronize to the amplitude modulations in the speech envelope (here: syllable rate synchronization) by resetting their activity so that important features of the speech signal arrive at periods of high excitability (indicated by "+"). Oscillations at lower frequencies (theta, top waveform) top-down impact oscillations at higher frequencies (gamma, bottom waveform) through cross-frequency coupling. Figure adapted from Tune & Obleser (2022).

It has been hypothesized that the distinct yet interconnected oscillatory rates allow for speech to be analyzed in parallel at multiple timescales (i.e. multi-time resolution processing). This process is presumed to be functionally lateralized (Arnal et al., 2015; Boemio et al., 2005; Giraud & Poeppel, 2012b; Poeppel, 2003). An initial theory proposed that hemispheric specialization arises from differences in the spectrotemporal processing properties between the left and the right hemisphere. It was hypothesized that the left hemisphere is better suited for temporal information processing, whereas the right hemisphere is better suited for spectral information processing (Zatorre & Belin, 2001). However, the "asymmetric sampling in time" (AST) hypothesis (Poeppel, 2003) posited that both hemispheres are equally equipped for temporal information processing, but that they differ in their sensitivity to slow versus fast modulation rates. According to the AST hypothesis, slow temporal rates subserving syllabic processing are preferentially processed in the right hemisphere, whereas fast temporal rates subserving phonemic processing are preferentially processed in the left hemisphere or bilaterally.

The aforementioned interpretation of neural synchronization as an encoding mechanism of the incoming speech signal is partly the result of bottom-up synchronization to the speech signal, but also assumes active linguistic processing. Even though this linguistic interpretation has received strong

empirical support (Doelling et al., 2014; Peelle et al., 2013; Peelle & Davis, 2012), it is worth mentioning that an alternative explanation suggests a purely stimulus-driven response depending on only the acoustic characteristics of the auditory stimulus without active linguistic processing (Alexandrou, 2018). Nevertheless, a detailed explanation of this alternative interpretation falls outside the scope of the current work.

In sum, over the past decades, a great deal of research has been devoted to the (neural) processes underlying speech perception and intelligibility and how these ultimately contribute to reading development. Considering this brief overview of the literature on the topic, it should come as no surprise that difficulties with (neural) auditory temporal processing might give rise to cascading difficulties with phonological processing and consequently reading development.

1.3 Developmental dyslexia

As a consequence of formal reading instruction and sufficient practice throughout the initial years of primary school, most children attain fluent reading skills. However, a proportion of children experiences severe difficulties with reading and will go on to receive the diagnosis of developmental dyslexia.

1.3.1 Definition

Developmental dyslexia (henceforth, dyslexia) is one of the most common developmental disorders, with an estimated prevalence around 7% (Peterson & Pennington, 2015; Yang et al., 2022). The prevalence of dyslexia largely depends on the adopted definition. In the current thesis we define dyslexia as a developmental disorder marked by severe and persistent difficulties in reading and/or spelling, despite adequate instruction and opportunities and intact sensory abilities (Peterson & Pennington, 2012, 2015). This definition comprises the three criteria implemented in clinical practice in Flanders to receive the diagnosis of dyslexia. That is, reading and spelling problems are required to be (1) severe, meaning that performance lies well below the expected age norms, (2) persistent and resistant to instruction and targeted intervention and (3) not better accounted for by external factors such as

inadequate instruction, insufficient opportunities, or sensory impairments (Ghesquière, 2014). Dyslexia has a strong genetic component, with prevalence rates going up to 40 to 60% in children who have a first-degree relative with dyslexia (Grigorenko, 2001). Notably, the underlying cognitive factors of dyslexia largely overlap with those of other developmental disorders such as attention deficit hyperactivity disorder, and with other specific learning disabilities such as dyscalculia and dysphasia (Landerl & Moll, 2010; Willcutt & Pennington, 2000). As a result, dyslexia is frequently comorbid, meaning that it co-occurs with these other disorders.

1.3.2 Etiology

Dyslexia is characterized by a complex etiology. Over the last decades, numerous theories have been proposed to explain the mechanisms underlying the development of dyslexia, from the phonological deficit theory (Snowling, 2000; Vellutino et al., 2004) to visual (Livingstone et al., 1991; Stein, 2019) and auditory processing deficit theories (Goswami, 2011; Tallal, 1980) (for an overview see Vellutino et al. 2004, and Goswami, 2015). The research field recognizes that no single deficit is necessary or sufficient to develop dyslexia, but rather that dyslexia has a multifactorial etiology with several cognitive, neurobiological, genetic and environmental factors contributing to its development (Menghini et al., 2010; Pennington, 2006; Peters & Ansari, 2019; Peterson & Pennington, 2015; van Bergen et al., 2014).

Phonological deficit theory

Throughout the years, the phonological deficit theory has received most support (Snowling, 2000; Vellutino et al., 2004). This theory assigns the reading and spelling difficulties in dyslexia to underlying phonological processing difficulties. More specifically, it is assumed that people with dyslexia have difficulties with the representation, retrieval and/or storage of phonological units. This in turn impacts phonological processing skills such as phonological awareness, rapid automatized naming and verbal short-term memory, as well as the learning of grapheme-to-phoneme correspondences. Considering the importance of these skills for future reading abilities, it is clear that a deficit in phonological processing would greatly impede reading development (see **1.1.1**). In support of the phonological deficit theory, a great

deal of research has provided evidence for poor phonological processing skills in people with dyslexia, even prior to the onset of formal reading acquisition (Boets et al., 2010; Clayton et al., 2020; De Jong & Van der Leij, 2003). These phonological processing difficulties have consistently been reported across languages and orthographies (Ziegler & Goswami, 2005). Even though not all individuals with dyslexia display poor phonological processing, prevalence rates are typically high, varying from around 50% to 100% (Hazan et al., 2009; Law et al., 2014; Ramus et al., 2003; Reid et al., 2007; Saksida et al., 2016; White et al., 2006).

Auditory temporal processing deficits

Even though somewhat debated, over the last decades increasing evidence has demonstrated that phonological processing difficulties in dyslexia might be related to an underlying auditory temporal processing deficit (Farmer & Klein, 1995; Goswami, 2011; Tallal, 1980).

Initial theories supporting auditory temporal processing deficits in dyslexia such as the Rapid Auditory Processing Deficit (RAPD) theory suggested difficulties with processing brief sounds or sounds presented in rapid succession (Farmer & Klein, 1995; Tallal, 1980). Such a deficit was suggested to impact phonological representations through an inability to integrate rapidly presented acoustic information. Even though initially several studies provided support for this theory (De Martino et al., 2001; Farmer & Klein, 1995; Tallal, 1980), most studies have actually failed to demonstrate a rapid auditory processing deficit, or its relation with phonological skills (Breier et al., 2003; Bretherton & Holmes, 2003; Hämäläinen et al., 2013; Nittrouer, 1999; Rosen & Mangari, 2001).

More recently, the focus has shifted from a rapid auditory processing deficit to a deficit in processing the slow-rate, dynamic information in speech. This theory proposes that atypical auditory temporal processing interferes with the development of phonological skills that are important for reading acquisition. More specifically, it is suggested that atypical auditory temporal processing impedes the parsing of the speech signal into phonological units such as syllables and phonemes. A failure to accurately parse speech would affect speech perception and consequently the quality of phonological representations that underlie phonological processing skills and reading development (Goswami, 2018, 2019a).

A growing body of research has provided evidence for atypical processing of slow-rate dynamic information such as amplitude and frequency modulations in individuals with dyslexia (Poelmans et al., 2011; Stuart et al., 2006; Witton et al., 1998; Witton et al., 2002). However, the most prominent measures of dynamic information in the speech envelope are rise times (see **1.2.2**). Hence, in this line of research, a great deal of attention has been paid in particular to rise time sensitivity. Impaired rise time sensitivity has been demonstrated in both children (Goswami, 2011; Goswami et al., 2002; Poelmans et al., 2011; Richardson et al., 2004) and adults with dyslexia (Hämäläinen et al., 2005; Law et al., 2014; Leong et al., 2011). Moreover, rise time discrimination is already compromised in infants and pre-readers at risk for developing dyslexia (Kalashnikova et al., 2018; Law, Wouters, et al., 2017). Further demonstrating its importance, rise time discrimination is predictive of phonological awareness and literacy skills, even before the onset of formal reading instruction (Goswami et al., 2020; Richardson et al., 2004; Vanvooren et al., 2017). Rise time discrimination difficulties are consistently demonstrated across languages (Goswami, 2015). Rise time discrimination is hypothesized to impact the quality of phonological representations through impaired speech perception abilities (Goswami, 2018, 2019a). Speech-in-noise perception difficulties have indeed frequently been demonstrated in at risk pre-readers, as well as children and adults with dyslexia, and significantly contribute to later reading skills (Boets et al., 2011; Calcus et al., 2018; Dole et al., 2012; Ziegler et al., 2009). Prevalence rates of auditory and speech processing difficulties typically vary from around 45% to around 70% (Calcus et al., 2016, 2018; Law et al., 2014; Ramus et al., 2003; Van Hirtum et al., 2021; Van Hirtum, Moncada-Torres, et al., 2019).

Auditory temporal processing and speech perception in essence rely on the neural encoding of the speech signal (see **1.2.3**). In this respect, insights in how the dyslexic brain processes temporal information might provide us a better understanding of the specifics of the auditory temporal processing deficit in dyslexia. A conceptual framework that aimed to integrate the behavioral difficulties demonstrated by individuals with dyslexia with underlying neural oscillations is the Temporal Sampling Framework (TSF) of Goswami (2011). The TSF assigns phonological difficulties in dyslexia to an atypical neural synchronization of neural oscillations at slow or syllabic-rate modulations, specifically the delta and theta rate, to the speech envelope.

Over the years, the TSF has frequently been the subject of empirical investigations with mixed findings as a result (see Lizarazu et al. 2021, for a review). We provide a chronological overview of the studies investigating neural synchronization to temporal modulations in individuals with dyslexia in **Table 1.2**.

Table 1.2 Neural synchronization to temporal modulations in dyslexia

Study	Participants	Language	Method	Stimuli	Delta	Theta	Beta / Gamma
McAnally & Stein, (1997)	Adults	English	EEG	AM WN	/	/	DR < TR
Menell et al., (1999)	Adults	English	EEG	AM WN	/	/	DR < TR
Lehongre et al., (2011)	Adults	French	MEG	AM WN	/	/	DR < TR (in LH) DR > TR (in RH)
Hämäläinen et al., (2012)	Adults	English	MEG	AM WN	DR < TR (in RH)	DR = TR	DR = TR
Poelmans, Luts, Vandermosten, Boets, et al., (2012)	Adults	Dutch	EEG	AM SWN	/	DR = TR	DR < TR (in LH)
Lehongre et al., (2013)	Adults	French	EEG/fMRI	Speech	/	/	DR < TR (in LH)
Soltész et al., (2013)	Adults	English	EEG	AM tones	DR < TR	/	/
Vanvooren et al., (2014)	Pre-readers	Dutch	EEG	AM SWN	/	DR = TR	DR = TR
Lizarazu et al., (2015)	Children/adults	Spanish	MEG	AM WN	DR = TR	DR > TR	DR > TR (in RH)

Molinaro et al., (2016)	Children/adults	Spanish	MEG	Speech	DR < TR (in RH)	DR = TR	/
Power et al., (2016)	Children	English	EEG	Noise-vocoded speech	DR < TR	DR = TR	/
De Vos et al., (2017a)	Pre-readers Children	Dutch	EEG	AM SWN	/	DR = TR DR = TR	DR = TR DR > TR
De Vos et al., (2017b)	Adolescents	Dutch	EEG	AM SWN	/	DR = TR	DR > TR
Van Hirtum et al., (2019)	Adults	Dutch	EEG	AM WN	/	DR = TR	DR < TR
Marchesotti et al., (2020)	Adults	French	EEG	AM tones	/	/	DR < TR (in LH)
Granados Barbero et al., (2021)	Adolescents	Dutch	EEG	AM SWN	/	DR > TR	DR > TR
Lizarazu et al., (2021)	Adults	French	MEG	AM WN	DR < TR (in RH)	/	DR < TR (in LH)
Granados Barbero et al., (2022)	Pre-readers Children	Dutch	EEG	AM SWN	/	DR < TR DR < TR	DR > TR DR < TR
Keshavarzi et al., (2022)	Children	English	EEG	Rhythmic speech	DR < TR	DR = TR	/
Mandke et al., (2022)	Children	English	MEG	Speech	DR < TR	DR < TR	DR < TR
Mittag et al., (2022)	At risk infants	English	MEG	AM WN	/	DR < TR	DR = TR
Peter et al., (2023)	Children	English	EEG	AM WN	DR < TR	DR = TR	/

Overall, nearly all reviewed studies demonstrate an atypical neural synchronization in children and adults with dyslexia, in pre-readers who later on develop dyslexia and even in infants at risk for developing dyslexia. However, it is rather unclear which specific modulation rates are compromised. Our overview of the studies investigating neural synchronization in dyslexia exposes striking inconsistencies with respect to the specific modulation rates at play. The TSF proposed a deficit in syllabic processing mainly situated at the delta and theta rate. However, studies investigating theta rate synchronization failed to demonstrate a clear-cut deficit. Two studies revealed decreased theta synchronization in dyslexia (Granados Barbero et al., 2022; Mandke et al., 2022), while two other studies instead demonstrated increased theta synchronization (Granados Barbero et al., 2021; Lizarazu et al., 2015). Nevertheless, a growing number of studies have consistently reported decreased delta rate synchronization (Hämäläinen et al., 2012; Keshavarzi et al., 2022; Lizarazu, Scotto di Covella, et al., 2021; Mandke et al., 2022; Molinaro et al., 2016; Peter et al., 2023; Power et al., 2016; Soltész et al., 2013). Hence, individuals with dyslexia indeed seem to struggle to some extent with encoding prosodic and syllabic information. Despite the focus of the TSF on syllabic processing, several studies have additionally investigated phonemic processing considering that the core deficit in dyslexia is primarily situated at the level of the phoneme. However, studies investigating beta and low-gamma synchronization have demonstrated both decreased (Granados Barbero et al., 2022; Lehongre et al., 2011, 2013; Lizarazu, Scotto di Covella, et al., 2021; Mandke et al., 2022; Menell et al., 1999; Poelmans, Luts, Vandermosten, Boets, et al., 2012) and increased synchronization (De Vos et al., 2017a, 2017b; Granados Barbero et al., 2022; Lizarazu et al., 2015), therefore also failing to reveal a well-defined deficit.

Apart from overall increased or decreased neural synchronization, several of the reviewed studies have additionally reported atypical hemispheric specialization in dyslexia. At syllable rate, several studies have reported a reduced right hemispheric bias (Granados Barbero et al., 2022; Lizarazu et al., 2015; Mandke et al., 2022). At phoneme rate, results are again inconsistent. Several studies have demonstrated a reduced left hemispheric (Lehongre et al., 2011, 2013; Lizarazu, Scotto di Covella, et al., 2021; Mandke et al., 2022; Poelmans, Luts, Vandermosten, Boets, et al., 2012), but

also an increased right hemispheric bias (Granados Barbero et al., 2022; Lizarazu et al., 2015).

Notably, most studies did not take into account the importance of rise times for sustaining neural synchronization to the speech envelope (see **1.2.3**). Only a few recent studies have investigated the impact of rise times on neural synchronization in dyslexia, demonstrating decreased synchronization to rise time cues in adults with dyslexia (Lizarazu, Lallier, et al., 2021; Van Hirtum, Ghesquière, et al., 2019). These studies caution not to overlook difficulties with rise time sensitivity at the neural level.

In sum, even though the neural auditory temporal processing deficit is not yet fully unraveled, it is evident that individuals with dyslexia experience difficulties with encoding the speech signal, persisting from childhood into adulthood. We further investigate the specific mechanisms underlying this neural auditory temporal processing deficit in Chapter 3.

1.4 Improving auditory temporal processing in dyslexia

A major goal in dyslexia research is unquestionably the development of targeted interventions to improve reading difficulties. In general, interventions largely focus on phonics instruction. However, our overview of the literature shows that in a subgroup of individuals with dyslexia phonological difficulties can be allocated to an auditory temporal processing deficit. Therefore, it might be beneficial to combine the more conventional phonics-based trainings with an intervention aiming to improve auditory temporal processing. In the following section we will provide a brief overview of the already existing intervention strategies (**1.4.1** and **1.4.2**), followed by an introduction to the enhanced speech intervention proposed in the present doctoral research (**1.4.3**). Lastly, we will discuss a critical issue in intervention programs and suggest a way to overcome this (**1.4.4**).

1.4.1 Phonics-based interventions

Over the last decades, it has become increasingly clear that most individuals with dyslexia experience phonological processing difficulties (Snowling,

2000; Vellutino et al., 2004). Consequentially, most researchers have focused on the development of interventions targeting phonological processing. Phonics-based interventions are generally considered successful in remediating phonological and reading difficulties in dyslexia, especially when they provide explicit and systematic phonics instruction and phoneme blending exercises (Bus & Van Ijzendoorn, 1999; Ehri et al., 2001; Galuschka et al., 2014; National Institute of Child Health and Human Development, 2000; Snowling & Hulme, 2011; Verhoeven et al., 2020). Moreover, phonics-based interventions have a great potential for digital game-based application, and can therefore easily be implemented even in younger children (Richardson & Lyytinen, 2014).

Despite the well-established efficacy of phonics-based interventions, the achievement gap between dyslexic and typical readers tends to persist into adolescence (Ferrer et al., 2015). Phonics-based interventions by definition rely on the accurate perception of the presented phonemes. Hence, although presently uninvestigated, auditory temporal processing difficulties and their related speech perception difficulties might disrupt the otherwise beneficial impact of phonics instruction. Combining phonics-based interventions with an auditory intervention specifically targeting the auditory temporal processing deficit in dyslexia might offer a solution to this problem.

1.4.2 Auditory-based interventions

Initial auditory interventions primarily focused on improving rapid auditory processing in line with the RAPD theory, which proposed that a difficulty with processing brief and rapidly presented sounds impairs phonological representations in dyslexia (Tallal, 1980). The most widely implemented training resulting from the RAPD theory is the Fast ForWord program (Scientific Learning Corporation, 1998). In Fast ForWord, rapid auditory processing was trained by tasks such as temporal order judgement tasks, and speech perception was facilitated by language exercises in which speech was acoustically modified to amplify and extend brief events. Even though Fast ForWord initially seemed to improve auditory processing and reading skills (Gaab et al., 2007; Merzenich et al., 1996; Tallal et al., 1996; Temple et al., 2003), the included language exercises obscured the specific effect of the auditory training. Hence, the impact of Fast ForWord on reading skills has been heavily debated (Cohen et al., 2005; McArthur et al., 2008).

As the focus of research on auditory temporal processing deficits in dyslexia changed from rapid to slow-rate, dynamic auditory processing (see **1.3.2**), so did the focus of auditory-based interventions. Correspondingly, several interventions have been developed that target slow-rate acoustic features in speech such as amplitude rise times. Rise times are closely related to speech rhythm (Goswami et al., 2002; Goswami, 2018) and therefore a number of interventions aimed to improve temporal processing by targeting rhythm skills. Musical and rhythm-based interventions include tasks such as music activities, tapping or drumming in time to a beat or poetry and rise time discrimination tasks. Such musical and rhythm-based interventions, in isolation or combined with reading training, have been shown to improve auditory temporal processing, as well as phonological and reading skills (Bhide et al., 2013; Cancer et al., 2022; Chobert et al., 2014; Degé & Schwarzer, 2011; Flaugnacco et al., 2015; Harrison et al., 2018; Thomson et al., 2013). Despite their positive outcomes, most of the above auditory interventions require a great deal of effort and are tremendously time-consuming, which makes them suboptimal for use in younger children with dyslexia.

An alternative approach primed sentences with their slow amplitude envelope (< 8 Hz), which was suggested to improve atypical neural synchronization in dyslexia (Ríos-López et al., 2017). Priming improved pseudoword recognition and correlated with reading skills. Even though priming did not improve auditory processing in the long term, it offers useful insights into potential new ways to remediate reading difficulties by targeting synchronization to speech. More recently, a technique has been proposed that targets synchronization to speech in real-time, offering a possible solution to the problem of time-consuming auditory interventions (Van Hirtum et al., 2021; Van Hirtum, Moncada-Torres, et al., 2019).

1.4.3 Envelope Enhancement

Based on the observed difficulties with rise time sensitivity of individuals with dyslexia and the crucial role of rise times in the neural encoding of speech and consequently speech perception (see **1.2.3**), Van Hirtum, Moncada-Torres, et al. (2019) investigated an algorithm that specifically accentuates rise times in the speech envelope, Envelope Enhancement (EE).

EE (Geurts & Wouters, 1999; Koning & Wouters, 2012, 2016) is, along with other envelope enhancement strategies, based on the notion that altering the speech envelope might improve speech intelligibility (Schroeder, 1981). Initial studies on envelope enhancement focused on altering the speech envelope as a whole by means of compression and expansion. Even though manipulating the whole envelope initially seemed to be beneficial for speech intelligibility (Clarkson & Bahgat, 1991; Langhans & Strube, 1982), it was also demonstrated that speech compression and expansion did not sufficiently improve speech intelligibility (Plomp, 1988; van Buuren et al., 1999). Therefore, the focus of envelope enhancement shifted to the enhancement of specific parts of the speech signal instead of the speech envelope as a whole.

EE is one such strategy in which solely onset cues or rise times are emphasized (Geurts & Wouters, 1999; Koning & Wouters, 2012, 2016). The EE algorithm was originally developed for cochlear implant users and aims to mimic the rapid adaptation in the probability of discharge at the synapse to the auditory nerve fiber (ANF) at the onset of a stimulus (Delgutte, 1980, 1997). To this end, EE amplifies onsets in the speech envelope in each frequency band separately, which accentuates the onsets in speech without altering other parts of the speech signal. Results showed that EE improved speech perception in both vocoder simulations and in cochlear implant users (Koning & Wouters, 2012, 2016).

Even though the adaptation effect at the synapse to the ANF is intact in dyslexia, individuals with dyslexia experience difficulties at higher levels in the auditory system that EE might potentially restore. Van Hirtum, Moncada-Torres, et al. (2019) hypothesized that EE might improve atypical auditory temporal processing and speech perception in dyslexia by facilitating the detection of rise times and allegedly enhancing the suboptimal neural entrainment to the speech envelope in dyslexia in real-time (see **Figure 1.4**). EE implemented in a speech-in-noise perception task improved speech perception abilities in both children (Van Hirtum et al., 2021) and adults with dyslexia (Van Hirtum, Moncada-Torres, et al., 2019). Notably, this improvement occurred in the absence of any instruction and after only limited exposure and can thus easily be implemented as an intervention for dyslexia. In the present doctoral research, we investigate the effect of EE as an intervention on neural synchronization (Chapter 3) and rise time discrimination (Chapter 4).

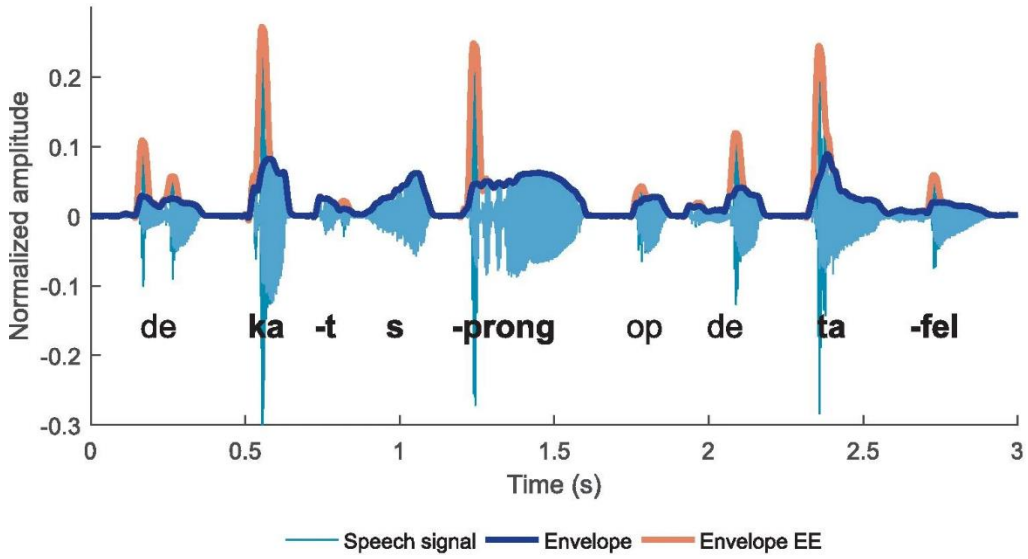


Figure 1.4: Envelope Enhancement. The speech envelope of the Dutch sentence "De kat sprong op de tafel" (English: "The cat jumped on the table") is enhanced at approximately syllable rate. The envelope of the speech signal is depicted in dark blue, the envelope of the enhanced speech signal in red. Figure reproduced from Van Hirtum et al. (2021).

1.4.4 The dyslexia paradox

A critical issue in interventions for dyslexia is the striking discrepancy between the optimal time window for interventions and when these interventions are actually provided. This discrepancy is described as “the dyslexia paradox” (Ozernov-Palchik & Gaab, 2016).

Research has shown that already at the start of formal reading acquisition, there is an achievement gap between children with dyslexia and their typically reading peers. Furthermore, this gap persists into adolescence (Ferrer et al., 2015). The achievement gap not only relates to literacy outcomes, but poses serious consequences for psychosocial well-being, as well as later educational and professional performance (Abbott-Jones, 2019; Ihbour et al., 2021; Livingston et al., 2018; Wilmot et al., 2022). This highlights the importance of early identification and intervention, even as soon as kindergarten, to offer the potential to reduce or close the gap and thereby diminish the consequences of reading difficulties. The importance of early interventions is further supported by structural brain research that indicated a natural plasticity window for reading during the first years of primary school (Phan et al., 2021). Indeed, a number of studies have

supported the efficacy of early and preventive interventions over interventions delivered at a later age (Hall et al., 2022; Lonigan et al., 2013; Lovett et al., 2017; Wanzek & Vaughn, 2007).

The importance of early identification and intervention for dyslexia stands in sharp contrast to clinical practice, where children typically experience several years of significant struggle with reading development before a diagnosis is received and targeted interventions are provided. In order to optimally support children with dyslexia, it is imperative to move away from the current wait-to-fail approach and instead focus on more preventive intervention strategies. In the present research, we investigate the effects of a preventive combined auditory and phonics-based intervention on neural synchronization (Chapter 3) and rise time discrimination (Chapter 4).

1.5 Techniques to assess neural auditory processing

In the following section we will consider the methodological background of the present research. We will give an overview of the most commonly used techniques in auditory neuroimaging (**1.5.1**), followed by a more detailed description of the method in the current research, namely auditory steady-state responses (**1.5.2**).

1.5.1 Neuroimaging techniques to assess auditory processing

Over the past decades, an increasing amount of neuroimaging techniques has become available that allows us to study the structure and function of the human brain. A first group of neuroimaging techniques allows the visualization of brain structures, i.e. structural imaging techniques. This includes techniques such as computed tomography (CT), magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) (Noggle & Davis, 2021). While these techniques are equipped to measure the anatomical properties of the brain, they cannot measure brain function. Therefore, a second group of neuroimaging techniques allows the mapping of functional brain activity, i.e. functional imaging techniques. On the one hand, techniques such as functional magnetic resonance imaging (fMRI)

measure hemodynamic activity. A second set of functional imaging techniques rather measure electrical or magnetic activity, such as electroencephalography (EEG) and magnetoencephalography (MEG) (Boly et al., 2016). The above-mentioned techniques vary widely in their respective spectral and temporal resolution, and the selection of the appropriate technique is decisive in answering research questions.

In the present doctoral research we investigate auditory temporal processing, meaning that, in order to answer our research questions, we require a technique with high temporal resolution. EEG offers a temporal resolution in the order of milliseconds and is therefore the most appropriate technique for the current research. Another advantage of EEG is its sensitivity to both tangential and radial sources as well as to deeper sources such as the brainstem, even though the sensitivity of EEG to deeper subcortical structures is lower compared to cortical structures (Ahlfors et al., 2010). This allows EEG to measure activity along the entire auditory system. Additionally, EEG has a relatively low cost and is easy to use in practice, which is of utmost importance when targeting a population of young children. In the present research we assessed auditory temporal processing using EEG and more specifically auditory steady-state responses (ASSRs).

1.5.2 Auditory steady-state responses

The auditory steady-state response (ASSR) is a periodic electrophysiological response of the brain that results from stimulation with a periodically varying acoustic signal (Rance, 2008, **Figure 1.5**). This response has the same periodicity as the acoustic signal and is thus a prime tool to objectively measure the ability of the auditory system to phase-lock or synchronize to the rhythm at which the presented stimulus is modulated (Picton, 2010; Picton et al., 2003). Considering that ASSRs' frequency components remain constant in amplitude and phase over a long time period, they can easily be measured in the frequency domain. Here, ASSRs show peaks in activity at both the modulation frequency and its harmonics (John et al., 2003; Picton, 2010).

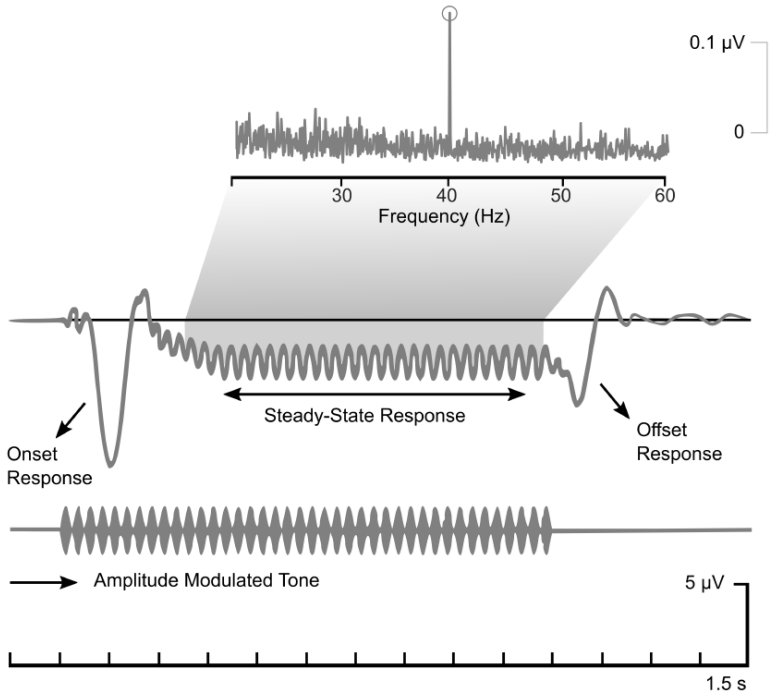


Figure 1.5: Example of transient and steady-state response to a one second amplitude modulated tone at 40 Hz. The on- and offset of the tone evoke a transient response. Following the transient response at the onset, there is a steady-state response (shaded area), that can be identified as a peak at the modulation frequency in the frequency domain. Figure redrawn and adapted from Picton (2010).

In general, ASSR response amplitudes decrease with increasing modulation frequencies, except for peaks around 40 and 90 Hz (Galambos et al., 1981; Purcell et al., 2004). Even though there is still ongoing debate on the exact neural generators of ASSR activity, it is generally agreed upon that the modulation frequency determines the location of the neural generators in the auditory pathway. Whereas cortical sources are predominantly sensitive to lower modulation frequencies (< 25 Hz), higher modulation frequencies (80 – 100 Hz) trigger subcortical sources, i.e. the brainstem (Farahani et al., 2017; Giraud et al., 2000).

The stimuli most commonly used to elicit ASSRs are sinusoidal amplitude modulated stimuli (SAM) (Picton, 2010; Rance, 2008). SAM stimuli consist of a carrier frequency whose amplitude is modulated at a certain modulation frequency and at a certain modulation depth. The carrier frequency can be a pure tone, or a more complex signal such as white or speech-weighted noise and determines the location of activation on the basilar membrane The modulation frequency refers to the rate at which the carrier signal is modulated in amplitude and determines the location of the neural generator

in the auditory pathway. The modulation depth is the degree of modulation of the carrier signal at the modulation frequency. In the frequency spectrum, the SAM only contains energy at the carrier frequency, and the two side bands separated from the carrier frequency by the modulation frequency (Picton, 2010).

