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Auditory processing in dyslexia: electrophysiology and psychophysics

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Auditory processing in dyslexia: electrophysiology and psychophysics

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Voorwoord

Het schrijven van het voorwoord voor dit doctoraat is het moment waar ik lange tijd naar uitgekeken heb. Niet alleen is het voorwoord het meest gelezen stukje tekst in een doctoraat, het is ook het laatste stukje tekst dat geschreven wordt en symboliseert het succesvol afronden van een project waar je jaren lang dag en nacht mee bezig ben geweest. Het is dan ook de ideale plaats om iedereen te bedanken die tijdens deze periode belangrijk is geweest.

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Abstract

Developmental dyslexia is characterized by severe difficulties in reading and spelling despite normal intelligence, education and intense remedial effort. Until now, the exact origin of this disorder remains unknown. One theory suggests that the reading and spelling problems in dyslexia are caused by a fundamental deficit in auditory temporal processing. That is, reduced sensitivity to temporal acoustic cues during the crucial phase of reading acquisition may impair the accuracy of which speech sounds are mapped onto their corresponding written symbols and this may cause reading and spelling difficulties in individuals with dyslexia.

In the brain, temporal information is encoded by neural oscillations that phase-lock to the rhythm of the temporal variation. Spontaneous neural oscillations in certain frequency bands in the EEG coincide with the time windows in which important acoustic information about the modulation of syllables (~4 Hz) and phonemes (~20 Hz) is processed. It has been suggested that temporal information within these time windows is processed asymmetrically in the brain, with a right hemispheric preference for processing syllabic-rate acoustic information and a left hemispheric preference for processing phonemic-rate acoustic information. In this context, it has recently been proposed that neural oscillatory activity in response to syllabic- and phonemic-rate information deviates in individuals with dyslexia.

The aim of this PhD project was to investigate the nature of the auditory temporal processing deficit in dyslexia by means of electrophysiological and psychophysical techniques. In the first part of this project, we aimed to determine an objective electrophysiological marker for the auditory temporal processing deficit in dyslexia by means of auditory steady-state brain responses (ASSRs). Moreover, we focused on three research questions. *First*, we examined whether adults with dyslexia have different electrophysiological responses to phonemic- (20 Hz) and/or syllabic-rate (4 Hz) modulations, or to a reference modulation rate (80 Hz). Results demonstrated that adults with dyslexia display deviant responses specifically to the phonemic-rate modulation, but not to syllabic or higher modulation rates. Moreover, phonemic-rate group differences reflected in lower responses at electrodes over the left hemisphere as well as in lower coherence between and within hemispheres. Furthermore, a

significant relation between phonemic-rate ASSRs and psychophysical tests of speech-in-noise perception and phonological awareness was obtained. These results suggest that in adults with dyslexia, phonemic-rate acoustic information is less accurately sampled into phonemic representations and that this problem may result in difficulties perceiving speech and processing phonological information.

Second, because not much is known about phonemic- and syllabic-rate ASSRs, we examined whether these ASSRs are influenced by the side of stimulus presentation or whether slow-rate ASSRs are rather influenced by a functional hemispheric specialization to process phonemic- or syllabic-rate modulations. Results demonstrated that for 80 and 20 Hz ASSRs the highest responses could be recorded at electrodes over the same hemisphere as the side of stimulus presentation. In contrast, for 4 Hz ASSRs functional lateralization was observed. ASSRs were higher in the right hemisphere, independent of which ear was stimulated. These results may imply that both hemispheres are sensitive to process phonemic-rate information whereas the right hemisphere displays the strongest activity to syllabic-rate modulations.

Third, the relation between functional phonemic- and syllabic-rate processing and anatomical cortical white matter pathways was examined. Functional processing of phonemic-rate modulations related to structural white matter properties of regions that are involved in speech perception and this relation was different for normal-reading and dyslexic adults. These results indicate that in individuals with dyslexia functional phonemic-rate processing problems may relate to anatomical differences in the brain.

The second part of this project aimed to elucidate the auditory temporal processing deficit in 12-year old children with dyslexia using psychophysical measures. We demonstrated that children with dyslexia are less sensitive than normal-reading children to slowly varying temporal auditory information, speech-in-noise perception, phonological awareness and reading. Furthermore, correlations were found between auditory temporal processing and phonological awareness, and between speech-in-noise perception and reading. Together, these results confirm that children with dyslexia have difficulties at all levels of the auditory temporal processing deficit theory.

In general, this project demonstrates that individuals with dyslexia process temporal acoustic information that occurs in important time windows for phonological processing, less accurately compared to normal-reading persons. Moreover, it seems

that in individuals with dyslexia phoneme-level acoustic information is insufficiently integrated in the phonological pathway involved in speech perception.

Korte inhoud

Dyslexie wordt gekenmerkt door ernstige problemen met lezen en schrijven, ondanks een normale intelligentie, voldoende onderwijs en remediëring. Tot op heden is de precieze oorzaak van dyslexie nog niet bekend. De auditief temporele verwerkingstheorie suggereert dat de lees- en spellingmoeilijkheden van mensen met dyslexie veroorzaakt worden door een verstoorde verwerking van auditief temporele informatie. Verminderde gevoeligheid voor auditief temporele informatie zou in de cruciale fase van leesontwikkeling een invloed hebben op hoe accuraat spraakklanken aan letters gekoppeld worden, en zou dus aan de basis kunnen liggen van de lees- en spellingproblemen bij dyslexie.

In de hersenen wordt temporele informatie verwerkt op basis van neurale oscillaties. Oscillaties in verschillende frequentiebanden in het EEG vallen samen met de tijdsvensters waarin belangrijke akoestische informatie over de modulatie van lettergrepen (~4 Hz) en fonemen (~20 Hz) verwerkt wordt. De verwerking van temporele informatie in deze tijdsvensters gebeurt asymmetrisch in de hersenen. Modulaties rond de lettergreepfrequentie lijken eerder in de rechter hemisfeer verwerkt te worden, terwijl modulaties rond de foneemfrequentie eerder in de linker hemisfeer verwerkt worden. Recentelijk werd gesuggereerd dat de auditief temporele verwerkingsproblemen bij mensen met dyslexie gelinkt zijn aan een ander activatiepatroon van deze oscillaties.

Het doel van dit doctoraatsonderzoek was de aard van het auditief temporele verwerkingsprobleem in dyslexie te onderzoeken met zowel elektrofysiologische als psychofysische maten. In het eerste deel van dit project werd met behulp van auditory steady-state hersenresponsen (ASSRs) gezocht naar een objectieve elektrofysiologische maat om het auditief temporele verwerkingsprobleem bij mensen met dyslexie vast te stellen. Hierbij werden drie vraagstellingen onderzocht. *Ten eerste* werd nagegaan of mensen met dyslexie andere neurale responsen vertonen voor modulaties rond de lettergreep- (4 Hz) en/of de foneemfrequentie (20 Hz), en voor referentie modulatiefrequentie (80 Hz). Resultaten wezen uit dat volwassenen met dyslexie moeilijkheden hadden met de verwerking van auditieve informatie op de foneemfrequentie, terwijl auditieve informatieverwerking op de

lettergreepfrequentie en voor de hogere modulatiefrequentie normaal was. Dit groepsverschil voor foneemniveau informatie uitte zich in lagere responsen in de linker hemisfeer, alsook in lagere coherentie tussen en binnen beide hemisferen. Tenslotte correleerden foneemniveau ASSRs met psychofysische maten voor fonologisch bewustzijn en spraak perceptie. Deze resultaten zouden erop kunnen wijzen dat de fonologische en spraak perceptie problemen van mensen met dyslexie het gevolg zijn van minder accurate foneemrepresentaties die ontstaan doordat basale akoestische informatie op een andere manier verzameld wordt.

Omdat er niet veel bekend is over de responskenmerken van deze ASSRs, werd op *de tweede plaats* onderzocht of foneem- en lettergreepniveau ASSRs beïnvloed worden door de manier waarop de stimulus wordt aangeboden of dat er sprake is van een functionele specialisatie van beide hemisferen voor het verwerken van deze modulatiefrequenties. Resultaten toonden aan dat voor 80 en 20 Hz ASSRs de hoogste responsen opgemeten worden in dezelfde hemisfeer waar de stimulus wordt aangeboden en dat de hemisfeer waarin de hoogste responsen worden opgemeten dus verschilt voor stimuli aangeboden aan het linker of het rechter oor. Voor 4 Hz ASSRs daarentegen werd een functionele lateralisatie gevonden. Responsen waren steeds hoger in de rechter hemisfeer, onafhankelijk van aan welk oor de stimulus werd aangeboden. Dit zou erop kunnen wijzen dat beide hemisferen gevoelig zijn voor de verwerking van foneemniveau informatie, terwijl de rechter hemisfeer de grootste activiteit vertoont bij het verwerken van lettergreepniveau informatie.

Ten derde werd nagegaan of de functionele verwerking van temporele informatie op de lettergreep- en/of foneemfrequentie gerelateerd kan worden aan anatomische hersenpaden die belangrijk zijn voor spraakverstaan. We vonden dat de functionele verwerking van foneemniveau modulaties relateerde aan de structurele kenmerken van witte materie paden die instaan voor de verwerking van spraak, en dat deze relatie verschillend was voor normaal-lezende en dyslectische volwassenen. Dit zou erop kunnen wijzen dat bij mensen met dyslexie de functionele problemen met de verwerking van foneemniveau informatie gerelateerd zijn aan anatomische verschillen in de hersenen.

In het tweede deel van dit project wilden we ook op psychofysisch niveau de relatie tussen auditief temporele verwerking, spraakperceptie, fonologisch bewustzijn en lezen na gegaan bij 12-jarige kinderen met dyslexie. Resultaten toonden aan dat kinderen met dyslexie moeilijkheden hadden met de verwerking van verschillende auditief temporele verwerkingstaken, maar ook met spraakperceptie, fonologisch bewustzijn en lezen. Correlaties werden gevonden tussen auditief temporele

verwerkingstaken en fonologisch bewustzijn, en tussen spraakperceptie en lezen. Deze resultaten wijzen erop dat kinderen met dyslexie moeilijkheden vertonen op alle niveaus van de auditief temporele verwerkingsdeficit theorie.

Algemeen tonen deze resultaten aan dat mensen met dyslexie moeilijkheden hebben met de verwerking van temporele akoestische informatie die voorkomt in belangrijke tijdsvensters voor fonologische verwerking. Dit probleem zou ervoor kunnen zorgen dat bij mensen met dyslexie foneemniveau informatie onvoldoende wordt geïntegreerd in het fonologische systeem dat betrokken is bij spraakperceptie.

Acronyms and abbreviations

ABR	Auditory Brainstem Response
AEP	Auditory Evoked Potential
AF	Arcuate Fasciculus
AM	Amplitude-Modulated
AMFR	Amplitude Modulation Following Response
APEX 3	Application for PsychoElectrical eXperiments, version 3
ASSR	Auditory Steady-State Response
AST	Asymmetrical Sampling over Time
BE	Bilateral, diotic stimulus presentation
CC	Corpus Callosum
CCsplenium	Splenium of the Corpus Callosum
Cz	Vertex
CT	X-ray Computed Tomography
CVC	Consontant-Vowel-Consonant
dB	Decibel
dB HL	Decibel Hearing Level
dB SPL	Decibel Sound Pressure Level
DTI	Diffusion Tensor Imaging
e.g.	exempli gratia: for example
EEG	ElectroEncephaloGram
EFR	Envelope Following Response
ELR	Early Latency Response
EMT	Een Minuut Test
ERP	Event-Related Potential
et al.	et alia: and others
ExpORL	Experimental Oto-Rhino-Laryngology
FA	Fractional Anisotropy
FFR	Frequency Following Response

FFT	Fast Fourier Transform
FM	Frequency-Modulated
fMRI	functional Magnetic Resonance Imaging
Fpz	High forehead
HG	Heschl's Gyrus
Hz	Hertz
ID	Intensity Discrimination
i.e.	id est: that is
IFG	Inferior Frontal Gyrus
IFGop	Opercular part of the Inferior Frontal Gyrus
kHz	Kilohertz
KU Leuven	Katholieke Universiteit Leuven
kOhm	kiloOhm
LE	Left ear stimulus presentation
LH	Left Hemisphere
LI	Laterality Index
LIST	Leuven Intelligibility Sentence Test
LLR	Late Latency Response
MEG	MagnetoEncephaloGram
MLR	Middle Latency Response
MRI	Magnetic Resonance Imaging
Ms	Milliseconds
nHL	normal Hearing Level
nV	nanoVolt
NVA	Nederlandse Vereniging voor Audiologie
Oz	Occiput
PA	Phonological Awareness
PAC	Primary Auditory Cortex
PET	Positron Emission Tomography
PT	Planum Temporale
RAN	Rapid Automatic Naming
RE	Right Ear stimulus presentation
RH	Right Hemisphere

RM-ANOVA	Repeated Measures Analyses Of VAriance
RMS	Root-Mean-Square
SAC	Secondary Auditory Cortex
SD	Standard Deviation
SE	Standard Error of the mean
SLF	Superior Longitudinal Fasciculus
SNR	Signal-to-Noise Ratio
SOMA	Setup ORL for Multichannel ASSR
SPECT	Single Photon Emission Tomography
SPIN	SPeech-In-Noise
SPSS	Statistical Package for the Social Sciences
SRT	Speech Reception Threshold
STGa	Anterior part of the Superior Temporal Gyrus
STGp	Posterior part of the Superior Temporal Gyrus
STS	Superior Temporal Sulcus
VSTM	Verbal Short Term Memory

Table of contents

Voorwoord ..... **v**

Abstract ..... **viii**

Korte inhoud ..... **xi**

Acronyms and abbreviations ..... **xiv**

Table of contents ..... **xvii**

Chapter 1 General introduction **1**

1.1. Motivation *1*

1.2. Reading acquisition and developmental dyslexia *3*

1.2.1. Theories about the origin of dyslexia 4

1.2.1.1. The phonological deficit theory 4

1.2.1.2. The general sensory deficit theory 6

1.2.1.3. The auditory temporal processing theory 6

1.3. Auditory temporal processing in dyslexia *7*

1.3.1. The influence of auditory temporal perception on speech perception and reading 8

1.3.2. Psychophysical evidence for an auditory temporal processing deficit underlying dyslexia 10

1.3.3. Neurophysiological evidence for an auditory temporal processing deficit underlying dyslexia 12

1.4. Auditory temporal processing in the brain *13*

1.4.1. The auditory system 13

1.4.2. Sensitivity of the auditory system to auditory temporal information 15

1.4.2.1. Animal studies 16

1.4.2.2. Studies in humans 17

1.4.3. Overview of objective techniques applied in auditory neuroscience 18

1.4.4. Auditory evoked potentials 19
1.4.4.1. Transient responses 20
1.4.4.2. Sustained responses 23

1.5. Auditory steady-state responses *23*
1.5.1. Definition 23
1.5.2. ASSR stimuli 24
1.5.3. ASSR recording and response detection in the EEG 25
1.5.4. ASSR response measures 27
1.5.5. Stimulus parameters 29
1.5.6. ASSR generation 32
1.5.6.1. Physiological model 33
1.5.6.2. Neural ASSR generators 34

1.6. Research objectives *36*

1.7. Thesis outline *37*

Chapter 2 Auditory steady-state responses as a neural correlate for temporal processing in adults with dyslexia 39