In some contexts acquisition time is of crucial importance. For example, obtaining ASSRs as quickly as possible is a great advantage in clinical practice or when testing a pediatric population that is generally difficult to test. Increased response amplitudes shorten the time needed to obtain significant responses (John et al., 2002) and therefore several studies have aimed to optimize SAM stimuli in order to increase response strengths (John et al., 2002, 2003, 2004; Prendergast et al., 2010). Using exponential envelopes with a power *N* to modulate the carrier signal proved to increase response strengths in adults (John et al., 2002, 2003; Prendergast et al., 2010; Van Hirtum, Ghesquière et al., 2019) and young infants (John et al., 2004). With increasing *N*, rise- and fall times decrease and rise- and fall slopes increase (see **Figure 1.6**). Furthermore, these pulsatile stimuli with steeper slopes or shorter rise times have been argued to more accurately represent our acoustic world and are thus deemed more appropriate to investigate auditory processing (Prendergast et al., 2010). In the frequency spectrum, pulsatile stimuli are slightly less frequency specific, with a peak at the carrier frequency and an increasing number of side bands with increasing exponent power. Side bands are separated from the carrier frequency by 1 to *N* times the modulation frequency. In Chapter 2, we investigate the potential of pulsatile stimuli in pre-readers and beginning readers.

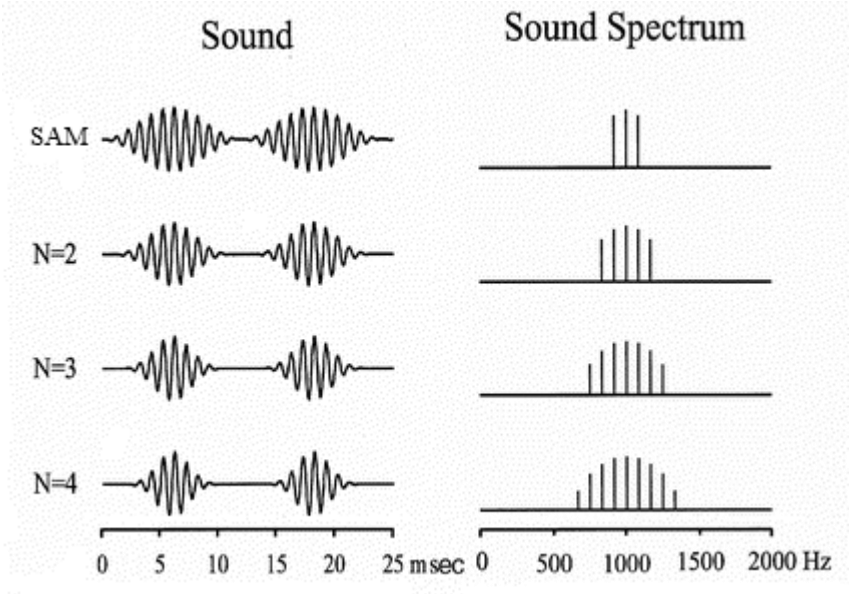


Figure 1.6: SAM and pulsatile stimuli to elicit ASSRs. *N* determines the power of the exponential envelope used to modulate the carrier frequency. Increasing the value of *N* decreases rise- and fall times and increases rise- and fall slopes. Increasing *N* increases the number of side bands in the frequency spectrum. Figure adapted from John et al. (2002).

1.6 ASSRs in dyslexia research

It is clear that ASSRs are an important tool to investigate how the auditory system processes the temporal modulations relevant to speech perception. Importantly, in this respect ASSRs might provide us critical insights into the neural markers of disorders that are related to atypical auditory temporal processing, such as dyslexia. Indeed, ASSR studies have already contributed to our understanding of the neurophysiological mechanisms underlying the development of dyslexia (De Vos et al., 2017a, 2017b; Granados Barbero et al., 2021, 2022; Lehongre et al., 2011; Marchesotti et al., 2020; McAnally & Stein, 1997; Menell et al., 1999; Mittag et al., 2022; Peter et al., 2023; Poelmans, Luts, Vandermosten, Boets, et al., 2012; Van Hirtum, Ghesquière, et al., 2019) (also see **1.3.2**). Whereas most of these studies used SAM stimuli, the study by Van Hirtum, Ghesquière, et al. (2019) demonstrated that pulsatile stimuli might be more suited to uncover the neural markers of dyslexia. Therefore, future research might benefit from the use of pulsatile stimuli. In Chapter 3, we use pulsatile stimuli to investigate the neural markers underlying the development of dyslexia.

1.7 The current doctoral research

The general aim of dyslexia research is the prevention of reading failure. A precise definition of the mechanisms underlying the development of dyslexia might contribute to the improvement of intervention strategies, which could in turn potentially reduce or even prevent reading failure. We can identify a few gaps in the literature that need to be filled in order to address this general aim. Although atypical (neural) auditory temporal processing has been demonstrated to relate to dyslexia, the specific mechanisms underlying this deficit are still unclear. Additionally, even though interventions have the potential to promote reading and its underlying mechanisms, they are often provided untimely. To meet these gaps, the current doctoral research has two overarching aims. The **first overarching aim** is to identify the neurophysiological markers of the auditory temporal processing deficit in dyslexia. The **second overarching aim** is to investigate the impact of a preventive intervention on the auditory temporal processing deficit in dyslexia. Even though the auditory temporal processing deficit is only a single deficit in a further complex and multifactorial etiology, targeting this deficit might still contribute to reducing reading failure.

To address our overarching aims, we conducted three studies. As to aim 1 (neurophysiological markers), we examined the suitability of acoustic stimuli with an increased potential to uncover the neural markers behind dyslexia in pre-reading to beginning reading children (Chapter 2). Next, we investigated the neurophysiological markers of auditory temporal processing in dyslexia in pre-reading to beginning reading children using the stimuli from Chapter 2 (Chapter 3). As to aim 2 (intervention), we assessed the additive impact of a preventive intervention combining enhanced speech with phonics-based training on neural synchronization (Chapter 3) and rise time discrimination (Chapter 4) in pre-readers at cognitive risk for dyslexia. Whereas investigating the impact of the intervention was the primary aim of Chapter 3, the investigation of neurophysiological markers underlying dyslexia was originally a secondary analysis in this same chapter. Nevertheless, we believe that the significance of the results of this initial secondary analysis justify its presentation as a separate aim of the doctoral research.

ASSRs are a valuable tool in order to investigate the auditory temporal processing deficit in dyslexia. Most studies that used ASSRs to characterize the auditory processing deficit in dyslexia used SAM stimuli to evoke ASSRs. However, it has recently been argued that more pulsatile stimuli with steeper slopes or sharper rise times have a greater potential to uncover the neurophysiological mechanisms behind dyslexia (Van Hirtum, Ghesquière, et al., 2019). A thorough investigation of the suitability of pulsatile stimuli in pre-reading and beginning reading children, a crucial age range for developmental reading research, remains to be performed. Therefore, in **Chapter 2**, we longitudinally investigate pulsatile stimuli in this age range in a large sample of typically reading children.

In **Chapter 3**, we build on Chapter 2 and use the pulsatile stimuli to characterize the auditory temporal processing deficit in dyslexia. The pulsatile stimuli allow us to investigate the impact of rise times on neural synchronization in dyslexia. This is an often overlooked, yet crucial line of research, since neural synchronization to rise times might be the specific neurophysiological deficit at play in dyslexia (Lizarazu, Lallier, et al., 2021; Van Hirtum, Ghesquière, et al., 2019). To this end, we longitudinally investigated neural synchronization to pulsatile and SAM stimuli in pre-reading to beginning reading children with dyslexia and typical readers. However, the primary goal of this longitudinal study was to introduce a preventive intervention that combined an enhanced speech intervention, designed to exaggerate rise times in the speech envelope and therefore addressing the auditory temporal sampling deficit, with a phonics-based intervention. We investigated its impact in pre-readers at cognitive risk for dyslexia, immediately post-intervention and after one year of formal reading instruction.

Chapter 4 is closely related to Chapter 3. The objective of Chapter 4 is to investigate the short- and long-term impact of the preventive intervention combining enhanced speech and phonics-based training on rise time discrimination. Impaired rise time discrimination is considered a core aspect of the auditory temporal processing deficit with cascading effects on reading-related skills (Goswami, 2018, 2019a; Lallier et al., 2018). Therefore, improving rise time discrimination might be a crucial step towards overcoming reading difficulties.

In summary, the current doctoral research aims to address several gaps in the literature based on recent research. The project novelty lies in the investigation of neural synchronization to rise times in children with dyslexia, as well as the implementation of an enhanced speech intervention already in pre-readers at cognitive risk for dyslexia. This has a potential impact on the understanding of the auditory processing deficit in dyslexia and is anticipated to contribute to the improvement of interventions for dyslexia.

The current doctoral research was part of a larger longitudinal study investigating the neurocognitive impact of a preventive intervention in pre-readers at cognitive risk for dyslexia. Whereas the focus of the current doctoral thesis is on auditory temporal processing, the neuroanatomical and behavioral outcomes of the intervention are described in other doctoral research projects (Economou, 2022; Vanden Bempt, 2023). The work described in this doctoral thesis was undertaken within the Dyslexia Research Collaboration Leuven (DYSCO), a collaboration between the research group of Experimental Oto-Rhinolaryngology at the Faculty of Medicine and the Parenting and Special Education research unit at the Faculty of Psychology and Educational Sciences. All research protocols were approved by the Medical Ethical Committee of the Leuven University Hospital (B322201836276).

Chapter 2

Pulsatile stimuli in a pediatric population

The content of this chapter is under revision for NeuroImage as: Van Herck, S., Economou, M., Vanden Bempt, F., Ghesquière, P., Vandermosten, M. & Wouters, J. Pulsatile modulation greatly enhances neural synchronization at syllable rate in children.

Abstract

Neural processing of the speech envelope is of crucial importance for speech perception and comprehension. This envelope processing is often investigated by measuring neural synchronization to sinusoidal amplitude modulated stimuli at different modulation frequencies. However, it has been argued that these stimuli lack ecological validity. Pulsatile amplitude

modulated stimuli, on the other hand, are suggested to be more ecologically valid and efficient, and have increased potential to uncover the neural mechanisms behind some developmental disorders such a dyslexia. Nonetheless, pulsatile stimuli have not yet been investigated in pre-reading and beginning reading children, which is a crucial age for developmental reading research. We performed a longitudinal study to examine the potential of pulsatile stimuli in this age range. Fifty-two typically reading children were tested at three time points from the middle of their last year of kindergarten (5 years old) to the end of first grade (7 years old). Using electroencephalography, we measured neural synchronization to syllable rate and phoneme rate sinusoidal and pulsatile amplitude modulated stimuli. Our results revealed that the pulsatile stimuli significantly enhance neural synchronization at syllable rate, compared to the sinusoidal stimuli. Additionally, the pulsatile stimuli at syllable rate elicited a different hemispheric specialization, more closely resembling natural speech envelope tracking. We postulate that using the pulsatile stimuli greatly increases EEG data acquisition efficiency compared to the common sinusoidal amplitude modulated stimuli in research in younger children and in developmental reading research.

2.1 Introduction

Speech perception and comprehension are skills that people often take for granted. Nevertheless, the auditory perception of a complex and dynamic signal such as natural speech depends on several processes. It is generally agreed upon that the ability of the auditory system to process the speech envelope, which contains temporal modulations in the speech signal below 50 Hz (Rosen, 1992), is crucial for speech perception (Drullman et al., 1994; Shannon et al., 1995). Amplitude modulation rates in the speech envelope coincide with linguistically meaningful units such as phonemes (gamma and beta range; > 30 Hz and 13-30 Hz respectively), syllables (theta and delta range; 4-8 Hz and < 4 Hz respectively) and intonational phrase boundaries (delta range; < 4 Hz) (Ghitza, 2011; Ghitza & Greenberg, 2009; Meyer, 2018; Poeppel, 2003). The neural mechanism proposed to underlie their perception is neural synchronization, which refers to the phase-locking of neural oscillations to temporal modulations in the speech envelope (Peelle &

Davis, 2012). Successful neural synchronization is indeed strongly associated with speech perception and intelligibility (Ghitza & Greenberg, 2009; Giraud & Poeppel, 2012a; Luo & Poeppel, 2007; Peelle & Davis, 2012; Riecke et al., 2018). Furthermore, influential speech perception theories such as the 'asymmetric sampling in time' or AST theory suggest a hemispheric specialization in which slow temporal rates are preferentially processed in the left hemisphere, whereas fast temporal rates are preferentially processed in the right hemisphere or bilaterally (Poeppel, 2003).

Over the past decades, several electrophysiological paradigms have been developed in order to investigate the neural processing of the speech envelope. One such paradigm involves measuring the brain's response to natural speech (Aiken & Picton, 2008; Vanthornhout et al., 2018). Although ecologically relevant, using real speech poses a few challenges such as disentangling aspects of the neural response that are associated with comprehension from those associated with actual envelope processing (Gransier & Wouters, 2021). Gransier & Wouters (2021) argue that despite the importance of using real speech for understanding how it is processed by the brain, this stimulus is suboptimal to investigate (deficits in) envelope processing. A paradigm that allows to investigate envelope processing without having to face these challenges involves sinusoidally amplitude modulated (SAM) sounds (Alaerts et al., 2009; Rees et al., 1986; Wang et al., 2012). Such stimuli evoke Auditory Steady-State Responses (ASSRs), which measure how well the auditory system phase-locks or synchronizes to a stimulus rhythm (Picton et al., 2003). Measuring ASSRs to multiple frequencies provides insight into how the auditory system processes the temporal modulations relevant to speech perception. However, it has been argued that SAM stimuli do not accurately represent the features of our acoustic world and are suboptimal for investigating speech processing (Prendergast et al., 2010). Prendergast et al. (2010) stated that the speech envelope mainly consists of short pulsatile bursts of energy rather than gradual transitions such as those in SAM stimuli. These sharper edges or rise times in speech are specifically important for neural synchronization to the speech envelope. Rise times trigger neural oscillations to accurately synchronize to the temporal modulations in the speech signal (Gross et al., 2013) and it is specifically their sharpness that facilitates synchronization (Doelling et al., 2014). In this respect, more pulsatile stimuli with sharper

rise times might better represent the features of our acoustic world and are hence more ecologically valid and suitable to investigate speech processing (Prendergast et al., 2010).

Aforementioned pulsatile stimuli have already been developed and implemented in a few studies (John et al., 2002, 2003, 2004; Prendergast et al., 2010; Van Hirtum, Ghesquière, et al., 2019). In these studies, the envelope shape of SAM sounds was varied (semi-)exponentially, leading to a rise time reduction of the stimuli without affecting the rate at which the envelope is amplitude modulated. Exponentially modulated tonal stimuli significantly increase steady-state responses compared to SAM stimuli with the same modulation frequencies in both adults (John et al., 2002; Prendergast et al., 2010) and young infants (John et al., 2004). It is argued that stronger responses such as the ones obtained by the pulsatile stimuli allow for more rapid and accurate detection of responses (John et al., 2002, 2004) and are more suitable for investigations of neural synchronization (Prendergast et al., 2010). A study by Van Hirtum, Ghesquière, et al. (2019) confirmed stronger responses to pulsatile, in their case modulated noise stimuli, at least in typically reading adults and at modulation frequencies of 4, 10 and 40 Hz. Additionally, the authors demonstrated an atypical neural synchronization in people with dyslexia, a developmental reading disorder, only when using the pulsatile stimuli, and not when using the SAM stimuli. Atypical neural synchronization is suggested to contribute to the development of dyslexia (Goswami, 2011), and by using the pulsatile stimuli, Van Hirtum, Ghesquière, et al. (2019) now allocated this to a deficit with neural synchronization to sharper rise times specifically. Hence, using pulsatile stimuli instead of SAM stimuli is also beneficial for uncovering the neural mechanisms behind developmental disorders such as dyslexia.

Researchers aiming to uncover these neural mechanisms often focus on the pre-reading to beginning reading age range, considering that there is a natural plasticity window for reading in this period (Phan et al., 2021) and that research during this period allows to uncover the causal mechanisms behind the disorder. The pulsatile stimuli could prove invaluable for such investigations. Not only are these stimuli suggested to make detection of responses more efficient (John et al., 2002, 2004), which is of particular interest in pediatric populations in which acquiring extensive electrophysiological (EEG) data can be challenging. As Prendergast et al. (2010) suggested, they are also more suitable for representing our real

acoustic world. Despite these clear advantages of the pulsatile stimuli over SAM stimuli with respect to ecological validity and efficiency, only very few studies in children have included these kinds of stimuli. Most studies investigating neural synchronization to the speech envelope in children included only regular SAM stimuli (De Vos et al., 2017a, 2020; Lizarazu et al., 2015; Vanvooren et al., 2014, 2015). To the best of our knowledge, only the study of John et al. (2004) investigated the application of pulsatile stimuli in young children, and confirmed stronger responses to these stimuli in newborn infants. However, a thorough investigation of pulsatile stimuli in pre-reading to beginning reading age still remains to be performed before their application in research in younger children and developmental reading research aiming to uncover neural precursors of dyslexia.

To this end, we designed a longitudinal study that investigates responses to pulsatile stimuli in Dutch-speaking pre-reading to beginning reading children with typical reading skills. We longitudinally investigated ASSRs to SAM stimuli and pulsatile (PULS) stimuli with envelope shapes in which the rise times were fixed to 30 ms. Measurements took place in the middle (T0) and at the end (T1) of the last year of kindergarten, and at the end of first grade (T2), after approximately one year of formal reading instruction. We included 4 Hz (syllable rate) and 20 Hz (phoneme rate) modulations considering their frequent application in reading research and direct links to linguistically meaningful units (De Vos et al., 2017a, 2017b; Poelmans, Luts, Vandermosten, Boets, et al., 2012; Van Hirtum, Ghesquière, et al., 2019; Vanvooren et al., 2014). In line with the study of Van Hirtum, Ghesquière, et al. (2019), we hypothesized to find stronger ASSR responses to the PULS stimuli compared to the SAM stimuli. We suggest that the physiological basis for these hypothesized stronger responses lies in the enhancement of the probability of discharge at the synapse to the auditory nerve fiber at the onset of a stimulus, which is more prominent for steeper stimulus onset slopes (Delgutte, 1980, 1997; Geurts & Wouters, 1999). Furthermore, we hypothesize stronger responses to the PULS stimuli to be more marked at 4 Hz, considering that the difference between the rise times of the SAM and PULS stimuli is much greater at 4 Hz than at 20 Hz. Based on Van Hirtum, Ghesquière, et al. (2019), we did not expect stimulus type to impact hemispheric specialization. Furthermore, we hypothesized that the PULS stimuli, because of their stronger responses, might reveal more subtle maturational effects that are possibly not revealed by the SAM stimuli.

Investigating maturation of neural synchronization is not a primary goal in the current study, but examining the suitability of the PULS stimuli across pre-reading and beginning reading stages is an important prerequisite for future longitudinal developmental reading research, where investigating maturation of neural synchronization is a primary goal.

2.2 Materials and Methods

2.2.1 Participants

Fifty-two children (31 male) participated in the current study. The children were recruited from a large preventive reading intervention study in children at cognitive risk for developing dyslexia in which EEG measurements were collected (N=91) (see Economou, Van Herck, et al., 2022; Van Herck, Vanden Bempt, et al., 2022; Vanden Bempt et al., 2021; Vanden Bempt, Economou, et al., 2022). All children in the current study were retrospectively classified as typical readers based on standardized word reading (Brus & Voeten, 1973; Verhoeven, 1995) and pseudoword reading tasks (van den Bos et al., 1994), and a standardized spelling task (Deloof, 2006) at the start of third grade. In total, third grade reading data were obtained for 78 of the children that participated in the intervention study with EEG measurements. Of the 78 participating children, 26 were classified as dyslexic readers, meaning that they scored below the 10^{th} percentile on at least one of the reading or spelling tasks, and below the 25^{th} percentile on all other reading and spelling tasks, and were not included in the current study. All remaining children (n = 52) were classified as typical readers and included in the current study. In the course of the intervention study, all children received some kind of (reading) intervention between T0 and T1, which is outside the scope of the current study, but which is thoroughly described in Economou et al. (2022), Van Herck, Vanden Bempt, et al. (2022), Van Herck, Economou, Vanden Bempt, Glatz et al. (2022) and Vanden Bempt et al. (2021, 2022). Of the sample included in the current study, 17 children belonged to a group receiving a phonics-based training and a story-listening game with auditory training, 22 children received a phonics-based training and a story-listening game without auditory training, and 13 children received a control game combined with the story-listening

game without auditory training. All children were native Dutch speakers with bilateral normal hearing, had neither history of brain damage or neurological disorders, nor (preliminary) diagnosis of autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD), did not receive any speech therapy due to language and/or articulatory problems and had already received a total pre-primary schooling period of at least 20 months by the start of the longitudinal study. All children scored above a norm score of 75.3 on the Raven's Colored Progressive Matrices (Raven et al., 1984). See **Table 2.1** for participant characteristics.

In the course of the longitudinal study, EEG measurements were collected at three time points, corresponding to the time points implemented in the intervention study from which the participants were recruited. Data were collected at T0 (age: *M* = 5 years, 5 months; *SD* = 3 months; middle of third year of kindergarten), T1 (age: *M* = 5 years, 10 months, *SD* = 3 months; end of third year of kindergarten) and T2 (age: *M* = 7 years, 0 months; *SD* = 3 months; end of first grade of primary school). Even though the intervention is not of interest for the current study, we use the longitudinally collected EEG data from all three time points in order to investigate neural synchronization across development from pre-reading to beginning reading age.

At T0, we collected EEG data in all children. Measurements of 14 out of 208 conditions (four conditions per child) were excluded for the following reasons: (1) excessive noise levels, meaning that the mean peak-to-peak amplitude across epochs of the combined left or right channel (see **2.2.2**) exceeded a threshold of six times the median of the mean peak-to-peak amplitudes across all channels, in line with earlier work in our research lab (2) measurement was ended prematurely, (3) data of the specific condition was not collected, (4) uncertainty about the child's hearing of the stimulus. Note that in case of excluded conditions, available conditions of a child are still included in analyses. At T1, five children discontinued participation. Additionally, 5 out of 188 conditions were excluded. Six children discontinued participation at T2. Here, 4 out of 184 conditions were excluded.

The study was approved by the Medical Ethical Committee of the University Hospital of Leuven, KU Leuven, and signed informed consents were obtained for all participants in line with the Declaration of Helsinki.

Table 2.1: Participant characteristics

Characteristic	Levels	(*N* = 52)	
		M	*SD*
Age T0 (months)		65	3
Non-verbal IQ[a]		101	14
Sex	Male/Female	31/21	
SES[b]	Low/Middle/High	14/16/22	
Handedness	Left/Ambidextrous/Right	5/4/43	

Note. *M* = group mean, *SD* = standard deviation, SES = socio-economic status. For categorical data (i.e. sex, SES and handedness) the numbers in each group are reported instead of *M* and *SD*.
[a] Reported scores are standardized scores based on the *M* and *SD* of a large scale screening in the last year of kindergarten (N=1225) (*M* = 98.15, *SD* = 16.66)
[b] SES is based on the parental educational level of the mother

2.2.2 EEG measures

Recording parameters

EEG signals were recorded with the BioSemi ActiveTwo system using 64 active Ag/AgCL electrodes mounted in head caps according to the 10-20 electrode system. A sample rate of 16384 Hz was used. The system uses a built-in low-pass filter with a cutoff frequency of 3276 Hz. This sampling rate, even though relatively high considering the frequencies of interest in the current study, ensures comparability within our research lab and allows for accurate modelling of artifacts. Electrode offsets were kept between -25 mV and 25 mV. Recordings were carried out in a double-walled soundproof booth with Faraday cage. Children sat down in a comfortable chair during the measurement while watching a soundless movie of their choice. This passive listening paradigm has previously been used in pediatric ASSR studies (De Vos et al., 2017a; Vanvooren et al., 2014) and ensures a similar level of alertness and attention across subjects throughout the measurement. An experienced test leader accompanied the child in the EEG cabin for the entire duration of the measurement.

For each subject, we collected four EEG measurements (two modulation frequencies x two stimulus types). Each condition lasted approximately 9 minutes (532.48 sec).

Auditory Steady State Responses

Stimuli used to evoke ASSRs consisted of continuous amplitude modulated speech-weighted noise. The carrier noise was adopted from the "Leuven Intelligibility Sentence Test" (LIST; Van Wieringen & Wouters, 2008). This represents the long-term average speech spectrum of 730 sentences of a female speaker. The speech-weighted noise was 100% amplitude modulated at approximately 4 and 20 Hz (exact frequencies 3.91 and 19.53 Hz) (Vanvooren et al., 2015), to measure neural synchronization of theta and beta oscillations respectively. For each modulation frequency, we created two conditions or stimulus types, see **Figure 2.1** . In the sinusoidal amplitude modulated condition (SAM) a sinusoidal envelope modulation was implemented. In the pulsatile condition (PULS), an envelope shape was applied with a linear rise time (the time it takes to go from minimal to maximal amplitude) fixed at 30 ms, no plateau, and a fall time fixed at 10 ms, without affecting amplitude modulation rates at 4 and 20 Hz. The PULS stimuli are similar to those used in the study of Van Hirtum, Ghesquière, et al. (2019), except for the use of white noise instead of speech-weighted noise in their study. All stimuli were created so that the SAM and PULS stimuli were equal in RMS level in windows of approximately 30 ms, which for the PULS stimuli only contained the samples of the signal containing energy (rise and fall times). This resulted in the spectral representations as illustrated in **Figure 2.1**. Spectra of all stimuli were very similar, apart from a difference of approximately 10 dB between the 4 Hz SAM and 4 Hz PULS stimulus. This difference was normalized during the calibration procedure in which the stimuli were matched in peak-to-peak level. All stimuli were presented monaurally at 70 dBpeSPL through a calibrated ER-3B insert earphone to the right ear.

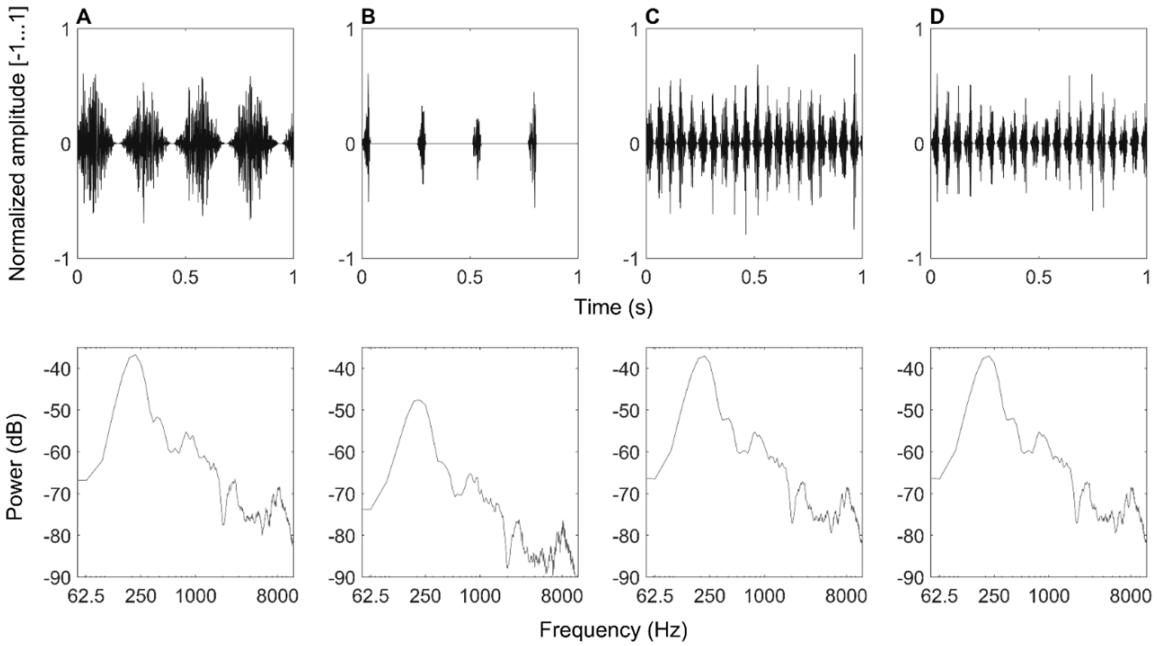


Figure 2.1: SAM and PULS stimuli. A 1 second waveform (upper panels) and spectral representation (lower panels) of the (A) 4 Hz SAM, (B) 4 Hz PULS, (C) 20 Hz SAM and (D) 20 Hz PULS stimuli.

Preprocessing

Preprocessing was performed in Matlab R2016b (The MathWorks Inc, 2016). First, the EEG signal was high-pass filtered with a second-order Butterworth filter with a cutoff frequency of 2 Hz to remove the DC component. After filtering, the signals were averaged across a pre-selected electrode configuration into one recording channel representing the left hemisphere and one channel representing the right hemisphere. Nine electrodes in the left (TP7, P1, P3, P5, P7, P9, PO3, PO7, and O1) and nine electrodes in the right hemisphere (TP8, P2, P4, P6, P8, P10, PO4, PO8, and O2) were included. This configuration was based on previous research showing that these electrodes are most sensitive to pick up ASSRs in children (Vanvooren et al., 2014). The suitability of this electrode configuration was confirmed in the current dataset by calculating the average number of significant responses for all electrode pairs and all conditions included in the study. The average was 87% and 89% for 4 and 20 Hz respectively. Next, the signal was segmented into epochs of 1.024 seconds. We then applied an epoch-based artifact rejection to remove muscle potentials and other artifacts. The aim was to obtain 448 epochs per subject with the lowest

amount of artifacts in all channels. Epochs with the highest maximum absolute amplitude were removed until 448 epochs remained per electrode. Hence, the amplitude rejection level was set on an individual basis,. The remaining 448 epochs were re-referenced to Cz. A fast Fourier transform (FFT) algorithm was applied to calculate the complex frequency spectrum for each of the remaining epochs (**Figure 2.2**). From the complex frequency spectrum, we obtained the response power, amplitude and phase corresponding to the modulation frequencies used during the experiment (i.e. 4 and 20 Hz, the response spectrum). Mean response amplitudes and phases were computed by vector averaging the complex response spectrum across epochs. The neural background noise was calculated based on the "standard deviation of the mean" (Gransier et al., 2017). This measure assumes that the measured ASSR, as present in the response spectrum, consists out of both the steady state response, constant in phase and amplitude over time, and the neural background activity, varying randomly in phase and amplitude over time. The "standard deviation of the mean", calculated as the standard deviation over epochs divided by the square root of the number of epochs, therefore directly reflects the average amplitude across epochs of the neural background activity (Gransier et al., 2017). This measure, compared to the "neighboring bins estimate", does not underestimate neural background noise when it is higher in the bin of interest compared to the neighboring bins. At both syllable and phoneme rates, noise decreased over time. Median noise values at 4 Hz were 0.335 μV, 0.330 μV and 0.311 μV for T0, T1 and T2 respectively. Median noise values at 20 Hz were 0.065 μV, 0.066 μV and 0.063 μV for T0, T1 and T2 respectively. Finally, a one sample Hotelling T^2 test combining amplitude and phase was performed to determine whether the synchronized activity differed significantly from the neural background activity and hence whether a reliable ASSR (i.e. significant response) was present in the EEG signal (Picton et al., 2003). This test was performed at the modulation frequency bin.

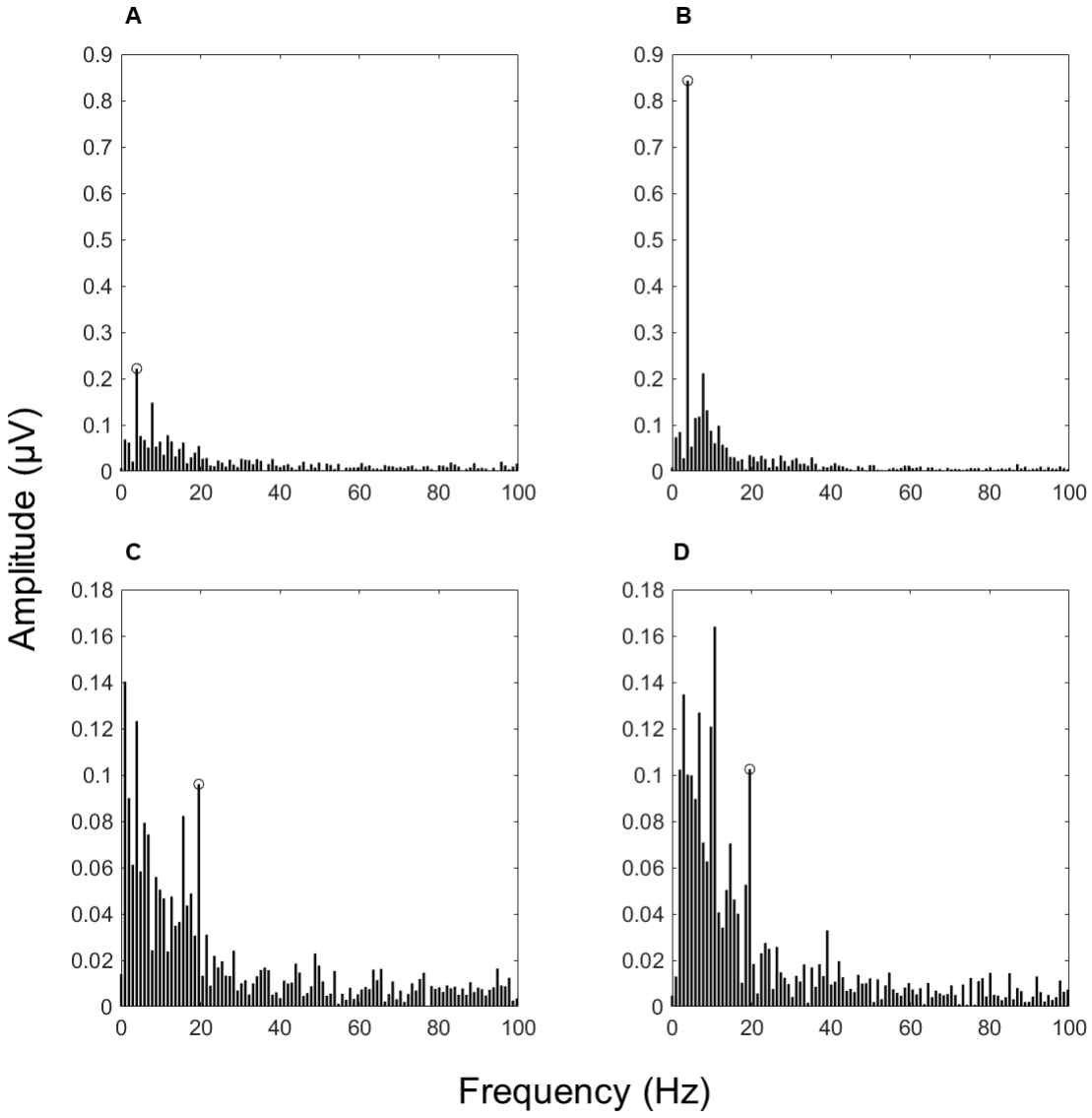


Figure 2.2: Frequency spectra of the EEG signals. The frequency spectrum of the recorded EEG of one randomly selected subject after preprocessing for the (A) 4 Hz SAM, (B) 4 Hz PULS, (C) 20 Hz SAM and (D) 20 Hz PULS conditions. The circle indicates the stimulation frequency in that specific condition.

2.2.3 Statistical analyses

Statistical analysis was performed in R (version 3.5.1) (R Core Team, 2018). Prior to analysis, the assumption of normality of the residuals was assessed using Kolmogorov-Smirnov tests. Levene tests were performed to test for homogeneity of variance. Both assumptions were violated, hence we adopted robust estimation methods for the analyses.

To assess the effects of the stimulus types on neural synchronization, as well as the impact of stimulus type on hemispheric specialization and maturation or development, robust linear mixed-effects models (robustlmm package) (Koller, 2016) were fitted for each modulation frequency (4 and 20 Hz) separately. Stimulus type (SAM and PULS), hemisphere (left and right) and test phase (T0, T1 and T2) were included in the model as fixed effects. A random intercept was included per subject to account for repeated measures. P values with a significance level of $p < .05$ for the fixed effects and their interactions in the model were obtained by means of bootstrapping as suggested by Koller (2016). Considering that all children included in the current study received some kind of (reading) intervention, we ruled out the impact of the intervention on our research question. Therefore, we additionally fitted models with intervention group added as a covariate. There were no significant effects regarding the intervention group factor (all $p > .05$). To further confirm that the intervention had a negligible impact, we subsequently compared the models including the intervention group factor to the models without the intervention group factor. Comparison of these models demonstrated no differences between both, so we opted for the model without intervention group included as a covariate for further analyses.

We used a parametric bootstrapping approach with 1000 simulations. Post-hoc comparisons on the interactions were performed using estimated marginal means with a Holm correction for multiple comparisons. Descriptives are reported as medians and interquartile ranges.

2.3 Results

2.3.1 Response amplitudes

Descriptive data for ASSR response amplitudes are provided in **Table 2.2** and an illustration of the raw data can be found in **Figure 2.3** (4 Hz) and **Figure 2.4** (20 Hz). For 4 Hz response amplitudes, a significant main effect of test phase ($\chi^2(2) = 40.37$, $p < .001$) was found. Overall, 4 Hz response amplitudes were significantly smaller at T0 ($z = -6.757$, $p < .001$, 95 % asymptotic CI [-0.472, -0.225]) and T1 ($z = -5.506$, $p < .001$, 95 % asymptotic CI [-0.416, -0.164]) compared to T2, while response amplitudes did not differ between T0 and T1 ($z = -1.133$, $p = .257$, 95 % asymptotic CI

[-0.183, 0.066]). Apart from the main effect of test phase, the interaction between stimulus type and hemisphere was also significant ($\chi^2(1) = 24.50$, $p < .001$). Overall, there were larger responses to the PULS than to the SAM stimuli, in both the left ($z = 27.053$, $p < .001$, 95 % asymptotic CI [1.447, 1.742]) and right ($z = 19.152$, $p < .001$, 95 % asymptotic CI [0.982, 1.276]) hemisphere. Additionally, whereas in response to the SAM stimuli there was an overall larger response in the right hemisphere compared to the left hemisphere ($z = 3.344$, $p < .001$, 95 % asymptotic CI [0.050, 0.347]), the opposite pattern, i.e. a larger response in the left hemisphere, was found in response to the PULS stimuli ($z = 4.578$, $p < .001$, 95 % asymptotic CI [0.121, 0.413]). None of the interaction effects with test phase was significant (all $p > .05$).

John et al. (2004) already emphasized that stimuli that elicit increased response amplitudes should shorten the time needed to measure significant ASSRs. The authors state that for stimuli with increased amplitudes you only need $1/X^2$ of the time to reach the same signal-to-noise ratio (SNR), with X representing the ratio of the response amplitudes of the two stimuli. In the current study, the average response amplitude of the 4 Hz SAM stimuli is 1.12 μV, whereas that of the 4 Hz PULS stimuli is 2.52 μV. Hence, the time required to reach a certain SNR when using the PULS stimuli is $1/(2.52/1.12)^2$, which equals 0.20 or 20% of the time required to reach this same SNR when using the SAM stimuli.

For 20 Hz response amplitudes, only the main effect of test phase reached significance ($\chi^2(2) = 21.10$, $p < .001$) (see **Figure 2.4**). Similar to this main effect at 4 Hz, response amplitudes at 20 Hz did not differ between T0 and T1 ($z = -1.615$, $p = .106$, 95 % asymptotic CI [-0.039, 0.008]), while they were significantly smaller at T0 ($z = -4.750$, $p < .001$, 95 % asymptotic CI [-0.070, -0.023]) and T1 ($z = -3.106$, $p = .004$, 95 % asymptotic CI [-0.054, -0.007]) compared to T2. None of the other effects reached significance (all $p > .05$).

Table 2.2: Descriptives of response amplitudes (in μV) for all frequencies, stimulus types, hemispheres and test phases separately

Modulation frequency	Stimulus type	Hemisphere	T0		T1		T2	
			Mdn	*IQR*	*Mdn*	*IQR*	*Mdn*	*IQR*
4 Hz	SAM	Left	0.81	0.60	0.96	0.69	1.20	0.64
		Right	1.10	0.66	1.06	0.64	1.33	0.47
	PULS	Left	2.46	1.09	2.43	1.07	2.85	1.17
		Right	2.21	0.93	2.15	0.86	2.42	0.90
20 Hz	SAM	Left	0.30	0.30	0.28	0.26	0.32	0.24
		Right	0.29	0.27	0.30	0.26	0.36	0.23
	PULS	Left	0.28	0.25	0.31	0.28	0.34	0.23
		Right	0.27	0.21	0.27	0.26	0.33	0.25

Mdn = median, *IQR* = interquartile range

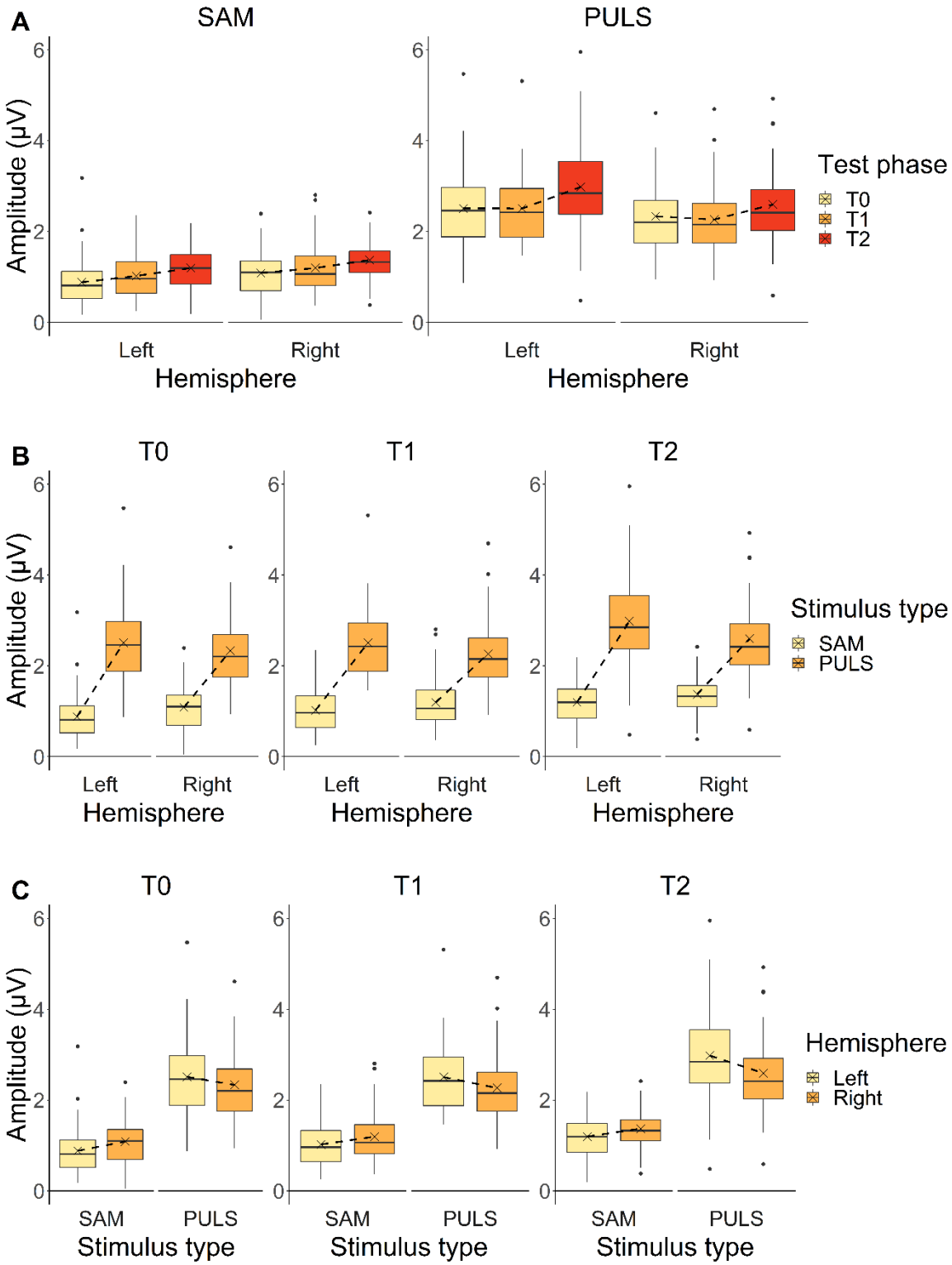


Figure 2.3: Response amplitudes for the different stimulus types, hemispheres and test phases at 4 Hz. Crosses indicate raw data mean response amplitudes. Individual points represent outliers, determined as all individual points below Q1 – 1.5 x IQR / above Q3 + 1.5 x IQR. All three panels are different representations of the same data. The three panels depict the different significant effects found at 4 Hz. Dashed lines are used to clearly indicate the effect of interest. Panel A depicts the main effect of test phase. Panel

B depicts the difference between the SAM and PULS stimulus types. Panel C depicts the interaction between stimulus type and hemisphere.

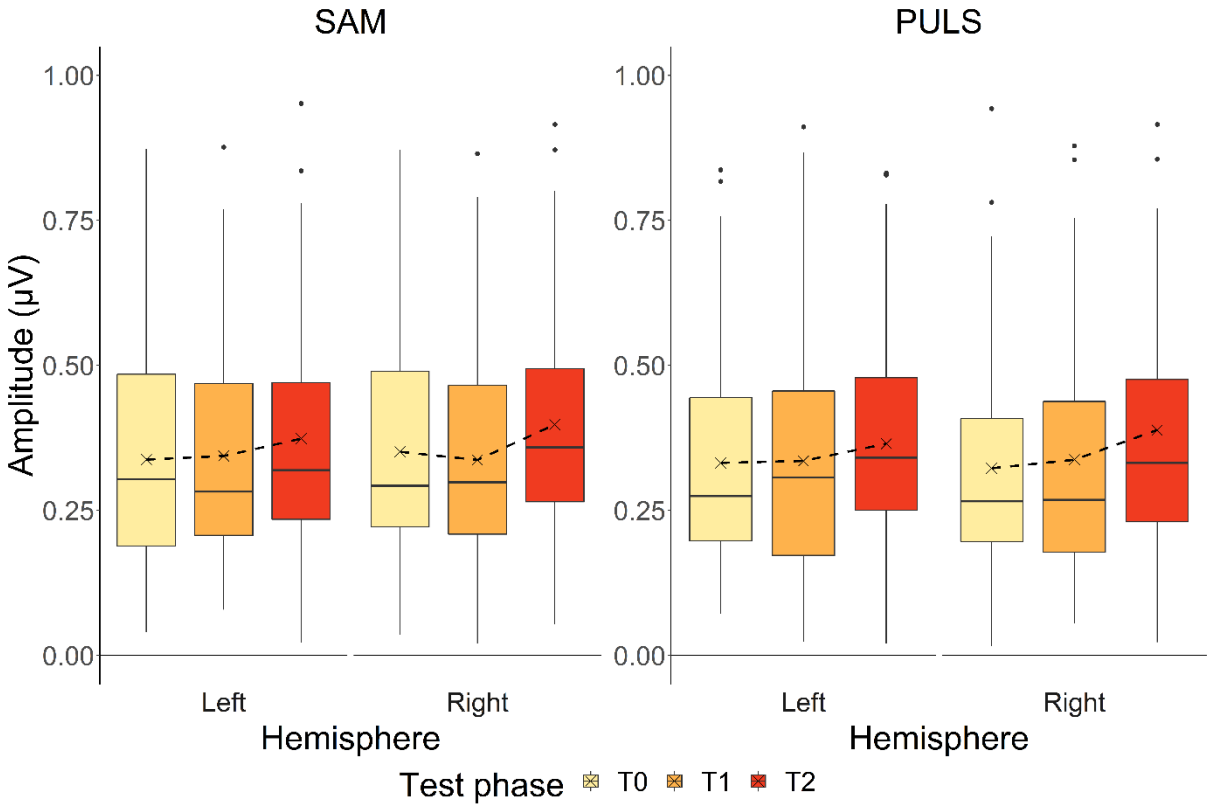


Figure 2.4: Response amplitudes for the different stimulus types, hemispheres and test phases at 20 Hz, demonstrating the test phase differences. Crosses indicate raw data mean response amplitudes. Individual points represent outliers, determined as all individual points below Q1 – 1.5 x IQR / above Q3 + 1.5 x IQR. The dashed lines connect the means of the three test phases to clearly depict the main effect of test phase.

2.3.2 Percentage significant responses

As a consequence of the significantly larger responses to the PULS compared to the SAM stimuli at 4 Hz, the question arose whether the percentage of significant responses would be higher for it. The percentage significant responses, averaged over hemispheres and test phases was 82% for the 4 Hz SAM and 99% for the 4 Hz PULS stimuli.

2.4 Discussion

Measuring neural synchronization to SAM sounds by means of ASSR is a useful technique to investigate envelope processing (Alaerts et al., 2009; Picton, 2010; Picton et al., 2003; Rees et al., 1986; Wang et al., 2012). However, it has been argued that pulsatile stimuli with sharper rise times are more ecologically valid (Prendergast et al., 2010), and additionally, that they induce stronger responses than regular SAM sounds and are hence more efficient for response detection (John et al., 2002, 2004; Prendergast et al., 2010; Van Hirtum et al., 2019). Interestingly, pulsatile stimuli have also been demonstrated to be effective for uncovering the neural mechanisms behind developmental disorders such as dyslexia (Van Hirtum, Ghesquière, et al., 2019). If, however, we aim to apply pulsatile stimuli in developmental reading research aiming to uncover neural precursors of dyslexia, we first need to investigate their potential in the crucial age range of pre-reading to beginning reading age (Phan et al., 2021), which was the objective of the current longitudinal study. We compared responses to PULS and SAM stimuli from the middle of the last year of kindergarten (5 year olds) to the end of first grade (7 year olds) in Dutch-speaking typically reading children. Neural synchronization was measured at syllable (4 Hz) and phoneme rate (20 Hz) using both SAM and PULS stimuli.

Our results revealed stronger synchronization to the PULS compared to the SAM stimuli, only at 4 Hz. At this same frequency, stimulus type impacted hemispheric specialization in the sense that responses at 4 Hz were lateralized to the right hemisphere with the SAM stimuli, but lateralized to the left hemisphere with the PULS stimuli. At both 4 and 20 Hz, there was an increase in synchronization from T0 and T1 to T2.

2.4.1 Synchronization to syllable rate information

PULS stimuli enhance synchronization

In the current study, responses at 4 Hz to the PULS stimuli were significantly enhanced compared to responses to the SAM stimuli. Whereas the median response amplitude was 1.10 μV for the SAM stimuli, the response for the PULS stimuli was significantly larger with a median response amplitude of 2.42 μV. These results thus support previous studies demonstrating

increased responses to pulsatile stimuli (John et al., 2002, 2004; Prendergast et al., 2010; Van Hirtum et al., 2019), now extending this finding to pre-reading to beginning reading children. We hypothesized that stronger responses to the PULS stimuli could be related to discharge probabilities at the synapse to the auditory nerve fiber. This discharge probability peaks at stimulus onsets and is more prominent for steeper stimulus onset slopes (Delgutte, 1980, 1997; Geurts & Wouters, 1999), such as in the PULS stimuli. Nevertheless, we did not explicitly investigate the physiological basis of the findings in the current study, which would make an interesting research question for future research.

This finding entails multiple benefits. First, with respect to EEG data acquisition, the use of PULS stimuli should be more efficient than the use of SAM stimuli. As suggested by John et al. (2002) and John et al. (2004), using pulsatile stimuli should significantly shorten the time needed to measure significant ASSRs because of the increased response amplitudes to the stimuli. In the current study, we demonstrated that using the PULS stimuli reduced this time by 80%. A more efficient response detection is particularly convenient in a pediatric population such as our pre-reading to beginning reading children. EEG data acquisition requires considerable effort from both the child and the researcher. Sitting still and staying attentive during an EEG measurement for an extended period of time is a challenge for most children, and the resulting poor data quality is often frustrating for researchers. Stimuli that shorten the time needed to obtain significant ASSRs could ease the process for participating children and executing researchers. Furthermore, a shortened acquisition time can be decisive when applied in clinical environments where duration of tests is an important factor. Hence, the current results exert a major impact on both EEG research, especially in pediatric populations, and on clinical practice.

Second, the PULS stimuli at syllable rate might significantly contribute to, for example, developmental reading research. Van Hirtum, Ghesquière, et al. (2019) revealed an atypical neural synchronization in dyslexic young adults only when using the PULS stimuli, and not when using the SAM stimuli. The authors thus demonstrated the added value of the PULS stimuli to reading research. An important period for developmental reading research is from pre-reading to beginning reading age, since research during this period allows to uncover causal neural mechanisms behind the disorder. We now demonstrated significantly stronger and more efficiently evoked

responses to the PULS stimuli at syllable rate in this specific age range. Hence, the PULS stimuli are especially promising for reading research conducted in younger children, with the potential of uncovering the neural precursors behind dyslexia.

Third, this increased synchronization to the PULS stimuli provides an explanation for the efficacy of speech envelope enhancement (EE) as a technique to improve speech perception (Van Hirtum et al., 2021; Van Hirtum, Moncada-Torres, et al., 2019). EE was originally developed for use in cochlear implant users (Geurts & Wouters, 1999; Koning & Wouters, 2012, 2016) and specifically accentuates rise times in the speech envelope, which should facilitate their detection. More recently, Van Hirtum, Moncada-Torres, et al. (2019) and Van Hirtum et al. (2021) demonstrated that applying EE in a speech-in-noise task instantaneously improved speech perception in young adults. The researchers hypothesized that EE, due to the accentuated rise times in the speech signal, enhanced synchronization to speech, hence resulting in improved speech perception. EE bears strong similarities to our PULS stimuli, since both techniques emphasize the temporal dynamics of the speech envelope, more specifically by sharpening the rise times. Importantly, amplified rise times in EE occur at approximately syllable rate (Van Hirtum, Moncada-Torres, et al., 2019), whereas our results demonstrated that sharper, pulsatile stimuli enhance synchronization specifically at this rate. Therefore, it is highly plausible that EE indeed enhances synchronization to the speech signal, hence resulting in improved speech perception. An interesting question for future research is to investigate whether using EE on speech indeed enhances synchronization to the same extent as our PULS stimuli.

Whereas we could demonstrate clear differences in responses between the SAM and PULS stimuli at 4 Hz, at 20 Hz, responses to both stimulus types were similar. This is not surprising if we look at the rise times of the stimuli. At 4 Hz, the pulsatile modulation decreased the rise time of the stimulus from 125 ms for the SAM stimulus to 30 ms for the PULS stimulus, creating a much more sudden onset for the PULS stimulus. On the contrary, for 20 Hz, the rise time of the PULS stimulus (30 ms) only differed slightly from that of the SAM stimulus (25 ms). Hence, at 20 Hz there is almost no difference between the rise times of the SAM and the PULS stimuli, which is why we propose that we were not able to demonstrate differences in neural responses to both stimuli.

Hemispheric specialization is sensitive to stimulus type

Hemispheric specialization in the current study was sensitive to stimulus type. At 4 Hz, we demonstrated a rightward lateralization in response to the SAM stimuli, and a leftward lateralization in response to the PULS stimuli.

This result was rather unexpected given the consistency with which rightward lateralization is demonstrated at 4 Hz (De Vos et al., 2017a; Lizarazu et al., 2015; Luo & Poeppel, 2007; Poelmans et al., 2012; Vanvooren et al., 2014, 2015). The study by Van Hirtum, Ghesquière, et al., (2019) who used very similar pulsatile stimuli to the ones in the current study could not confirm any effects of stimulus type on lateralization. Their study, however, included young adults, while the current study focused on pre-reading to beginning reading children. It is possible that the link between stimulus type and lateralization is only present in younger children in which the auditory system's sensitivity to syllable rate modulations is still developing (read more about this further on in the discussion), but does not persist into (young) adulthood. Indeed, lateralization has already been shown to undergo development over time (Ríos-López et al., 2020; Yamazaki et al., 2018).

An important question that remains to be answered is what the cause is of this specific pattern of hemispheric specialization. To the best of our knowledge, no studies have yet uncovered a leftward lateralization at 4 Hz with similar, pulsatile stimuli. However, even though rightward lateralization at theta rate is quite consistent, more recently, it has been shown that this rightward lateralization may diminish or even reverse under specific processing demands (Assaneo et al., 2019). Specifically, Assaneo et al. (2019) demonstrated that whereas right hemispheric synchronization at syllable rate reflects an intrinsic, bottom-up, oscillatory response, left hemispheric synchronization reflects a top-down mechanism from non-auditory cortical areas related to different factors such as speech intelligibility or attention. These top-down influences to the left hemisphere may reverse the classical rightward lateralization to syllable rate modulations. This agrees with studies such as the one by Peelle et al. (2013) that showed a leftward lateralization at syllable rate in response to intelligible sentences. Hence, hemispheric specialization does not only occur due to asymmetric temporal sampling of purely acoustic features (Poeppel, 2003), but can be influenced by other cues such as linguistic content and attention

(Assaneo et al., 2019; Peelle et al., 2013). It is unlikely that factors such as these contributed to the leftward lateralization to the PULS stimuli in the current study, but we do propose that cues unrelated to the rhythmic properties of the signal contribute to hemispheric specialization, at least in younger children.

An influential theory by Zatorre & Belin (2001) that preceded the AST theory (Poeppel, 2003) proposed that the left hemisphere is better suited for processing temporal information, whereas the right hemisphere is better suited for processing spectral information. Our results can be interpreted with respect to this proposal. Reducing the rise time of the envelope shape to create the PULS stimuli cut the PULS stimuli down to only temporal cues (Doelling et al., 2014; Van Hirtum, Ghesquière, et al., 2019), whereas this was not the case for the SAM stimuli. The much stronger temporal information in the PULS stimuli compared to the SAM stimuli might have caused the leftward lateralization, consistent with the proposal by Zatorre and Belin (2001). Whereas the SAM stimuli possess smooth temporal modulation transitions of about 125 ms, the transitions in the PULS stimuli are much more sudden, namely about 30 ms. The slope of the PULS stimuli is therefore much steeper, creating a stronger temporal cue. This observation may be related to the increased discharge probability to the auditory nerve fiber at the onset of a stimulus, with a higher increase for steeper stimulus onset slopes (Delgutte, 1997; Geurts & Wouters, 1999). However, this remains a hypothesis, and future research should aim to uncover the specific mechanisms behind the effect of stimulus type on hemispheric specialization. Such a study should preferably longitudinally investigate different stimulus types to uncover at what point in development leftward lateralization to PULS stimuli evolves to rightward lateralization. At least one extra stimulus type should be included that falls somewhere in between the purely temporal PULS stimulus and the SAM stimulus to investigate whether a gradual transition from leftward to rightward lateralization can be exposed in younger children.

Additionally, one might suggest that the leftward lateralization to the PULS stimuli is merely the consequence of a contralateral processing preference based on an anatomical cross-over to the contralateral side (Bailey, 2010). However, hemispheric specialization may be the result of anatomical preference, as well as functional preference based on acoustic properties of the auditory system (Poeppel, 2003). In ASSR literature, rightward

lateralization in response to theta rate stimulation has already been demonstrated with all stimulation modalities: monaural right ear stimulation, monaural left ear stimulation and bilateral stimulation (De Vos et al., 2017b; Poelmans, Luts, Vandermosten, Ghesquière, et al., 2012). In line with this, several studies have shown rightward lateralization to right ear stimulation with similar ASSR stimuli as those implemented in the current study, in both adults (Poelmans, Luts, Vandermosten, Ghesquière, et al., 2012; Vanvooren et al., 2014) and children (De Vos et al., 2017a; Granados Barbero et al., 2022; Vanvooren et al., 2015). This supports lateralization based on functional preference over anatomical preference. Furthermore, if the leftward lateralization in response to the PULS stimuli were due to purely anatomical contralateral lateralization, we would have expected to uncover this same pattern for the SAM stimuli. In contrast, responses to the SAM stimuli are lateralized to the right hemisphere. Therefore, we suggest that the current pattern of differential lateralization between SAM and PULS stimuli reflects substantial differences in central auditory processing rather than a confound resulting from right ear stimulation in the current study. Ideally, we would have included additional monaural left ear and bilateral stimulation modalities in the current study, but this was not possible due to time constraints and the young age of the children.

Even though our PULS stimuli contain no linguistic information, the pattern of hemispheric specialization in response to these stimuli aligns well with that in response to stimuli with higher language processing demands due to the presence of linguistic or semantic information (Assaneo et al., 2019; Peelle et al., 2013). Interestingly, it has been demonstrated that the strength of speech entrainment in the left auditory cortex is associated with speech intelligibility (Ahissar et al., 2001; Zoefel et al., 2018), while this is not the case for the right auditory cortex (Peelle et al., 2013). Taken together, we might suggest that a leftward lateralization, as seen in response to our PULS stimuli, more closely resembles natural speech envelope tracking. We propose that the PULS stimuli might be more ecologically valid than the SAM stimuli (Prendergast et al., 2010). However, this interpretation should be treated with caution. In order to empirically support this claim, we recommend future research to compare hemispheric specialization to the PULS stimuli and natural speech in the same population, at both scalp and source levels.

Synchronization to syllable rate information increases with age

Our results demonstrated a developmental increase in neural synchronization to syllable rate modulations. More specifically, at 4 Hz, responses were stronger at T2, compared to T0 and T1. There was no change in response between T0 and T1. These findings did not differ between SAM and PULS stimulus types.

This developmental increase in response is consistent with a study by Kolozsvári et al. (2021), who cross-sectionally demonstrated an increase from childhood to adulthood in coherence values between the brain signal measured with magneto-encephalography (MEG) and speech. The authors suggested this as evidence for an improved ability of the brain to track speech with age. Nonetheless, most previous studies on the topic showed either a decrease in syllable rate responses from childhood to adulthood (Tlumak et al., 2012; Vanvooren et al., 2015), or no difference at all (Lizarazu et al., 2015). However, all of these studies cross-sectionally compared children with adults, whereas in the current study we longitudinally investigated development from pre-reading (5 years old) to beginning reading (7 years old) age. A possibility is that at this time, the sensitivity of the auditory system to syllable rate information is indeed still developing, and that a maturational decrease in response will only occur at a later point in development. Another study that looked at the same age range as the current study is the one by De Vos et al. (2017a). The authors could also not confirm a decrease in response from 5 to 7 years. However, in their study responses did also not increase as in the current study, but remained similar. A direct comparison between our results and those of De Vos et al. (2017a) is however complicated, considering that the authors used a different response measure and the studied populations slightly differed between our respective studies. Even though all children in the current study were classified as typical readers, they were recruited from an intervention study in children at cognitive risk for dyslexia. The increasing syllable rate synchronization could therefore also be specific to this population of children at risk for dyslexia that eventually develop typical reading skills. However, it has already been shown that (family) risk for dyslexia does not contribute to neural synchronization at both syllable and phoneme rate (De Vos et al., 2017a).

Despite inconsistencies in the literature, we suggest that our data demonstrate an ongoing development of the auditory system's sensitivity to syllable rate information in pre-readers to beginning readers. Interestingly, even though few empirical investigations have considered the relation between theta rate synchronization and phonological skills, the Spectral Amplitude Modulation Phase Hierarchy (S-AMPH) modeling approach by Leong & Goswami (2015) demonstrated that modulation rates centered around 5 Hz, or syllable rate, support the parsing of syllables in child-directed speech. As a result, it is conceivable that in children syllable rate synchronization would be related to phonological skills, at least at the larger phonological unit of the syllable.

2.4.2 Synchronization to phoneme rate information increases with age

Similar to our results at 4 Hz, responses at 20 Hz increased from T0 and T1 to T2, whereas responses did not change between T0 and T1. At 20 Hz, the findings did also not differ between SAM and PULS stimulus types.

This developmental increase is consistent with studies who also reported increasing phoneme rate responses during childhood (De Vos et al., 2017a) and from childhood to adulthood (Lizarazu et al., 2015), although both Vanvooren et al. (2015) and Tlumak et al. (2012) reported no differences at this frequency between childhood and adulthood. Rather than maturation, this increasing sensitivity to phoneme rate modulations in the current study could be attributed to the development of phoneme awareness in beginning readers (De Vos et al., 2017a). The increase of 20 Hz response amplitudes occurs around the onset of formal reading instruction, and phoneme awareness is known to emerge as a consequence of reading acquisition (Goswami & Bryant, 1990). The link between increasing phoneme rate synchronization and the development of phoneme awareness is further supported by correlations between phoneme rate synchronization and behavioral phoneme awareness scores (Lizarazu et al., 2015). Indeed, phoneme rate synchronization has often been shown to correlate with phonological awareness measures (De Vos et al., 2017b; Lizarazu et al., 2015; Van Hirtum, Ghesquière, et al., 2019). However, because some of the children in the current study received some kind of phonics-based training in between T0 and T1, we should remain careful in our interpretation of

increasing phoneme rate synchronization as a consequence of purely formal reading instruction. Interestingly, an over-synchronization at phoneme rate is linked with dyslexia (De Vos et al., 2017a, 2017b; Lizarazu et al., 2015), hence suggesting that there is an optimal level of synchronization that becomes dysfunctional when exceeded.

2.4.3 Limitations

We need to acknowledge a few limitations in the current study. First, a limitation that goes up for all electrophysiological studies in young children is the dropout and data quality. In the current study, some conditions for which data were acquired could not be included because noise levels were too high to process the data or because the measurement was prematurely ended because the child was not willing to proceed anymore. However, using the PULS stimuli might alleviate some practical concerns such as these, by making data collection more time efficient.