2.1. Introduction *40*

2.2. Methods *43*
2.2.1. Participants 43
2.2.2. Psychophysical measures 44
2.2.3. ASSR stimulus parameters 45
2.2.4. ASSR recording parameters 45
2.2.5. ASSR data analysis 46
2.2.6. Statistical analyses 47

2.3. Results *49*
2.3.1. Response-strength 49
2.3.2. Coherence 50
2.3.3. Correlations 53

2.4. Discussion *55*

Chapter 3 Auditory steady-state response asymmetry: the influence of stimulation side on response-strengths 59

3.1. Introduction *60*

3.2. Methods *61*
3.2.1. Participants 61
3.2.2. Stimulus parameters 61
3.2.3. Experimental protocol 62
3.2.4. ASSR recording parameters 62
3.2.5. ASSR data analysis 63
3.2.6. Statistical analyses 64

3.3. Results *65*
3.3.1. Response-strength 65
3.3.2. Laterality 67

3.4. Discussion *69*

Chapter 4 The relation between auditory steady-state responses and structural white matter density in adults with dyslexia 73

4.1. Introduction *75*
4.1.1. Cortical auditory and phonological processing in normal readers 76
4.1.2. Cortical auditory and phonological processing in dyslexic readers 79
4.1.3. Hypotheses 81

4.2. Methods *83*
4.2.1. Participants 83
4.2.2. Structural measures: DTI 84
4.2.2.1. Data acquisition 84
4.2.2.2. Data processing 85
4.2.3. Electrophysiological measures: ASSR 86
4.2.3.1. Stimuli 86
4.2.3.2. Data acquisition 87
4.2.3.3. Data processing 87
4.2.4. Statistical analyses 88

4.3. Results *88*
4.3.1. DTI-measures in dyslexic versus normal readers 88
4.3.2. ASSRs to phonemic- and syllabic-rate modulations in dyslexic versus normal readers 90
4.3.3. Correlations of DTI- with ASSR-measures 91

4.4. Discussion *92*
4.4.1. Structural lateralization in normal and dyslexic readers 93

4.4.2. Functional phonemic- and syllabic-rate processing in normal and dyslexic readers 94
4.4.3. Does FA-lateralization in STGp relate to functional phonemic- and syllabic-rate processing in normal and dyslexic readers? 95
4.4.4. Does FA in CCsplenium relate to functional phonemic- and syllabic-rate processing in normal and dyslexic readers? 98
4.4.5. An integrative model for dyslexia? 99
4.4.6. Conclusion 101

Chapter 5 Auditory temporal processing in children with dyslexia 103

5.1. Introduction 104

5.2. Methods 107
5.2.1. Participants 107
5.2.2. Experimental setup 108
5.2.3. Tasks 109
5.2.3.1. Auditory processing tasks 109
5.2.3.2. Speech-in-noise perception 110
5.2.3.3. Phonological Awareness 111
5.2.4. Statistical analyses 112

5.3. Results 112
5.3.1. No differences between low-risk and high-risk normal-reading children 112
5.3.2. Performance of dyslexic versus normal-reading children 113
5.3.3. Relations between slow-rate auditory processing, speech perception, phonological awareness and literacy measures 115

5.4. Discussion 116

Chapter 6 General conclusions and future research directions 121

6.1. General discussion of research findings 121
6.1.1. Low-frequency ASSRs as a tool to measure neurophysiological responsiveness to auditory temporal information 122
6.1.2. Phonemic- versus syllabic-rate processes in speech perception 125
6.1.3. Auditory temporal processing in normal-reading and dyslexic adults 126
6.1.4. Auditory temporal processing in normal reading and dyslexic children 128

6.1.5. Alternative explanations for auditory processing problems in dyslexia 130
6.1.6. Clinical implications 131

6.2. General limitations 132

6.3. Future research directions 133
6.3.1. Optimizing ASSR recordings and analyses 133
6.3.2. Neurophysiological syllabic- and phonemic-rate processing in normal-reading and dyslexic individuals 134
6.3.3. Elucidating the relation between functional and structural brain measures during reading development 135

6.4. General conclusions 136

References 138

List of publications 173

Curriculum vitae 179

Chapter 1
General introduction

1.1. Motivation

Human language is a highly elaborated communication system. Whereas animals communicate via auditory signs, humans also master the ability to correspond via written language. Since the existence of written script, knowledge is written down and spread across distance and time. Whereas in former times only elites mastered the ability to read and write, at present every child learns to read and write, already at a young age. However, unlike spoken language acquisition, a child is not born with the natural ability to develop written language skills. Reading and writing acquisition depends on the explicit instruction about the link between the spoken and written language system. Although most children make a relatively effortless transition from to spoken to written language, a substantial amount of children encounter great difficulties learning to read and write without any obvious reason, referred to as developmental dyslexia (Dehaene, 2009; Snowling, 2000).

Until now, the exact cause of dyslexia remains unknown. The most common finding in dyslexia research is that the reading and spelling problems of individuals with dyslexia are related to difficulties with phonological processing (Snowling, 2000). However, it has also been hypothesized that the underlying cause of these phonological problems can be allocated to a sensory dysfunction in the auditory domain (for reviews see Farmer & Klein, 1995; Bailey & Snowling, 2002; Hämäläinen et al., 2012b). A low-level auditory dysfunction to process temporal information (i.e. changing over time) is thought to cause a cascade of problems influencing how the spoken language system is linked to the written language system. A recent longitudinal study proved that children with dyslexia have pre-reading deficits in auditory processing, speech perception and phonology, but more importantly, that low-level auditory processing and speech perception in kindergarten uniquely contribute to growth in reading ability (Boets et al., 2011a).

Given the theoretical importance of auditory temporal sensitivity in reading acquisition, auditory processing and speech perception skills in relation to dyslexia

have received increasing attention. However, results are often unclear in that auditory temporal processing problems are only observed in a subgroup of individuals with dyslexia (e.g. Ramus, 2003; Rosen, 2003), or to certain stimulus features (e.g. Witton et al., 2002). This diversity may in part be explained by the fact that most studies assessed auditory sensitivity with psychophysical tests, and performance may be biased by uncontrolled higher order cognitive processes such as attention, motivation, or decision making processes. Therefore, the application of a new neurophysiological technique to the field of dyslexia research may open new avenues to assess auditory sensitivity with only a small bias of cognitive processes (for reviews see Kujala & Näätänen, 2001; Leppänen & Lyytinen, 1997). Compared to behavioural measures, neurophysiologic techniques appear to be more sensitive to differentiate between dyslexic and normal readers, as they even reveal sensory deficits in dyslexics who perform adequately on analogous psychophysical tasks (Stoodley et al., 2006). Exploring the neurophysiological underpinnings of the auditory temporal processing deficit in dyslexia, was the main focus of this research project.

Alternatively, only a limited amount of studies assessed auditory temporal sensitivity with tasks measuring several aspects of temporal auditory stimuli (e.g. Boets et al., 2006; Witton et al., 2002). Given that speech is a redundant signal containing a variety of temporal information, some temporal cues may be more directly related to speech perception abilities than previously assumed (e.g. Goswami et al., 2002). Therefore, psychophysical studies investigating the nature of the auditory temporal processing deficit with a broader range of stimuli are thus necessary to elucidate the direct relation between auditory temporal processing, speech perception and phonology in individuals with dyslexia. This formed the second focus of this project.

In this chapter, a general introduction on reading and developmental dyslexia (1.2) and the influence of auditory temporal sensitivity on reading and dyslexia (1.3) is provided. Furthermore, an overview of neural processing of auditory temporal modulations (1.4) and more specifically auditory steady-state responses (1.5) is described.

1.2. Reading acquisition and developmental dyslexia

Reading is the ability to acquire meaning from a series of written symbols that represent spoken language. Unlike spoken language, a child is not born with the ability to read. Reading acquisition only starts when a child enters school and explicitly learns to decode written text into its corresponding spoken form. Decoding starts with the instruction that every written symbol (grapheme) corresponds to a speech sound (phoneme) and is thought to be processed by two reading strategies. Initial reading is performed in an indirect, *sublexical* manner in which written words are decoded by linking their component letters to their corresponding speech sounds (i.e. phonological decoding), and meaning is accessed based on the resulting phonological code. This initial sublexical decoding strategy develops into an automated and more efficient *lexical* reading strategy for words that are frequently encountered. This direct, lexical reading manner accesses the phonological code of these words by a fast recognition of their visual word image, without the intermediate step of single letter-to-sound decoding (Perry et al., 2010; Coltheart et al., 2001). In adults, both reading strategies are fully developed and simultaneously active during reading. Even though proficient readers have a predominant lexical reading strategy, they still rely on sublexical decoding skills to read unfamiliar words and pseudowords (Coltheart et al., 2001; Dehaene, 2009).

Given that reading skills only develop after the explicit instruction about the correspondence between spoken and written language, the foundations for reading already develop implicitly before a child learns to read, at the level of spoken language perception. That is, reading acquisition builds upon phonological awareness, the awareness that spoken language consists of segments that can be mapped on written symbols. In an alphabetical language, these segments are the smallest meaningful units of language, i.e. phonemes. However, before phoneme awareness emerges and explicit phoneme representations are built, a gradual development from large (words, syllables) to small (phonemes) phonological units occurs (Anthony et al., 2003; Ziegler & Goswami, 2005; Goswami, 2002). Studies have shown that phonological processing skills, before and after reading acquisition, have a strong predictive value for later reading proficiency (e.g. Boets et al., 2011a; Goswami, 2008). Given that pre-readers only process spoken language, it is clear that phonological development depends on auditory perception skills (McBride-Chang, 1996). Before a child can link phonemes to graphemes, the auditory system must be able to accurately process acoustic cues that are crucial for speech perception (for a detailed explanation see 1.3.1).

Despite the complexity of the auditory, phonological and reading development, the majority of children are able to master fluent reading skills. However, 5-10% of the population suffers from severe reading and writing problems despite normal intelligence, education and intense remedial effort. This is defined as developmental dyslexia (Vellutino et al., 2004; Gersons-Wolfensberger & Ruijssenaars, 1997). The diagnosis of developmental dyslexia is in current practice in Flanders based on three criteria. Reading and spelling problems are classified as dyslexia when (*i*) they cannot be explained by other factors such as a low IQ, mental retardation, emotional disturbance, visual or hearing impairments, or cultural, social, or economic environments (*exclusionary* criterion), (*ii*) they are *severe* compared to a norm group (i.e. below percentile 10) (severity criterion), and when (*iii*) low reading and/or spelling performance is *persistent and resistant* to educational effort and intense didactical intervention.

1.2.1. Theories about the origin of dyslexia

Until now, the exact origin of this disorder remains largely unknown. In dyslexia research, a number of theories about the cause of dyslexia exist. These theories are not necessarily competing, but rather attempt to explain the reading and spelling problems in dyslexia from different research perspectives and backgrounds. In the framework of this doctoral research, two approaches will here be discussed in more detail.

1.2.1.1. The phonological deficit theory

One of the most consistent findings in individuals with dyslexia is their difficulty with processing phonological information (e.g. Mann & Liberman, 1984; Wagner & Torgesen, 1987; Snowling, 2000; Ramus et al., 2003). This observation was the foundation of the *phonological deficit theory*, which suggests that the reading and writing problems in dyslexia are caused by a cognitive deficit in the development and the use of phonological representations (Snowling, 2000; Vellutino et al., 2004). This deficit was found in three aspects of phonological processing (Wagner & Torgesen, 1987).

First, individuals with dyslexia demonstrate poor *phonological awareness*. Phonological awareness (PA) refers to the consciousness about the sound structure of language, and the ability to manipulate these language segments (Rack, 1994; Snowling, 2000). Classical tasks to measure PA are deleting phonemes from words (phoneme deletion) or exchange the initial letters of two words (spoonerisms).

Second, individuals with dyslexia have a poor verbal short-term memory. The verbal short-term memory (VSTM) is responsible for retaining verbal information as phonological codes over a short period. This is a necessary step before information can be consolidated to long-term memory. Poor VSTM hence manifests by low memory span for verbal items and poor nonword repetition (repetition of valid words without a meaning). Poor VSTM may also affect performance on a variety of tasks other than memory tasks, such as list learning, story recall, paired-associate learning, but also performance on phonological awareness tasks such as spoonerisms (e.g. Vellutino et al., 1975).

Third, individuals with dyslexia are slower in retrieving phonological codes from long-term memory. This ability depends on recoding a visual item into a sound-based representation by retrieving its lexical concept from long-term memory and is commonly assessed with a *rapid automatic naming* task (RAN) (Wolf & Bowers, 1999; Wolf & Bowers, 2000).

Given that these three aspects of phonology are closely linked together, it is unclear what the exact nature of the phonological deficit underlying dyslexia is. The question thus remains whether phonological representations themselves are degraded, or whether the ability to retrieve them from or store them into working and/or long-term memory is limited (e.g. Ramus & Szenkovits, 2008). According to the phonological deficit theory, these phonological problems result in a failure to mentally map letters to phonemes, and lead to reading and spelling impairments and problems with phonological tasks. Despite other theories about the cause of dyslexia, impaired phonological processing is the most consistent finding in individuals with dyslexia (Ramus et al., 2003), as it is observed for different age groups (Shaywitz et al., 2007) and in different languages (Ziegler & Goswami, 2005). Neuroimaging studies suggest that the neural underpinning of this problem may be allocated to a neurological dysfunction of certain left-hemisphere perisylvian brain areas (Shaywitz, 1998; McCandliss & Noble, 2003; Paulesu et al., 2001).

1.2.1.2. The general sensory deficit theory

The idea of a phonological deficit as the primary source of the reading and spelling problems in dyslexia, has however been challenged by theories that allocate the phonological problems in dyslexia to a *fundamental deficit in basic perceptual mechanisms* (e.g. Ramus, 2003; Wright et al., 2000). This theory incorporates separate theories that assign the reading and spelling problems in dyslexia to a magnocellular visual dysfunction (e.g. Boets et al., 2011b; Cornelissen et al., 1995; Eden et al., 1996; Hari et al., 2001; Livingstone et al., 1991; Lovegrove et al., 1980; Skottun & Skoyles, 2008; Stein & Walsh, 1997; Stein, 2001), a tactile dysfunction (e.g. Stoodley et al., 2000), a cerebellar/motor dysfunction (e.g. Nicolson et al., 2001), an attentional dysfunction (e.g. Hari & Renvall, 2001), or an auditory dysfunction (e.g. Tallal, 1980; 1993; Talcott et al., 1999; Witton et al., 1998).

Given the broad scope of dysfunctions covered by this theory, it is unlikely that the reading and spelling problems in dyslexia are the result of a single deficit. Instead, it may be that these problems are the outcome of a multidimensional deficit, for which the expression of reading and spelling problems are determined by an accumulation of multiple risk factors in different cognitive or sensory domains (e.g. Pennington, 2006; Ramus et al., 2003; Snowling, 2008).

Without ignoring the possibility of different factors underlying the development of dyslexia, the present research project focused on investigating the possibility of a low-level auditory processing deficit as underlying factor for the reading and spelling problems in dyslexia.

1.2.1.3. The auditory temporal processing theory

In the auditory domain, poor auditory and speech processing may affect the way phonological representations of speech sounds are assembled during childhood and may influence subsequent language and literacy development (Bailey & Snowling, 2002).