Second, despite the advantages of using amplitude modulated stimuli to investigate neural synchronization, we are only able to measure one specific modulation frequency at a time in this way. This approach is time-consuming, but moreover, insufficient to cover the auditory system's and brain's response to a frequency band (David et al., 2022; Gransier & Wouters, 2021). Gransier and Wouters (2021) developed the Temporal Envelope Speech Tracking or TEMPEST framework. The TEMPEST framework provides a solution to aforementioned issues and allows evaluation of the overall envelope processing ability of the auditory system using stimuli that contain a range of envelope modulations. Furthermore, different parameters of the stimuli, such as the envelope shape, can be adjusted, which allows for a more efficient evaluation of the effect of different rise times on neural synchronization. Hence, it would be a good idea for future studies to make use of the TEMPEST stimuli.

2.5 Conclusion

Our results show that pulsatile stimuli with sharper rise times enhance neural synchronization to 4 Hz amplitude modulations and greatly improve the efficiency of data acquisition (John et al., 2002, 2004). This provides an

explanation for the improved speech perception in response to EE (Van Hirtum et al., 2021; Van Hirtum, Moncada-Torres, et al., 2019). Additionally, at 4 Hz, using pulsatile stimuli resulted in a different hemispheric specialization, more closely resembling natural speech envelope tracking. Distilling the stimuli down to only temporal information, as is the case for the PULS stimuli, is hypothesized to have contributed to this. Further studies are required to investigate the specifics of the differential hemispheric specialization. Nevertheless, these results significantly contribute to the literature on envelope shapes with reduced rise times and demonstrate the applicability of PULS stimuli in pre-reading to beginning reading age. The greatest novelty of the current study lies in the empirical demonstration of an increased efficiency of data acquisition across a wide range of pre-reading and beginning reading stages, which could have major implications on future pediatric EEG studies and clinical practice.

Chapter 3

Dyslexia and intervention effects on neural synchronization

The content of this chapter has been published as: Van Herck, S., Economou, M., Vanden Bempt, F., Glatz, T., Ghesquière, P., Vandermosten, M., & Wouters, J. (2022). Neural synchronization and intervention in pre-readers who later on develop dyslexia. *European Journal of Neuroscience*

Abstract

A growing number of studies has investigated temporal processing deficits in dyslexia. These studies largely focus on neural synchronization to speech. However, the importance of rise times for neural synchronization is often overlooked. Furthermore, targeted interventions, phonics-based and auditory, are being developed, but little is known about their impact. The current study investigated the impact of a 12-week tablet-based intervention. Children at risk for dyslexia received phonics-based training, either with (*n*=31) or without (*n*=31) auditory training, or engaged in active control

training (*n*=29). Additionally, neural synchronization and processing of rise times was longitudinally investigated in children with dyslexia (*n*=26) and typical readers (*n*=52) from pre-reading (5 years) to beginning reading age (7 years). The three time points in the longitudinal study correspond to intervention pre-test, post-test, and consolidation, approximately one year after completing the intervention. At each time point neural synchronization was measured to sinusoidal stimuli and pulsatile stimuli with shortened rise times at syllable (4 Hz) and phoneme rates (20 Hz). Our results revealed no impact on neural synchronization at syllable and phoneme rate of the phonics-based and auditory training. However, we did reveal atypical hemispheric specialization at both syllable and phoneme rates in children with dyslexia. This was detected even before the onset of reading acquisition, pointing towards a possible causal rather than consequential mechanism in dyslexia. This study contributes to our understanding of the temporal processing deficits underlying the development of dyslexia, but also shows that the development of targeted interventions is still a work in progress.

3.1 Introduction

Literacy plays a significant role in today's culture. Unlike spoken language, the acquisition of written language relies on formal reading instruction (Rastle et al., 2021). Consequently, the majority of children will eventually attain fluent reading skills. However, around 7% of children are eventually diagnosed with developmental dyslexia, meaning that they experience severe and persistent difficulties in reading and/or spelling despite adequate instruction and intelligence and intact sensory abilities (Peterson & Pennington, 2012, 2015).

Targeted reading interventions promote reading and related skills and can support readers with dyslexia. Reading interventions are most successful when they provide explicit and systematic phonics instruction (National Institute of Child Health and Human Development, 2000). Although there is strong empirical support for the efficacy of phonics-based interventions (Galuschka et al., 2014; Snowling & Hulme, 2011; Wanzek & Vaughn, 2007), in practice they are often provided at a time that does not allow children with dyslexia to optimally benefit from them (Ozernov-Palchik & Gaab, 2016). Already in first grade there is an achievement gap between

dyslexic and typical readers that persists into adolescence (Ferrer et al., 2015). This calls for early interventions, even as early as kindergarten, with the potential to reduce or even close this gap. Indeed, early reading interventions administered during kindergarten and around the onset of formal literacy education are most effective (Wanzek & Vaughn, 2007). Furthermore, structural brain research demonstrates a natural plasticity window for reading within the first years of primary school and thus further argues for the implementation of early interventions (Phan et al., 2021). Nonetheless, interventions are usually only provided after several years of reading instruction and clear reading failure, hence when the most effective time for intervention has already passed. This has been labeled the "dyslexia paradox" (Ozernov-Palchik & Gaab, 2016).

Phonics-based interventions, which include systematic and explicit instruction of letter-sound relations and phoneme blending exercises, have been developed to target the decoding difficulties in dyslexia caused by phonological processing problems (Snowling & Hulme, 2011). This phonological processing deficit is the most widely agreed upon cognitive origin of dyslexia (Snowling, 2000; Vellutino et al., 2004). More recently, phonological difficulties have been associated with an (auditory) temporal processing deficit, and more specifically an atypical temporal sampling of speech by neural oscillations (Goswami, 2011). The temporal sampling framework (TSF) of Goswami (2011) suggests that neural synchronization of slow-rate oscillations to the temporal modulations of the speech envelope is atypical in dyslexia. This affects children's phonological development and as a result impedes reading development. Cortical oscillatory frequencies coincide with important amplitude modulation rates in the speech envelope and successful synchronization of neural oscillations to these temporal modulations plays a key role in speech perception and intelligibility (Ghitza & Greenberg, 2009; Giraud & Poeppel, 2012a; Peelle & Davis, 2012). Specifically, synchronization in the delta (< 4 Hz) and theta (4-8 Hz) ranges is linked to syllable rate processing, whereas synchronization in the beta (13-30 Hz) and gamma (> 30 Hz) ranges is associated with phoneme rate processing (Ghitza, 2011; Ghitza & Greenberg, 2009; Poeppel, 2003). Speech perception theories have furthermore proposed hemispheric specialization patterns. The prominent 'asymmetric sampling in time' (AST) hypothesis (Poeppel, 2003) for example, assigns right hemispheric dominance to syllable rate modulations and a bilateral or left hemispheric

dominance to phoneme rate modulations (Boemio et al., 2005; Giraud & Poeppel, 2012b; Poeppel, 2003). Considering the importance of neural synchronization for speech segmentation and intelligibility (Doelling et al., 2014; Giraud & Poeppel, 2012a), it has been hypothesized that atypical neural synchronization or hemispheric specialization at these rates in dyslexia could be harmful for speech perception and consequently phonological and reading development (Goswami, 2019a).

Over the past years, several studies have investigated the temporal processing deficit in both adults and children with dyslexia (see Lizarazu, Scotto di Covella, et al. 2021 for a review). Studies investigating syllable rate processing provided solid evidence for atypical delta synchronization (Keshavarzi et al., 2022; Mandke et al., 2022; Power et al., 2016; Soltész et al., 2013) mostly located in the right hemisphere (Hämäläinen et al., 2012; Lizarazu, Scotto di Covella, et al., 2021; Molinaro et al., 2016). People with dyslexia rather consistently show decreased delta synchronization compared to controls. Results at theta rate are rather inconsistent. Two studies demonstrated decreased theta synchronization in dyslexia (Granados Barbero et al., 2022; Mandke et al., 2022), while two other studies demonstrated increased theta synchronization (Granados Barbero et al., 2021; Lizarazu et al., 2015). In the study of Lizarazu et al. (2015), the dyslexia group also failed to demonstrate a right hemispheric lateralization at the theta rate. In the study of Granados Barbero et al. (2022), children with dyslexia demonstrated a belated rightward hemispheric specialization. Using a source analysis methodology, the authors demonstrated a significantly weaker rightward lateralization in children with dyslexia compared to typical readers, Notably, the dyslexic readers caught up with typical readers by the age of 9, pointing towards a late maturation process of hemispheric specialization in dyslexia. Results for phonemic processing in the beta and low-gamma range are also rather inconclusive. Studies demonstrated decreased synchronization (Granados Barbero et al., 2022; Mandke et al., 2022; Menell et al., 1999) mostly located in the left hemisphere (Lehongre et al., 2011, 2013; Lizarazu, Scotto di Covella, et al., 2021; Poelmans, Luts, Vandermosten, Boets, et al., 2012), increased synchronization (De Vos et al., 2017a, 2017b; Granados Barbero et al., 2022), at times restricted to the right hemisphere (Lizarazu et al., 2015), and even typical synchronization (Hämäläinen et al., 2012; Vanvooren et al., 2014). Although not yet fully unraveled, it is hypothesized that people with dyslexia display atypical

neural synchronization and differential hemispheric specialization when compared to their typically developing peers. What most studies investigating the temporal processing deficits in dyslexia did not take into account is the importance of amplitude rise times (also called "edges") for sustaining synchronization to the speech signal. Amplitude rise times (from here on rise times) indicate the time it takes to reach peak amplitude in the speech envelope and are most prominent at syllable onsets (Goswami, 2018, 2019b). Rise times, similar to amplitude, are one of the measures of the dynamics in the speech envelope. The dynamics in the speech envelope are characterized by the modulation depth at the modulation frequency and rise times of amplitude variations in the envelope. Rise times facilitate temporal sampling of speech by triggering a phase reset of neural oscillations, causing them to synchronize to the temporal modulations present in the speech signal (Gross et al., 2013). It is specifically the sharpness of the edges or rise times that facilitates synchronization (Doelling et al., 2014).

At the behavioral level, difficulties with rise time discrimination and its link with reading development are commonly demonstrated in children (Goswami et al., 2002, 2011; Law et al., 2017; Poelmans et al., 2011; Richardson et al., 2004; Vanvooren et al., 2017) and adults (Hämäläinen et al., 2005; Law et al., 2014; Leong et al., 2011) with dyslexia. However, to the best of our knowledge only two studies have investigated the impact of rise times on neural synchronization in dyslexia (Lizarazu, Lallier, et al., 2021; Van Hirtum, Ghesquière, et al., 2019). Lizarazu, Lallier, et al. (2021) demonstrated that whereas in typical readers, rise times in the speech signal phase reset slow-rate oscillations (delta and theta), thereby enhancing their synchronization to speech, this mechanism was impaired in dyslexia. The study by Van Hirtum et al. (2019) showed a deficit in neural synchronization at alpha and beta rate in dyslexia only when the rise times of the stimuli were shortened. This study used Auditory Steady-State Responses (ASSRs) as a tool to measure neural synchronization (Picton et al., 2003). The studies of Lizarazu, Lallier, et al. (2021) and Van Hirtum, Ghesquière, et al. (2019) provide evidence for the impact of rise times on neural synchronization in dyslexia, although studies on the subject are rather scarce and evidence is currently limited to cross-sectional studies in adults. Investigating the impact of rise times on temporal processing in children before the onset of reading acquisition might allow us to establish whether this is a symptom or a possible cause of dyslexia. A recent study by Van Herck, Economou, Vanden

Bempt, Ghesquière, et al. (2022) investigated the stimuli of Van Hirtum, Ghesquière, et al. (2019) in children and demonstrated that stimuli with shortened rise times elicit much stronger ASSR responses than regular sinusoidal amplitude modulated stimuli at syllable rate, thereby enhancing their sensitivity. Hence, the authors postulated that using stimuli with shortened rise times might be preferable in developmental reading research to examine the neural mechanisms behind dyslexia. Furthermore, in typically reading children the stimuli with shortened rise times elicited a leftward lateralization at syllable rate, in contrast to the rightward lateralization suggested by AST (Poeppel, 2003). This was proposed to be evoked by the much stronger temporal information in these stimuli, in line with the theory by Zatorre & Belin (2001) that assigned temporal information processing to the left hemisphere. Therefore, using stimuli with shortened rise times might also help unravel the mechanisms behind atypical hemispheric specialization in dyslexia.

Aforementioned studies investigating the temporal processing deficit in dyslexia have improved our understanding of the specific mechanisms involved in the development of dyslexia, and furthermore contribute to the development of more targeted interventions specifically addressing the mechanisms at play. Such targeted interventions addressing the temporal processing deficit for example train auditory temporal processing and rhythm skills and have been shown to improve phonological and literacy development (Bhide et al., 2013; Cancer et al., 2021; Cancer & Antonietti, 2022; Degé & Schwarzer, 2011; Flaugnacco et al., 2015; Harrison et al., 2018). Another promising auditory intervention is the envelope enhancement (EE) intervention of Van Herck, Vanden Bempt, et al. (2022), Vanden Bempt, Economou, et al. (2022) and Vanden Bempt, Van Herck, et al. (2022) in which children listen to natural speech of which the speech envelope is enhanced. EE was originally developed for use in cochlear implant users (Geurts & Wouters, 1999; Koning & Wouters, 2012, 2016) and specifically accentuates rise times in the speech envelope, which facilitates their detection. EE has already been shown to improve speech perception in a speech-in-noise task passively and instantaneously in both children and adults with dyslexia (Van Hirtum et al., 2021; Van Hirtum, Moncada-Torres, et al., 2019). Van Herck, Vanden Bempt, et al. (2022) investigated the impact of EE combined with phonics-based instruction as an intervention for pre-readers with an elevated cognitive risk of developing dyslexia in a behavioral

rise time discrimination task. Notably, listening to stories that were envelope enhanced during an intervention in kindergarten, improved children's rise time sensitivity by the start of formal reading instruction, while the groups that listened to non-enhanced stories demonstrated improved rise time sensitivity only after one year of formal reading instruction in first grade (Van Herck, Vanden Bempt, et al., 2022). The authors concluded that the EE intervention improves rise time discrimination at a crucial time in development, namely prior to the onset of reading instruction and during the most sensitive period for intervention (Ozernov-Palchik & Gaab, 2016; Phan et al., 2021) and that this might give children at risk for dyslexia a head start at the start of reading acquisition. Despite its impact on rise time sensitivity (Van Herck, Vanden Bempt, et al., 2022), the EE intervention did not promote speech perception, phonological awareness, or productive letter knowledge (Vanden Bempt, Van Herck, et al., 2022). However, the neural aspects of the EE intervention remain to be investigated.

Despite these recent advances in our understanding of the temporal processing deficit and the development of more targeted interventions for the mechanisms at play, there are still some unresolved questions. First, to our knowledge, no study has yet investigated whether interventions can improve neural synchronization in dyslexia. Providing interventions would be particularly valuable early on in development (Ozernov-Palchik & Gaab, 2016; Phan et al., 2021). Not only is there a need to examine the impact of the frequently administered phonics-based interventions on neural synchronization, but also of an auditory training such as the EE intervention. EE specifically addresses the temporal processing deficit by accentuating rise times in the speech envelope and thereby supposedly enhancing suboptimal neural synchronization (Van Hirtum, Moncada-Torres, et al., 2019). EE has already been demonstrated to improve behavioral rise time discrimination (Van Herck, Vanden Bempt, et al., 2022), but its efficacy remains to be investigated at the neural level. Second, despite the solid evidence for a deficit in the processing of rise times at the behavioral level in children with dyslexia and its link with later phonology and literacy performance (Goswami et al., 2002, 2011; Law et al., 2017; Poelmans et al., 2011; Richardson et al., 2004; Vanvooren et al., 2017), the neural processing of rise times has not yet been investigated in children with dyslexia. Such an investigation would provide even more valuable insights into the temporal processing deficit, especially when integrated in a longitudinal investigation

that enables us to exclude that the observed differences are a consequence of the disorder.

To this end we designed a longitudinal study with a twofold objective. Our first aim was to investigate the impact of an early intervention combining a phonics-based training and EE on neural synchronization in Dutch pre-readers at cognitive risk for dyslexia (intervention research question). Secondly, we aimed to investigate the role of atypical neural processing of rise times in reading development (reading groups research question). To answer these aims, we longitudinally investigated ASSRs in children with an elevated cognitive risk of developing dyslexia at pre-reading (5 years old) and beginning reading age (7 years old) and more specifically prior to, immediately following and approximately one year after a digital home-based intervention. Children's reading skills were measured in third grade. We specifically measured ASSRs in response to 4 Hz (theta; syllable rate) and 20 Hz (beta; phoneme rate) amplitude modulated stimuli with varying rise times, namely sinusoidal amplitude modulated (SAM) stimuli and pulsatile stimuli with shortened rise times (PULS). ASSRs were measured in 1) children receiving phonics-based training and an envelope enhanced story-listening game, 2) children receiving phonics-based training and a non-enhanced story-listening game and 3) children playing an immersive control game that did not directly train literacy skills and the non-enhanced story-listening game. This group design allowed us to disentangle the effects of the EE and phonics-based training and the inclusion of an active control group eliminated possible placebo effects. Apart from the intervention groups, the third grade reading data allowed for retrospective classification of these children in two reading groups, dyslexic and typical readers, for the purpose of the second research aim of the study.

3.2 Materials and Methods

3.2.1 Participants

The total sample consisted of 91 children with an elevated cognitive risk of developing dyslexia. All children were native Dutch speakers with bilateral normal hearing, neither history of brain damage or neurological disorders, nor (preliminary) diagnosis of autism spectrum disorder (ASD) or attention

deficit hyperactivity disorder (ADHD), did not receive any therapy due to language and/or articulatory problems and had already received a total schooling period of at least 20 months. All children scored above a norm score of 75.3 on the Raven's Colored Progressive Matrices (Raven et al., 1984). Furthermore, to be classified as having an elevated cognitive risk for dyslexia, the children needed to score below the 30th percentile on two out of three reading precursors during a large-scale screening phase (*N*=1225) organized in the last year of kindergarten in Flanders (Belgium) (Verwimp et al., 2020). These measures were phonological awareness (PA), letter knowledge (LK) and rapid automatized naming (RAN), the strongest cognitive pre-literacy predictors of dyslexia (Caravolas et al., 2012; Clayton et al., 2020; Ozernov-Palchik & Gaab, 2016). Since the phonics-based training predominantly focused on grapheme-phoneme coupling, children scoring below the 30th percentile on PA and RAN were additionally required to have LK below the 40th percentile. This ensured that children could optimally benefit from the phonics-based training. A detailed description of the sample and screening tasks and procedure can be found in previous publications (Economou, Van Herck, et al., 2022; Van Herck, Vanden Bempt, et al., 2022; Vanden Bempt et al., 2021; Verwimp et al., 2020).

At pre-test, all 91 children were invited for EEG data collection, during which each child participated in four EEG conditions, resulting in a total of 364 EEG conditions at pre-test. At post-test, seven children discontinued participation, resulting in 336 EEG conditions. At consolidation test, two children that did not participate at post-test returned, while an additional seven children discontinued participation at consolidation test. This resulted in a total of 12 children not participating at consolidation test, and 316 EEG conditions. Furthermore, at each test phase, measurements of some of the EEG conditions were excluded for the following reasons: (1) excessive noise levels, (2) measurement was ended prematurely, (3) data of the specific condition was not collected, (4) uncertainty about the child's hearing of the stimulus. As a result, measurements of 30 out of 364 conditions were excluded at pre-test, 14 out of 336 at post-test, and five out of 316 at consolidation test. Note that in case of excluded conditions, available conditions of a child are still included in the analyses. Third grade reading data were collected for 78 children. A detailed description of the participant flow can be found in **Figure 3.1**.

For the intervention research question, all 91 children of the total sample were included. We included three experimental groups that each received a slightly different intervention program: (1) a phonics-based training and envelope enhanced speech group (GGEE), (2) a phonics-based training and non-envelope enhanced speech group (GGNE) and (3) an active control group (ACNE). This was a pseudo-randomized group assignment at the individual level based on the factors birth trimester, sex, and educational environment (i.e. school) and the resulting groups did not differ in age (months), non-verbal IQ, sex, socio-economic status (SES) and handedness. The intervention groups had comparable intervention exposure (see **Table 3.1** for demographic data).

For the reading groups research question, only the children with available third grade reading data were included, as these data were required for the dyslexia versus typical reading classification. This left us with a sample of 78 children. Based on the acquired reading and spelling data, children were classified as dyslexic if they scored below the 10th percentile on at least one of the included reading or spelling tasks, and below the 25th percentile on all other tasks. All remaining children were classified as typical readers. The tasks included standardized word reading (Brus & Voeten, 1973; Verhoeven, 1995) and pseudoword reading tasks (van den Bos et al., 1994) and a standardized spelling task (Deloof, 2006). This classification resulted in a sample of 26 children with dyslexia (DR) and 52 typically reading children (TR). At pre-test, the groups did not differ in age (months), non-verbal IQ, phonological awareness (PA), productive and receptive letter knowledge (LK), sex, SES and handedness. The groups only differed slightly on rapid automatized naming (RAN) (see demographic data in **Table 3.2**). Even though the TR children are classified as such based on the available third grade reading data, it is important to keep in mind that they were initially screened in kindergarten for an elevated cognitive risk of developing dyslexia. Therefore, the TR group is not an accurate representation of the general typical reading population, which might provide an explanation for their similar pre-reading cognitive profile to the DR group.

For both research questions, available data from all children are included in the analyses, since the statistical analyses used in the current study (robust linear mixed-effects models) are robust to missing data.

The study was approved by the Medical Ethical Committee of the University Hospital of Leuven, KU Leuven, and signed informed consents were obtained for all participants (Katholieke Universiteit Leuven; approval number B322201836276).

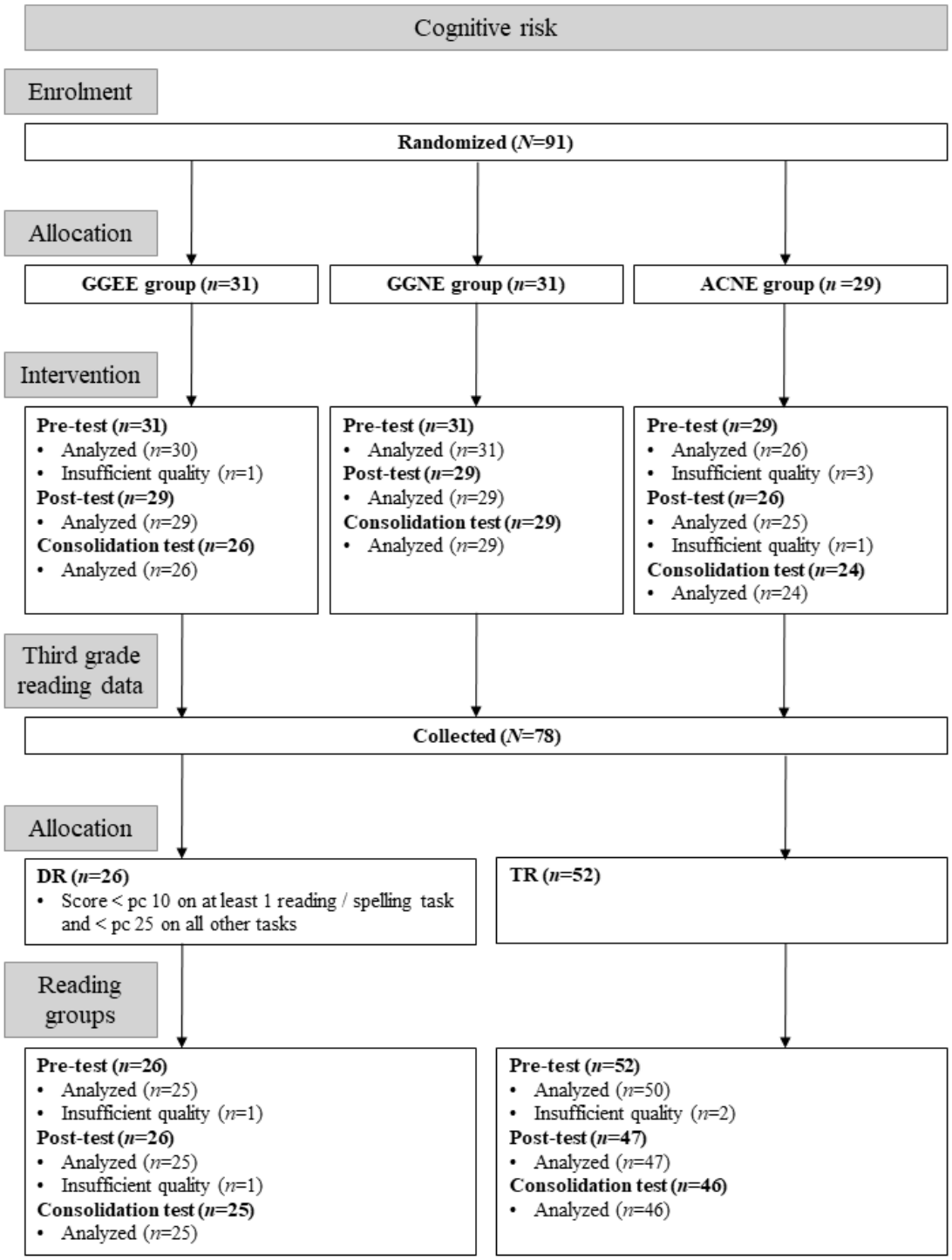


Figure 3.1: Participant flow in the study

Table 3.1: Participant characteristics intervention groups

Characteristic	Levels	GGEE (*n*=31)		GGNE (*n*=31)		ACNE (*n*=29)		Group comparison	
		M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*-value
Age pre-test (months)		65	3	65	3	65	4	$F(2,88) = 0.27$	$p = .764$
Non-verbal IQ[a]		101	14	101	17	96	13	$F(2,88) = 0.98$	$p = .378$
Sex	Male/Female	19/12		15/16		16/13		$\chi^2(2, N=91) = 1.04$	$p = .594$
SES[b]	Low/Middle/High/Missing	8/9/14/0		7/12/12/0		8/15/5/1			$p = .190$
Handedness	Left/Ambidexter/Right	1/1/29		2/1/28		2/2/25			$p = .859$
Story listening game exposure (hours)		10.5	3.0	11.2	2.8	11.4	1.9	$F(2,84) = 0.99$	$p = .370$
Phonics-based training / control game exposure (hours)		16.1	5.3	16.0	5.3	17.1	4.8	$F(2,88) = 0.41$	$p = .670$

Note. GG = GraphoGame, EE = envelope enhanced, NE = not envelope enhanced. AC = active control, *M* = group mean, *SD* = standard deviation, SES = socio-economic status. For categorical data (i.e. sex, SES and handedness) the numbers in each group are reported instead of *M* and *SD*, and group comparisons are done using Chi-squared tests (sex) or Fishers's exact tests (SES and handedness) instead of one-way ANOVA.

[a] Reported scores are standardized scores based on the *M* and *SD* of the total group of screened children (*M* = 98.15, *SD* = 16.66)

[b] SES is based on the parental educational level of the mother

Table 3.2: Participant characteristics reading groups

Characteristic	Levels	TR (*n*=52)		DR (*n*=26)		Group comparison	
		M	*SD*	*M*	*SD*	*F*	*p*-value
Age at pre-test (months)		65	3	65	3	$F(1,76) = 0.02$	$p = .896$
Non-verbal IQ[a]		101	14	96	14	$F(1,76) = 2.15$	$p = .147$
PA[b]		3	3	2	3	$\chi^2(1) = 2.57$	$p = .110$
RAN[c]		0.55	0.10	0.49	0.11	$F(1,75) = 4.75$	$p < .05$
LK productive[d]		2.00	4.00	1.50	2.00	$\chi^2(1) = 2.82$	$p = .090$
LK receptive[d]		6.50	3.22	5.29	2.46	$F(1,70) = 2.53$	$p = .120$
Sex	Male/Female	31/21		14/12		$\chi^2(1, N=78) = 0.06$	$p = .808$
SES[e]	Low/Middle/High	14/16/22		5/13/8			$p = .299$
Handedness	Left/Ambidexter/Right	4/1/47		0/3/23			$p = .071$
Intervention group	GGEE/GGNE/ACNE	17/22/13		11/7/8		$\chi^2(1, N=78) = 1.76$	$p = .410$

Note. TR = typically reading children, DR = children with dyslexia, *M* = group mean, *SD* = standard deviation, PA = phonological awareness, RAN = rapid automatized naming, LK = letter knowledge, SES = socio-economic status, GG = GraphoGame, EE = envelope enhanced, NE = not envelope enhanced, AC = active control. For non-normally distributed data (i.e. phonological awareness and active letter knowledge), the median and interquartile range are presented instead of the mean and standard deviation, and group comparisons are calculated using Kruskal-Wallis rank sum tests instead of one-way ANOVA. For categorical data (i.e. sex, SES, handedness and intervention group) the numbers in each group are reported instead of *M* and *SD*, and group comparisons are done using Chi-squared tests (sex and intervention group) or Fishers's exact tests (SES and handedness) instead of one-way ANOVA.

[a] Reported scores are standardized scores based on the *M* and *SD* of the total group of screened children (*M* = 98.15, *SD* = 16.66)

[b] The maximum score for the PA measure was 10

[c] RAN raw score was defined as the number of items named correctly per second

[d] The maximum score for the LK productive and LK receptive measures was 16

[e] SES is based on the parental educational level of the mother

3.2.2 Procedure

The data described in the current study were collected as part of a larger longitudinal intervention project (*N*=149) in which additional behavioral and neuroanatomical assessments were carried out. Additional findings from the intervention study were reported in previous publications (Economou, Van Herck, et al., 2022; Van Herck, Vanden Bempt, et al., 2022; Vanden Bempt et al., 2021). The intervention study comprised a pre-test, intervention, post-test, consolidation test and dyslexia status test. Important to note is that the dyslexia status test is not a clinical diagnosis, but rather a classification based on the acquired third grade reading and spelling data. EEG measurements at pre-test, post-test and consolidation test were collected in our university research lab, while behavioral assessments (dyslexia status test) were carried out at school in a quiet test room. The intervention took place at home.

In their last year of kindergarten, all children performed an initial baseline measurement of the outcome measure (i.e. ASSRs) at pre-test. Afterwards, all children performed the tablet-based intervention at home in which they were instructed to independently play the intervention games for six days a week for a total period of 12 weeks. During this intervention, the GGEE and GGNE groups played GraphoGame for 15 minutes daily in combination with actively listening to stories that were either envelope enhanced (EE; GGEE group) or non-enhanced (NE; GGNE group) for approximately 10 minutes. The ACNE group played control games for 15 minutes and listened to non-enhanced stories for 10 minutes. For more details on the practical aspects of the home-based intervention, see Economou, Van Herck, et al (2022), Van Herck, Vanden Bempt, et al. (2022) and Vanden Bempt et al. (2021). Post-test took place shortly after the intervention, at the end of the last year of kindergarten. Consolidation test took place on average 1 year and 2 months after post-test, after approximately one year of formal reading instruction in first grade. In between post-test and consolidation test, the children received home schooling in first grade, due to the COVID-19 pandemic. At the start of their third year of primary school, approximately 1 year and 2 months after consolidation test, the children participated in the dyslexia status test.

3.2.3 Interventions

Envelope Enhancement

Signal processing of spoken stories was performed in MATLAB R2016b (The MathWorks Inc, 2016). The stimuli and signal processing are identical to those reported in the study by Van Herck, Vanden Bempt, et al. (2022). Several ways exist to implement a speech processing algorithm such as EE. The one adopted in the current study is only one manner to introduce EE, but has shown to be effective in children and adults with dyslexia (Van Hirtum et al., 2021; Van Hirtum, Moncada-Torres, et al., 2019). These studies, however, did not use EE as intervention, but implemented it in a speech-in-noise task during the assessment.

As a first step in the signal processing, the original signal $s(t)$ was resampled to $f_{sampling} = 16$ kHz and subsequently split into frames of 128 samples with a frame advance of 32 samples. A frame-based fast Fourier transform preceded by Hann windowing transformed the signal to the time-frequency domain. Upon this, the frequency bins were combined by means of a weighted sum of their powers, mapping them to 23 critical channels. The frequency limits of these channels were defined according to the critical bandwidths of Fastl and Zwicker (2007). The envelope of each channel $E(t,k)$ was obtained by taking the square root per channel. A slow envelope of each channel $E_{slow}(t,k)$ was obtained as follows. The envelope $E(t,k)$ was low-pass filtered with a fourth-order Butterworth filter with a cutoff frequency of 20 Hz, which gave a signal with higher time delay when reacting to sudden increases in $E(t,k)$. This low-pass filtered version of $E(t,k)$ was then half-wave rectified and amplified by a factor of $A_{slow} = 8$ to obtain $E_{slow}(t,k)$. The latter step ensured a higher level of $E_{slow}(t,k)$ than that of $E(t,k)$ at quasi-stationary parts, while the level of $E(t,k)$ was higher than that of $E_{slow}(t,k)$ at sudden increases in energy (i.e. onsets). As such, subtracting $E_{slow}(t,k)$ from $E(t,k)$ yields a signal with peaks at the onsets of the envelope $E(t,k)$, and negative values at stationary parts of $E(t,k)$. A peak envelope signal $E_{peak}(t,k)$ could therefore be obtained by subtracting $E_{slow}(t,k)$ from $E(t,k)$, followed by half-wave rectification and amplification by a factor of $A_{peak} = 3.5$. The eventual peak signal in the time domain $p(t)$ was obtained by mapping the 23 bands back to 128 frequency bins, followed by an inverse fast Fourier transform after which the

frames were recombined by a weighted overlap-add method. Finally, $p(t)$ was added to the original signal $s(t)$, resulting in the envelope enhanced signal $s_{EE}(t)$, see **Figure 3.2**.

The EE signal processing was applied on age-appropriate stories that were embedded in a tablet-based story-listening game. Two versions of the game were created, one in which the stories were envelope enhanced (EE) and one without enhancement (NE). Regardless of the version of the story-listening game, the children were instructed to listen to stories for approximately 10 minutes daily. For more details on the story-listening game and its feasibility, enjoyment and its impact on language comprehension, see Vanden Bempt, Economou, et al. (2022) and Van Herck, Vanden Bempt, et al. (2022).

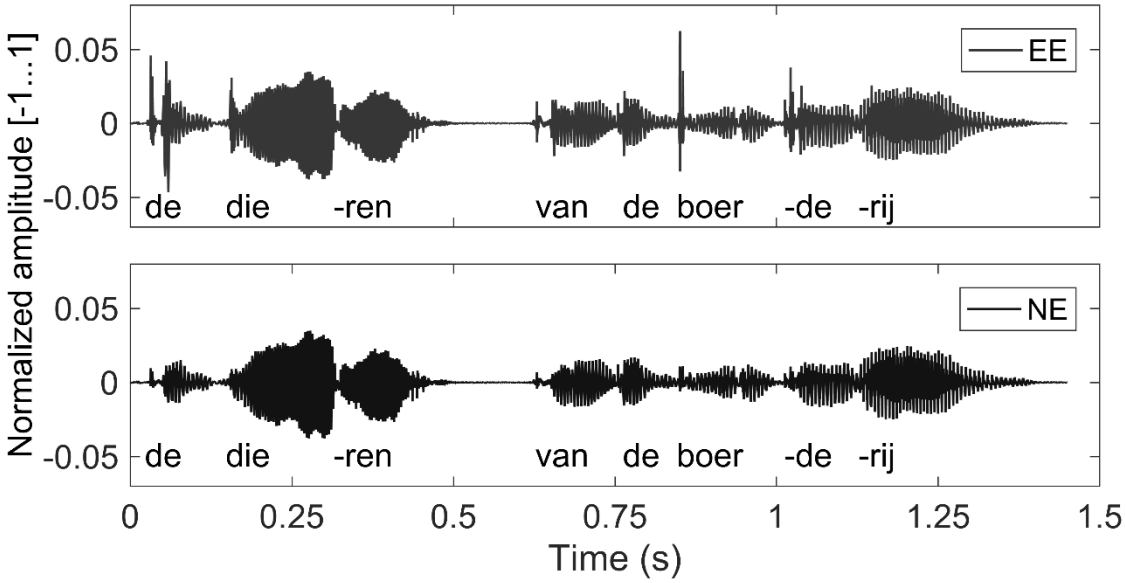


Figure 3.2: EE/NE stimulus. A waveform of a Dutch utterance (English translation: 'the animals from the farm') from one of the stories as EE stimulus (upper) and NE stimulus (lower)

GraphoGame

For the purpose of the current study we adapted the GraphoGame interface (Richardson & Lyytinen, 2014) to a tablet-based Flemish version (GraphoGame-Flemish; GG-FL) (Glatz et al., 2021). The training consisted of an introduction of graphemes, visual and auditory discrimination of graphemes and phonemes respectively, and eventually built up to grapheme-

phoneme coupling, phoneme blending and counting, spelling and early reading. During the 12-week intervention, the children spent 15 minutes per day on GraphoGame-Flemish. A detailed description of the training content can be found in Glatz et al. (2021).

Control Game

The control game consisted of six commercially available tablet-based games, namely Lego City My City, LegoDuploTown, LegoDuploTrains, Playmobile horseriding game, Playmobil Police and Lego Heartlake Rush. Children could choose the games they played each day, provided that they played the games for the instructed 15 minutes per day, identical to GraphoGame-Flemish.

3.2.4 EEG measures

Recording parameters

EEG signals were recorded with the BioSemi ActiveTwo system using 64 active Ag/AgCL electrodes mounted in head caps according to the 10-20 electrode system. Electrode offsets were kept between -25 mV and 25 mV. All recordings were administered in a double-walled soundproof booth with Faraday cage. During the measurement, children were seated in a comfortable chair while watching a soundless movie without subtitles of their choice. This passive listening paradigm ensures a similar level of alertness and attention across subjects throughout the measurement in pediatric ASSR studies (De Vos et al., 2017a; Vanvooren et al., 2014). Measurements were embedded in a different child-friendly protocol in each test phase. An experienced test leader accompanying the child in the EEG cabin monitored alertness and movement.

For each subject, we collected four EEG conditions (two modulation frequencies x two stimulus types). Each condition lasted approximately 9 minutes (532.48 seconds).

Auditory Steady State Responses

ASSRs measure how well the auditory system synchronizes to a stimulus rhythm (Picton et al., 2003). In the current study, we used a speech-weighted noise as carrier noise to evoke ASSRs. This carrier noise was adopted from

the "Leuven Intelligibility Sentence Test" (LIST; Van Wieringen & Wouters, 2008) and represents the long-term average speech spectrum of 730 sentences of a female speaker. The speech-weighted noise was 100% amplitude modulated at approximately 4 and 20 Hz to measure neural synchronization of theta and beta oscillations respectively. For each modulation frequency, we created two conditions or stimulus types (see **Figure 3.3**): (1) a sinusoidal amplitude modulated condition (SAM) in which a sinusoidal envelope modulation was implemented, and (2) a pulsatile condition (PULS) in which the envelope shape was fixed at 30 ms and 10 ms for rise time and decay time respectively. This resulted in a reduced rise time, without affecting amplitude modulation rates at 4 and 20 Hz. The inclusion of the PULS stimuli allows us to investigate the neural synchronization to rise times.

All stimuli were presented monaurally at 70 dBpeSPL through a calibrated ER-3B insert earphone to the right ear.

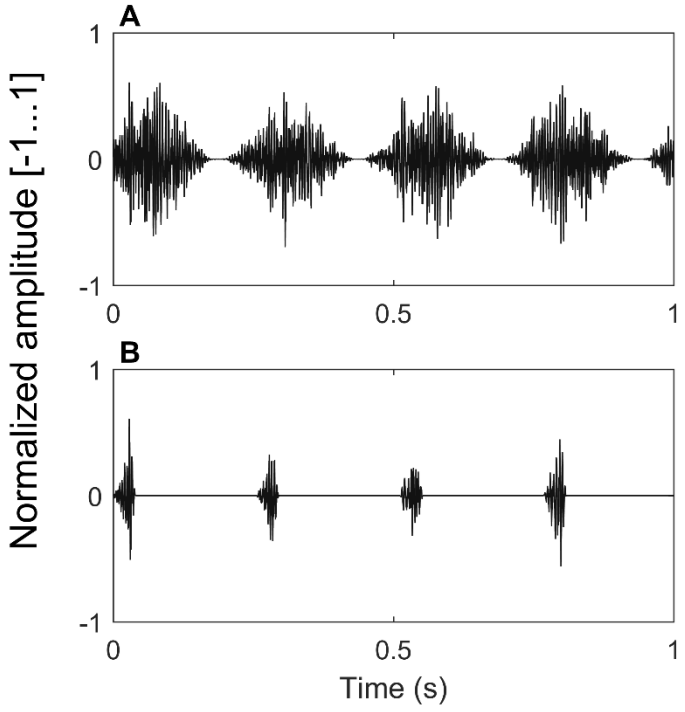


Figure 3.3: SAM and PULS stimulus at 4 Hz. A 1 second waveform of the 4 Hz (A) SAM stimulus and (B) PULS stimulus

Preprocessing

Preprocessing of the recorded EEG data was done in Matlab R2016b (The MathWorks Inc, 2016). First, we used a high-pass filter with a second-order Butterworth filter with a cutoff frequency of 2 Hz to remove the direct current (DC) component. After filtering, the signals were averaged across two pre-selected electrode configurations, resulting in an artificial left (TP7, P1, P3, P5, P7, P9, PO3, PO7, and O1) and right channel (TP8, P2, P4, P6, P8, P10, PO4, PO8, and O2). This configuration was based on previous research showing that these electrodes are most sensitive to pick up ASSRs in children (Vanvooren et al., 2014). Vanvooren et al. (2014) set a criterion for the sensitivity of an electrode selection so that only electrode pairs with an average amount of significant responses above 70% for all conditions can be included. This criterion was met in the current study, thereby confirming the suitability of the electrode selection in the current dataset. The average number of significant responses for all electrode pairs and all conditions was 87% and 89% for 4 and 20 Hz respectively. Next, the signal was divided into epochs of 1.024 seconds on which we then applied an epoch-based artifact rejection to remove muscle potentials and other artifacts. The amplitude rejection level for artifact rejection was set on an individual basis, until 448 epochs remained per electrode, in line with previous ASSR studies in children (De Vos et al., 2017a; Vanvooren et al., 2014, 2015). The aim was to obtain 448 epochs per subject with the lowest amount of artifacts in all channels. Artifact-free epochs were re-referenced to electrode Cz. A fast Fourier transform (FFT) algorithm was applied to calculate the complex frequency spectrum for each of the remaining epochs. From the complex frequency spectrum, we obtained the response power, amplitude and phase corresponding to the modulation frequencies used during the experiment (i.e. 4 and 20 Hz, the response spectrum). Mean response amplitudes and phases were computed by vector averaging the complex response spectrum across epochs. The noise amplitude was calculated as the standard deviation of the FFT bin corresponding to the modulation frequency across epochs divided by the square root of the number of epochs. Finally, a one sample Hotelling T^2 test combining amplitude and phase was performed to determine whether the synchronized activity differed significantly from the neural background activity and hence whether a reliable ASSR (i.e. significant response) was present in the EEG signal (Picton et al., 2003).

3.2.5 Statistical analyses

Statistical analysis was performed in R (version 3.5.1) (R Core Team, 2018). Prior to analysis, Kolmogorov-Smirnov tests were used to assess the assumption of normality, and Levene tests were performed to test for homogeneity of variance. Both assumptions were violated, hence we adopted robust estimation methods for analysis.

As we did not aim to compare responses across the modulation frequencies, robust linear mixed-effects models (robustlmm package) (Koller, 2016) were built for each modulation frequency (4 and 20 Hz), outcome measure (response and noise amplitudes) and research question (intervention and reading group) separately. Noise levels determine the precision of the ASSR amplitudes. Therefore, even though there are no hypotheses linked to the noise levels, both response and noise amplitudes are considered in the manuscript. Stimulus type (SAM and PULS), hemisphere (left and right), test phase (pre-test, post-test and consolidation test) and intervention group (GGEE, GGNE and ACNE) or reading group (DR and TR) were included in the model as fixed effects and the overarching 4-way interaction was considered. By-subject random intercepts accounted for within-subject observations. The results presented here specifically focus on the effects of intervention and reading groups and possible interaction effects with stimulus type, hemisphere and test phase. The main effects of and interaction effects between stimulus type, hemisphere and test phase will not be discussed since these results apply to all groups and hence do not answer our research questions. These results are the subject of another study by Van Herck, Economou, Vanden Bempt, Ghesquière, et al. (2022).

For statistical inference, p-values with a significance level of $p < .05$ were obtained by means of bootstrapping with 1000 simulations for the fixed effects and their interactions in the model. Post-hoc comparisons on the interactions were performed using estimated marginal means (EMMs) with a Holm correction for multiple comparison.

3.3 Results

3.3.1 Effects related to the intervention

Response amplitudes

For 4 Hz response amplitudes (**Figure 3.4**, boxplots outlined in black), the robust linear mixed-effects model indicated a significant interaction between intervention group and test phase ($\chi^2(4) = 12.54$, $p = .013$). Only in the GGNE group there were larger responses at consolidation test compared to pre-test ($z = 6.09$, $p < .001$, 95 % asymptotic CI [0.22, 0.65], Δamplitude = 0.44 μV) and post-test ($z = 3.73$, $p = .003$, 95 % asymptotic CI [0.05, 0.49], Δamplitude = 0.27 μV). In none of the other groups did this increase in response reach significance, nor did any of the groups differ from the other at any of the test phases (all $p > .05$). No other effects with intervention group were found (all $p > .05$).

At 20 Hz (**Figure 3.5**, boxplots outlined in black), no main effect of intervention group, nor any interaction with this factor was found (all $p > .05$).

Noise amplitudes

For 4 Hz noise amplitudes (**Figure 3.4**, boxplots outlined in grey), we found no main effect of intervention group, nor any interaction effects with this factor (all $p > .05$).

At 20 Hz (**Figure 3.5**, boxplots outlined in grey), a significant main effect of intervention group was found, revealing smaller noise amplitudes in the GGEE compared to the ACNE group only ($z = -2.69$, $p = .022$, 95 % asymptotic CI [-0.02, -0.01], Δamplitude = -0.01 μV).

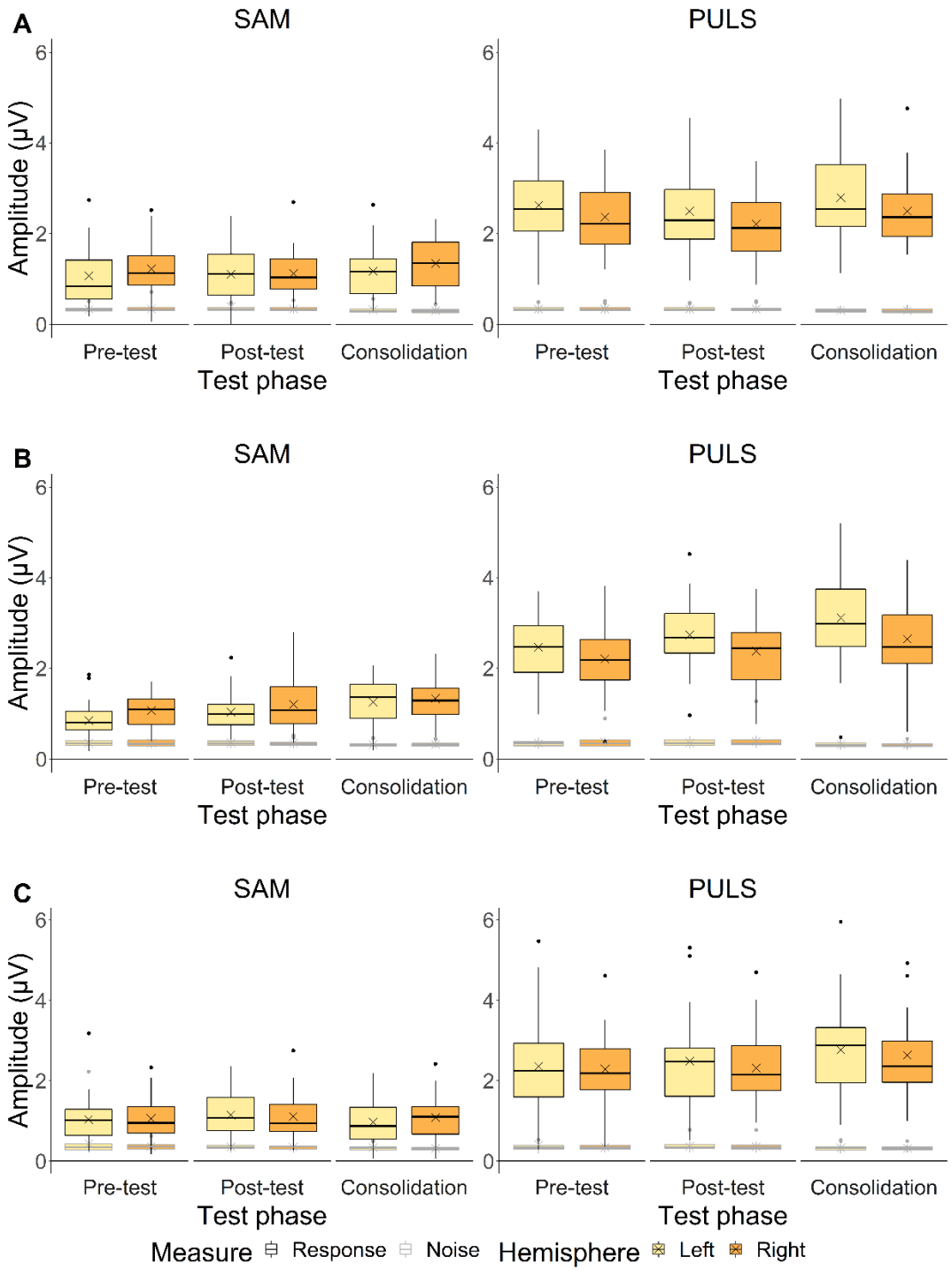


Figure 3.4: Response and noise amplitudes at 4 Hz for the GGEE, GGNE and ACNE groups. Panel A represents ASSR raw data in amplitude (µV) for the GGEE group, panel B for the GGNE group and panel C for the ACNE group. Crosses indicate raw data mean response and noise amplitudes.

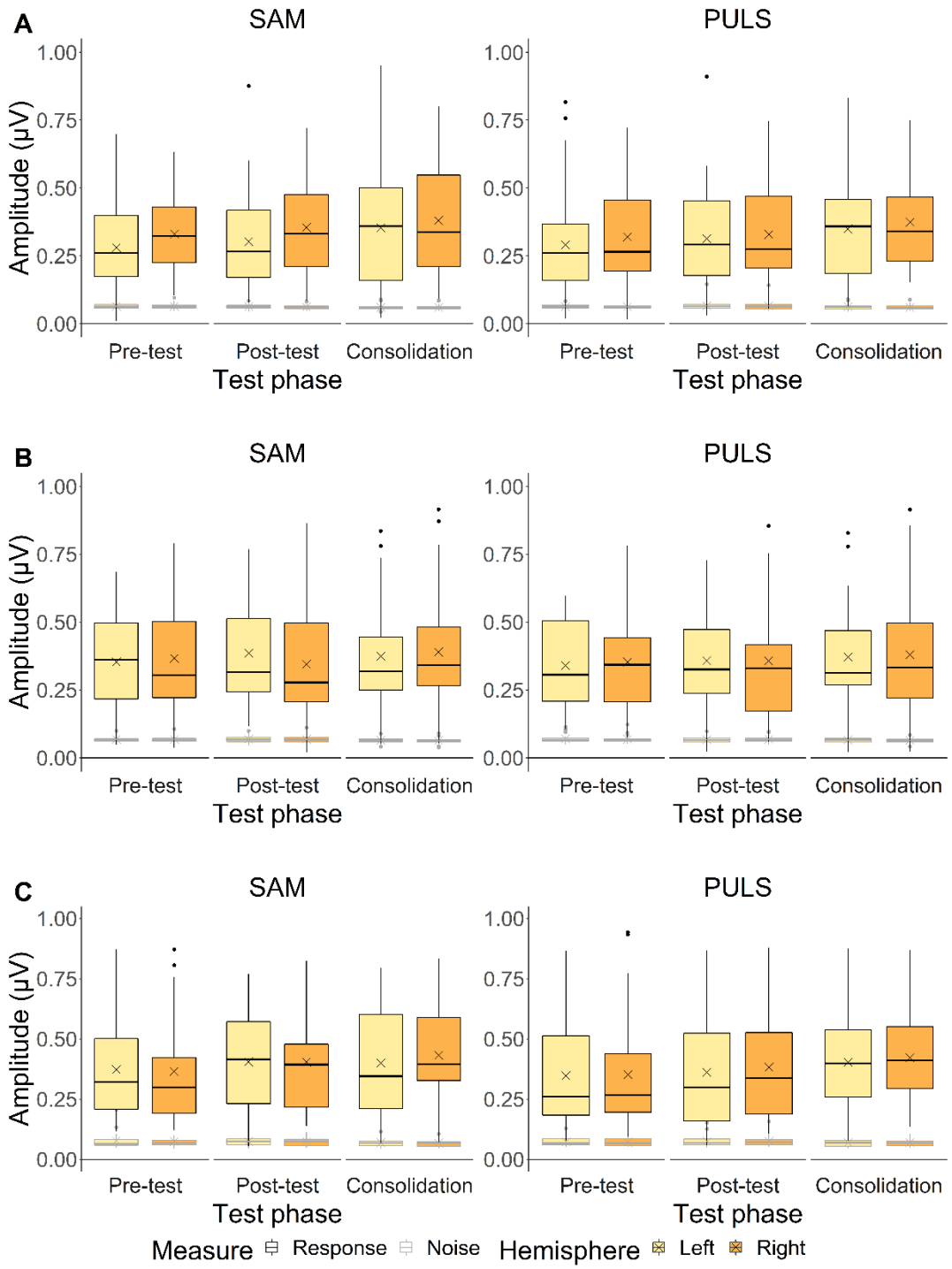


Figure 3.5: Response and noise amplitudes at 20 Hz for the GGEE, GGNE and ACNE groups. Panel A represents ASSR raw data in amplitude (μV) for the GGEE group, panel B for the GGNE group and panel C for the ACNE group. Crosses indicate raw data mean response and noise amplitudes.

3.3.2 Effects related to dyslexia

Because we were not able to demonstrate intervention effects in the current study, we opted to establish new groups based on third grade reading and spelling data and perform analyses on the resulting reading groups. We fitted models with both intervention group and reading group added as covariate. The interactions between intervention and reading group did not reach significance (all $p > .05$). To further confirm that the intervention had a negligible impact, we subsequently compared two models, one with and one without intervention group as a covariate. Comparison of these models demonstrated no differences between both, so we opted for the simpler model without intervention group included as a covariate for further analyses.

Response amplitudes

For 4 Hz response amplitudes (**Figure 3.6**, boxplots outlined in black), a significant interaction between reading group, stimulus type and hemisphere was found ($\chi^2(1) = 3.79$, $p = .048$). This interaction indicated that in typical readers, the SAM stimuli elicited larger responses in the right hemisphere compared to the left hemisphere ($z = 3.11$, $p = .013$, 95 % asymptotic CI [0.02, 0.38], Δamplitude = 0.20 μV), whereas the PULS stimuli elicited larger responses in the left compared to the right hemisphere ($z = 4.25$, $p < .001$, 95 % asymptotic CI [0.09, 0.45], Δamplitude = 0.27 μV). In children with dyslexia however, there was no hemispheric specialization to any of the stimulus types (all $p > .05$). No other effects including the factor reading group were found (all $p > .05$).

At 20 Hz (**Figure 3.7**, boxplots outlined in black), we found a significant interaction between reading group and hemisphere ($\chi^2(1) = 4.73$, $p = .027$). We confirmed a rightward lateralization in children with dyslexia only ($z = 3.36$, $p = .003$, 95 % asymptotic CI [0.01, 0.06], Δamplitude = 0.04 μV), while there was bilateral processing in typical readers ($p > .05$). No other effects with reading group reached significance (all $p > .05$).

Noise amplitudes

For 4 Hz noise amplitudes (**Figure 3.6**, boxplots outlined in grey) and 20 Hz noise amplitudes (**Figure 3.7**, boxplots outlined in grey), no effects including the factor reading group were found (all $p > .05$).

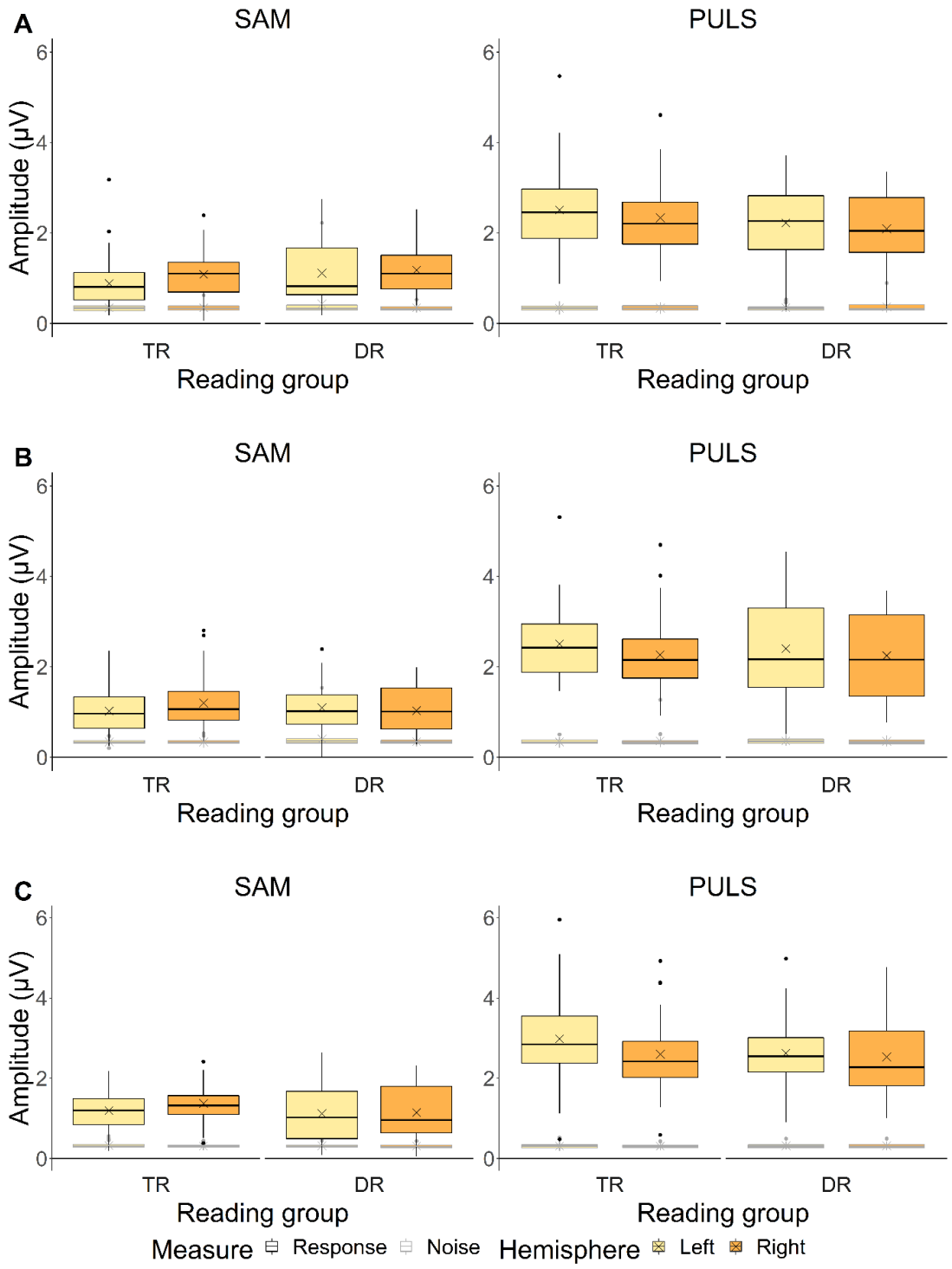


Figure 3.6: Response and noise amplitudes at 4 Hz for the TR and DR groups. Panel A represents ASSR raw data in amplitude (μV) at pre-test, panel B at post-test and panel C at consolidation test. Crosses indicate raw data mean response and noise amplitudes.

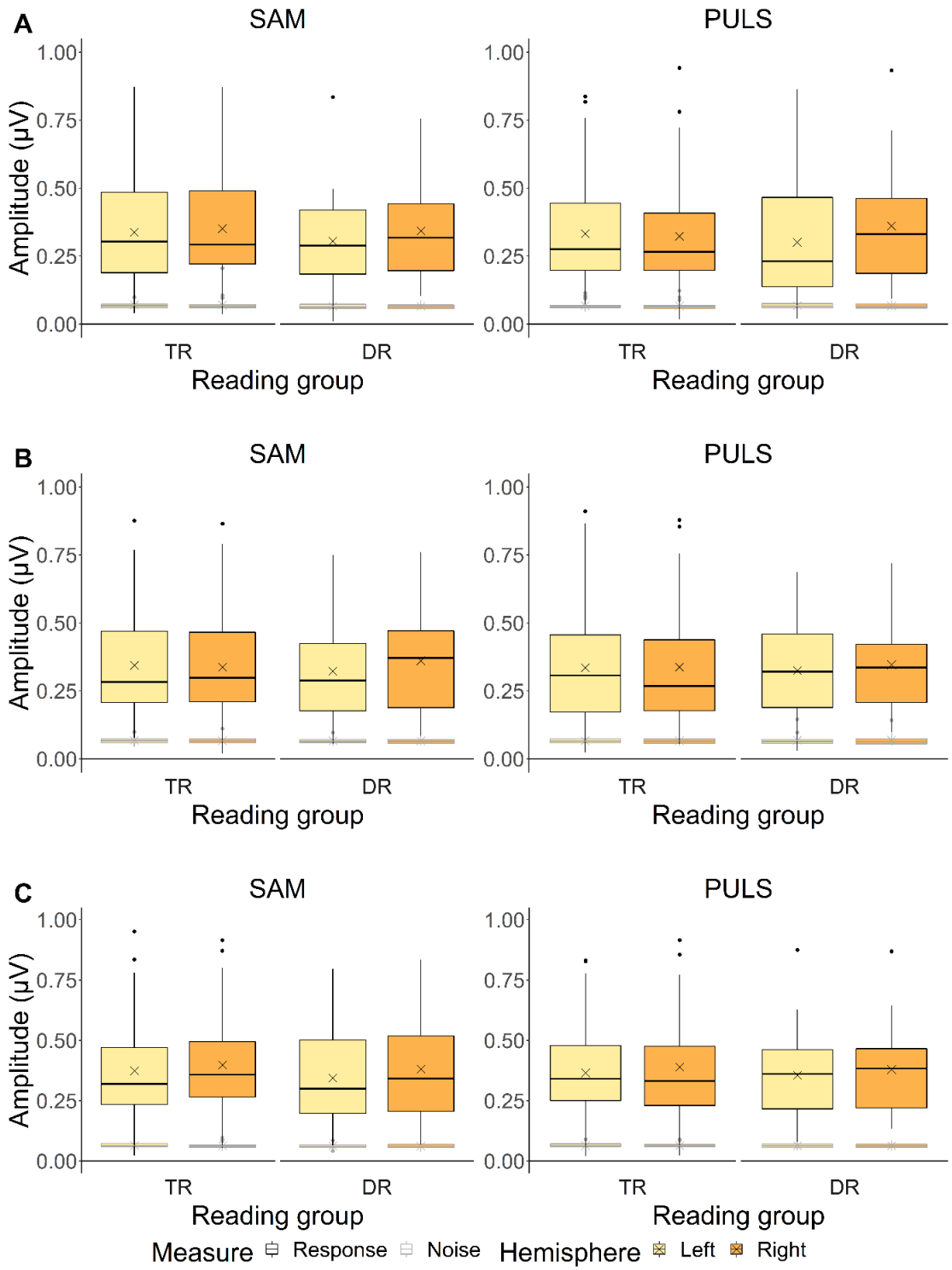


Figure 3.7: Response and noise amplitudes at 20 Hz for the TR and DR groups. Panel A represents ASSR raw data in amplitude (μV) at pre-test, panel B at post-test and panel C at consolidation test. Crosses indicate raw data mean response and noise amplitudes.

3.4 Discussion

Dyslexia has been associated with atypical neural synchronization and hemispheric specialization to temporal modulations in the speech envelope (Goswami, 2011; see Lizarazu, Scotto di Covella, et al. 2021 for a review). This is considered to adversely impact speech perception and consequently phonological and reading development (Goswami, 2019a). There is a need to investigate the impact of interventions for dyslexia on the temporal processing deficit, as well as to develop new interventions that specifically target the mechanisms at play (i.e. atypical neural synchronization), such as the EE intervention (Van Herck, Vanden Bempt, et al., 2022). Therefore, the first objective of the study was to investigate the impact of an early combined phonics-based training and EE intervention on neural synchronization in pre-readers at cognitive risk for dyslexia. Furthermore, amplitude rise times exert an impact on (atypical) neural synchronization in dyslexia (Lizarazu, Lallier, et al., 2021; Van Hirtum, Ghesquière, et al., 2019). Nonetheless, little is known about the causality of the neural processing of rise times in reading development. Accordingly, the second aim of the present study was to longitudinally investigate neural processing of rise times throughout the first years of reading development.