Individuals with dyslexia have been found to have difficulties with a wide range of auditory stimuli. On the one hand studies find evidence for deficiencies in processing low-level auditory information that is *non-temporal* in nature (i.e. information that does not vary over time), such as the perception of stimulus intensity, frequency, and duration (e.g. Ahissar et al., 2006; Huttunen et al., 2007;

Leppänen et al., 2010; Thomson et al., 2006; for a review see Hämäläinen et al., 2012b), or the perception of phoneme length (e.g. Leppänen et al., 1999; 2002; Pennala et al., 2010; Richardson et al., 2003).

On the other hand, several studies have focused on a deficit in processing dynamic information (i.e. changing over time), often referred to as *temporal* processing (for a review, see Farmer & Klein, 1995; McArthur & Bishop, 2001). In literature, the term "auditory temporal processing" has been used in conflicting contexts. Whereas the auditory deficit in dyslexia was originally allocated to processing transient information that is brief or rapidly presented (e.g. stop consonants) (e.g. Tallal, 1980; Tallal et al., 1993), more recent studies agree that the nature of the auditory temporal processing deficit in dyslexia rather relates to temporal, dynamic modulations (e.g. Talcott et al., 2000; 2003; Witton et al., 1998; 2000). Given the importance of temporal auditory cues in carrying information in speech (see 1.3.1 for more details), an impairment at this level may provoke a cascade of effects resulting in reading and spelling problems (see Figure 1.1). Therefore, the auditory temporal processing deficit theory is the starting point of the present project.

1.3. Auditory temporal processing in dyslexia

An important question is how precisely auditory temporal processing abilities influence the establishment of the fine-grained phonological representations that underpin reading development. Given that auditory temporal cues are crucial elements in spoken language comprehension (Shannon et al., 1995), it is assumed that auditory perception and phonology are mediated by speech perception (see Figure 1.1). This section will give an overview of how these processing levels interact (1.3.1), and will review what the existing evidence for this theory is at the psychophysical (1.3.2) as well as at the neurophysiological (1.3.3) level.

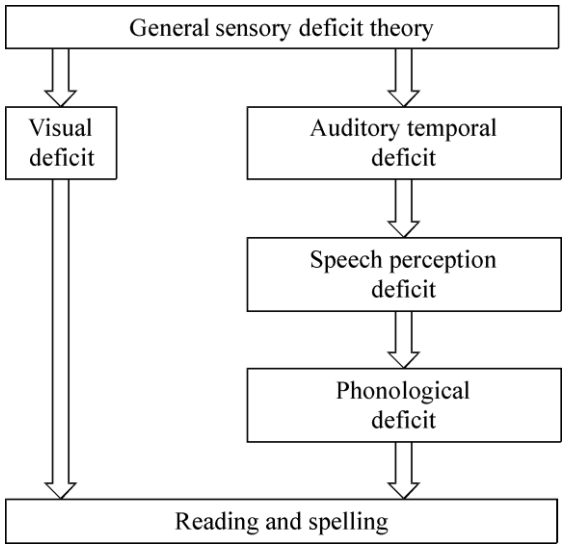


Figure 1.1 A causal model for dyslexia, as proposed by the general sensory theory for dyslexia. Adapted from Ramus (2001).

1.3.1. The influence of auditory temporal perception on speech perception and reading

Acoustically, speech can be described as a signal that varies in amplitude and frequency over time. Based on the multiple timescales of these fluctuations, the speech signal can be partitioned in three distinct levels: fine structure, periodicity and envelope cues (Rosen, 1992). The *fine structure* of the speech signal corresponds to the rapid changes of the sound pressure waveform (above 250 Hz) that carry information about the formant patterns and determine the spectral content of the sound. The *periodicity* of the speech signal is characterized by the fundamental frequency of the speaker at rates between 70 and 500 Hz and is created by the opening and closing of the vocal folds during voiced speech. Finally, speech *envelope* information corresponds to the slow modulations (below 50 Hz) of the speech signal and describes the changes in the overall amplitude of the pressure waveform.

Studies have shown that while speech perception remains possible when fine structure and periodicity information is reduced, the reduction of temporal envelope

information is detrimental for speech intelligibility (Shannon et al., 1995; Drullman et al., 1994). The slow modulations of the temporal envelope information are thus thought to provide crucial information for speech intelligibility.

To decode the meaning of speech, it is mandatory to identify single words, phrases, and sentences. This process is preceded by a pre-lexical processing level at which acoustic-phonetic information is categorized and integrated along multiple timescales. These time windows differ temporally with respect to the length on which the auditory cues act and are linguistically classified as to whether they convey cues relevant for suprasegmental or segmental information (Obrig et al., 2010). That is, suprasegmental information about for example speech prosody and stress, occurs in time windows of ± 150-300 ms, whereas segmental information about, for example, phoneme identity occurs in time windows of ± 20-80 ms (Obrig et al., 2010; Pöppel et al., 2008). Extraction of segmental and suprasegmental information from the continuous speech stream is guided by two classes of acoustic cues in the temporal envelope of speech.

First, the temporal envelope of sounds contains steady-state acoustic cues that indicate global amplitude changes over time (i.e., amplitude modulations, AM). *Amplitude modulation* rates near 4 Hz (± 250 ms) and 20 Hz (± 50 ms) signal the time windows in which, respectively, suprasegmental and segmental acoustic cues occur in speech (Pöppel, 2003). Within these time windows, acoustic information is processed and integrated into an acoustic-phonetic construct.

Second, the temporal envelope of sounds contains transient acoustic cues, such as a sound's *onset time* (also referred to as rise time), that mark the occurrence of a transient acoustic event in the signal. In natural speech, sound onset times comprise a combination of dynamic cues such as changes in intensity, duration, and fundamental frequency, which are important for segmenting speech into regularly occurring chunks, such as syllables, onsets or rimes and for analyzing prosodic patterns and syllable stress (Goswami et al., 2010), but also for phoneme discrimination (Goswami et al., 2011b). Unlike AM, whose rate determines syllabic- or phonemic-rate integration, onset time has a general role at both the syllabic and the phonemic level. Yet, it is important to note that both temporal envelope cues are not completely independent in that the onset time of AM stimuli varies with their modulation rate.

Speech perception and the representation of phonological units can thus be affected by (*i*) how precise temporal envelope cues that signal segmental and suprasegmental

units are processed, and (*ii*) how well acoustic cues occurring within these segmental and suprasegmental time windows are integrated.

1.3.2. Psychophysical evidence for an auditory temporal processing deficit underlying dyslexia

The *auditory temporal processing* deficit theory of dyslexia has been examined with a variety of stimuli and tasks (for a review see Hämäläinen et al., 2012b). Psychophysical studies investigating *sound onset* time perception found significantly poorer performance of individuals with dyslexia compared to normal-reading individuals (children: Richardson et al., 2004; adults: Hämäläinen et al., 2005; Pasquini et al., 2007). Additionally, performance on onset time detection tasks was related to reading, spelling, and phonological awareness abilities (e.g. Goswami et al., 2002; Hämäläinen et al., 2005; Muneaux et al., 2004; Pasquini et al., 2007; Richardson et al., 2004). Similarly, *AM detection* studies demonstrated elevated AM detection thresholds for modulation rates between 4 and 1024 Hz in children (Lorenzi et al., 2000; Rocheron et al., 2002) and adults (McAnally et al., 1997; Menell et al., 1999) with dyslexia. However, contradicting results were found for AM rates at the lower end of the temporal envelope modulations. Even though in children the largest group differences were found near 4 Hz, results in adults were less clear. Witton et al. (2002) found elevated 20 Hz AM detection thresholds in dyslexic adults, but observed comparable 2 Hz AM thresholds between both groups. In contrast, Stuart et al. (2006), found elevated AM detection thresholds in dyslexic adults in the slow AM range at 1 Hz, but not at 100 Hz. In addition to temporal changes in amplitude, individuals with dyslexia also seem to be impaired in processing signals fluctuating in frequency over time (i.e. *frequency modulation*, FM). Studies have found poorer performance to slow-rate FM signals in adults (Witton et al., 2000) and children (Talcott et al., 2000; Boets et al., 2006) with dyslexia compared to their normal-reading peers. Sensitivity to slow-rate FM related to pseudoword-reading and phonological awareness (Witton et al., 1998; Boets et al., 2008; Boets et al., 2011a; Witton et al., 2002; Stuart et al., 2006; Talcott et al., 1999).

In agreement with the auditory temporal processing deficit theory, group differences are less consistently found for tasks evaluating *non-temporal* stimulus cues such as intensity and duration discrimination (e.g. Pasquini et al., 2007; Thomson &

Goswami, 2008; Richardson et al., 2004), suggesting that the deficit in dyslexia is specific to stimuli containing a temporal auditory aspect. However, it should be noted that individuals with dyslexia sometimes demonstrate lower performance on frequency discrimination tasks (e.g. Banai & Ahissar, 2004; Banai & Ahissar, 2006; Halliday & Bishop, 2006a; Halliday & Bishop, 2006b), even though these tasks do not require the analysis of temporal information.

If, as described in 1.3.1, an auditory temporal processing deficit is indeed one of the possible risk factors for poor phonological representations in dyslexia via *speech perception* (see Figure 1.1), individuals with dyslexia should demonstrate speech perception problems in addition to difficulties processing auditory temporal and phonological information. Indeed, studies examining speech perception in individuals with dyslexia found evidence for a (subtle) speech perception problem in dyslexia, on categorical perception (e.g. Bogliotti et al., 2008; Manis et al., 1997; Serniclaes et al., 2005; Serniclaes et al., 2001; Serniclaes et al., 2004; for a review, see Vandermosten et al., 2011) or speech-in-noise perception tasks (e.g. Bradlow et al., 2003; Chandrasekaran et al., 2009; Wible et al., 2002; Ziegler et al., 2009). Furthermore, speech perception performance predicted 28–44% of unique variance for phonological decoding and 18–37% for reading (Ziegler et al., 2009). Nonetheless, studies disagree about the exact origin of the speech perception problem in dyslexia. Based on their finding of a speech-in-noise perception deficit in children with dyslexia, Ziegler et al. (2009) hypothesized that the speech perception problems in dyslexia relate to an inability to extract and integrate crucial auditory information from a complex or noisy signal. Contrary to the auditory temporal processing deficit theory, this hypothesis states that the main deficit in dyslexia is not at the level of temporal auditory perception per se but relates rather to the integration of acoustic information into a phonological construct. Alternatively, Vandermosten et al. (2010; 2011) demonstrated that the categorical perception problems of children and adults with dyslexia are specific to speech and nonspeech contrasts that are manipulated in their temporal cues, supporting the idea that reduced sensitivity to auditory temporal cues affects speech perception abilities and results in underspecified phoneme categories. Evidence for the direct relation between temporal processing and speech perception problems in dyslexia comes from a longitudinal study, demonstrating that children with dyslexia already have pre-reading deficits in auditory processing, speech perception and phonology (Boets et al., 2006; 2007), but more importantly, that low-level auditory temporal processing and speech perception in kindergarten uniquely contribute to growth in reading ability (Boets et al., 2011a).

1.3.3. Neurophysiological evidence for an auditory temporal processing deficit underlying dyslexia

Despite the growing number of behavioural studies indicating reduced sensitivity to auditory temporal cues in individuals with dyslexia, the neural mechanisms underlying this deficit are still unclear. It has recently been proposed that the auditory temporal processing problems in dyslexia result from a neural dysfunction to engage spontaneous oscillatory brain activity to phase-lock to the temporal information in the envelope of sounds (Goswami, 2011). Several electroencephalographic (EEG) and magnetoencephalographic (MEG) studies confirm this approach as they found neurophysiological deviances between normal-reading and dyslexic individuals to a variety of temporal stimuli, including sound onset time, AM and FM.

EEG studies examining sound onset sensitivity found evidence for deviant event-related potentials (ERPs, see 1.4.4) in individuals with dyslexia (Hämäläinen et al., 2007; 2008; 2011; Stefanics et al., 2011). Source analysis specified that in normal-reading participants ERP components to sound onset time stimuli were lateralized to the left hemisphere, whereas in dyslexic participants no ERP lateralization was found due to significantly lower amplitudes in the left hemisphere compared to normal readers (Khan et al., 2011).

Similar findings were observed in response to AM stimuli. Phonemic-rate modulations were found to be less lateralized to the left hemisphere in dyslexic compared to normal-reading participants, and related to phonological performance (Lehongre et al., 2011). Additionally, group differences were found for processing of syllabic-rate modulations. In normal readers, these modulations were consistently found to be more prominently processed in the right hemisphere, whereas dyslexic readers rather showed a symmetrical organization (Abrams et al., 2008; 2009; Hämäläinen et al., 2012a). In response to FM stimuli, ERPs were lower to 20 Hz but not to 240 Hz FM in adults with dyslexia, even though these participants did not demonstrate different psychophysical performances (Stoodley et al., 2006).

Overall, these studies indicate a neurophysiological disturbance in processing auditory temporal information, suggesting that the integration of auditory information into the phonological system is not optimal in dyslexia. However, the exact origin of this neural dysfunction along the auditory pathway is still unknown.

1.4. Auditory temporal processing in the brain

Although most of the above-mentioned studies found evidence for neurophysiological differences between normal-reading and dyslexic persons in response to auditory temporal information, the exact neural origin of this deficit is still unknown. A possible reason for this is the complexity of the human auditory system. In this section, the anatomy of the auditory system will be described (1.4.1) and studies examining its sensitivity to temporal information will be reviewed (1.4.2). Furthermore, an overview of the existing neurophysiological techniques to assess auditory temporal sensitivity in the auditory system will be given (1.4.3). Given the scope of this doctoral thesis, this section will conclude with a description of auditory evoked potentials (1.4.4).

1.4.1. The auditory system

The *auditory system* comprises all structures that a sound encounters between its first contact with the ear until its mental interpretation. The *peripheral* part of the auditory system consists of the outer ear, the middle ear and the inner ear. In the outer ear, sound waves arrive at the pinna and travel through the ear canal to the tympanic membrane (also called the eardrum). In the middle ear, the vibrations of the tympanic membrane are transmitted by the malleus, the incus and the stapes, to the oval window in the inner ear. In the inner ear, the movement of the membrane of the oval window displaces the fluid in the inner ear to the round window, and a pressure difference is applied across the basilar membrane, which causes the stereocilia of the hair cells to bend (see 1.5.6.1 and Figure 1.10). This stimulates the hair cells, which in turn initiate neural action potentials in the auditory nerve. Whereas the cochlea is involved in encoding the spectral content of a sound, information about the sound's intensity and time structure is also encoded. Information about the level is provided by the fact that higher stimulus intensities produce larger basilar membrane movements. Temporal information is encoded because the temporal vibration pattern of the basilar membrane and the subsequent neural firing rate follows temporal properties of the acoustic stimulus.

Neural information from the auditory nerve travels to the *cochlear nucleus.* The cochlear nucleus' large network of interconnections and complex physiology suggests that it refines the sound code coming from the auditory periphery. From the

cochlear nuclei, a contralateral (on the opposite side compared to the side of stimulus presentation) and an ipsilateral (on the same side compared to the side of stimulus presentation) pathway departs to the left and right *olivary complex* (see Figure 1.3). This implies that from this level forward, information from both ears is combined, a feature important for processes such as the spatial localization of sounds.