Our results revealed no intervention effects on neural synchronization at syllable and phoneme rate. We did find evidence for an atypical hemispheric specialization at syllable and phoneme rate in children with dyslexia. In typical readers, at syllable rate, the SAM stimuli elicited larger responses in the right compared to the left hemisphere, whereas the PULS stimuli elicited larger responses in the left compared to the right hemisphere. In children with dyslexia, no evidence for any hemispheric specialization was found. Furthermore, at phoneme rate, our results revealed a right hemispheric specialization in children with dyslexia only. These patterns of atypical hemispheric specialization at syllable and phoneme rate were unrelated to the neural processing of rise times.

3.4.1 No intervention effects on neural synchronization to syllable and phoneme rate information

The current study aimed to investigate the impact of an early intervention combining phonics-based training and an EE intervention, with the latter specifically designed to target temporal processing deficits in dyslexia. The current study could not demonstrate clear intervention effects on neural synchronization at syllable and phoneme rates. Results only showed an increase in syllable rate processing from pre-test to consolidation test, limited to the GGNE group. This effect, however, was rather small, considering that in none of the test phases the three groups significantly differed from each other. Furthermore, if the effect was truly related to the GraphoGame intervention, we would have expected to uncover the same pattern in the GGEE group, as it is rather unlikely that the EE intervention would have prevented such an increased synchronization from occurring. Therefore, instead of the intervention, we attribute this group difference to random variation within our sample and/or other factors that we might not have explored in the current study. Random individual variability between the GGNE and other groups has already been suggested in the study by Economou, Vanden Bempt, et al. (2022), investigating cortical plasticity following our GraphoGame intervention.

Contrary to our expectations, listening to EE stories did not elicit an intervention effect on neural synchronization to syllable and phoneme rate modulations. We suggest that this is related to the specific mechanisms at play in the temporal processing deficit. While EE was originally suggested to enhance suboptimal neural synchronization to speech (Van Hirtum et al., 2021; Van Hirtum, Moncada-Torres, et al., 2019), we could not confirm a decreased synchronization to speech-like stimuli in children with dyslexia in the current study. This might potentially be related to the fact that the typical reading group in the current study was also at cognitive risk for developing dyslexia at pre-reading age. The underlying deficit we demonstrated seems to entail a more complex pattern of atypical hemispheric specialization (read more about this further on in the discussion), which is unlikely to be resolved by the current EE intervention. Nonetheless, in adults with dyslexia, decreased neural synchronization is demonstrated more regularly (Lehongre et al., 2011, 2013; Lizarazu, Scotto di Covella, et al., 2021; Mandke et al., 2022; Menell et al., 1999; Poelmans, Luts, Vandermosten, Boets, et al.,

2012; Van Hirtum, Ghesquière, et al., 2019). In this case, EE could possibly normalize reduced neural synchronization. However, we aimed to specifically design an intervention that could be implemented in younger children, considering that this is the most optimal age for interventions and intervening in adults is unlikely to close the gap between typical and dyslexic readers (Ferrer et al., 2015; Ozernov-Palchik & Gaab, 2016; Phan et al., 2021). Hence, even though the current EE intervention might be more effective in adults with dyslexia who do demonstrate reduced neural synchronization, it seems suboptimal for pre-reading children at risk for dyslexia. This is consistent with the study by Vanden Bempt, Van Herck, et al (2022) which also failed to demonstrate an EE-driven effect on speech perception and other reading-related skills in a largely overlapping population. Speech perception is strongly related to neural synchronization (Ghitza & Greenberg, 2009; Giraud & Poeppel, 2012a; Peelle & Davis, 2012), so the lack of an EE intervention effect on neural synchronization putatively explains the absence of a boosting effect on speech perception and related skills.

Apart from the EE intervention, the current study also investigated the impact of GraphoGame, a frequently implemented phonics-based training (Economou, Van Herck, et al., 2022; Glatz, 2018; Lovio et al., 2012; Van Herck, Vanden Bempt, et al., 2022; Vanden Bempt et al., 2021). Even though we expected the phonics-based training to influence phoneme rate processing, considering that formal reading instruction induces increased phoneme rate synchronization (De Vos et al., 2017a), we could not demonstrate an impact of GraphoGame on neural synchronization. However, this finding agrees with the behavioral results in the study of Vanden Bempt et al. (2021) (see **Appendix 3A** for descriptives of the behavioral data). Vanden Bempt et al. (2021) demonstrated that even though playing GraphoGame induced significant short-term increases in productive and receptive letter knowledge and word decoding, it did not evoke a transfer effect on phonological abilities. Beta oscillations (13-30 Hz) are specifically related to phonetic features or phoneme processing (Ghitza, 2011; Leong & Goswami, 2015) and have been found to be associated with phonological awareness (De Vos et al., 2017a, 2017b; Poelmans, Luts, Vandermosten, Boets, et al., 2012). Consequently, it is unsurprising that if GraphoGame did not elicit measurable growth in phonological awareness (Vanden Bempt et al., 2021), there is also no impact on phoneme rate neural synchronization.

Stimulus-induced noise at phoneme rate (20 Hz) demonstrated a minor, but general difference between the intervention groups. Noise levels were smaller in the GGEE, compared to the ACNE group. It is unclear what might have caused this difference between the groups, as it seems unrelated to aspects of the intervention. Therefore, we suggest that this group difference is another manifestation of the random variation present within our study sample.

3.4.2 Atypical hemispheric specialization at syllable and phoneme rate in children with dyslexia

Our results at syllable rate (4 Hz; theta range) showed that in typical readers the SAM and PULS stimuli elicited a different hemispheric specialization. Whereas responses to SAM stimuli were lateralized to the right hemisphere, responses to PULS stimuli were lateralized to the left hemisphere. Interestingly, responses to both stimulus types were processed bilaterally in children with dyslexia.

While there is strong support for atypical hemispheric specialization at syllable rate when considering the delta range (Hämäläinen et al., 2012; Lizarazu, Scotto di Covella, et al., 2021; Molinaro et al., 2016), evidence in the theta range is far more restricted. Yet, the current study is not the first in revealing an atypical hemispheric specialization in the theta range in dyslexia (Granados Barbero et al., 2022; Lizarazu et al., 2015; Mandke et al., 2022). Consistent with the current results for the SAM stimuli, the studies of Lizarazu et al. (2015) and Mandke et al. (2022) demonstrated a rightward lateralization at syllable rate in typical readers, but a lack thereof in dyslexic readers. A plausible interpretation for this finding can be found in Granados Barbero et al. (2022), who attributed a weaker rightward lateralization in children with dyslexia to a late maturation process that normalized by the age of nine. The children in the current study were only 7-8 years old at the latest test phase, but the data indeed seem consistent with a late maturation for lateralization, which might impact reading development.

We did not only reveal an atypical hemispheric specialization at syllable rate in response to the SAM stimuli, but also in response to the PULS stimuli, which were designed to specifically assess the neural processing of rise times. Whereas the SAM stimuli were lateralized to the right hemisphere, in

line with the AST hypothesis (Poeppel, 2003), the PULS stimuli elicited a leftward lateralization in typical readers (Van Herck, Economou, Vanden Bempt, Ghesquière, et al., 2022). If a leftward lateralization in response to the PULS stimuli is indeed evoked by stronger temporal information in these stimuli, as hypothesized by Van Herck, Economou, Vanden Bempt, Ghesquière, et al. (2022), the lack of such a leftward lateralization in children with dyslexia might imply a reduced sensitivity to the increased temporal information in the PULS stimuli. This would furthermore confirm a deficit in the neural processing of rise times. However, our results rather point to a more global deficit in hemispheric specialization at syllable rate at this age. Children with dyslexia demonstrated an atypical hemispheric specialization in response to both SAM and PULS stimuli, therefore contradicting the claim that the deficit is specifically linked to the processing of shorter rise times in the PULS stimuli.

This is confirmed by our results at phoneme rate (20 Hz), demonstrating a bilateral processing in typical readers, but a rightward lateralization in children with dyslexia. This finding was the same for both the SAM and PULS stimuli, so it seems to be unrelated to the neural processing of rise times. Whereas bilateral processing is considered to aid speech processing (Boemio et al., 2005), multiple studies have failed to demonstrate this in readers with dyslexia and rather demonstrated a right hemispheric preference for processing phoneme rate modulations (Granados Barbero et al., 2022; Lehongre et al., 2011; Lizarazu et al., 2015), consistent with our results. The current study is the first to establish this atypical hemispheric specialization already at pre-reading age.

Taken together, the current study demonstrated atypical hemispheric specialization at both syllable and phoneme rates of speech in children with dyslexia. Given that both hemispheres are not equally sensitive to syllable and phoneme rate modulations, and hemispheric specialization is therefore important for successful speech processing (Boemio et al., 2005; Giraud & Poeppel, 2012b; Poeppel, 2003), one might suggest that a disruption of this lateralization, as seen in the current study, might affect the efficiency of the auditory processing of speech (Lehongre et al., 2013). This is consistent with the temporal sampling framework of dyslexia, that assigns phonological difficulties, and as a result, reading difficulties, essentially to an atypical temporal sampling of speech (Goswami, 2011). Links between hemispheric specialization and literacy measures are briefly explored in **Appendix 3B.**

Importantly, we demonstrated an atypical hemispheric specialization across all test phases included in the current study, ranging from pre-reading (5 years old) to beginning reading age (7 years old). With this longitudinal design, we aimed to disentangle causal from consequential effects. Considering that the deficits were present already before the onset of reading acquisition, we postulate that an atypical hemispheric specialization might be a potential cause, rather than a consequence of developing dyslexia.

Despite these valuable insights into the deficits underlying the development of dyslexia, we could not confirm the impact of rise times on neural synchronization in children as the studies of Lizarazu, Lallier, et al. (2021) and Van Hirtum, Ghesquière, et al. (2019) did in adults. A possibility is that the impact of rise times on neural synchronization only develops at a later age. Another possibility and an important factor to take into account is that our results might be related to the comparison of children with dyslexia to typical readers who had a cognitive risk of developing dyslexia at pre-reading age. This means that our typical readers are not a true representation of the general population of typical readers and might be outperformed by the latter. We propose that the group differences in the current study might be enhanced when comparing children with dyslexia to true typical readers, or that group differences that we failed to reveal might emerge. Nonetheless, the current study provides an important glance on the deficits underlying the development of dyslexia.

3.4.3 Limitations

A few limitations should be noted in the current study. A first limitation concerns the reading groups comparison. All children included in the analyses for this research question received some kind of intervention in their last year of kindergarten and are thus not typical children with dyslexia or typical readers. Since we could not demonstrate intervention effects and statistical analyses showed no differences between a model with and without intervention group as a covariate, we omitted the intervention group factor in subsequent reading group analyses. However, absence of evidence is not evidence of absence. Ideally we would have compared children that did not (yet) receive some kind of intervention, which could be addressed in future research.

Inherent to measuring ASSRs is that we are only able to measure one specific modulation frequency at a time. We defined syllable and phoneme rate modulations as 4 and 20 Hz modulations respectively. However, a growing number of studies point towards deficits in the delta instead of theta range for syllable rate processing (Hämäläinen et al., 2012; Lizarazu, Scotto di Covella, et al., 2021; Molinaro et al., 2016; Power et al., 2016; Soltész et al., 2013) and in the gamma instead of beta range for phoneme rate processing (Lehongre et al., 2011, 2013; Lizarazu et al., 2015; Lizarazu, Scotto di Covella, et al., 2021). We suggest future research to therefore include delta rate measurements, e.g. at 2 Hz, and gamma rate measurements, e.g. at 30 Hz. Alternatively, these issues can be addressed by implementing the recently developed Temporal Envelope Speech Tracking or TEMPEST stimulus framework (Gransier & Wouters, 2021), which allows the evaluation of a range of envelope modulations concurrently within one stimulus.

3.5 Conclusion

In conclusion, the current study investigated (1) the impact of an early intervention combining phonics-based and EE training in pre-reading children at cognitive risk for developing dyslexia, and (2) the role of atypical neural processing of rise times in reading development. Performing a phonics-based and/or EE training had no impact on neural synchronization at syllable and phoneme rate, thereby urging for the development of interventions that are more successful in remediating the temporal processing difficulties related to the development of dyslexia. Whereas we could not demonstrate a deficit in the neural processing of rise times, our results did reveal a more global atypical hemispheric specialization at both syllable and phoneme rates, even before the onset of formal reading acquisition. Overall, the current study contributes to our understanding of the specific temporal processing mechanisms involved in the development of dyslexia, but also exposes that the development of targeted interventions is still a work in progress.

Appendix 3A

Behavioral data are the subject of Vanden Bempt et al. (2021), (2023) and Vanden Bempt, Van Herck, et al. (2022). Descriptives of the phonological and literacy measures assessed at pre-test, post-test and consolidation test for the three intervention groups are summarized in **Table 3.3**.

Table 3.3: Descriptives of phonological and literacy measures collected at pre-test, post-test and consolidation test for the three intervention groups

Test	GGEE						GGNE						ACNE					
	Pre		Post		Cons		Pre		Post		Cons		Pre		Post		Cons	
	Mdn	*IQR*	*Mdn*	*IQR*	*Mdn*	*IQR*	*Mdn*	*IQR*	*Mdn*	*IQR*	*Mdn*	*IQR*	*Mdn*	*IQR*	*Mdn*	*IQR*	*Mdn*	*IQR*
PA[a]	3.00	2.50	6.00	5.50	11.5	9.25	3.00	3.00	6.00	5.00	14.0	8.75	3.00	2.00	5.00	4.50	11.50	10.75
RAN[b]	0.51	0.14	0.59	0.21	0.88	0.21	0.53	0.05	0.68	0.18	1.01	0.16	0.55	0.20	0.71	0.25	1.03	0.32
vSTM[c]	10.00	5.50	11.00	3.50	11.00	5.00	10.00	5.00	12.00	5.00	12.00	5.25	10.00	5.00	11.00	4.25	13.00	4.00
LKr[d]	6.00	3.00	13.50	6.00	/	/	5.00	5.00	13.00	6.00	/	/	6.00	3.00	7.00	5.00	/	/
LKp[d]	2.00	2.00	6.00	5.50	/	/	2.00	4.00	8.00	4.00	/	/	3.00	4.00	3.00	3.75	/	/
DMT[e]	0.00	0.00	0.00	1.50	27.00	26.25	0.00	0.00	1.00	2.00	36.50	19.75	0.00	0.00	0.00	0.00	29.50	20.50
LVS[f]	/	/	/	/	42.50	16.50	/	/	/	/	49.00	8.50	/	/	/	/	44.00	16.50

Note. *Mdn* = median, *IQR* = interquartile range, PA = phonological awareness, RAN = rapid automatized naming, vSTM = verbal short-term memory, LK = letter knowledge (r = receptive, p = productive), DMT = Drie Minuten Toets (word reading), LVS = Leerlingvolgsysteem (spelling)

[a] The maximum score for the PA measure was 10

[b] RAN raw score was defined as the number of items named correctly per second

[c] The maximum score for the vSTM measure was 24

[d] The maximum score for the LKp and LKr measures was 16

[e] DMT raw score was defined as the number of correctly read words per minute

[f] The maximum score for the LVS measure was 60

Appendix 3B

The links between hemispheric specialization, measured by the lateralization index (LI), as defined in Gransier et al. (2021), and several literacy measures (word reading, non-word reading and spelling) assessed at the start of third grade were explored using Spearman's correlations. At 4 Hz we separately investigated correlations for the SAM and PULS stimuli, based on the results of the robust mixed model analyses. There were no significant correlations between 4 Hz LI and literacy measures for the DR group for both SAM and PULS stimuli. In contrast, for the TR group, while no significant correlations were found for the SAM stimuli, 4 Hz LI was significantly correlated with non-word reading for the PULS stimuli (r_s = -0.28, p = .046), indicating that more bilateral and leftward lateralization is related to better non-word reading in the TR group. At 20 Hz, responses to the SAM and PULS stimuli were combined, based on the results of the robust mixed model analyses. Similarly to the results at 4 Hz, there were no significant correlations between 20 Hz LI and literacy measures for the DR group. For the TR group, the correlation between 20 Hz LI and word reading came very close to significance (r_s = -0.27, p = 0.052), also indicating that more bilateral and leftward lateralization is related to better word reading scores in the TR group.

These exploratory analyses support the results of the robust mixed model analyses in Chapter 3. Considering that hemispheric specialization is related to both word and non-word reading scores in the TR group, this confirms hemispheric specialization as an important contributing factor to reading (development). Remarkably, at 4 Hz no relations were found for the SAM stimuli, whereas a significant correlation was present for the PULS stimuli. This further confirms the potential of the PULS stimuli for (developmental) reading investigations.

Chapter 4

Intervention effects on rise time discrimination

The content of this chapter has been published as: Van Herck, S., Vanden Bempt, F., Economou, M., Vanderauwera, J., Glatz, T., Dieudonné, B., Vandermosten, M., Ghesquière, P. & Wouters, J. (2022). Ahead of maturation: Enhanced speech envelope training boosts rise time discrimination in pre-readers at cognitive risk for dyslexia. *Developmental Science.*

Abstract

Dyslexia has frequently been related to atypical auditory temporal processing and speech perception. Results of studies emphasizing speech onset cues and reinforcing the temporal structure of the speech envelope, i.e.

envelope enhancement, demonstrated reduced speech perception deficits in individuals with dyslexia. The use of this strategy as auditory intervention might thus reduce some of the deficits related to dyslexia. Importantly, reading-skill interventions are most effective when they are provided during kindergarten and first grade. Hence, we provided a tablet-based 12-week auditory and phonics-based intervention to pre-readers at cognitive risk for dyslexia and investigated the effect on auditory temporal processing with a rise time discrimination task. Ninety-one pre-readers at cognitive risk for dyslexia (aged 5-6) were assigned to two groups receiving a phonics-based intervention and playing a story listening game either with (n = 31) or without (n = 31) envelope enhancement or a third group playing control games and listening to non-enhanced stories (n = 29). Rise time discrimination was measured directly before, directly after and one year after the intervention. While the groups listening to non-enhanced stories mainly improved after the intervention during first grade, the group listening to enhanced stories improved during the intervention in kindergarten and subsequently remained stable during first grade. Hence, an envelope enhancement intervention improves auditory processing skills important for the development of phonological skills. This occurred before the onset of reading instruction, preceding the maturational improvement of these skills, hence potentially giving at risk children a head start when learning to read.

4.1 Introduction

Developmental dyslexia is a learning disability, which manifests through severe and persistent difficulties in reading and/or spelling that cannot be explained by low intelligence, insufficient instruction or sensory disabilities (Peterson & Pennington, 2012; Vellutino et al., 2004). Dyslexia has a multifactorial etiology with several cognitive and neural factors contributing to its development (Menghini et al., 2010; Pennington, 2006; van Bergen et al., 2014). Within this multifactorial framework, deviant phonological processing has been considered a core deficit (Ramus et al., 2003) and therefore phonics instruction is considered the best approach for learning to read (National Institute of Child Health and Human Development, 2000). By some, this phonological deficit has been assigned to difficulties with auditory

perception, allocated to the processing of temporal information (i.e. changes over time) (Farmer & Klein, 1995).

Initial theories that assigned phonological difficulties to auditory deficits focused primarily on deficits in rapid auditory processing. Specifically, difficulties were suggested with processing brief or rapidly presented auditory stimuli (Farmer & Klein, 1995; Tallal, 1980). More recently, this focus has shifted to a deficit in processing the slow-rate dynamic information in speech (Goswami et al., 2002; Poelmans et al., 2011; Richardson et al., 2004). The latter studies emphasize the importance of amplitude rise times in the speech envelope. The speech envelope contains modulations in the speech signal between 2 and 50 Hz (Rosen, 1992). Amplitude rise times indicate the time until the envelope reaches its maximum amplitude (Goswami, 2019b). A cascading effect can explain how deficits in processing temporal cues such as rise times contribute to (the development of) dyslexia. Rise times provide cues for the segmentation of the speech signal into its constituting elements such as syllables and phonemes. This process is mediated by entrainment to the speech signal. Rise times provide important cues for this entrainment, since they aid in distinguishing different rates of amplitude modulations in the speech signal (Goswami, 2011; Gross et al., 2013; Peelle & Davis, 2012). This entrainment is known to aid speech segmentation and intelligibility (Doelling et al., 2014; Giraud & Poeppel, 2012a; Gross et al., 2013; Luo & Poeppel, 2007), but it has been suggested to be compromised in dyslexia (Goswami, 2011). As such, the failure to accurately and efficiently use rise time cues by people with dyslexia would impact neural entrainment, speech perception, and consequently phonological and reading development (Goswami et al., 2010; Power et al., 2016; Ziegler et al., 2009).

At the behavioral level, difficulties with discriminating rise times have been established in both adults (Hämäläinen et al., 2005; Law et al., 2014; Leong et al., 2011) and children with dyslexia. Even preceding the start of formal reading instruction rise time discrimination (RTD) can differentiate between children at high family risk for dyslexia and control children at low family risk for dyslexia (Law, Wouters, et al., 2017). Furthermore, a study by (Law et al. (2014) revealed rise time discrimination deficits in 58% of the dyslexic adult participants in their study, highlighting the importance of auditory processing in dyslexia. At the neurophysiological level, a study by Van Hirtum, Ghesquière, et al. (2019) also revealed an impaired tracking of rise

time cues in young adults with dyslexia by comparing neural synchronization to stimuli with differing rise times.

Apart from deficits in rise time discrimination at both the behavioral and neurophysiological level, clear links have been established between rise time discrimination and reading-related skills such as phonological awareness, even preceding the onset of formal reading instruction (Goswami et al., 2020; Vanvooren et al., 2017). A longitudinal study by Vanvooren et al. (2017) established a link between pre-reading children's performance on rise time discrimination and later phonology and literacy performance. This study confirmed that basic auditory processing already exerts an influence on phonology and literacy before the onset of formal reading instruction and that these basic auditory processes like rise time discrimination have a profound impact on reading development. Goswami et al. (2020) even postulated rise time discrimination to be the core contributor to the development of phonological awareness. For rise time discrimination to affect phonological awareness through speech perception abilities, there should be a link established between basic auditory processing such as the processing of rise time cues and speech perception.

Even though this link has not always been clearly demonstrated (Law et al., 2014; Poelmans et al., 2011), two recent studies by Van Hirtum et al. (2021) and Van Hirtum, Moncada-Torres, et al. (2019) revealed that difficulties with processing temporal cues in the speech envelope have a considerable impact on speech perception in both children and adults with dyslexia. The researchers accentuated rise times in the speech envelope by means of a method referred to as Envelope Enhancement (EE), originally developed for use in cochlear implant users (Geurts & Wouters, 1999; Koning & Wouters, 2012, 2016). This method amplifies onsets in the speech envelope, which facilitates the rise times' detection. The impact of this envelope enhancement was investigated on speech perception in a speech-in-noise task with vocoded speech, in which there is only limited temporal fine structure and spectral information, and in natural speech. Accentuating the rise times was found to improve speech perception in this task. Specifically, participants with dyslexia benefitted more from EE than the typical readers, so that EE closed the initial gap in performance between the groups. This effect occurred passively (i.e. without explicit instruction) and instantaneously (i.e. after only limited exposure) and the benefits provided by EE were similar in the natural and vocoded speech conditions. Hence, difficulties in processing

envelope cues indeed contribute to the speech perception deficits that people with dyslexia often, but not always, experience. Emphasizing rise time cues in the speech envelope allegedly enhances the suboptimal entrainment of neural oscillations to the speech signal in people with dyslexia, thereby improving their speech perception (Doelling et al., 2014; Gross et al., 2013; Van Hirtum et al., 2021; Van Hirtum, Moncada-Torres, et al., 2019). Considering its ability to normalize speech perception in children with dyslexia as demonstrated via a speech-in-noise task and the importance of speech perception for phonological and reading development, EE has been suggested as a potential intervention strategy (Van Hirtum et al., 2021).

A meta-analysis by Wanzek & Vaughn (2007) revealed the highest effects for early reading interventions administered during kindergarten and first grade on reading-related skills including phonological awareness, word reading, spelling, fluency and comprehension. Thus, interventions should preferably be provided at an early age. Yet, dyslexia is usually only diagnosed after several years of reading/writing instruction, when reading and writing impairments show to be severe (usually in second grade or later) and hence interventions are mainly provided after the period in which they would be most effective. This paradox is called the 'dyslexia paradox' (Ozernov-Palchik & Gaab, 2016) and clearly indicates the importance of preventive intervention.

Meta-analyses have provided most support for phonics-based interventions, especially when they include explicit and systematic phonics instruction and when they are provided at an early age (Bus & Van Ijzendoorn, 1999; National Institute of Child Health and Human Development, 2000; Richardson & Lyytinen, 2014; Snowling & Hulme, 2011; Verhoeven et al., 2020). Previous studies already demonstrated positive effects of GraphoGame, a frequently implemented phonics-based intervention, in pre-reading children at risk for dyslexia (Lovio et al., 2012; Vanden Bempt et al., 2021). Despite the positive impact of phonics-based interventions, children with dyslexia do not consistently reach the reading level of their typical reading peers, even when the interventions are provided at an early age (McTigue et al., 2019). The meta-analysis of McTigue et al. (2019) on GraphoGame demonstrated that even though some studies provided evidence for improved sublexical skills (e.g. letter sound knowledge and phonological processing), there is overall little evidence for an impact on word reading. Up to the present moment, it is unclear whether children

experiencing auditory processing difficulties sufficiently benefit from phonics-based interventions. Phonics-based interventions rely on the accurate perception of the phonemes presented during the intervention. Auditory processing difficulties may lead to atypical phoneme perception (Vandermosten et al., 2010, 2011), and so far it is unclear how this impacts the effectivity of phonics-based interventions. Hence, providing phonics-based interventions alone might be insufficient for this population, but there may be a benefit in combining them with alternative intervention strategies.

Auditory intervention strategies might provide a solution to this. Musical and rhythm-based interventions that train temporal processing and rhythm skills have already been shown to provide benefits to phonological and literacy development (Bhide et al., 2013; Degé & Schwarzer, 2011; Flaugnacco et al., 2015; Harrison et al., 2018). Apart from these auditory interventions, we believe that EE also shows potential as an intervention strategy. EE might enable children with dyslexia to benefit more from phonics-based interventions by improving speech perception and hence improving the perception of phonemes and consequently the phoneme representations. EE has proven to be effective during a speech-in-noise task in children with dyslexia, and does not require children to have any reading experience, making it particularly well suited for early intervention (Van Hirtum et al., 2021).

Notwithstanding the promising results using EE during a speech-in-noise task in adults and children with dyslexia (Van Hirtum et al., 2021; Van Hirtum, Moncada-Torres, et al., 2019), its potential to be used as an intervention strategy has not yet been investigated. Considering its suggested impact on the efficacy of phonics-based interventions in people with auditory processing deficits, it might be an additional benefit to combine EE with a phonics-based intervention. Therefore, the goal of this study was to explore the additive auditory perceptive effects of an intervention combining EE and phonics-based training in Dutch-speaking pre-readers at cognitive risk for dyslexia prior to the onset of reading instruction. Our 12-week intervention combined a tablet-based Flemish version of GraphoGame, a frequently implemented phonics-based intervention, initially developed for children from first grade struggling with acquiring basic decoding skills (McTigue et al., 2019; Richardson & Lyytinen, 2014), with an auditory story-game intervention in which the stories were envelope enhanced. We implemented an EE strategy adapted from the one of Koning and Wouters (2012). The

outcome measure of this study is rise time discrimination, which has been proposed as a contributor to one of the core deficits in dyslexia, namely the sensitivity to temporal cues in the speech envelope (Farmer & Klein, 1995; Goswami et al., 2002, 2020; Goswami, 2011; Hämäläinen et al., 2013; Poelmans et al., 2011; Van Hirtum et al., 2021; Van Hirtum, Ghesquière, et al., 2019; Vanvooren et al., 2017).

Considering the speech perception improvement by EE in both children and adults with dyslexia (Van Hirtum et al., 2021; Van Hirtum, Moncada-Torres, et al., 2019), we expected EE to also boost basic auditory processing. EE specifically accentuates rise times in the speech envelope. Thus, we hypothesize an enhanced rise time sensitivity in children at cognitive risk for dyslexia directly after the intervention, with potential long term maintenance. We do not expect GraphoGame to impact this performance. To the best of our knowledge, no study has yet investigated the ability of EE to improve basic auditory processing in children at risk for dyslexia, prior to the onset of reading instruction. This could result in the development of more appropriate interventions targeting an important deficit in dyslexia.

4.2 Materials and Methods

4.2.1 Participants

Participants for the current study were recruited during a large-scale screening phase in children attending the last year of kindergarten. Parents of children attending kindergarten in Flanders (Belgium) were contacted by sending an information letter and video. From the 1900 children who received parental consent for participation in the screening, 1225 children were eventually assessed based on a few exclusion criteria. All children had to be native Dutch speakers with bilateral normal hearing, neither history of brain damage or neurological disorders, nor (preliminary) diagnosis of autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD), did not receive any therapy due to language and/or articulatory problems and had already received a total schooling period of at least 20 months. Children with incomplete or unreliable test scores, as well as children scoring below the 10th percentile on non-verbal IQ, i.e. below a norm score of 75.3 on the Raven's Colored Progressive Matrices (Raven et

al., 1984), were further excluded, leaving us with a sample of 1091 children. From these 1091 children, 119 children were eventually defined as having an elevated cognitive risk for dyslexia, defined as scoring below the 30th percentile on two out of three reading-related measures. These measures were phonological awareness (PA), letter knowledge (LK) and rapid automatized naming (RAN), the strongest cognitive pre-literacy predictors of dyslexia (Caravolas et al., 2012; Clayton et al., 2020; Ozernov-Palchik & Gaab, 2016). Children scoring below the 30th percentile on PA and RAN were additionally required to have LK below the 40th percentile. A detailed description of the screening tasks and procedure can be found in Verwimp et al. (2020). From the 119 children at cognitive risk for developing dyslexia, 91 participated in the current study. Eight children did not return for post-test and 12 children did not return for consolidation test, resulting in a sample of 83 and 79 children at post-test and consolidation test respectively. Seventy-six of the children have all three test phases complete. However, data from all 91 children are included for one or more test phases, since statistical analyses are robust to missing data. Due to technical issues with the tablets used for the intervention, EE data from four children were lost

4.2.2 Procedure

Through a block randomization the 91 selected children were randomly assigned to one of three experimental groups for the intervention study. The first experimental group was instructed to perform a phonics-based training (i.e. GraphoGame, GG) for 15 minutes in combination with actively listening to stories that were envelope enhanced (EE) for 10 minutes (i.e. GGEE group; $n_{pre\text{-}test} = 31$, $n_{post\text{-}test} = 29$, $n_{consolidation\ test} = 26$). Children in the second experimental group also played GraphoGame for 15 minutes, but listened to stories without envelope enhancement (NE) for 10 minutes (i.e. GGNE group; $n_{pre\text{-}test} = 31$, $n_{post\text{-}test} = 28$, $n_{consolidation\ test} = 29$). Children in the third experimental group constituted the active control group. They played control games for 15 minutes and actively listened to stories without envelope enhancement (NE) for 10 minutes (i.e. ACNE group; $n_{pre\text{-}test} = 29$, $n_{post\text{-}test} = 26$, $n_{consolidation\ test} = 24$). The block randomization assured that the three experimental groups were balanced with respect to birth trimester, sex, and educational environment (i.e. school) and did not differ in age (months), non-

verbal IQ, sex and socio-economic status (SES) (see **Table 4.1** for participant characteristics).

The intervention study had a longitudinal design with a pre-test, intervention, post-test, and consolidation test. All children performed an initial baseline measurement of the outcome measure (i.e. rise time discrimination). Afterwards, they were instructed to carry out the tablet-based intervention at home in which the children played the games for six days a week for a total period of 12 weeks. Not all children played the games according to our instructions (i.e. 6 days per week for 12 weeks), so intervention duration was not strictly 12 weeks for all children, but rather on average 14 weeks. For the EE intervention children completed on average 91% of the intervention, while for GraphoGame on average 89% was completed.

To complete the intervention, all children received a Samsung Galaxy Tab E9.6 tablet in combination with an Audiotechnica ATHM20x headphone. Our research group calibrated the tablets and headphones for sound level for the EE intervention. Following the intervention, children returned for a post-test in which they were again tested for rise time discrimination. Post-test took place on average 1.5 week after the end of the intervention. On average 1 year and 2 months after the post-test, after roughly one year of formal reading instruction in first grade, the children returned for a consolidation test in which their rise time discrimination was again investigated. A chi-squared test revealed no differences between the three experimental groups in terms of drop-out ($\chi^2(2, N=12) = 1.5$, $p = .47$).