From the superior olivary complex, information is transmitted to the *inferior colliculus*, the *medial geniculate body* and the *auditory cortex*. In the past the auditory cortex, was described as primary and secondary. However, current terminology uses the image of a core with at least two concentric areas surrounding it, the belt and the parabelt regions (see Figure 1.2) (for a review see Kaas et al., 1999; Kaas & Hackett, 2000). The core is thought to correspond to the primary auditory cortex (PAC), located in the medial and intermediate part of Heschl's gyrus (HG). The belt and parabelt extend into neighbouring sulci, with belt regions corresponding to the secondary auditory cortex (SAC), located in the lateral part of HG, and parabelt regions corresponding to the planum temporale (PT) and possibly also the posterior part of the superior temporal gyrus (STGp) and an area located in front of HG, in the anterior part of STG (STGa) (Gourevitch et al., 2008; Sweet et al., 2005). In the auditory cortex, acoustic information travels ipsilaterally from the core areas to the surrounding belt that relays information to parabelt regions and travels then contralaterally via the *corpus callosum* to the opposite auditory cortex for further processing. Auditory cortical regions combine and integrate information from lower levels in the auditory pathway into complex auditory patterns (Yost, 2000; Bailey, 2010; Moore, 1997).

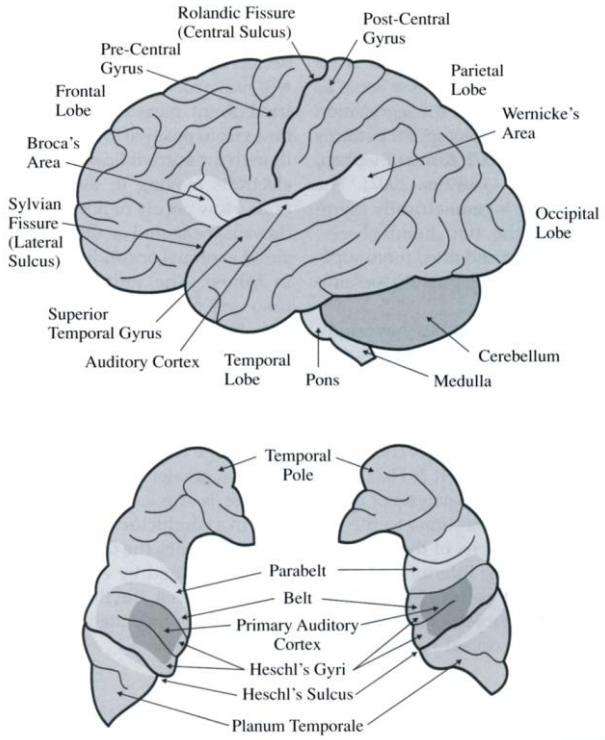


Figure 1.2 The human auditory cortex. The upper part of this figure shows the left side of the human brain. The human auditory cortex is located on the superior surface of the temporal lobe within the Sylvian fissure. The lower part of this figure depicts the top view of the left and right temporal lobes. From Picton (2011).

1.4.2. Sensitivity of the auditory system to auditory temporal information

The auditory system encodes temporal envelope information by engaging neural oscillations to phase-lock to the rhythm of the temporal variation (Buzsaki & Draguhn, 2004). Neural phase-locking can be measured when a sufficient number of neurons (around 10^5 to 10^7) oscillate synchronously (Eggermont & Ponton, 2002; Hämäläinen et al., 1993). Whereas the entire auditory system is sensitive to the temporal envelope of sounds, it is generally assumed that the highest possible rate to which neurons are sensitive reduces along the ascending auditory pathway (see Figure 1.3).

1.4.2.1. Animal studies

Much of our understanding of the neurophysiology underlying coding of amplitude modulations comes from animal studies (see Figure 1.3). These studies demonstrated that neurons along the auditory pathway differ in their ability to phase-lock to auditory stimuli at certain rates. Moreover, auditory nerve fibers are able to phase-lock to modulations as high as 3–4 kHz, whereas the phase-locking cut-offs for neurons in the *cochlear nucleus* lie between 750 and 1500 Hz (Frisina et al., 1990; Rhode & Greenberg, 1994; Zhao & Liang, 1997). At the level of the *superior olivary complex*, neurons are most responsive to AM rates around 500 Hz (Kuwada & Batra, 1999), while neurons in the inferior colliculus respond preferentially to AM rates between 50 and 150 Hz (Rees & Moller, 1987; Langner & Schreiner, 1988). At the *cortical level*, neurons are most sensitive to modulation rates between 2 to 30 Hz (Joris et al., 2004; Schreiner & Urbas, 1986; 1988). Moreover, neurons located in auditory fields posterior to primary regions tend to encode slower variations in signal amplitude than primary auditory cortical neurons (Heil & Irvine, 1998). Kuwada et al. (2002) demonstrated activity in the auditory cortex to modulations between 10 and 20 Hz.

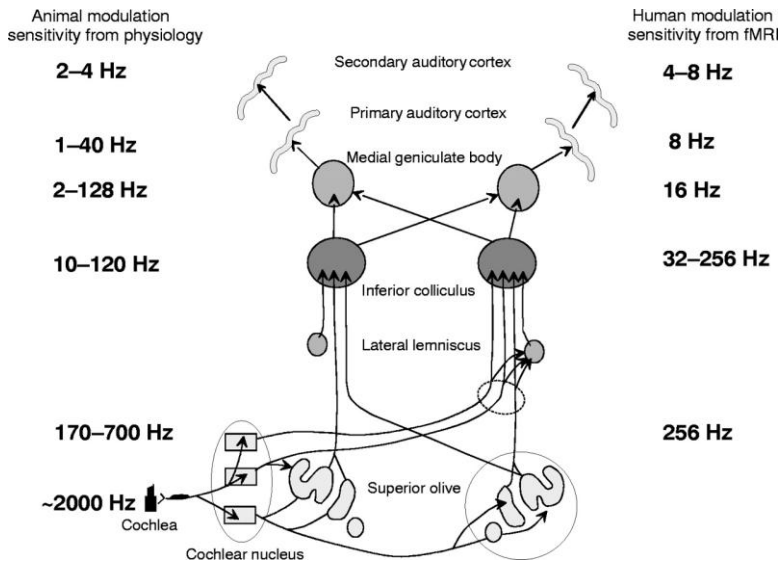


Figure 1.3 Sensitivity to different rates of amplitude modulation at different nuclei along the auditory pathway in animals and in humans. From Palmer & Summerfield (2002).

1.4.2.2. Studies in humans

In humans, however, remarkable similarities with the animal auditory system were found (see Figure 1.3). In an fMRI study, Giraud et al. (2000) investigated the neural representation of the temporal envelope of sounds with white noises, amplitude modulated at 4, 8, 16, 32, 64, 128, and 256 Hz. The authors reported subcortical activation in the superior olivary complex (256 Hz), the right inferior colliculus (32-256 Hz) and the left medial geniculate body (16 Hz) to right ear stimulation. Additionally, cortical activity was measured in Heschl's gyrus (8 Hz) and the posterior regions of the temporal sulcus and the superior temporal gyrus (4-8 Hz).

Based on the response characteristics of evoked potentials measured with intracerebral recordings in the context of epilepsy research, Liégeois-Chauvel and colleagues specified the role of important cortical regions for auditory temporal processing (see Figure 1.2). Similar to the results of Giraud et al. (2000), SAC and STGp demonstrated the highest activity to 4 and 8 Hz modulation rates, while PAC was sensitive to a broader range of amplitude modulation rates up to 32 Hz (Liégeois-Chauvel et al., 2004). This selective temporal sensitivity in SAC and STGp suggests the existence of a processing hierarchy from large unspecialized groups of neurons towards smaller specialized groups. The fact that the relatively high temporal resolution of PAC (compared to SAC and STGp) is not maintained in secondary and associative areas suggests that the analysis of complex sounds, including fast temporal changes, may depend on the encoded information of the primary cortex (Liégeois-Chauvel et al., 2004; Fishman et al., 2001; Giraud et al., 2000).

In addition to these hierarchical differences between cortical structures, the left and right auditory cortical areas (PAC, SAC, STGp and STGa) are thought to differ in their capacity to follow slow temporal modulations (Liégeois-Chauvel et al., 2004). That is, whereas activity in PAC was equal for both hemispheres, activity in SAC and STGp was higher in the left than in the right hemisphere, suggesting that the left hemispheric SAC and STGp are more sensitive to differentiate between temporal envelope modulations (Liégeois-Chauvel et al., 2004; Gourevitch et al., 2008; Giraud et al., 2000). These findings correspond to models assigning a greater temporal resolution to the left hemisphere (e.g. Belin et al., 1998; Zatorre & Belin, 2001). Alternatively, these findings agree with the "Asymmetrical Sampling in Time" (AST) model of Pöppel and colleagues that argues that the left hemisphere is preferential responsive to auditory temporal signals between 12-50 Hz

(corresponding to a temporal change every 20-80 ms) whereas the right auditory cortex is most sensitive to process acoustic modulations at a lower rate, between 3-7 Hz (150-300 ms) (Pöppel, 2003).

1.4.3. Overview of objective techniques applied in auditory neuroscience

In neuroscience, the anatomy and function of the brain is modelled with a variety of techniques. In this section, an overview of the most commonly used techniques is provided. A detailed description of all other techniques is provided by Laureys et al. (2002).

In general, these techniques are categorized based on the activity they measure. A first class of techniques are techniques that measure the *anatomical* properties of the brain, such as X-ray computed tomography (CT), magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI). A second class of techniques are those that measure functional brain activity (see Figure 1.4). To this class belong neuroimaging techniques that evaluate brain activity based on the *hemodynamic activity*, such as single photon emission tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), and neurophysiological techniques that evaluate brain activity based on the *electrical or magnetic activity* of the brain, such as the electroencephalography (EEG) and the magnetoencephalography (MEG).

These functional techniques differ in their sensitivity to measure temporal changes (temporal resolution) or on their accuracy to discriminate between spatial regions (spatial resolution). Whereas hemodynamic responses are slow to build up and are therefore less specific to measure the time course of the response, electrical responses are very precise in measuring the time course of the response but are recorded at the scalp and have therefore a poorer spatial resolution. Thus, the selection of technique depends mainly on the research question. In the field of neuro- and psycholinguistic research, electrophysiological approaches dominate. This stems from four important properties of the EEG technique: (*i*) excellent temporal resolution in the range of milliseconds (compared to methods based on hemodynamic activity), (*ii*) relatively low experimental constraints (Friederici, 2004), (*iii*) sensitivity to both tangential and radial oriented sources (compared to MEG that only measures tangential sources) (Nunez & Srinivasan, 2006), and (*iv*) a

relative high sensitivity to deep sources (compared to MEG that is mainly sensitive to cortical sources). These properties are important in that good temporal resolution allows monitoring temporally sequential sub-processes in language comprehension, whereas low experimental constraints are an important requisite to extend this research to difficult testable participant samples such as young children or clinical groups. Additionally, EEG's sensitivity to tangential and radial oriented sources, as well as to deep sources such as the midbrain and brainstem are beneficial to measure activity along the entire auditory pathway and to sources of which their orientation is still unknown. Assessment of auditory functions in the EEG will be discussed in more detail in the following paragraphs.

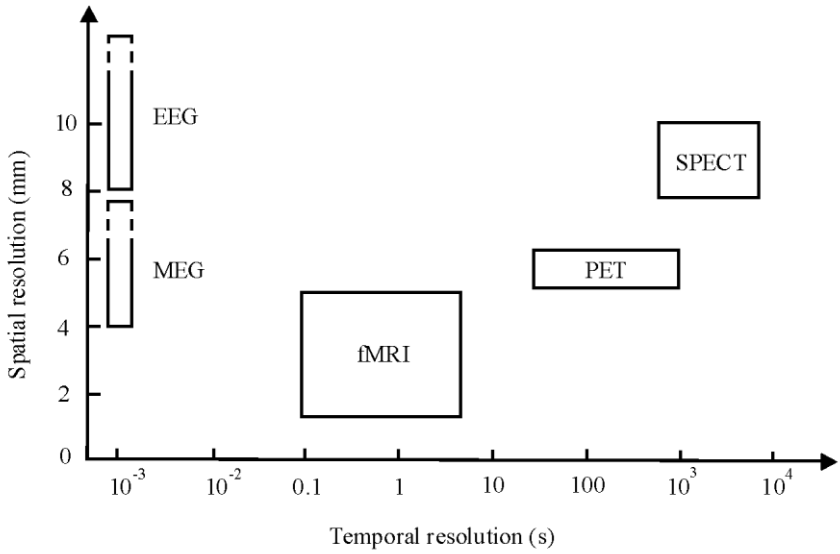


Figure 1.4 Approximation of the resolution in time and space of the most commonly employed techniques in auditory neuroscience. Adapted from Laureys et al. (2002).

1.4.4. Auditory evoked potentials

Compared to other neurological techniques, the main advantage of assessing the integrity of the auditory system with auditory evoked potentials (AEPs) is that the status of the entire auditory system, from the brainstem to the cortex, can be evaluated with a high temporal resolution. This section provides an overview of the

most commonly used evoked potentials in auditory neuroscience. In literature, AEPs can be classified in two classes: transient, described in 1.4.4.1 and steady-state responses, described in 1.4.4.2. A more detailed review on the AEPs can be found in Picton (2011) and Rance (2008).

1.4.4.1. Transient responses

Transient responses are evoked by a change in the auditory stimulus. These responses are also known as event-related responses, because they are time-locked to a transient event and reflect neural stimulus encoding from the sensory to the cognitive level. Transient stimulus events can be the onset or decay of a sound, a change in frequency, amplitude or phase. According to their post-stimulus latency, three classes of transient responses can be identified: early (0 to 10 ms), middle (10 to 50 ms), and late (50 to 250 ms) latency responses (Rance, 2008).

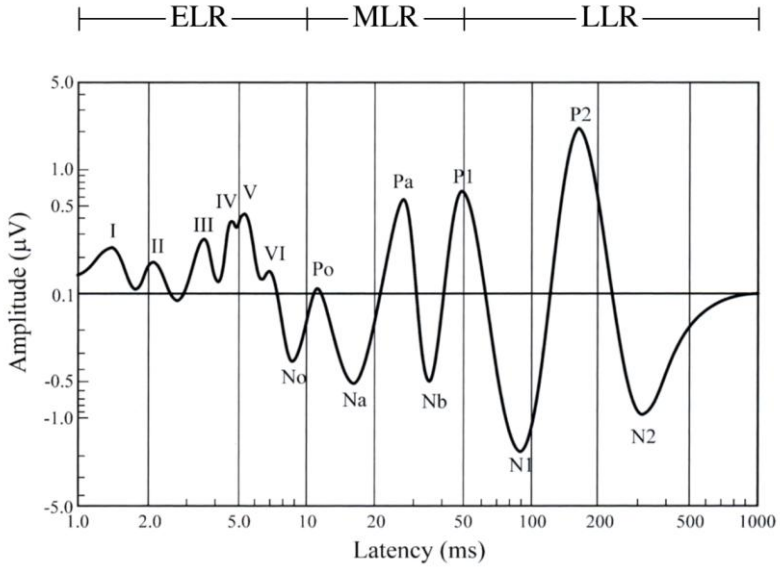


Figure 1.5 Auditory evoked potentials. Amplitudes and latencies are plotted on a logarithmic scale. Adapted from Picton (2011).

Early latency responses

Early latency responses are AEPs that occur within the first 10 ms after stimulus onset. One of the most important early latency responses is the auditory brainstem response (ABR). This response is characterized by a wave with 7 positive peaks. The most commonly used stimuli to evoke an ABR are clicks or tone bursts, optimally presented at a rate between 10-30/s. At relatively high stimulus levels (e.g. 70 dB nHL) and with click stimuli, the first peak (wave I) has a latency around 1.5 ms, with subsequent ABR waves appearing roughly at intervals of 1.0 ms (see Figure 1.5). The largest of these waves is wave V, with a typical latency around 5.6 ms. As mentioned in its name, these responses are thought to be generated in the brainstem. Waves I and II are assumed to be generated at the distal and proximal portion of the auditory nerve, respectively. Later waves appear to have multiple generators within the auditory brainstem up to the inferior colliculus. ABR components are classically evaluated based on their peak latency and the inter-peak latencies of waves I, III and V. ABRs are not affected by sleep state or most medications. The most common application of ABR is in the context of hearing screening and diagnosis, where they are assessed to objectively determine hearing thresholds (Picton, 2011; Hall, 2007).

Middle latency responses

Middle latency responses (MLRs) are AEPs that occur between 10 and 50 ms after stimulus onset, using click or tone burst stimulation. This time window is characterized by a sequence of negative and positive peaks called N0, P0, Na, Pa, Nb, and Pb (or P50), with latencies of 8 ms, 12 ms, 18 ms, 30 ms, 40 ms and 50 ms respectively. The earliest of these MRLs, N0 and P0 are thought to represent activity in the thalamus or thalamocortical radiations, whereas the Na and Pa waves likely represent activation near the primary auditory cortex on Heschl's gyrus (Borgmann et al., 2001; Pantev et al., 1996). The Pa wave is generated anterior to N1 (see late latency responses). The exact neural generators of the Nb and Pb component are not clear. Intracerebral recordings found sources successively located along Heschl's gyrus from postero-medial to antero-lateral (from primary to secondary auditory areas) (Liégeois-Chauvel et al., 1994). MEG studies suggested that the source underlying Pb is located more anterior and lateral to that of Na/Pa, probably in secondary areas (Yoshiura et al., 1995; Hall, 2007), or within the planum temporale (Reite et al., 1988). Sleep and medication may influence the amplitude and latency of MLRs and thus must be carefully assessed. MLRs are assessed in the context of

auditory processing disorders above level of the brainstem (Hall, 2007). The final wave of the MLR is also a component of the first wave of the auditory late latency response (LLR). When analyzed as part of the MLR, the final wave is designated Pb or P50. When analyzed as part of the LLR, the same peak is referred to as P1.

Late latency responses

Late latency (or long-latency) responses (LLRs) are AEPs that occur later than 50 ms after stimulus onset. They are optimally evoked by tone burst stimuli of relatively long duration (more than 10 ms), but can also be elicited by complex stimuli such as short speech tokens. Within this time window, the main components are the P1, N1, P2 and N2, occurring 50-80 ms, 100-150 ms, 150-200 ms and 180-250 ms after stimulus onset, respectively. Studies suggested that the neural source of P1 is located in Heschl's gyrus (Godey et al., 2001; Liégeois-Chauvel et al., 1994), while the N1 wave is thought to be located in lateral parts of Heschl's gyrus and the planum temporale (Godey et al., 2001). The P2 wave represents activity in the planum temporale and/or in the posterior region of the temporal sulcus (Godey et al., 2001). Finally, the main source underlying the N2 wave has also been located in the supratemporal plane, anterior to the source of N1 (Céponiene et al., 2002; Sussman et al., 2008).

In auditory neuroscience, the two most prominently used components are the Acoustic Change Complex (ACC) and the Mismatch Negativity (MMN). The ACC refers to the N1-P2 response in response to an acoustic change in stimulation (e.g. Martin & Boothroyd, 1999). The MMN is a negative deflection resulting from the difference waveform between rare (i.e. deviant) and frequently (i.e. standard) presented stimuli, and represents a preattentive change detection process (Näätänen, 2000; Näätänen et al., 2011).

LLRs are easily affected by both sleep state and medications, especially sedatives. Amongst other purposes, LLRs are used to assess the integrity of the cortical auditory system, to diagnose auditory processing disorders, to asses speech perception skills, to evaluate auditory and visual attention to novel stimuli, and to evaluate other neuropsychiatric conditions (Hall, 2007).

1.4.4.2. Sustained responses

In contrast to these transient responses, which resume their resting-state activity after encoding certain stimulus properties, sustained responses are evoked continuously in the EEG. In this class of AEPs also belong the cochlear microphonic, the frequency following response (FFR) and the sustained cortical negative potential occurring during prolonged sound (for more details see Rance, 2008). In response to a continuous, regularly changing stimulus, a steady-state response is evoked. Steady-state responses can be recorded in the auditory, visual and the somatosensory system. Of particular interest for this project is the Auditory Stead-State Response (ASSR), which will be described in detail in section 1.5.

1.5. Auditory steady-state responses

This section provides an overview of the recording aspects of ASSRs. The definition of the ASSR is explained in 1.5.1. Commonly used stimuli to evoke ASSRs and the details about ASSR recording are described in 1.5.2 and 1.5.3 respectively. Subsequently, ASSR response measures (1.5.4) and details about the influence of stimulus parameters on these measures (1.5.5) are provided. Finally, the neural sources of ASSRs are provided in 1.5.6.

1.5.1. Definition

The auditory steady-state response (ASSR) is a neural oscillatory response that is evoked by a periodically varying, continuous signal. The ASSR is a complex waveform with exactly the same periodicity as the acoustic stimulus and measures the accuracy with which the auditory system follows variations in amplitude and/or frequency (Picton, 2011; Rance, 2008). In literature, a variety of terms is used to define this response, including auditory steady-state evoked potential (ASSEP), envelope following response (EFR) and amplitude modulation following response (AMFR).

1.5.2. ASSR stimuli

Whereas transient responses are evoked by stimuli that do not have a periodic nature, steady-state responses are evoked by *continuously, periodic or repetitive stimuli*. Classically, ASSRs are evoked by sinusoidal AM or FM signals, because these are well-controlled stimuli in which the temporal characteristics are determined by the modulating waveform. Modulated signals consist of a *carrier signal* that varies in amplitude or frequency over time, a *modulation rate* that determines the rate of the amplitude or frequency variation, and a *modulation depth* that describes the degree of modulation.

For an AM stimulus, the modulation depth describes the ratio of the maximum amplitude to the minimum amplitude in the AM signal. Hence, when the modulation is 100% the amplitude envelope decreases to zero every modulation cycle (see Figure 1.6, upper panel). The most important characteristic of an AM stimulus is its relatively simple frequency spectrum that only contains energy at the carrier frequency and at two sidebands, separated from the carrier frequency by the modulation frequency (carrier frequency plus and minus the modulation frequency) (Joris et al., 2004). A relatively more complex frequency spectrum is found for FM stimuli (see Figure 1.6, lower panel). For a FM stimulus, the modulation depth describes the difference between the maximum and minimum frequencies divided by the carrier frequency. Hence, as the depth of a FM stimulus increases the number of components in the frequency spectrum also increases, and the frequency specificity of the stimulus decreases (Picton et al., 1987a; Maiste & Picton, 1989). The frequency specificity of a stimulus has important implications for the response characteristics of ASSRs (see 1.5.5) and may be a crucial factor in the field of objective response audiometry. In addition to these stimuli, ASSRs can also be evoked by repeated clicks or tone bursts, or by more complex waveforms consisting of a combination of AM and FM (e.g. mixed modulation or independent amplitude and frequency modulation (IAFM)). These stimuli are described in more detail in Hall & Swanepoel (2010), Rance (2008), and Picton (2011).

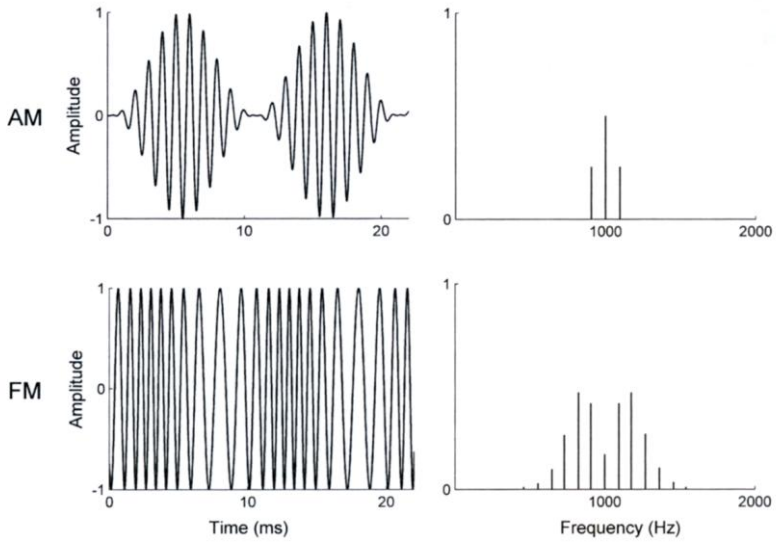


Figure 1.6 Amplitude and frequency modulation in the time- and in the frequency-domain. The top row indicates a 1000 Hz tone 100% AM at 90 Hz. The bottom row depicts a 1000 Hz tone, 50% FM at 90 Hz. Adapted from Hall & Swanepoel (2010).

1.5.3. ASSR recording and response detection in the EEG

ASSRs can be recorded in the EEG using scalp electrodes. An international recognized system for describing and applying electrode positions for EEG recordings is the 10-10 system (Figure 1.7) (American Clinical Neurophysiology Society, 2006), or its modified version the 10-20 system (Malmivuo & Plonsey, 1995). This system is designed to place electrodes at approximately equal distances from each other over the scalp. Dependent on the modulation rate and the participant's age the optimal locations for placement of electrodes to record ASSRs may vary (Herdman et al., 2002; John & Picton, 2000a; van der Reijden et al., 2005). Common electrode placements for single channel ASSR recordings are the vertex (Cz) or high forehead (Fpz) for the active or noninverting electrode, with the reference or inverting electrode placed at the neck or occiput (Oz). The ground electrode is often placed at one of the mastoids, the side of the neck, the clavicle or Pz (e.g. John et al., 2001b; Lins & Picton, 1995; Luts & Wouters, 2005).

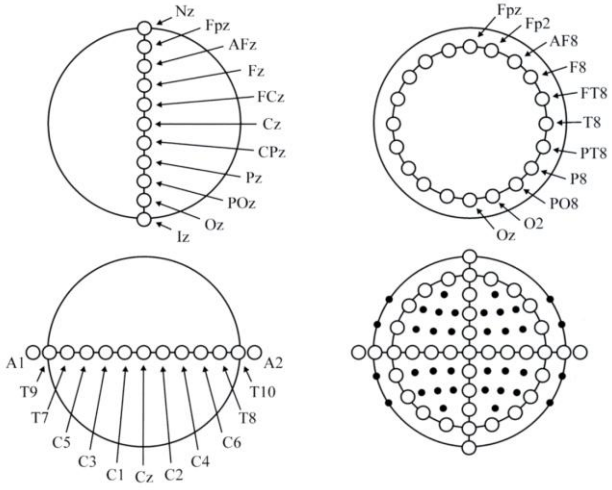


Figure 1.7 Electrode positions according to the 10-10 system for electrode placement. From Picton (2011).

The scalp-recorded EEG signal is a small voltage signal, expressed in units such as millivolts (mV), microvolts (µV) or even nanovolts (nV). Besides the EEG, scalp electrodes also record a certain degree of measurement noise, induced by currents in the recording circuits. For good EEG measurements, it is important to reduce this noise as much as possible. Therefore two techniques are applied to the incoming EEG: differential amplification and filtering. During differential amplification, measurement noise is cancelled out by comparing the signals coming from two electrodes. By calculating the potential difference between two electrodes, potentials that are common for both electrodes disappear and only the difference potential maintains. A differential amplifier considers one electrode as a reference electrode (in literature referred to as “reference”, “inverting” or “-” electrode) whereas all other electrodes are “active” (in literature also referred to as “non-inverting” or “+”) electrodes (Burkard et al., 2007; Picton, 2011). Subsequently, the EEG signal is filtered for those frequencies that contribute little to the signal of interest (for details see Picton, 2011). To represent the remaining EEG signal as a time-domain voltage signal, it is amplified and an analog-to-digital (AD) conversion is carried out. The continuously recorded EEG signal is then stored in the computer’s memory as a series of digital segments, known as epochs. Every data epoch is linked to a stimulus buffer to compare the correspondence between the recorded signal and the stimulus.

Epochs are combined into larger data segments, called sweeps. Sweeps are then averaged and submitted to a Fast Fourier Transformation (FFT) analysis. A sweep-based analysis is necessary to increase the frequency resolution of the amplitude spectra in the FFT, on which ASSRs are evaluated. The FFT algorithm converts the recorded time domain signal into its constituent frequency components. After this conversion, amplitude values are provided for each of the frequencies in the amplitude spectrum.

1.5.4. ASSR response measures

In contrast to transient AEPs, which are evaluated in the time domain by measuring the amplitude and latency of the peaks and troughs, ASSRs can be analyzed more precisely in the frequency domain. In this section, the response measures that are applied in this doctoral thesis are described. These measures are however only a few of the possible measures to evaluate ASSRs. A detailed description of other ASSR measures is provided in Rance (2008), and Picton (2011).

Amplitude and signal-to-noise ratio

Frequency domain analyses evaluate the amplitude of every frequency component in the EEG. Besides energy at the modulation frequency of this stimulus (i.e. the ASSR), the amplitude spectrum of the EEG also contains energy of spontaneous EEG activity. Spontaneous EEG rhythms reflect cognitive brain states such as attention, alertness, drowsiness, sleep but are also involved in active cognitive processes such as memory, cross-modal integration and motor functioning. Spontaneous EEG oscillations can be classified in frequency bands, including the delta (1.5-4 Hz), theta (4-10 Hz), alpha (8-12 Hz), beta (10-30 Hz) and gamma (30-80 Hz) bands (Buzsaki & Draguhn, 2004). Hence, given that ASSRs are recorded from electrodes at the scalp, the recorded responses are a combination of the actual ASSR (i.e. signal) and the spontaneous EEG activity (i.e. noise) at the modulation frequency. Therefore, response-strength analyses are often performed based on a *signal-to-noise ratio* (SNR). The SNR, often expressed in dB, is defined as the ratio between the power of the signal (P_{signal}) and the power of the background noise (P_{noise}) and is calculated as:

$$\mathrm{SNR} = 10 * \log_{10}\left(\frac{P_{signal}}{P_{noise}}\right)$$

An SNR of 3 dB indicates that the power of the ASSR is approximately twice that of the background noise. Alternatively, a negative SNR or a SNR of 0 dB indicates that a response is embedded in the noise. The SNR can be used to determine whether a response is statistically present or not, using the *F*-ratio statistic. The F-test calculates the *F*-ratio of the response power at the signal frequency bin to the mean power of *n* adjacent frequency bins, where *n* is the number of noise bins used to create the noise estimate (Lins et al., 1996; Rance, 2008). If no response is present, the ratio is distributed as F with degrees of freedom 2 and 2*n*. If the *F*-ratio exceeds a predefined threshold of the *F*(2, 2*N*) distribution, the response is considered present (Figure 1.8). At the neurophysiological level, the strength of an ASSR (whether expressed in amplitude or SNR) depends on either the number of neurons that phase-lock to the modulation or alternatively on the synchrony of neural firing within a neural generator.