Table 4.1: Participant characteristics

Characteristic	Levels	GGEE (n = 31)		GGNE (n = 31)		ACNE (n = 26)		Group comparison	
		M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*-value
Age pre-test (months)		65	3	65	3	65	4	$F(2,88) = 0.27$	$p = .764$
Non-verbal IQ[a]		101	14	101	17	96	13	$F(2,88) = 0.98$	$p = .378$
Sex	Male/Female	19/12		15/16		16/13		$\chi^2(2, N=91) = 1.04$	$p = .594$
SES[b]	Low/Middle/High/Missing	8/9/14/0		7/12/12/0		8/15/5/1		$\chi^2(2, N=91) = 6.10$	$p = .192$

Note. GG = GraphoGame, EE = envelope enhanced, NE = not envelope enhanced, AC = active control, *M* = group mean, *SD* = standard deviation, SES = socio-economic status. For categorical data (i.e. sex, SES) the numbers in each group are reported instead of *M* and *SD*, and group comparisons are done using chi-squared tests instead of one-way ANOVA.

[a] Reported scores are standardized scores based on the *M* and *SD* of the total group of screened children (*M* = 98.15, *SD* = 16.66)

[b] SES is based on the parental educational level of the mother

4.2.3 Interventions

Envelope Enhancement

Signal processing of 72 spoken stories was performed in MATLAB R2016b (The MathWorks Inc, 2016). The signal processing methods here were adapted from those in the study of Koning and Wouters (2012). As a first step in the signal processing, the original signal $s(t)$ was resampled to $f_{sampling} = 16$ kHz and subsequently split into frames of 128 samples with a frame advance of 32 samples. A frame-based fast Fourier transform preceded by Hann windowing transformed the signal to the time-frequency domain. Upon this, the frequency bins were combined by means of a weighted sum of their powers, mapping them to 23 critical channels. The frequency limits of these channels were defined according to the critical bandwidths of Fastl and Zwicker (2007). The envelope of each channel $E(t,k)$ was obtained by taking the square root per channel. A slow envelope of each channel $E_{slow}(t,k)$ was obtained as follows. The envelope $E(t,k)$ was low-pass filtered with a fourth-order Butterworth filter with a cutoff frequency of 20 Hz, which gave a signal with higher time delay when reacting to sudden increases in $E(t,k)$. This low-pass filtered version of $E(t,k)$ was then half-wave rectified and amplified by a factor of $A_{slow} = 8$ to obtain $E_{slow}(t,k)$. The latter step ensured a higher level of $E_{slow}(t,k)$ than that of $E(t,k)$ at quasi-stationary parts, while the level of $E(t,k)$ was higher than that of $E_{slow}(t,k)$ at sudden increases in energy (i.e. onsets). As such, subtracting $E_{slow}(t,k)$ from $E(t,k)$ yields a signal with peaks at the onsets of the envelope $E(t,k)$, and negative values at stationary parts of $E(t,k)$. A peak envelope signal $E_{peak}(t,k)$ could therefore be obtained by subtracting $E_{slow}(t,k)$ from $E(t,k)$, followed by half-wave rectification and amplification by a factor of $A_{peak} = 3.5$. The eventual peak signal in the time domain $p(t)$ was obtained by mapping the 23 bands back to 128 frequency bins, followed by an inverse fast Fourier transform after which the frames were recombined by a weighted overlap-add method. Finally, $p(t)$ was added to the original signal $s(t)$, resulting in the envelope enhanced signal $s_{EE}(t)$, see **Figure 4.1**.

Eighty-seven age-appropriate stories ranging from 3 to 16 minutes were selected from 18 book series. Nine professionals with knowledge of standard Dutch recorded these stories. The stories were then combined with

appropriate images and included in a tablet-game. Two versions of the game were created, one in which the stories were enhanced with the envelope enhancement signal processing strategy (EE) and one without enhancement (NE). The game consisted of 18 themes or book series that each contained four story sessions. Each story session contained one long or two short stories. The children played one story session per day. Hence, in total there were 72 playing days, covering the entire 12-week intervention period with one day off every week. At the end of each story, the children answered questions about its content to ensure active listening. To ensure continued motivation, children earned coins for every correct response, allowing them to buy gadgets for their game character. The children's progress was logged online to allow the researchers to monitor it.

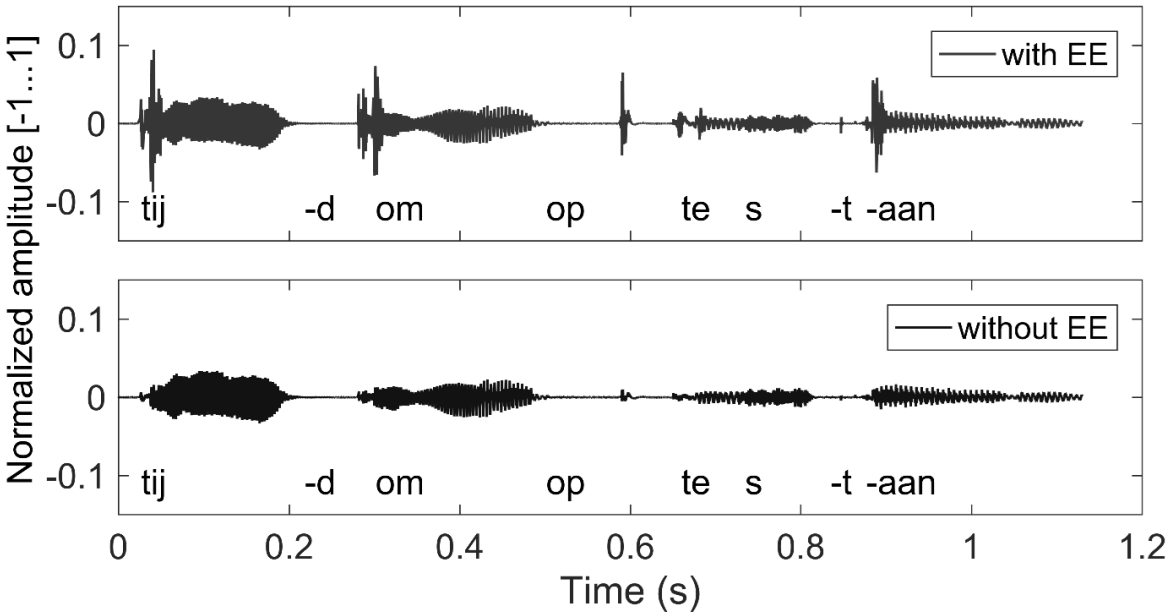


Figure 4.1; EE/NE stimulus. A waveform of a Dutch sentence (English translation: 'time to get up') from one of the stories with EE (upper) and without EE (lower)

GraphoGame

GraphoGame Flemish (Glatz et al., 2021) consisted of mini-games divided over three module types namely, grapheme modules, phonology modules, and reading modules. The different mini-games aimed at training or

assessing different skills, such as introducing new graphemes, visual discrimination of graphemes, auditory identification of phonemes within words, phoneme blending, spelling, phoneme counting, reading of syllables and words, general purpose levels in which grapheme-phoneme correspondences and single word reading are practiced and repeated and playing motivation assessment. The game's content was slowly increasing in difficulty, and was enough to span the extended 12-week intervention period. During the 12-week intervention, the children needed to progress through the game content, but they were able to go back to play previous levels at all times. To increase motivation, children earned coins when progressing though the game, which enabled them to buy gadgets for their game character in an in-game store. The results from the GraphoGame sessions were logged online and were accessible to the research group in order to follow up the children's progress throughout the game. GraphoGame Flemish is described in detail in Glatz et al. (2021).

Control Game

The control game consisted of six commercially available applications, namely Lego City My City, LegoDuploTown, LegoDuploTrains, Playmobile horseriding game, Playmobil Police and Lego Heartlake Rush. The children were not instructed to play any particular game, as long as they played according to the schedule (i.e. 6 days per week for a period of 12 weeks). Identical to GraphoGame, children played the control games for 15 minutes per day. The choice for these games was based on a few criteria. They (1) were at least as immersive as GraphoGame, (2) were age-appropriate, and (3) were shown by an internal pilot study to not train reading, and to induce the same placebo effect for attention span as GraphoGame.

4.2.4 Measures: Pre-test, Post-test and Consolidation Test

Rise Time Discrimination Task

Auditory perception was investigated using a rise time discrimination task identical to the one used in Vanvooren et al. (2017), which measures the participants' sensitivity to differences in rise times. The task was performed in a soundproof booth. Prior to performing the rise time discrimination task,

all participants were screened for hearing loss by means of an audiometric pure-tone detection task at .25, .5, 1, 2, 4 and 8 kHz. The Fletcher Index (FI) was calculated as the average threshold at .5, 1 and 2 kHz (Fletcher, 1950). Stimuli were presented monaurally to the right ear over calibrated Sennheiser HDA 200 headphones at 70 dB SPL, unless the FI to the right ear exceeded 20 dB HL. In this case, the increased hearing thresholds were compensated for by increasing the level of the stimuli with FI – 20 dB SPL, so that the adjusted presentation level equals 70 + (FI-20) dB SPL. This was the case for three out of 91 children at pre-test, seven out of 83 at post-test, and six out of 79 at consolidation test. Rise time discrimination was estimated with a two-down, one-up adaptive staircase procedure, targeting the threshold corresponding to 70.7 % correct responses (Levitt, 1971). This procedure was embedded within a three-alternative forced-choice oddity paradigm and presented as an interactive computer gamification using APEX software (Francart et al., 2008; Laneau et al., 2005). A threshold run was terminated after eight reversals and the average of the last four reversals was taken as the threshold. Each participant completed the task two times, thus obtaining two thresholds. To guarantee understanding of the task, the participants completed a practice run prior to the two actual threshold runs. Hence, the participants were already familiarized with the task. Stimuli comprised speech-weighted noise with a linear rise and fall time. The total duration of the stimuli was fixed at 800 ms, including a fixed linear fall time of 75 ms. The rise times varied logarithmically between 15 and 699 ms in 50 steps, with the stimulus with the shortest rise time (15 ms) as the reference stimulus in each trial. The recorded threshold is the rise time of the target stimulus at which the children can still reliably discriminate between the target and the reference stimulus. Analyses were performed on the best threshold (i.e. the lowest threshold) of the two obtained thresholds (Law, Vandermosten, et al., 2017).

4.2.5 Statistical analysis

All statistical analyses were performed in R (version 3.5.1) (R Core Team, 2018). Prior to analyses, the assumption of normality of the residuals was assessed using Kolmogorov-Smirnov tests. To ensure the assumption of homogeneity of variance, Levene tests were performed. For the rise time discrimination task, both the assumptions of normality of the residuals and

homogeneity of variance were violated, steering us towards a semi-parametric approach for data analysis.

This main analysis investigated the short- and long-term effects of the auditory and phonics-based interventions using generalized estimating equations (GEE) (geepack package) (Halekoh et al., 2006; Zeger & Liang, 1986). Based on the distribution of the dependent variable (i.e. RTD threshold), a Gamma Family with a log link, which exponentiates the linear predictors to make the model fit in a linear form, was specified. Considering the repeated measures design, an autoregressive correlation structure was specified, accounting for the correlation between repeated observations from a given subject. Missing values were reported to the model.

For analyses, the interaction between intervention group and test phase was considered. In order to disentangle short- and long-term intervention effects between the different intervention groups, we performed post-hoc comparisons using estimated marginal means (EMMs) with a Holm correction for multiple comparisons. In an additional analysis, the number of hours the groups spent listening to the stories and the number of hours the groups played either GG or CG were investigated using One-way ANOVAs, since residuals were normally distributed for these measures. Considering the non-normality of the residuals for the rise time discrimination task, all descriptives are reported as medians and interquartile ranges, whereas intervention durations are reported as means and standard deviations.

4.3 Results

Descriptive data for the RTD thresholds are provided in **Table 4.2** and an illustration of the thresholds for all groups and test phases can be found in **Figure 4.2**. We observed a significant interaction effect between group and test phase ($\chi^2(4) = 11$, p = .026). The interaction effect showed that whereas all groups improved significantly from pre-test to consolidation test (GGEE: $z = 6.05$, $p < .001$, 95 % asymptotic CI [1.57, 4.33], GGNE: $z = 4.72$, $p < .001$, 95 % asymptotic CI [1.29, 3.75]; ACNE: $z = 4.00$, $p = .002$, 95 % asymptotic CI [1.22, 5.98]), only the GGEE group's performance was significantly enhanced at post-test ($z = 5.15$, $p < .001$, 95 % asymptotic CI [1.39, 4.07]). An improvement in the GGNE group took place during first

grade (z = 3.12, p = 0.044, 95 % asymptotic CI [0.99, 2.89]), and the ACNE group's improvement during this same time period came close to significance (z = 2.99, p = .063, 95 % asymptotic CI [0.95, 4.44]). Despite the differences between the groups regarding the period in which the main improvement took place, none of the groups differed from the other at the three test phases, although at post-test the difference between GGEE and ACNE almost reached significance with the ACNE group performing worse than the GGEE group (z = -2.94, p = .073, 95% asymptotic CI [0.28, 1.06]). See **Figure 4.3** for the GEE model predictions.

Table 4.2: Descriptives of RTD thresholds (in ms) for the three intervention groups in the three separate test phases

Group	Pre-test		Post-test		Consolidation test	
	Mdn	*IQR*	*Mdn*	*IQR*	*Mdn*	*IQR*
GGEE	278	272	81	84	84.5	106
GGNE	119	136	92	113	60	61
ACNE	175	395	140	241	55	44

Note. *Mdn* = median; *IQR* = interquartile range

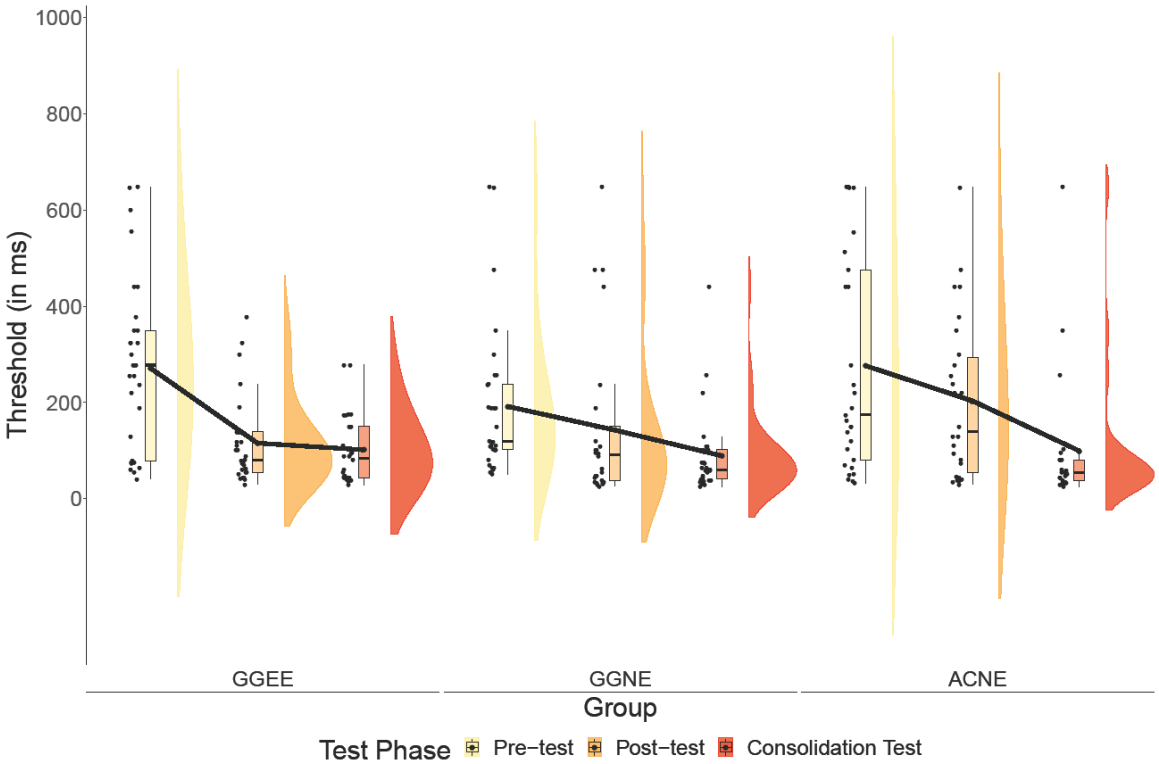


Figure 4.2: RTD thresholds as a function of intervention group and test phase. From left to right we depict individual subjects' thresholds, boxplots and probability distributions for the three intervention groups and the three test phases. The solid black line connects the means of the three intervention groups at each test phase.

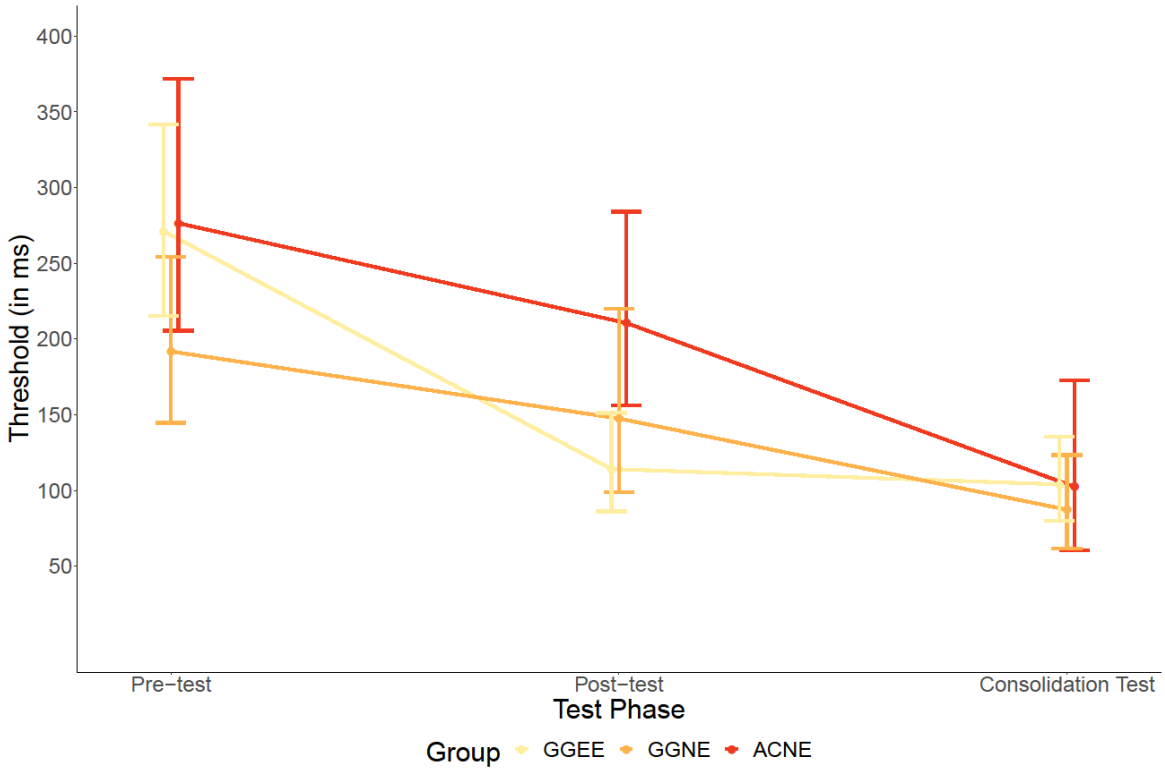


Figure 4.3: GEE model predictions. Fitted values and 95% CIs are depicted for the three groups in the three test phases.

We furthermore compared the amount of hours the children in the different groups spent listening to the EE (GGEE group) or NE (GGNE and ACNE group) stories and the amount of hours they played GG (GGEE and GGNE group) or CG (ACNE group). The groups did not differ with respect to story listening ($F(2,84) = 0.99$, $p = 0.37$) or GG/CG ($F(2.88) = 0.41$, $p = 0.67$). See **Table 4.3** for intervention duration descriptives.

Table 4.3: Descriptives of hours of EE/NE stories listened to and duration of GraphoGame and control game for the three intervention groups

Intervention	GGEE		GGNE		ACNE	
	M	*SD*	*M*	*SD*	*M*	*SD*
EE/NE Stories	10.5	3.0	11.2	2.8	11.4	1.9
GG/CG	16.1	5.3	16.0	5.3	17.1	4.8

Note: *M* = mean; *SD* = standard deviation

4.4 Discussion

The ‘dyslexia paradox’ often undermines the effectiveness of dyslexia remediation (Ozernov-Palchik & Gaab, 2016). In order to address this paradox, interventions should be administered preventively. Dyslexia remediation generally focuses on grapheme-phoneme correspondences with phonics-based interventions (National Institute of Child Health and Human Development, 2000). However, it is unclear whether children with dyslexia who experience auditory processing difficulties sufficiently benefit from these phonics-based interventions. This creates the need for interventions that (1) also target the auditory perceptive difficulties seen in dyslexia on top of the phonics-based interventions and that (2) can easily be administered prior to the onset of reading instruction. Therefore, the present longitudinal study investigated a combined auditory and phonics-based intervention administered before the onset of reading instruction. Its impact was investigated in Dutch children at cognitive risk for dyslexia on an auditory temporal perceptive task, namely rise time discrimination. To our knowledge, this study is the first to investigate EE as an intervention strategy in pre-readers at cognitive risk for dyslexia. Here, we demonstrated that the EE intervention in kindergarten directly boosts rise time discrimination, leading to improved rise time sensitivity at the start of reading acquisition while children without EE training only display rise time sensitivity improvement at a later moment in development.

We hypothesized that receiving the EE training would enhance children’s rise time sensitivity, whereas GraphoGame was not hypothesized to impact rise time discrimination. This EE-related improvement was expected to be demonstrated directly after the intervention, with potential long-term maintenance. Our results displayed an interesting distinction between the groups regarding the time period in which they mainly improved. In this study, EE provided an effect on rise time discrimination that could be measured immediately following the intervention, as demonstrated by the significant improvement following the intervention in the GGEE group. Previous studies by Van Hirtum et al. (2021) and Van Hirtum, Moncada-Torres, et al. (2019) already revealed the ability of EE to improve speech perception instantaneously and passively. The authors suggested that after long-term repeated exposure during intervention, EE might have an even

stronger impact. In the current study we investigated the effect of such a repeated EE exposure on rise time discrimination and confirmed its impact on this measure. In contrast, the GGNE and ACNE groups did not significantly improve during the intervention period. Despite these differences in response to the intervention, the groups were not significantly different at post-test, although the difference between the GGEE and ACNE group tended towards significance, with the GGEE group performing better than the ACNE group. Even though we might have expected a clearer distinction between the group receiving the EE intervention and the groups not receiving this intervention, EE nonetheless provided a marked improvement that was not demonstrated by the other two groups.

During first grade, when no intervention was taking place anymore, there was an improvement in the GGNE and ACNE groups only, hence they caught up with the GGEE group, reflected by no group differences at consolidation test. This improvement in the GGNE and ACNE groups seems to reflect maturation. Indeed, rise time discrimination has previously been found to improve with age in children with dyslexia, although to a lesser extent compared to typically developing children (Goswami et al., 2020). Apart from maturation, one might suggest that learning to read and the accompanying phonological awareness development improve auditory processing by refining acoustic contrasts in language (Kuppen et al., 2011). However, previous longitudinal studies have demonstrated that basic auditory processing impacts phonological awareness, but not the other way around, thereby contradicting this latter hypothesis (Goswami et al., 2020; Thomson et al., 2013). Our findings with respect to the phonics-based intervention further corroborate this statement and are in line with our expectations for the GraphoGame intervention. Considering the difference between the GGEE and GGNE groups, and the similar performance of the GGNE and ACNE groups, our phonics-based intervention did not seem to improve rise time discrimination. Hence, learning to read during the intervention did not impact rise time discrimination, making it unlikely that learning to read during first grade will exert an impact. One might also propose that the improvement in the GGNE and ACNE groups is consequential to possibly improved general abilities such as attention that could be attributed to the games played during the intervention (Franceschini et al., 2013; Stevens et al., 2013). However, if this were the case, we hypothesize that the improved rise time discrimination performance should

already have been present at post-test, directly after having completed the intervention. Considering, based on the analyses, that performance only improved by consolidation test, it is unlikely that general abilities trained during the intervention contributed to the improved performance of the GGNE and ACNE groups. This supports the maturation hypothesis of rise time discrimination.

Considering that maturation in rise time discrimination performance has already been demonstrated until at least the age of 12 with a similar task to the one we used (Goswami et al., 2020; Kuppen & Goswami, 2016), we expected the GGEE group to also further improve during first grade, hence maintaining its enhanced rise time sensitivity. The lack of further improvement in the GGEE group might be suggested to represent a ceiling effect that cannot be exceeded at this young age but might allow children to further improve at an older age. A fourth follow-up measurement would however be needed to confirm this hypothesis.

However, the importance of our findings lies in the fact that the EE intervention allows rise time discrimination to improve at a crucial time in development, namely right before the start of formal reading instruction. An issue with reading instruction, and as we previously suggested also with phonics-based interventions, is that they both rely on the accurate perception of presented phonemes. Thus, auditory processing deficits that impact phoneme perception could underlie reading development difficulties among some children with (a risk for) dyslexia. This could complicate their reading progress (Ziegler et al., 2009). The currently investigated EE intervention provided an improvement immediately following the intervention in the auditory processing of rise times, which provide important cues for phonetic discrimination (Goswami et al., 2011; Thomson et al., 2013). Accordingly, our intervention might have the potential to strengthen phoneme representations, which are of great importance for learning to read (Snowling & Hulme, 1994). Even more important, we demonstrated that the EE intervention allows for early intervention by implementation in children's stories embedded in a game. More specifically, it shows potential to be implemented before the onset of formal reading instruction and thus during the most sensitive period for intervention (Ozernov-Palchik & Gaab, 2016). This enables us to intervene during a time period of great importance for brain plasticity (Gilmore et al., 2018), and a period in which the foundation is being set for later phonological awareness and reading development

(Carroll et al., 2003; Snowling & Hulme, 2011). In this way, children receiving the EE intervention might have an advantage on the children not receiving this intervention at the onset of formal reading instruction. The latter group will start reading acquisition with unimproved rise time sensitivity that is possibly worse than that of typically developing children. This might complicate their reading progress. For the children receiving the EE intervention this deficit is reduced by the time reading acquisition starts. Our EE intervention hence may tackle both the requirements we set forth for interventions, (1) it improves the auditory perceptive difficulties and (2) it can be administered prior to the onset of reading instruction as to improve rise time discrimination at a crucial time in development.

Altogether, all groups clearly improved in rise time discrimination performance from pre-test (kindergarten) to consolidation test (end of first grade). Considering that the GGNE and ACNE groups only improved after the intervention had already finished, we postulate that this was the consequence of maturation during first grade. In the GGEE group, the EE intervention provided a clear improvement, immediately following the intervention. Importantly, this even preceded the maturational effect in the other groups who only demonstrated this improvement during first grade.

4.4.1 Limitations

Despite our promising findings the current study has a few limitations that need to be addressed. First, an important caveat is that it remains to be investigated whether the EE-induced improvement in rise time discrimination will in turn impact speech perception and phonological awareness in order to eventually improve reading performance in the investigated at risk children. However, previous longitudinal studies that have shown clear links between basic auditory processing such as rise time discrimination and later phonological awareness and reading allow us to hypothesize that this cascading effect should indeed be uncovered (Goswami et al., 2020; Vanvooren et al., 2017).

Another consideration is that in the current investigation there was no control group of typically developing children, and thus all children in this study are at cognitive risk for dyslexia. Consequently, we are unable to compare the developmental trajectories of typically developing children and children at

cognitive risk for dyslexia. Previous longitudinal studies have already indicated differences between children with dyslexia and their controls in both the speed of rise time discrimination development (Goswami et al., 2020) and the trajectory of their development (Kuppen & Goswami, 2016). Notwithstanding the fact that our data are inadequate to directly test a possible differentiation between children at cognitive risk for dyslexia and typically developing children, the main message of our study remains that an EE intervention allows for improved rise time discrimination performance immediately following the intervention, even before the onset of reading instruction. It might be suggested that EE will have a similar effect in typically developing children, considering its potential to also increase speech perception in children without dyslexia (Van Hirtum et al., 2021), but this remains to be tested in future studies. However, administering the intervention to both typically developing and at risk children would not be recommended because it would possibly only enlarge the gap in performance between these groups. An additional reason for not administering the intervention to typically developing children is that this would be an inefficient use of resources, especially when there are many children with (a risk for) dyslexia who could benefit from the provided interventions.

4.5 Conclusion

Our results show that speech envelope enhancement as an intervention for pre-readers at cognitive risk for dyslexia directly improves rise time discrimination, in contrast to the maturation of this process, which takes place at a later moment in development. Envelope enhancement affects basic auditory processing even before the onset of formal reading instruction. The significance here is that the EE intervention allows for interventions during the most effective intervention period. This is consistent with previous studies who already demonstrated the potential of GraphoGame to be used in pre-reading children at risk for dyslexia (Lovio et al., 2012; Vanden Bempt et al., 2021). Further studies are required to investigate whether the improvement in rise time discrimination will also carry through to speech perception, phonological awareness and reading performance in order to mitigate (the occurrence of) dyslexia. Nevertheless, these results provide a first glimpse on a way to preventively tackle the auditory processing deficits

that might be experienced by children at cognitive risk for dyslexia. Within a few years, we hope to have accumulated follow-up data from the children in this study. This will enable us to clearly distinguish between children that will have developed dyslexia as well as typically developing children. This will allow us to reanalyze our data by redefining the groups into dyslexic and typical reading groups and will even further clarify the significance of our EE intervention.

Chapter 5

General Discussion

5.1 Summary of aims and main findings

One of the main aims of dyslexia research is preventing reading failure. This requires targeted and preferably preventive interventions. A growing body of research indicates an underlying auditory temporal processing deficit in (a subgroup of individuals with) dyslexia. Hence, remediating auditory processing difficulties can potentially promote reading-related skills. Nonetheless, a more thorough understanding of the mechanisms underlying atypical auditory temporal processing is required to improve existing intervention strategies. With this in mind, the current research aimed to (1) identify the neurophysiological markers of the auditory temporal processing deficit in dyslexia and (2) to investigate the impact of a preventive intervention on auditory temporal processing.

By means of EEG, we first examined the suitability of acoustic stimuli that might support the identification of the neural markers underlying the auditory temporal processing deficit in young children (Chapter 2). We

confirmed the suitability of the PULS stimuli for research in pre-reading to beginning reading children. The pulsatile stimuli greatly enhanced neural synchronization to syllable rate modulations, thereby demonstrating a significant impact on data acquisition efficiency in a pediatric population. In addition, the pulsatile stimuli evoked a differential hemispheric specialization at syllable rate compared to the sinusoidal stimuli. There was no impact of the PULS stimuli on phoneme rate synchronization.

Consequently, what was originally a secondary analysis in Chapter 3, in fact provided us significant insights into neural auditory temporal processing in pre-reading to beginning reading children with and without dyslexia. The PULS stimuli were used to precisely characterize the auditory temporal processing deficit in dyslexia. We demonstrated atypical hemispheric specialization in children with dyslexia to both syllable and phoneme rate modulations, already before the onset of formal reading instruction. Atypical hemispheric specialization was found for both SAM and PULS stimuli. Hence, our results failed to confirm a deficit in the neural processing of rise times in (children with) dyslexia, but rather point to a more global deficit in hemispheric specialization.

The primary aim of Chapter 3 was to investigate the response to a preventive combined phonics- and auditory-based intervention on neural synchronization in pre-readers at cognitive risk for dyslexia. We revealed no intervention effects on neural synchronization at syllable or phoneme rate, thereby questioning the potential of the preventive intervention in its current form to remediate the auditory temporal processing deficit in dyslexia. Nonetheless, in Chapter 4 we investigated the intervention's impact on rise time discrimination and our results showed that the enhanced speech intervention, but not the phonics-based training, improved rise time discrimination in pre-readers at cognitive risk for dyslexia. Altogether, it seems like the development of targeted interventions is still a work in progress.

In the following sections we discuss the main findings of the current research. Furthermore, we provide an overview of the practical relevance and the limitations of the research. We conclude with an overview of future perspectives.

5.2 Neurophysiological markers of the auditory temporal processing deficit

The current research starts from the hypothesis that dyslexia is associated with atypical neural synchronization and hemispheric specialization to temporal modulations in the speech envelope. This is assumed to hamper reading development through cascading difficulties with speech perception and phonological awareness (Goswami, 2018, 2019a; Lallier et al., 2018). More specifically, within this framework, recent studies specifically assigned a crucial role to neural synchronization to rise times (Lizarazu, Lallier, et al., 2021; Van Hirtum, Ghesquière, et al., 2019). However, this latter research was limited to cross-sectional studies in adults and was unable to disentangle potential causal from consequential effects. Hence, the present research went beyond existing investigations of the auditory temporal processing deficit in dyslexia and, using pulsatile stimuli embedded in a longitudinal design, specifically explored the causal versus consequential effects of neural synchronization to rise times in children with dyslexia. In order to confirm the suitability of the pulsatile stimuli for this investigation of the auditory temporal processing deficit in children with dyslexia, we first explored their potential in a large population of typically reading pre- to beginning readers.