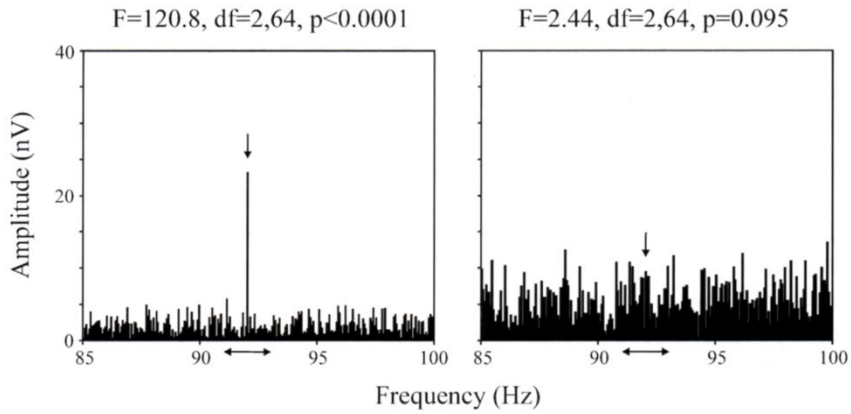


Figure 1.8 Detecting ASSRs in the EEG frequency spectrum. This figure depicts the EEG spectrum between 85 and 100 Hz of two different persons. ASSRs, as indicated with the arrow, were evoked by a 25 dB SPL 2kHz tone, amplitude modulated at 92 Hz. For the calculation of the response-SNR, the amplitude of the ASSR (↓) is compared to the average amplitude of n neighbouring frequency bins (↔) to determine the probability that a response might be within the expected range of amplitudes in the neighbouring frequency region of the spectrum. The response shown on the left is significantly different from the background EEG noise ($p < 0.05$). The response on the right, which amplitude is smaller and a higher level of background noise is recorded, is statistically not different from the background noise ($p > 0.05$). From Picton (2011).

Interelectrode phase coherence

Another response measure to evaluate ASSRs is inter-electrode phase coherence. Whereas amplitude and SNR measure neural functioning of individual group of neurons as measured at single electrodes, inter-electrode phase coherence allows studying the interaction between distant intra- and interhemispheric brain regions. It has been suggested that phase synchronization across spatially distinct brain regions is an important neuronal communication mechanism by dynamically linking neurons into functional networks, involved in the same underlying process (Womelsdorf et al., 2007). Phase coherence therefore provides crucial information about functional connectivity in the brain. Phase coherence is a correlation in the time domain between two signals, recorded simultaneously at different scalp electrodes at a given frequency or frequency band. According to the following formula, the coherence at frequency f between signals 1 and 2 indicated as C12(f) is calculated as the squared magnitude of the cross-spectral density of the signal pair W12(f), normalized by dividing with the product of the power spectra of the two signals, respectively W11(f) and W22(f) (Nunez & Srinivasan, 2006):

$$C_{12}(f) = \frac{|W_{12}(f)|^2}{(W_{11}(f) \times W_{22}(f))}$$

Coherence values range between zero and one. Low coherence indicates no synchronization between signals at different electrodes, which are a measure of underlying brain regions. High coherence indicates a high degree of synchronized neuronal activity. At the neurophysiological level, inter-electrode phase coherence varies with the degree of synchronization between distant neuronal ensembles.

1.5.5. Stimulus parameters

In general, ASSR stimuli have four defining parameters that influence the response measures of ASSRs: the modulation rate, the carrier signal, the modulation depth and the stimulus intensity. This section describes the influence of these parameters on recorded ASSR amplitudes.

Modulation rate

As described in 1.5.2, the modulation rate is the frequency at which the stimulus varies in amplitude, frequency or both. For AM and FM stimuli, the modulation rate corresponds to the modulation frequency, whereas for click or tone burst stimuli, the modulation rate refers to the frequency of the stimulus repetition (Rance, 2008). The modulation rate is an essential component of the ASSR stimulus, because it is exactly at this frequency that the neurophysiological response is evaluated in the frequency domain of the EEG. Furthermore, the modulation rate determines where in the auditory pathway the corresponding ASSR is generated (see 1.5.6 and Figure 1.3).

ASSRs have been investigated over a wide range of rates between 2 and 600 Hz (Purcell et al., 2004). The amplitude of the ASSR is known to vary with modulation rate. Similar to a decrease in background EEG power with increasing frequency, ASSR amplitudes decrease with increasing modulation rate (Figure 1.9). However, in certain frequency ranges local amplitude maxima can be found. It has been shown that the highest SNRs can be recorded in the 40 Hz region, followed by the frequency region between 80 and 100 Hz, where SNRs are already two to five times lower compared to the 40 Hz region in awake adults (Picton, 2011). Despite the high amplitude of ASSRs at modulation rates below 25 Hz, SNRs are low because of the high amplitude of the spontaneous background EEG (Picton, 2011). Purcell et al. (2004) and Picton (2011) provided a detailed overview over the possible physiological mechanisms underlying these local maxima.

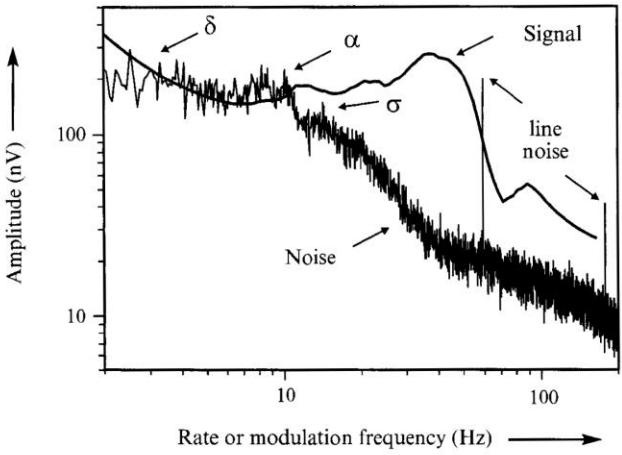


Figure 1.9 Representation of ASSR amplitude and spontaneous EEG activity at different modulation rates. Adapted from Picton et al. (2003).

Carrier signal

The carrier signal is the signal to which a modulation is applied. Carrier signals can be sinusoids or more complex signals such as noise. Depending on the frequency and the type of carrier signal, the response is initiated from a tonotopic area on the basilar membrane in the cochlea. That is, whereas the frequency of a sinusoid carrier signal activates a specific area of the basilar membrane, a broadband noise signal will activate a larger range of the basilar membrane (John et al., 1998). Given the frequency sensitivity of the basilar membrane, all frequencies between 125 and 8000 Hz can be used for the recording of ASSR (Rance, 2008).

ASSR amplitudes are influenced by the carrier frequency and this influence in turn depends on the modulation range (Purcell & Dajani, 2008). ASSR amplitudes were found to decrease with increasing carrier frequency in the 40 Hz domain (Galambos et al., 1981; Ross et al., 2003; Picton et al., 1987b). However, in the 80 Hz domain amplitudes are larger for frequencies between 1000 and 2000 Hz than for higher or lower carrier frequencies (John et al., 2001a).

Additionally, amplitudes are found to depend on the type of carrier signal. ASSR amplitudes were higher to broadband carrier signals (e.g. noise) than sinusoid carrier signals because of the broadband stimulation of the cochlea (Picton et al., 2003). For modulation rates below 40 Hz, response properties were found to depend only

weakly on the bandwidth of the carrier signal (Wang et al., 2011). However, more research is needed in this modulation range.

Stimulus modulation depth

ASSR amplitudes are influenced by the modulation depth of the stimulus. For AM, the modulation depth is defined as the ratio of the difference between the maximum and minimum amplitudes of the signal to the sum of the maximum and minimum amplitudes. The modulation depth can thus be varied between 0 (no modulation) and 100% (amplitude variation from zero to maximum amplitude). A higher modulation depth thus produces larger fluctuations in the stimulus envelope. The modulation depth has a direct influence on the frequency spectrum of the stimulus. By increasing the modulation depth, the spectral energy at the carrier frequency remains unchanged whereas the energy at the sidebands increases. Analogous, ASSR amplitudes increase linearly with an increase in modulation depth (Picton et al., 2003; Picton, 2011).

Stimulus intensity

The intensity of a stimulus refers to the Root-Mean-Square (RMS) level of the stimulus and is specified on a decibel (dB) scale. The stimulus intensity has a direct influence on the amplitude and phase of the ASSR. Increasing stimulus intensity increases the ASSR amplitude. This relation between stimulus intensity and ASSR amplitude is linear but may be steeper for intensities above 60 dB SPL (Picton et al., 2007). ASSR amplitudes however saturate at high intensity levels (~100 dB SPL) (Picton et al., 2003). Other factors influencing the relation between stimulus intensity and ASSR amplitude are stimulus type, modulation rate, carrier frequency and hearing impairment.

1.5.6. ASSR generation

As previously described, ASSRs generators vary for different modulation rates (see 1.4.2). Beside neuroimaging methods, evidence for different generators comes from the neurophysiological characteristics of the human auditory system in response to ASSRs across a large frequency range.

1.5.6.1. Physiological model

As previously described in 1.5.2 and depicted in Figure 1.6, modulated signals contain energy related to the carrier signal, but do not hold energy at the modulation frequency. The recorded response at the modulation frequency is achieved by the physiology of the human auditory system. In Figure 1.10, a schematic model for physiological transduction of an amplitude modulated signal is shown.

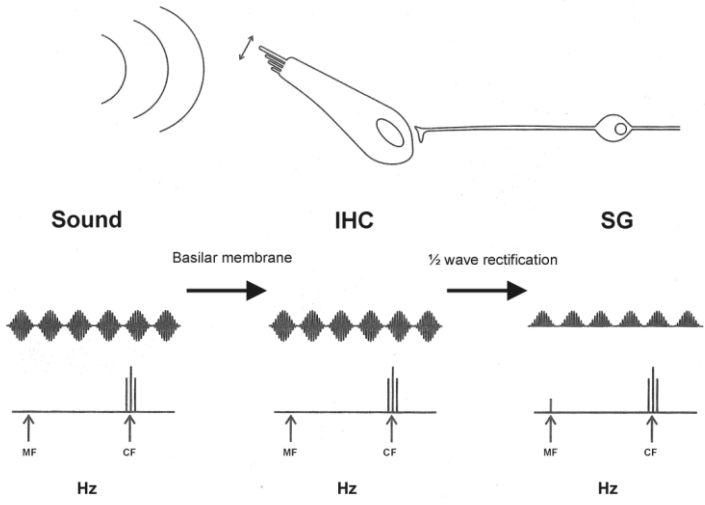


Figure 1.10 Transduction of an amplitude modulated signal into auditory nerve impulses rhythmically firing at the modulation rate. CF: Carrier frequency, MF: modulation frequency, IHC: inner hair cells, SG: spiral ganglion. From Rance (2008).

In the cochlea, the carrier frequency of a modulated sound activates a certain region of the tonotopically organized basilar membrane. This activation causes a group of hair cells to bend at the rhythm of the modulation, which in turn causes a change in the hair cell membrane potentials. At this level, compression occurs as the stimulus intensity increases. Hair cell transduction is larger when hair cells bend away from the basal body (depolarization) than when they bend towards it (hyperpolarisation). The inner hair cells then activate the ganglion cells that compose the auditory nerve. In the ganglion cells a complete rectification occurs as action potentials are only transmitted by depolarization of the inner hair cells. This results in a rhythmic

neurotransmitter release at the modulation rate and initiates a neurophysiological response at the modulation rate. Although the information of the carrier frequency itself is also transmitted to the auditory nerve, it is declined early in the auditory system as a result of the limited phase-locked firing capability of the auditory nerve fibers above 1000 Hz (Batra et al., 1986).

1.5.6.2. Neural ASSR generators

Neuroimaging studies indicate that as one ascends the auditory pathway from auditory nerve to the cortex, neurons become progressively less sensitive in following high modulation rates. Neurophysiological source estimates depart from the principle that scalp-recorded ASSRs represent the summed activity across all levels along the ascending auditory system, but that the recorded response reflects the activity of one or more dominant sources (Rance, 2008). Based on the recorded response characteristics, possible underlying sources can be estimated. Although the relation between modulation rate and ASSR generation should be regarded as a continuum, ASSRs are often categorized into three frequency ranges based on their underlying sources and response physiology.

ASSRs in the 80 Hz regions

Similar to neuroimaging studies, evidence exists that neurophysiological 80 Hz ASSRs are dominated by neurons in the auditory brainstem. Based on the superimposition theory and EEG studies investigating 80 Hz ASSR latencies, it was suggested that 80 Hz ASSRs result from the superimposition of auditory brainstem responses, predominantly ABR wave V, generated in the inferior colliculus (e.g. John & Picton, 2000a; Lins et al., 1995). Alternatively, a MEG study found a latency of 26 ms for the 80 Hz ASSR suggesting that this ASSR is related to a superimposition of the transient Na – Pa waves, with latencies of 20 and 30 ms respectively (Ross et al., 2000). Given that MEG is relatively insensitive in recording sources with a radial orientation and sources that are deeply located in the brain, it is possible that the reported latency values near 10 ms are the sum of the brainstem and cortical sources, whereas reported latencies near 25 ms are more strongly dominated by a (weak) cortical 80 Hz ASSR source. This was indeed confirmed by Herdman et al. (2002) that demonstrated a dominant brainstem source as well as a (weak) cortical source. Yet, the finding that 80 Hz ASSRs are not

influenced by sleep or anaesthesia (Aoyagi et al., 1993; Cohen et al., 1991) argues indirectly for minimal cortical contribution in the generation of this response.

ASSRs in the 40 Hz region

Compared to 80 Hz, the neural origin the 40 Hz modulations has been thought to be located at both the subcortical and cortical level in the auditory system (Ross et al., 2000; Herdman et al., 2002; Kuwada et al., 2002; Picton et al., 2003; Purcell et al., 2004; Bohorquez & Ozdamar, 2008). EEG studies reported latencies around 25 ms (Rickards & Clarck, 1984; Purcell et al., 2004), whereas with MEG latencies of 48 ms were found for 40 Hz ASSRs (Ross et al., 2000), suggesting overlapping fields from lower and higher order generators (Herdman et al., 2002). Indeed, studies found evidence that scalp-recorded 40 Hz ASSRs are the result of a periodic superimposition of MLRs recorded at a repetition rate of 40 Hz (e.g. Galambos et al., 1981; Gutschalk et al., 1999; Pantev et al., 1993; Stapells et al., 1988) or from a combination of wave V of the brainstem response, as well as MLRs such as the Pb wave (e.g. Bohorquez & Ozdamar, 2008; Ozdamar et al., 2007). The fact that 40 Hz ASSR amplitudes are reduced in amplitude during sleep and anaesthesia (Cohen et al., 1991; Picton et al., 1987b; Lins & Picton, 1995; Picton et al., 2003), favours at least some cortical contribution.

ASSRs below 25 Hz

Less is known about the exact neural sources of ASSRs to low-frequency modulations (below 25 Hz). MEG studies showed combined activation of both brainstem and cortical sources (Herdman et al., 2002). Purcell et al. (2004) confirmed that the brainstem still contributes at lower modulation frequencies, but with a main source of the lower frequency ASSR in the auditory cortex. Additionally they showed that responses to a 10 Hz modulation frequency are also generated in the auditory cortex. Furthermore, a limited number of latency studies have reported apparent latencies between 75 and 180 ms for modulation frequencies lower than 25 Hz, indicating predominantly primary and/or secondary auditory cortical generators (Rickards & Clarck, 1984; Rees et al., 1986; Stapells et al., 1987; Alaerts et al., 2009). These latencies are likely related to the latency of the P1-P2 waves of the transient response. Low-frequency ASSRs are known to be influenced by sleep and anaesthesia (Picton et al., 2003; Picton et al., 1987b), indicating a strong influence of cortical generators in this response.

1.6. Research objectives

The aim of this doctoral research project was to elucidate the auditory temporal processing deficit in dyslexia with electrophysiological as well as with psychophysical measures. In order to understand the causal influence of the auditory temporal processing deficit on reading and spelling, studies that examine the neural origin of auditory temporal processing problems are necessary. Finding an underlying neural cause for dyslexia, may have important implications for the detection and intervention of dyslexia. Given that the diagnosis of dyslexia is currently only provided after children demonstrate severe and persistent reading difficulties, the discovery of an objective neural marker for dyslexia may allow the detection of dyslexia, already before these children learn to read. This early detection inherently implies that auditory perception skills can be trained before children go to school and hence prevent that children are delayed in their reading and spelling development. Nonetheless, the auditory temporal processing deficit theory lacks evidence as to which auditory temporal cues are most sensitive to discriminate between normal-reading and dyslexic children and how these cues relate to speech perception and phonological processing.

The present doctoral project aims to elaborate on both of these topics. The ***first objective*** of this project was to determine an objective electrophysiological marker for the auditory temporal processing deficit in dyslexia by means of ASSRs. Moreover, we aimed to approach this objective from three points of view. First, given the importance of phonemic- and syllabic-rate modulations in speech perception (1.3.1), we aimed to explore neural phase-locking to these modulation rates in adults with dyslexia. Additionally, we intended to answer the question as to whether neural phonemic- and syllabic-rate phase-locking relates to psychophysical measures of speech perception and phonological awareness. Second, because of the evidence for different hemispheric sensitivity to phonemic- and syllabic-rate modulations (1.4.2), we aimed to systematically elucidate whether phonemic- and syllabic-rate ASSRs demonstrated a similar asymmetrical response pattern. Because of the complex nature of the human auditory system and the limited spatial resolution of ASSR measurements, asymmetry can be assessed by comparing responses evoked by stimuli presented to the left ear, to the right ear and simultaneously to both ears. Third, we aimed to investigate whether functional processing of phonemic- and syllabic-rate modulations in the brain can be associated with structural white matter pathways, connecting important auditory regions to the language network in the brain. If an auditory temporal processing deficit underlies

speech perception and phonological processing problems, reduced functional synchrony may relate to the structural measures underlying information transfer, i.e. white matter density.

The ***second objective*** of this project was to determine the nature of the auditory temporal processing deficit and its relation to speech perception, phonological awareness and reading in 12-year old children with dyslexia. Previous studies investigated auditory temporal processing and speech perception skills with a variety of stimuli, tasks and participant samples. Yet, this experimental diversity makes the comparison between studies difficult. Therefore, we aim to investigate auditory temporal sensitivity to the two most appropriate behavioural tests based on former studies (FM and onset time) (e.g. Boets et al., 2007; Goswami et al., 2002), in the same task and in the same participants and relate performance on these tasks to measures of speech perception, phonological awareness and reading.

1.7. Thesis outline

After this general introduction, this doctoral thesis consists of five chapters describing the results of the studies we performed as well as a general discussion of these results.

In **Chapter 2**, a study investigating electrophysiological AM sensitivity in adults with and without dyslexia is reported. ASSRs to phonemic- and syllabic-rate modulations were recorded in 30 normal-reading and 30 dyslexic adults. Besides measures of response-strength and phase coherence, ASSRs were related to psychophysical measures of speech-in-noise perception and phonological awareness. The material presented in this chapter has been published in Poelmans et al. (2012a).

Chapter 3 investigates the hypothesis of hemispheric lateralization of phonemic- and syllabic-rate modulations in a group of normal-reading adults. Because the results presented in Chapter 2 were based on monaural right ear stimulus presentation and literature reports an increasing amount of evidence for different hemispheric sensitivity to phonemic- and syllabic-rate modulations, this study systematically explored the influence of stimulation side on ipsilateral or contralateral recorded ASSRs. That is, ASSRs to phonemic- and syllabic-rate AM were recorded in normal-hearing adults to left ear, right ear or diotic stimulus presentation. This chapter is under second revision for publication (Poelmans et al., 2012b).

In **Chapter 4**, the relation between neural synchrony during auditory temporal processing and structural white matter integrity in important language-related structures was investigated in normal-reading and dyslexic adults. To examine whether functional neural synchrony operates on structural white matters pathways, coherence measures from Chapter 2 were associated with DTI data, recorded in the same participants. Based on these two neurological approaches, a combined structural and functional model for dyslexia is discussed. The material presented in this chapter is submitted as a joint first-author publication (Vandermosten et al., 2012b).

Chapter 5 presents evidence for a psychophysical auditory temporal processing deficit in a group of sixth grade children with dyslexia, measured with two different kinds of stimuli. Additionally, speech-in-noise perception abilities and their relation to phonological processing and reading ability were explored. The material presented in this chapter has been published in Poelmans et al. (2011).

In **Chapter 6**, these findings are discussed in the larger framework of dyslexia and future research directions are presented.

Chapter 2
Auditory steady-state responses as a neural correlate for temporal processing in adults with dyslexia

The content of this chapter has been published as: Poelmans, H., Luts, H., Vandermosten, M., Boets, B., Ghesquière, P., Wouters, J. (2012). Auditory steady state cortical responses indicate deviant phonemic-rate processing in adults with dyslexia. Ear and Hearing, 33 (1), 134-143.

Abstract

Speech intelligibility is strongly influenced by the ability to process temporal modulations. It is hypothesized that in dyslexia, deficient processing of rapidly-changing auditory information underlies a deficient development of phonological representations, causing reading and spelling problems. Low-frequency modulations between 4 and 20 Hz correspond to the processing rate of important phonological segments (syllables and phonemes respectively) in speech and therefore provide a bridge between low-level auditory and phonological processing. In the present study, temporal modulation processing was investigated by auditory steady state responses (ASSRs) in normal-reading and dyslexic adults. Multichannel ASSRs were recorded in normal-reading and dyslexic adults in response to speech-weighted noise stimuli amplitude modulated at 80, 20 and 4 Hz. The 80 Hz modulation is known to be primarily generated by the brainstem, whereas the 20 Hz and 4 Hz modulations are mainly generated in the cortex. Furthermore, the 20 and 4 Hz modulations provide an objective auditory performance measure related to phonemic-rate and syllabic-rate processing. In addition to neurophysiological measures, psychophysical tests of speech-in-noise perception and phonological awareness were assessed. Based on response-strength and phase coherence measures, normal-reading and dyslexic participants showed similar processing at the brainstem level. At the cortical level of the auditory system, dyslexic subjects demonstrated deviant phonemic-rate responses compared to normal readers, whereas no group differences were found for the syllabic-rate. Furthermore, a relation between phonemic-rate ASSRs and psychophysical tests of speech-in-noise perception and phonological awareness was obtained. These results suggest reduced cortical processing for phonemic-rate modulations in dyslexic adults, presumably resulting in limited integration of temporal information in the dorsal phonological pathway.

2.1. Introduction

Developmental dyslexia refers to a neurological disorder that manifests as a failure to acquire adequate reading and spelling skills despite normal intelligence, education and intense remedial effort and is thought to affect 5 to 10% of children (Vellutino et al., 2004). Until now, the exact origin of this disorder remains largely unknown. One theory suggests that the reading and writing problems in dyslexia are caused by a deficit in the development and the use of phonological representations, i.e., the abstract representation of speech sounds (e.g., Snowling, 2000; but see Ramus & Szenkovits, 2008). Prior to reading, phonological representations consist mainly at the syllable level, and it is only when learning to read that phoneme awareness emerges and explicit phoneme representations develop. Consequently, accurate syllable-level skills are necessary to allow stable phoneme-level representations (Ziegler & Goswami, 2005; e.g., Anthony et al., 2003). Yet, phonological awareness depends strongly on auditory perception skills (McBride-Chang, 1996). Within this context, it has been hypothesized that a fundamental deficit in low-level auditory temporal processing underlies the reading and spelling problems in dyslexia (e.g., Tallal, 1980; for a review, Farmer & Klein, 1995). Reduced sensitivity to "temporal", i.e., brief and dynamically changing, acoustic cues, the building blocks of spoken language, may result in less specified phonological representations, which in turn leads to a deficiency in reading and spelling skills (McBride-Chang, 1996).

Adequate temporal processing is one of the most important factors for speech intelligibility. It has been shown that adult listeners are able to accurately perceive speech with only limited spectral information (Shannon et al., 1995). The presence of temporal envelope cues, however, is crucial for speech perception. In continuous speech, the temporal envelope is characterized by multiple rates of amplitude modulations (AM), ranging from 2 to 50 Hz (Rosen, 1992). Particularly slower AM rates, between about 4 and 20 Hz, are important for segmenting speech into smaller units (Shannon et al., 1995; Drullman et al., 1994). Speech segmentation at the lower end of this AM range (near 4 Hz) has been found to be important for syllable-level information processing, whereas speech segmentation at the higher end of this range (near 20 Hz) provides important phoneme-level information (e.g., formant transitions in stop consonants) (Pöppel, 2003).

Several psychophysical studies have investigated AM processing in individuals with dyslexia. In children with dyslexia, elevated AM detection thresholds were observed for modulation frequencies between 4 and 1024 Hz, with the largest discrepancy

near 4 Hz, corresponding to the syllabic-rate of speech (Lorenzi et al., 2000; Rocheron et al., 2002). In adults with dyslexia, elevated AM detection thresholds were found over a wide range of modulation frequencies between 10 and 320 Hz, indicating AM processing difficulties for phonemic-rate modulation frequencies and for higher modulation frequencies which are less important for speech envelope processing (McAnally et al., 1997; Menell et al., 1999). However, contradicting results were found for AM at the lower end of the speech envelope modulations. Witton et al. (2002) found elevated 20 Hz AM detection thresholds in dyslexic adults, but observed comparable 2 Hz AM thresholds between both groups. Stuart et al. (2006) on the other hand, found elevated AM detection thresholds in dyslexic adults in the slow AM range at 1 Hz, but not at 100 Hz.

At the neurophysiological level, less is known about the nature of the temporal processing deficit in dyslexia. Temporal information is coded via neural oscillations that phase-lock to the rhythm of the modulation (Buzsaki & Draguhn, 2004). The ability of the neural system to align temporally to the temporal modulations of the speech envelope, reflected by the phase-locking strength, has been shown to be related to speech comprehension (Ahissar et al., 2001; Luo & Pöppel, 2007). Congruent with psychophysical results, smaller amplitude modulation following responses (AMFR) were observed for AM rates between 10 and 160 Hz, corresponding to phonemic-rate modulations and higher, in dyslexic compared to normal-reading adults (McAnally & Stein, 1997; Menell et al., 1999). Additionally, Abrams et al. (2009) demonstrated a lack of right-hemisphere dominance in temporal brain regions for processing syllabic-rate speech envelope fluctuations in children with dyslexia. Moreover, cortical measures of speech envelope processing predicted up to 41% of the variability in reading scores and 50% of phonological awareness, indicating a strong relation between speech envelope processing and reading ability (Abrams et al., 2009). However, not only is the degree of phase-locking important for temporal information processing, also the transmission of the temporal information throughout the auditory system contributes largely to how the temporal envelope of speech is processed. It has been suggested that phase synchronization across spatially distinct brain regions is an important neuronal communication mechanism by dynamically linking neurons into functional networks, which process task-relevant information (Womelsdorf et al., 2007). Phase coherence therefore provides crucial information about functional connectivity in the brain. Reading disability has been related to deviances in phase coherence. Studies found decreased EEG coherences at several EEG bands during rest (Marosi et al., 1995; Shiota et al., 2000; Barry et al., 2009) or during a visuo-spatial attention task

(Dhar et al., 2010) in individuals with a reading disability (not necessarily dyslexia). However, phase coherence has never been investigated in the auditory domain in a dyslexic population.

In the present study, electrophysiological correlates of AM processing were investigated in a group of normal-reading and dyslexic adults by means of auditory steady state responses (ASSRs). The ASSR is a neurophysiological oscillatory activity, which is typically evoked by amplitude or frequency modulated signals. ASSRs are phase-locked to exactly the same frequency as the modulation and provide an objective measure of the accuracy with which the auditory system processes variations in amplitude and/or frequency (Picton et al., 2003). Although the auditory stimulus activates the entire auditory system, from cochlea to cortex, the frequency of the modulation determines where in the auditory system the electrophysiological response is generated. For AM frequencies near 80 Hz, studies indicate a neural origin at the higher brainstem, whereas the neural origin of the 40 Hz ASSR has rather been located at both the subcortical and cortical level of the auditory system (John & Picton, 2000a; Picton et al., 2003; Bohorquez & Ozdamar, 2008). Less is known about the exact neural sources of ASSRs to low-frequency modulations (below 20 Hz). A limited number of ASSR studies reported predominantly primary and/or secondary auditory cortical generators for modulation frequencies lower than 25 Hz (Rickards & Clarck, 1984; Alaerts et al., 2009). Neuroimaging studies demonstrated that complex spectro-temporal signals like amplitude modulations (AM) and frequency modulations (FM) are processed in the bilateral dorsal superior temporal gyrus (STG) and superior temporal sulcus (STS) (Scott & Johnsrude, 2003). Yet, each hemisphere is specialized in analyzing at a different timescale (Pöppel, 2003): slow acoustic modulations between 3-7 Hz (150-300 ms) are hypothesized to be processed in the right auditory cortex, whereas the left auditory cortex is thought to be functionally more sensitive to auditory temporal signals between 12-50 Hz (20-80 ms). Because accurate AM detection is an essential requisite for precise speech processing, ASSRs to low modulation frequencies may be related to speech perception skills. Studies have shown that ASSRs to modulated tones or noises relate to word recognition scores in adults (Dimitrijevic et al., 2004; Alaerts et al., 2009).

The aim of the present study was to investigate AM processing objectively with multichannel ASSRs in normal-reading and dyslexic adults. By comparing ASSRs to modulation frequencies of 80, 20, and 4 Hz, we aimed to infer whether adults with dyslexia demonstrate AM processing difficulties for all modulation frequencies

or whether difficulties are limited to phonemic-rate (20 Hz) and/or syllabic-rate processing (4 Hz). Based on findings that phonemic-rate sensitivity builds upon syllabic-rate sensitivity (Ziegler & Goswami, 2005), we expected deviant responses at both modulation frequencies in adults with dyslexia. Additionally, the neural system of adults with and without dyslexia will be evaluated in terms of its efficiency to follow the periodicity of these modulations (i.e., response-strength), as well as its ability to functionally connect distant brain regions to process temporal information (i.e., phase coherence). Finally, psychophysical measures of speech-in-noise intelligibility and measures of phonological awareness were administered to examine their relationship with the ASSR measures of neural processing of temporal modulations.