5.2.1 Using pulsatile stimuli in a pediatric population

Our results in Chapter 2 indicated that the pulsatile stimuli significantly enhanced neural synchronization to syllable rate modulations. Using pulsatile stimuli contributes to the efficiency of data acquisition in children by reducing the time needed for obtaining significant ASSRs by 80%. We thereby demonstrated the potential of pulsatile stimuli over and above the investigation of neural synchronization to rise times in a pediatric population.

Our findings are consistent with earlier studies demonstrating increased neural synchronization in response to exponentially modulated envelopes in adults (John et al., 2002, 2003; Prendergast et al., 2010; Van Hirtum, Ghesquière, et al., 2019) and young infants (John et al., 2004). We were, to the best of our knowledge, the first to extend the existing literature to

children. John et al. (2002) suggested that response enhancement is related to the silent gaps in between the successive peaks of acoustic stimulation, which are longer for the pulsatile stimuli. The silent gaps could increase the probability that the refractory period, the recovery phase following the firing of neurons, has ended before the next stimulation peak. However, the recovery phase from firing is fast, and is therefore unlikely to contribute to enhanced responses, especially at a slow frequency of 4 Hz (Wang, 2010). We proposed that the reason for enhanced responses is related to the rapid adaptation effect at the synapse to the auditory nerve fiber (ANF). The more sudden the increase in intensity of the stimulus and hence the steeper the slope, the stronger the neural discharge probability at the synapse to the ANF (Delgutte, 1980, 1997; Geurts & Wouters, 1999). Notably, we did not investigate the physiological basis of enhanced responses, so this remains hypothetical until further investigated.

An additional finding relates to the reversed hemispheric specialization demonstrated by the PULS stimuli compared to the SAM stimuli. We were among the first studies to investigate hemispheric specialization using pulsatile stimuli (Van Hirtum, Ghesquière, et al., 2019), and we were the first to demonstrate this reversed hemispheric specialization. Our interpretation posited that the more sudden increases in intensity in the PULS stimuli compared to SAM stimuli created stronger temporal cues. In accordance with the theory by Zatorre & Belin (2001), this temporal information could elicit a leftward lateralization. Since lateralization has already been shown to develop over time, this effect could potentially be limited to younger children in which hemispheric specialization is not yet mature (Ríos-López et al., 2020; Yamazaki et al., 2018). This would explain the similar hemispheric specialization in response to both SAM and PULS stimuli in the study of Van Hirtum, Ghesquière, et al. (2019). Hemispheric specialization to PULS stimuli across development has however not yet been investigated, so future research should aim to elucidate this differential pattern of hemispheric specialization. Nonetheless, it is clear that factors unrelated to the modulation frequency determine response characteristics. This is consistent with studies demonstrating the impact of for example linguistic content and attention on response characteristics such as hemispheric specialization (Assaneo et al., 2019; Peelle et al., 2013). Interestingly, leftward lateralization more closely resembles speech envelope tracking

(Assaneo et al., 2019; Peelle et al., 2013) and might thus possibly indicate a stronger ecological validity of the PULS stimuli.

Altogether, our findings support the potential of pulsatile stimuli to elicit ASSRs in pediatric research. The benefit with respect to data acquisition efficiency is substantial and might thus encourage researchers to include PULS stimuli in their studies. Despite its clear advantages, the PULS stimuli do not seem to tap into the exact same mechanisms as SAM stimuli, at least in a pediatric population, and the underlying factors contributing to response enhancement are not yet fully understood. Therefore we encourage future research to investigate these differences before replacing the SAM by the PULS stimuli altogether.

5.2.2 Atypical hemispheric specialization in dyslexia

A main finding of Chapter 3 is that dyslexia is characterized by atypical hemispheric specialization at both syllable and phoneme rates, even before the onset of formal reading instruction. This indicates a possible causal mechanism or risk factor underlying the development of dyslexia. Our results agree with previous studies demonstrating atypical hemispheric specialization at syllable and phoneme rates in dyslexia (Granados Barbero et al., 2022; Lehongre et al., 2011; Lizarazu et al., 2015; Mandke et al., 2022) and is one of the first studies to already demonstrate this in pre-reading children.

Surprisingly, our results did not demonstrate a deficit with respect to the overall strength of neural synchronization, but rather indicated a more complex pattern of atypical hemispheric specialization. This contradicts the literature showing either decreased or increased synchronization at syllable and phoneme rates in dyslexia (De Vos et al., 2017a, 2017b; Granados Barbero et al., 2021, 2022; Lehongre et al., 2011, 2013; Lizarazu et al., 2015; Lizarazu, Scotto di Covella, et al., 2021; Mandke et al., 2022; Marchesotti et al., 2020; McAnally & Stein, 1997; Menell et al., 1999; Mittag et al., 2022; Poelmans et al., 2012; Van Hirtum, Ghesquière, et al., 2019). We suggest that the specific frequencies investigated in the current research can explain why our findings contradict the literature showing either decreased or increased neural synchronization in dyslexia. Whereas theta rate deficits in dyslexia are not reliably demonstrated, the existence of delta rate deficits

have received more support (Hämäläinen et al., 2012; Keshavarzi et al., 2022; Lizarazu, Scotto di Covella, et al., 2021; Mandke et al., 2022; Molinaro et al., 2016; Peter et al., 2023; Power et al., 2016; Soltész et al., 2013). Especially in children, where child-directed speech (CDS) contains more modulation energy at ~2 Hz (Leong & Goswami, 2015), and where awareness of larger phonological units occurring in speech at rates below 2 Hz develops well before that of smaller phonological units (Goswami & Bryant, 2016), the reliance on delta rate synchronization might outweigh that of theta rate synchronization. Indeed, research has demonstrated that delta rate synchronization seems to contribute to speech intelligibility in pre-readers (Ríos-López et al., 2020) as well as that it is predictive of later reading skills (Ríos-López et al., 2022). Additionally, languages differ in linguistic rhythm (Ramus et al., 1999) and this might impact the modulation frequencies essential to leverage the rhythmic regularities in speech. Dutch for example is a stress-timed language in which delta rate synchronization can be assumed to be fundamental to the perception of rhythm. Cross-language research on neural synchronization has shown that even though speech signals in all languages comprise relatively slow temporal modulations, there is a greater occurrence of secondary peaks in the 1-2 Hz range in stress-timed languages compared to syllable-timed languages (Varnet et al., 2017). Hence, there is an increased modulation energy in the delta frequency in stress-timed languages. This further contributes to the importance of delta rate synchronization over theta rate synchronization in our sample. On a similar note, the literature is inconclusive on what frequency is related to phoneme rate processing. Even though a frequency of 20 Hz corresponds to the duration of phonemes in speech (Crystal & House, 1988; Ghitza, 2011), phonemic sampling spans several frequencies from the beta to low-gamma range (Giraud & Poeppel, 2012b). Several studies have indeed confirmed deficits in the low-gamma instead of beta rate in dyslexia (Lehongre et al., 2011, 2013; Lizarazu et al., 2015; Lizarazu, Scotto di Covella, et al., 2021). Taken together, we strongly suggest future studies to investigate delta and gamma rate synchronization and their relation to reading skills.

Furthermore, we hypothesized that the neural processing of rise times specifically would be impaired in children with dyslexia, as had already been demonstrated in adults with dyslexia (Van Hirtum, Ghesquière, et al., 2019). Surprisingly, considering that atypical hemispheric specialization was not

restricted to the PULS stimuli, we could not confirm this hypothesis. Hence, we were unable to attribute dyslexia to a deficit in the neural processing of rise times. We propose that the specifics of the group comparison in Chapter 3 might have contributed to this. Firstly, both the dyslexic and the typical reading group had an elevated cognitive risk for developing dyslexia at the age of five. Therefore, despite the differentiation in reading and spelling scores in third grade, the cognitive profiles of both groups were very similar at the onset of the longitudinal study. Secondly, children in both groups received some kind of intervention. We did not demonstrate intervention effects on neural synchronization, but we cannot rule out the possibility that some intervention effects were not measurable with the current paradigm. Thirdly, the children with dyslexia were classified as such based only on reading and spelling scores in third grade and did not receive an official dyslexia diagnosis. Therefore, it is plausible that we were unable to demonstrate the hypothesized impaired neural synchronization to rise times in children with dyslexia due to these caveats in the group comparison.

Nevertheless, the findings in Chapter 3 provide an important glance on the deficits underlying the development of dyslexia. Hemispheric specialization is an important contributing factor to speech perception and intelligibility. The left and right hemisphere are differentially equipped for parsing the speech signal at slow versus fast timescales (Boemio et al., 2005; Doelling et al., 2014; Giraud & Poeppel, 2012b; Poeppel, 2003). Therefore, atypical hemispheric specialization could hamper the parsing of the speech signal and thereby ultimately complicate the development of phonological and reading skills. As a result, the present findings fit within the TSF (Goswami, 2011), in that respect that atypical neural synchronization is related to the development of dyslexia. However, we strongly suggest future studies to include additional modulation frequencies, as well as to perform careful group comparisons.

5.3 Preventive intervention impact on the auditory temporal processing deficit

Apart from identifying the neurophysiological markers of the auditory temporal processing deficit in dyslexia, a main aim of the current research

was to investigate the impact of a preventive intervention on the auditory temporal processing deficit. Recent studies already presented Envelope Enhancement (EE) as an algorithm to improve speech-in-noise perception in children and adults with dyslexia and suggested its potential as an intervention strategy (Van Hirtum et al., 2021; Van Hirtum, Moncada-Torres, et al., 2019). The current research extended the existing literature by developing an intervention in which EE was combined with phonics-based training and investigating its short- and long-term impact on behavioral rise time discrimination and neural synchronization.

We demonstrated that the EE intervention significantly improved rise time discrimination in pre-reading children at cognitive risk for dyslexia (Chapter 4), but we were unable to demonstrate an intervention effect on syllable and phoneme rate neural synchronization (Chapter 3). Therefore, looking across the conducted studies, the EE intervention does not seem to unequivocally improve auditory temporal processing in children at risk for dyslexia. This is further supported by the study by Vanden Bempt et al. (2022). This study was conducted as part of the larger longitudinal study and investigated the impact of the EE intervention on speech-in-noise perception and reading-related skills, namely phonological awareness and letter knowledge, in a largely overlapping population. The authors could not demonstrate an EE-driven effect on speech perception and reading-related skills. Considering the hypothesized cascading framework from neural synchronization through speech perception to phonological and reading skills (Goswami, 2018, 2019a; Lallier et al., 2018), the absence of an EE-driven boosting effect on speech perception and reading-related skills might be explained by the unaltered neural synchronization following the EE intervention.

Our findings with respect to neural synchronization contradict the results of Van Hirtum et al. (2021) and Van Hirtum, Moncada-Torres, et al. (2019) in which EE significantly improved speech-in-noise-perception in children and adults with dyslexia. However, whereas these studies used EE to enhance speech in the speech-in-noise task used to measure speech perception, we measured neural synchronization at the end of an extended period of listening to enhanced stories. Hence, the impact of EE might potentially be restricted to real-time implementation. This would not invalidate the potential of EE for dyslexia, but rather limit it to real-time implementation in for example assistive listening devices.

If the potential of EE is limited to real-time implementation, the question remains why rise time discrimination was significantly improved following the EE intervention (Chapter 4). Therefore, instead of a limitation to real-time implementation, we suggest that our findings are related to the mechanisms behind the EE algorithm. EE signal processing specifically detected and amplified onset peaks in the speech envelope, thereby facilitating the detection of rise times. As a result, the EE intervention directly trained rise time sensitivity but only indirectly trained skills such as neural synchronization, speech perception and reading-related skills (Vanden Bempt, Van Herck, et al., 2022). An enhanced rise time sensitivity did not seem to yield a transfer effect to these indirectly trained skills. It is possible that the duration of the current EE intervention was insufficient to exert an impact on neural synchronization. The total EE intervention lasted approximately 12 hours spread over 12 weeks. Although a review by Cancer and Antonietti (2022) could not confirm an impact of auditory training duration on intervention efficacy, we cannot rule out the possibility that increasing EE intervention duration or intensity might have altered neural synchronization. Another potential interpretation is that a transfer effect of rise time sensitivity on further skills is restricted to earlier stages in development, and that there may thus be a sensitive window for training auditory processing that precedes kindergarten. Indeed, sensitivity to auditory information already starts developing in utero (Hepper & Shahidullah, 1994) and important auditory skills such as native-language phoneme perception demonstrate a sensitive period within the first year of life (Kuhl, 2004).Additionally, evidence exists for impaired auditory processing already during the first year of life in infants at risk for dyslexia (Kalashnikova et al., 2018). This supports an early sensitive period for (training) auditory processing. A last interpretation is that the EE intervention seems to insufficiently address the specific neural auditory temporal processing deficits in (children with) dyslexia. Whereas the EE intervention directly targets rise time processing and was suggested to restore decreased neural synchronization in dyslexia (Van Hirtum, Moncada-Torres, et al., 2019), our findings in Chapter 3 did not demonstrate impaired neural processing of rise times, nor reduced neural synchronization in children with dyslexia. Rather, the underlying deficit seems to entail a more complex pattern of atypical hemispheric specialization, which the current EE intervention is unlikely to restore.

Nevertheless, the EE intervention did improve rise time discrimination in pre-readers at cognitive risk for dyslexia, which has frequently been found to be compromised in children with (a risk for) dyslexia (Goswami et al., 2002; Goswami, 2011; Hämäläinen et al., 2005; Kalashnikova et al., 2018; Law et al., 2014; Law, Vandermosten, et al., 2017). Furthermore, the story listening game design used for the EE intervention proved feasible and enjoyable for young children (Vanden Bempt, Economou, et al., 2022). This supports its potential as a preventive intervention tool. Therefore, we suggest that if the EE intervention were to address the specific neural auditory temporal processing deficits in dyslexia, it might potentially also yield transfer effects to indirectly trained skills such as neural synchronization, speech perception and reading-related skills. As previously suggested (see **5.2.2**), there is strong support for delta rate synchronization deficits, related to stressed syllable and prosodic information processing, over theta rate synchronization deficits, related to syllabic processing. Whereas the EE intervention in Chapters 3 and 4 emphasized syllable onsets in the speech envelope, future research could opt to emphasize solely the onsets of stressed syllables, to specifically target delta rate synchronization.

Apart from the EE intervention, the current research also investigated the impact of GraphoGame, a frequently implemented phonics-based training (Glatz, 2018; Lovio et al., 2012). Despite the well-established efficacy of phonics-based interventions on reading and related skills (Bus & Van Ijzendoorn, 1999; Ehri et al., 2001; Galuschka et al., 2014; National Institute of Child Health and Human Development, 2000; Snowling & Hulme, 2011), GraphoGame did not exert an impact on rise time discrimination (Chapter 4) or syllable and phoneme rate neural synchronization (Chapter 3). This corroborates earlier work that showed that auditory temporal processing is predictive of later phonological skills, but that phonological skills do not contribute to growth in auditory temporal processing (Goswami et al., 2020). Even though we hypothesized GraphoGame to influence phoneme rate synchronization, in a similar way as formal reading instruction does (De Vos et al., 2017a), the results in Chapter 3 could not confirm this hypothesis. This agrees with the study by Vanden Bempt et al. (2021), that failed to demonstrate a GraphoGame-driven boosting effect on phonological skills in a largely overlapping population as the one in Chapters 3 and 4. Nonetheless, the GraphoGame intervention did improve letter knowledge and word decoding (Vanden Bempt et al., 2021), supporting its potential as a

preventive intervention in children at risk for dyslexia. As GraphoGame did not have an impact on auditory temporal processing, this corroborates the hypothesis that solely providing phonics-based trainings might be insufficient for children in whom auditory temporal processing deficits underlie reading difficulties. This demonstrates the importance of auditory trainings properly targeting the auditory temporal processing deficit in dyslexia.

In summary, we recommend combining phonics-based training with auditory training, so that children experiencing auditory temporal processing deficits can also optimally benefit from interventions and are not withheld by their auditory processing difficulties. However, the EE intervention in its current form seems insufficient to remediate auditory temporal processing deficits. Future research should aim to ameliorate the current EE intervention by for example targeting delta rate synchronization and/or providing it earlier on in development, or could investigate the impact of a real-time EE implementation in assistive listening devices.

5.4 Clinical implications and relevance

Dyslexia research in general aims to identify the precursors of reading difficulties, improve early identification of at risk children and develop early and preventive interventions for those children in need. The overarching goal is to prevent reading failure. The findings of the current research contribute to these aims and carry important diagnostic and interventional relevance, as well as some clinical implications unrelated to dyslexia.

First, the current work demonstrates that atypical hemispheric specialization is already present at pre-reading age (5-6 years) in children who later on develop dyslexia. This provides relevant information on the nature of the auditory temporal processing deficit and is an important step towards the establishment of neurophysiological markers for dyslexia, which might improve early detection (Gabrieli et al., 2015; Ozernov-Palchik & Gaab, 2016). Whereas the current work demonstrates neurophysiological differences between pre-reading children with and without dyslexia at the group level, establishing a neurophysiological marker requires predictive value at the individual level (Gabrieli et al., 2015). Therefore, we encourage

future research to go from group level investigations to individualized predictions, for which the current research lacks data. Another challenge that comes with using electrophysiological markers for diagnostic purposes is the practical and financial feasibility of EEG as a screening tool in young children. The combination of neurophysiological markers with behavioral markers might help overcome at least some of these limitations. Even though not explicitly investigated, the screening test battery used in the current longitudinal study seems successful for dyslexia risk identification in pre-readers. As evident from Chapter 3, approximately one third of the children identified as at risk by the screening test battery was later classified as dyslexic based on third grade reading data. Therefore, behavioral screening could be the first step in a larger screening process, identifying children in which further neurophysiological screening might be advisable. Combining behavioral and neurophysiological markers increases the predictive accuracy of screening and a more targeted neurophysiological screening greatly reduces its financial burden. Furthermore, the potential of portable EEG devices to measure ASSRs has already been confirmed (Valentin et al., 2019) and hence portable EEG devices might increase the practical feasibility of neurophysiological screening.

Second, the current research carries implications for future dyslexia interventions. Our findings demonstrate that merely training phonological skills does not improve auditory temporal processing, thereby signifying the need for complementary auditory training to target auditory processing difficulties in dyslexia. In this respect, we investigated the potential of EE. Our findings indicate a boosting effect of EE on rise time discrimination, but no transfer effect to neural synchronization. Even though the EE intervention in its current form seems insufficient to remediate the cascading hierarchy of auditory processing difficulties, it does improve rise time discrimination, which has been found to be related to future reading problems (Goswami et al., 2020; Richardson et al., 2004; Vanvooren et al., 2017). Furthermore, its implementation in a story listening game proved to be highly feasible and enjoyable in pre-reading children (Vanden Bempt, Economou, et al., 2022), which is crucial in the context of preventive interventions. Therefore, provided that adjustments are made to the EE algorithm by for example targeting stressed syllables rather than syllabic processing, by increasing EE intervention duration and intensity, or by providing the intervention earlier on in development and future research confirms its impact, the EE

intervention might be a highly effective auditory preventive intervention tool.

Last, this work also carries an important contribution for clinical practice, unrelated to dyslexia. In Chapter 2 we demonstrated a remarkable increase in data acquisition efficiency when using the PULS compared to the SAM stimuli. Such an increased efficiency is crucial in contexts where timing is essential, such as in clinical practice where ASSRs are often used as an objective method to determine hearing thresholds (Luts et al., 2004; Picton et al., 2005). SAM stimuli have already been used in Belgian clinical practice to determine objective hearing thresholds for nearly 20 years, especially in case of referral to specialized medical services following failed initial hearing screening. A shift from SAM to PULS stimuli can therefore easily be implemented. Particularly in infants and children, where an objective technique is even more important but also more effortful compared to adults, timing becomes even more important. Thus, the contributions of the current research go beyond the field of dyslexia and are even applicable in clinical hearing screening.

5.5 Limitations and caveats

As is the case for any research project, the current research is constrained by a number of sample-related and methodological limitations. A first sample-related consideration relates to the intervention group comparisons in Chapters 3 and 4. Whereas we included an active control group to eliminate potential placebo effects, it would have been preferable to also include an at risk passive control group and a typically developing passive control group in order to compare the development of at risk and typically developing pre-readers. Both passive control groups were available in the larger longitudinal study and participated in behavioral and MRI testing, but due to time constraints in order to adhere to the strict testing and intervention schedule, we were unable to invite these groups to EEG testing. Therefore, time constraints, which are inherent to this kind of longitudinal research, are also a main limitation of the present research project. Another sample-related consideration relates to the group comparison of children with dyslexia and typically reading children in Chapter 3. The absence of measurable intervention effects in Chapter 3 allowed us to redefine the intervention

groups based on third grade reading and spelling data. However, even though we were unable to demonstrate intervention effects, we cannot disregard the fact that all children received some kind of intervention in kindergarten. Additionally, all children were at risk for developing dyslexia at the start of the last year of kindergarten. Consequentially, the typically reading children in Chapter 3 are not representative of true typical readers. It is important to address these factors in future work if we hope to confirm the underlying deficits related to the development of dyslexia.

An inevitable limitation in longitudinal studies is the dropout of participants over the course of the study. Our longitudinal design with pre-test, home-based intervention, post-test, consolidation test and dyslexia status test, required substantial commitment from both participants and their parents. As a result, seven participants discontinued participation at post-test. Whereas two of those children returned at consolidation test, another seven children discontinued participation. Third grade reading data were collected for 78 children of the 91 initially enrolled children. Despite the dropout of a number of participants over the course of the study, the data reported in this research are the result of successfully completing 254 EEG sessions, lasting approximately 3 hours each, that were scheduled, prepared and conducted, mainly during weekends and holidays considering the pediatric population. Apart from the data reported in the current research, another 56 EEG sessions were conducted at the time of post-test and consolidation test, which were not analyzed within the timeframe of the current research.

A related consideration is the intensity of the EEG test protocol. Despite the instatement of a child-friendly test protocol tailored to the pediatric population, each EEG testing moment lasted approximately 3 hours. However, this extensive testing time was required to address a few methodological limitations of pediatric neuroimaging studies. Acquiring EEG data in young children is very challenging and excessive motion and the resulting insufficient data quality are a common cause of data loss. By extending our recording time to 10 minutes (compared to the standard 5 minutes mostly recorded in adults) and offering frequent breaks in between conditions, we tried to prevent data loss due to insufficient data quality. Nonetheless, 30 data conditions (8%) at pre-test, 14 (4%) at post-test and five (2%) at consolidation test were deemed unusable for further analysis. The disadvantage of extensive recording times is that it limits the number of modulation frequencies that can be included in the testing protocol.

A last limitation that cannot be disregarded is the onset of the COVID-19 pandemic, causing full and partial school closures when our participants attended first grade in between March and June 2020. This period was characterized by great educational inequalities (Duroisin et al., 2021). In an attempt to evaluate the impact of school closures, we distributed online questionnaires to the parents of our participants assessing the home, school and therapeutic situation. No differences with respect to school attendance, homework, or parental support were found between the intervention groups (Vanden Bempt et al., 2023). Additionally, in the current research we mainly investigated auditory processing on which we presume that school closures have a rather limited effect. Nonetheless, it is highly probable that the COVID-19 pandemic exerted an impact on reading and spelling abilities of our participants, especially since they were already at risk for reading difficulties and schools were closed when they were in Grade 1, which is a crucial period for learning to read (see Donnelly & Patrinos, 2022 for an early review). To ensure a more or less reliable measure of reading and spelling skills, we conducted the dyslexia status test at the start of third grade instead of at the end of first grade as was initially scheduled. As a result, the children received one year of proper schooling without (or with very limited) school closures before their classification as children with and without dyslexia. Despite our substantial efforts to minimize the impact of the COVID-19 pandemic on our longitudinal study, it is very challenging to fully elucidate the impact of the pandemic on our research.

5.6 Future perspectives

The current research gives rise to a number of future research directions that we expect to further extend the impact of this research project. For instance, within the larger longitudinal study we also collected neuroanatomical data, as well as behavioral data of reading and spelling skills and speech-in-noise perception. Within the timeframe of the current research, we only analyzed the EEG and rise time discrimination data. However, combining the available data at hand to investigate their interrelations would provide even more valuable information on the underlying deficits of dyslexia. More specifically, modelling the interrelations between the neurophysiological, neuroanatomical and behavioral data (1) might elucidate the hypothesized

cascading framework from (neural) auditory temporal processing through speech perception to phonological and reading skills (Goswami, 2018, 2019a; Lallier et al., 2018) and (2) allow us to preliminarily investigate the heterogeneity of the deficits underlying the development of dyslexia. Nonetheless, the impact of the COVID-19 pandemic poses a major challenge if we hope to investigate the interplay with reading-related skills and future work should aim to address this.

Our findings provide important insights into the neural auditory temporal processing deficit underlying the development of dyslexia, but in order to precisely map the underlying deficits at the neural level, we recommend future research to also include delta rate modulations. Delta rate modulations are crucial for speech perception given that further temporal rates in the linguistic hierarchy are nested within the delta rate (Goswami, 2019b). Delta rate synchronization is especially important in young children, where CDS contains most energy at ~2 Hz (Leong & Goswami, 2015). However, an investigation in pre-readers remains to be performed in order to confirm it as a causative factor in dyslexia. In a similar vein, we advocate for an exploration of an EE intervention in which stressed syllable onsets instead of syllable onsets are accentuated. If delta rate synchronization deficits indeed partially underlie the development of dyslexia, this might be normalized by targeting the delta modulation rate specifically.

An intriguing question that the present work cannot answer is whether dyslexia is characterized by atypical cross-frequency coupling. Similar to the linguistic hierarchy, in which faster temporal rates (smaller phonological units) are nested within slower temporal rates (larger phonological units (Goswami, 2019b), neural oscillations display a nested hierarchy in which faster oscillations are nested within slower oscillations (Giraud & Poeppel, 2012a; Gross et al., 2013; Meyer, 2018). It is thus conceivable that atypical synchronization at slower frequencies would affect those at higher frequencies and that this would have detrimental effects on phonemic sensitivity (Lallier et al., 2018). Whereas, to the best of our knowledge, most studies, including the present work, investigated deficits at separate synchronization rates, investigating cross-frequency coupling between different rates is necessary to increase our understanding of the mechanisms underlying the development of dyslexia. While rise time discrimination is essential for sustaining cross-frequency coupling, it is commonly impaired in dyslexia (see **1.3.2**). The EE intervention in Chapter 4 directly improved

rise time sensitivity, and might therefore reinstate atypical cross-frequency coupling if this were to be demonstrated in dyslexia. The recently developed Temporal Envelope Speech Tracking or TEMPEST stimuli (David et al., 2022; Gransier & Wouters, 2021) provide an excellent framework to investigate cross-frequency coupling. Within the TEMPEST framework, a single stimulus allows for the evaluation of a range of envelope modulations, as well the impact of specific speech envelope parameters such as rise times. Therefore, we recommend future research to include the TEMPEST stimuli.

A last suggestion for future research is to investigate the benefit of source level analyses over scalp level analyses. The EEG activity recorded at the scalp electrodes is the result of brain activity generated at different locations in the brain (Nunez et al., 1997). Source level analyses might facilitate the neurophysiological interpretation of the results, especially in the case of hemispheric specialization, and may reduce the large inter-subject variability that is often observed with electrode level analyses, especially in young children.

5.7 General conclusion

The current research has contributed to our understanding of the neurophysiological markers of the auditory temporal processing deficit in dyslexia, and has provided new insights into the potential of preventive interventions to remediate these deficits. We first examined the suitability of a set of pulsatile acoustic stimuli with shortened rise times to identify the neural markers underlying the auditory temporal processing deficit in dyslexia. Over and above confirming their suitability for developmental reading research, this investigation demonstrated that pulsatile stimuli significantly enhance neural synchronization, which might have a major impact on pediatric EEG research and clinical practice. Furthermore, the pulsatile stimuli elicit a differential hemispheric specialization at syllable rate in pre-readers to beginning readers. We consequently used the pulsatile stimuli to investigate neural synchronization to rise times in dyslexia, but were unable to demonstrate atypical synchronization to rise times. However, regardless of rise time sensitivity, children with dyslexia demonstrated an atypical hemispheric specialization at both syllable and phoneme rates. This was already present at pre-reading age and persisted until beginning reading

age. Hence, the latter deficit seems to be causally related to the development of dyslexia. These findings emphasize the importance of (neural) auditory temporal processing for later literacy.

A second main aim of the present work was to investigate the impact of a preventive combined phonics-based and enhanced speech intervention. Whereas the EE intervention improved rise time discrimination in pre-reading children, it failed to yield transfer effects to neural synchronization. This suggests that the EE intervention in its current form, even though successful in improving rise time sensitivity already before the onset of reading instruction, insufficiently addresses the auditory temporal processing deficit in dyslexia. The phonics-based training did not exert an impact on auditory temporal processing. This highlights the importance of auditory trainings to remediate the auditory temporal processing deficit in dyslexia.

In sum, early identification and intervention are a vital first step towards reducing reading failure, but largely depend on a good understanding of the mechanisms underlying dyslexia. Although a number of questions remain unanswered, we are confident that the findings of the current research contribute to the understanding of the development of dyslexia and the potential of preventive interventions

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Scientific acknowledgements

The author gratefully acknowledges the promotor Prof. Dr. Jan Wouters, and the copromotors Prof. Dr Pol Ghesquière and Prof. Dr. Maaike Vandermosten for envisioning this research, their guidance and supervision while carrying out the work presented in this dissertation, and their contributions to Chapters 2, 3, and 4 as co-authors. A special thanks goes to Dr. Maria Economou and Femke Vanden Bempt for the close collaboration during participant recruitment and project management, as well as their contributions to Chapters 2, 3 and 4 as co-authors and to Prof. Dr. Jolijn Vanderauwera for help with project conceptualization, as well as the contribution to Chapter 4 as co-author. In addition, the author would like to thank Dr. Toivo Glatz for the GraphoGame Flemish implementation and contributions to Chapters 2 and 4, Ward Dehairs for programming the story listening game, Dr. Benjamin Dieudonné for the EE implementation and contribution to Chapter 4, and Dr. Tilde Van Hirtum for help with stimulus development. I would also like to thank Dr. Astrid De Vos and Dr. Sophie Vanvooren for their insightful feedback on performing pediatric EEG studies, and Dr. Astrid De Vos, Dr. Michael Hofmann and Dr. Raúl Granados Barbero for their help with ASSR processing.

I would further like to acknowledge Dr. Toivo Glatz, Dr. Tilde Van Hirtum, Dr. Lien Decruy, Dr. Klara Schevenels, Tine Arras, Dr. Astrid De Vos, Maud Goddefroy, Nele Baerts, Chloë vanden Hoff, Emma Smits, Sahn

Houtmeyers, Silke Lauwens, Caspar Konings, Laura Langhendries, Pauline Dauchy and Emma Coolens for their assistance during data collection.

Finally, I am most grateful to all the participating families and children for making this research possible.

Personal contributions

The current dissertation primarily reflects the work of the author. For all studies presented in the dissertation, Shauni Van Herck was responsible for the conceptualization of the studies, data acquisition and analysis, interpretation of results and writing of the manuscripts.

Conflict of interest statement

The author and co-authors declare no conflicts of interest. The work described in this dissertation was supported by the Research Council of KU Leuven (C14/17/046) and the Research Foundation Flanders (FWO) (12T4818N).

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Van Herck, S., Economou, M., Vanden Bempt, F., Glatz, T., Ghesquiere, P., Vandermosten, M., Wouters, J. (2022). Neural synchronization and intervention in pre-readers who later on develop dyslexia. European Journal of Neuroscience. doi: 10.1111/ejn.15894

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About the author

Shauni Van Herck was born in Turnhout (Belgium) on the 6th of January 1995. She received her secondary education (Latin-Modern languages) at the Sint Pietersinstituut in Turnhout and graduated in 2013. In 2016 she obtained a Bachelor's degree, and in 2018 a Master's degree in Theoretical and Experimental Psychology at Ghent University. Her Master's thesis was titled "Language switching behavior: the accuracy of self-reports and its relation to executive functions". Her Master's research internship was titled "Learning on a shorter timescale at the basis of a reduced modulation by global context in autism spectrum disorder".

In september 2018 she started her PhD as a research member of the group Experimental Oto-Rhino-Laryngology (ExpORL) at the Department of Neurosciences of KU Leuven, under the supervision of Prof. Dr. Jan Wouters, Prof. Dr. Pol Ghesquière and Prof. Dr. Maaike Vandermosten. During her PhD, she studied the neurophysiological mechanisms underlying dyslexia and the impact of preventive interventions.