2.2. Methods

2.2.1. Participants

In this study, 30 normal-reading and 30 dyslexic adults participated (Table 2.1). Participants were required to have adequate nonverbal intelligence, defined by a standard score above 85 on the Matrices subtest of the "Wechsler Adult Intelligence Scale" (WAIS-III: Wechsler, 1992). They were all native Dutch speakers, without a history of brain damage, language problems, psychiatric symptoms, visual problems or hearing loss. All participants were right-handed, assessed by the Edinburgh Handedness Inventory, and were required to have sufficiently good audiometric pure-tone hearing thresholds (i.e., 25 dB HL or less from 0.25-8.0 kHz) at the right ear. Participant groups were differentiated based on their history of reading problems and their current reading performance. Participants in the dyslexic group were required: (*i*) to have a formal diagnosis of developmental dyslexia assessed by a qualified psychologist and (*ii*) to demonstrate persistent adulthood reading difficulties by scoring below percentile 5 of a university norm group (Depessemier & Andries, 2009) on both a standardized word-reading (Brus & Voeten, 1973) and a pseudoword-reading test (Van den Bos et al., 1994). Participants of the normal-reading group on the other hand: (*i*) reported no history of reading difficulties; and (*ii*) scored above percentile 5 of the university norm group at the same standardized word-reading and pseudoword-reading tests. The normal-reading group thus covered the entire range of reading abilities, in the absence of dyslexia. All tests were approved by the Committee of Medical Ethics of Clinical Research of KU Leuven. All participants gave written informed consent.

Table 2.1 Participant characteristics (M ± SD)

	Normal-reading (*N* = 30)	Dyslexic (*N* = 30)
Gender (f/m)	20/10	22/8
Age (years)	21.4 ± 2.7	21.5 ± 2.7
Non-verbal IQ[a]	106 ± 10	108 ± 13
Word-reading[b]	101 ± 9	63 ± 10***
Pseudoword-reading[b]	63 ± 10	32 ± 5***
Spelling[a]	103 ± 10	72 ± 9***

[a]Standardized scores with population average (M = 100, SD = 15)
[b]Raw scores (words/min)
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

2.2.2. Psychophysical measures

Stimuli of all psychophysical tasks were presented to the right ear with Sennheiser HDA 200 headphones. Phonological awareness was assessed by a phoneme deletion and a spoonerisms task at 70 dB SPL. In the phoneme deletion task single spoken pseudowords were presented followed by a phoneme. Subjects had to identify the word that remained when that phoneme was omitted from the original word. In the spoonerisms task, two (pseudo)words were presented. Subjects were asked to exchange the two initial letters of both words. Performance of both tasks was assessed by the average response time (in milliseconds) of the correct answers. Response times of both tests were converted to z scores. The average of z scores of both tests for the whole group (N=60) was calculated as a composite score for phonological awareness. Note that higher composite scores represent inferior phonological awareness performance.

Speech-in-noise intelligibility was assessed for phonemes and sentences. In both tests, the level of the background noise was fixed at 70 dB SPL, whereas the speech level was varied. Speech and noises were presented with headphones to the right ear. The speech-in-noise test for phonemes consisted of CVC words presented in noise. The CVC words were obtained from Flemish recordings of the NVA list, consisting of 15 sublists of 33 target phonemes spoken by a male speaker (Wouters et al., 1994). The stationary NVA speech-weighted noise was used as masking noise. The percentage of correct perceived phonemes was measured for SNRs of -12, -9 and -6

dB. For every SNR two lists were administered and performance over both lists was averaged for each SNR. The Speech-Reception-Threshold (SRT) was obtained from a non-linear regression fit to a logistic function of the performance of each individual subject. In the speech-in-noise test for sentences, LIST-sentences (spoken by a female speaker) were presented in a stationary speech-weighted noise (van Wieringen & Wouters, 2008). To each subject, two lists of 10 sentences were presented. The SRT was determined adaptively by a one-up, one-down paradigm with a step size of 2 dB. A response was considered correct if all the key words of the sentence were repeated correctly. The SNRs of the last six sentences were averaged to compute the SRT and the SRTs of two subsequent tests were averaged to compute a mean SRT (van Wieringen & Wouters, 2008).

2.2.3. ASSR stimulus parameters

In this study, continuous amplitude modulated speech-weighted noise stimuli were created. The noise carriers were identical to the LIST noise (van Wieringen & Wouters, 2008). Noises were 100% amplitude modulated at adjusted modulation frequencies near 4, 20 and 80 Hz (exact frequencies: 3.91, 19.53 and 80.08 Hz respectively). The modulation frequencies of 4 and 20 Hz were selected because of their importance in speech intelligibility (Shannon et al., 1995), representing the syllable and phoneme rate respectively. Furthermore, they represent processing at the level of the cortex. The 80 Hz modulation frequency was selected as a reference condition, to investigate higher modulation frequencies that are less important for speech envelope processing. This modulation frequency also gives information about the integrity of processing at the level of the brainstem (e.g., John & Picton, 2000a; Herdman et al., 2002; Picton et al., 2003). Stimuli were generated in Matlab R14. In the experiment, all stimuli were presented with ER-3A insert phones, monaurally to the right ear at 70 dB SPL.

2.2.4. ASSR recording parameters

The continuous EEG was recorded by 10 surface Ag/AgCl electrodes on the scalp. Recording electrodes were placed in accordance with the international 10-20 system for electrode placement (Malmivuo & Plonsey, 1995), at (*1*) Oz, (*2*) P4, (*3*) P3, (*4*) F4, (*5*) F3, (*6*) M2, i.e., right mastoid (ipsilateral to acoustic stimulation), (*7*) M1,

i.e., left mastoid (contralateral to acoustic stimulation), (*8*) Fpz, with a reference electrode placed at Cz and ground electrode at the right clavicle. Inter-electrode impedances were kept below 5 kOhm at 30 Hz. The electrodes were connected to a low-noise Jaeger-Toennies multichannel amplifier. Each EEG channel was amplified with a gain of 50000 and band-pass filtered between 0.2 and 100 Hz (6 dB/octave), 2 and 100 Hz (6 dB/octave) and 20 and 300 Hz (6 dB/octave), for the 4, 20 and 80 Hz modulation frequencies respectively. Because the ASSR is a frequency-specific response, these filter settings only served to minimize the number of artifacts in the EEG. The amplified EEG signals were recorded and stimuli were presented by a RME Hammerfall DSP Multiface multichannel soundcard in combination with the experimental Setup ORL for Multichannel ASSR (SOMA) (Van Dun et al., 2008) at a sampling rate of 32 kHz and downsampled to 1 kHz. The continuous EEG was recorded in epochs. Each epoch consisted of 1024 samples (corresponding to 1.024 seconds). Sixteen successive epochs were clustered into a sweep. Online artifact rejection was set to 100 µV, to exclude muscle artifacts. For each stimulus, 18 artifact-free sweeps were recorded. EEG recordings were carried out in a double-walled and soundproof booth with a Faraday cage. Participants were asked to lie down on a bed and to watch a soundless movie to stay alert. Two ASSR recordings were carried out for each stimulus within the same session.

2.2.5. ASSR data analysis

Data analyses were performed by means of Matlab R14. Recorded data was divided in epochs. Ten percent of the epochs, i.e., those with the largest noise values, in each recording were rejected to exclude muscle artifacts. Sweeps were constructed by clustering 16 consecutive epochs. For each recording, the remaining 16 sweeps of EEG were weighted-averaged in the time domain and transformed into the frequency domain using a Fast Fourier Transform (FFT). The signal-to-noise ratio (SNR), as a measure of response-strength, was calculated by the log-transformation of the ratio between the response power at the tested modulation frequency and the power estimate of 40 neighbouring frequency bins on each side of the response-frequency bin (corresponding to approximately 2.44 Hz to the left and right side of the modulation frequency). A response was considered significant when the F-ratio statistic showed a significant difference ($p < 0.05$) between the response-power and the mean noise-power (John & Picton, 2000a), corresponding to a response-SNR of 4.85 dB. In the analyses, the baseline level of the response-SNRs was placed at 0 dB

because this indicates that no response can be detected in the EEG noise. Negative response-SNRs were transformed to the baseline level of 0 dB. Including negative response-SNRs in the analyses would falsely give more weight to non-significant responses and would therefore give a too optimistic view on possible group differences. Furthermore, phase coherence was calculated according to the following formula:

$$C_{12}(f) = \frac{|W_{12}(f)|^2}{(W_{11}(f) \times W_{22}(f))}$$

Phase coherence is a correlation in the time domain between two signals, recorded simultaneously at different scalp electrodes at a given frequency or frequency band. The coherence at frequency f between signals 1 and 2 indicated as $C_{12}(f)$ is calculated as the squared magnitude of the cross-spectral density of the signal pair $W_{12}(f)$, normalized by dividing with the product of the power spectra of the two signals, respectively $W_{11}(f)$ and $W_{22}(f)$ (Nunez & Srinivasan, 2006). Coherence values range between zero and one. Low coherence indicates no synchronization between underlying brain regions, whereas high coherence indicates a high degree of synchronized neuronal activity.

2.2.6. Statistical analyses

Statistical analyses were performed with the software SPSS 16 (SPSS, 2007). For each stimulus, a test and retest were recorded. Because there were no significant differences in response-SNR between the test and retest (paired t-test, $|t| < 1.99$, $p > 0.05$ for all electrodes and modulation frequencies), both recordings were linked together and FFT statistics were carried out over the linked data, i.e., after 32 sweeps. This prolonged duration resulted in better averaging of the data and higher response-SNRs. Normality of the response-SNRs and coherences was tested by a Kolmogorov-Smirnov test separately for all groups, modulation frequencies and electrodes. The significance level was set at $p < 0.01$, to adjust for multiple comparisons. All response-SNRs and coherence values were normally distributed according to this criterion.

Table 2.2 Average response-Signal-to-Noise-Ratios (response-SNRs) and percentage of subjects with nonsignificant responses for frontal, mastoid and parietal electrodes for modulation frequencies of 80, 20 and 4 Hz

	response-SNR (dB)			**% nonsignificant responses**		
	frontal	**Mastoid**	**parietal**	**frontal**	**mastoid**	**parietal**
80 Hz	10	16	17	22%	3%	4%
20 Hz	9	18	15	21%	3%	8%
4 Hz	7	12	11	27%	6%	14%

Some electrode positions were more sensitive in recording responses than others were. For the three modulation frequencies the highest response-SNRs were found at mastoid (M1, M2), parietal (P3, P4) and occipital (Oz) electrodes, whereas the smallest responses were recorded at frontal electrodes (F3, F4, Fpz). Additionally, at these frontal electrodes it was more difficult to record significant responses as evidenced by the higher number of subjects with nonsignificant responses (Table 2.2). Nonsignificant responses only indicate that a response is statistically not present but do not provide any quantitative information. Therefore, response-SNRs and coherence values of parietal and mastoid electrodes seem to be the most reliable measures for neural processing at the three tested modulation frequencies. To allow the comparison of right and left hemisphere responses, the midline occipital electrode (Oz) was excluded from the analyses. Summarizing, in the statistical analyses we focused on lateral parietal (P3, P4) and mastoid (M1, M2) electrodes. For these electrodes, response-SNRs and intrahemispheric (right: P4M2; left: P3M1) and interhemispheric coherence (parietal: P3P4; mastoid: M1M2) were evaluated (Figure 2.1). Note that in these analyses both significant and nonsignificant response-SNRs were included to also account for the worst performances.

In this study, group differences were assessed by a series of repeated measures analyses of variance (RM-ANOVA). All statistical tests were two-tailed ($\alpha = 0.05$). Reported p-values from the RM-ANOVA were Greenhouse-Geisser corrected and post-hoc analyses were Bonferroni corrected for multiple comparisons. Pearson correlations were calculated to determine the relationship between ASSR measures and measures of phonological awareness and speech-in-noise intelligibility.

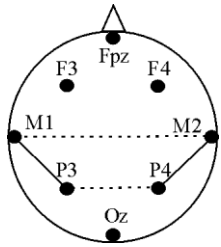


Figure 2.1 Schematic view of electrode positions and calculated coherence measures. Interhemispheric coherences are shown by dashed lines (M1M2, P3P4), intrahemispheric coherences are depicted in full lines (P4M2, P3M1).

2.3. Results

2.3.1. Response-strength

For the three tested modulation frequencies, a RM-ANOVA with factors Group (normal-reading vs. dyslexic), Laterality (right vs. left hemisphere) and Electrode (mastoid vs. parietal) was conducted.

For 80 Hz, no main effect of Electrode ($F(1,58) = 0.60$, $p = 0.440$, $\eta_p^2 = 0.01$), Group ($F(1,58) = 1.87$, $p = 0.177$, $\eta_p^2 = 0.03$) or any interaction with these factors (all $F < 0.41$, $p > 0.5$) was observed, suggesting no group difference in response-strength for the 80 Hz ASSR. Overall, a main effect of Laterality ($F(1,58) = 44.03$, $p < 0.001$, $\eta_p^2 = 0.43$) was found, demonstrating that ipsilateral right hemisphere responses were higher than contralateral left hemisphere responses (mean difference: 3.5 dB, SE: 0.5 dB) (Figure 2.2A). For 20 Hz, no main effect of Group ($F(1,58) = 2.35$, $p = 0.131$, $\eta_p^2 = 0.04$), but significant main effects of Laterality ($F(1,58) = 15.95$, $p < 0.001$, $\eta_p^2 = 0.22$) and Electrode ($F(1,58) = 56.48$, $p < 0.001$, $\eta_p^2 = 0.49$) were found. Additionally, a significant Laterality x Group ($F(1,58) = 4.36$, $p = 0.041$, $\eta_p^2 = 0.07$) interaction was observed. Post hoc analysis indicated that dyslexic adults had lower responses at left hemisphere electrodes than normal-reading adults (mean difference: 2.7 dB, SE: 1.3 dB, $t(58) = 2.04$, $p = 0.046$, $\eta_p^2 = 0.07$), whereas this group difference was not present for right hemisphere electrodes (mean difference: 1.1 dB, SE: 1.3 dB, $t(58) = 0.85$, $p = 0.397$, $\eta_p^2 = 0.01$) (Figure 2.2B). For 4 Hz, no main effect of Group ($F(1,58) = 0.77$, $p = 0.385$, $\eta_p^2 = 0.01$) or any interaction with this factor (all $F < 2.45$, $p > 0.1$) was found, suggesting no group differences for this modulation frequency (Figure 2.2C). Overall, a main effect of

Laterality ($F(1,58) = 12.43$, $p = 0.001$, $\eta_p^2 = 0.18$) and Electrode ($F(1,58) = 20.35$, $p < 0.001$; $\eta_p^2 = 0.26$), and a significant Laterality x Electrode interaction ($F(1,58) = 8.37$, $p = 0.005$; $\eta_p^2 = 0.13$) was found. At parietal electrodes, ipsilateral right hemisphere responses were higher than contralateral left hemisphere responses (mean difference: 2.0 dB, SE: 0.5 dB, $t(59) = 3.72$, $p < 0.001$, $\eta_p^2 = 0.19$), whereas this hemispheric difference was not present for mastoid electrodes (mean difference: 0.4 dB, SE: 0.3 dB, $t(59) = 1.23$, $p = 0.226$, $\eta_p^2 = 0.03$).

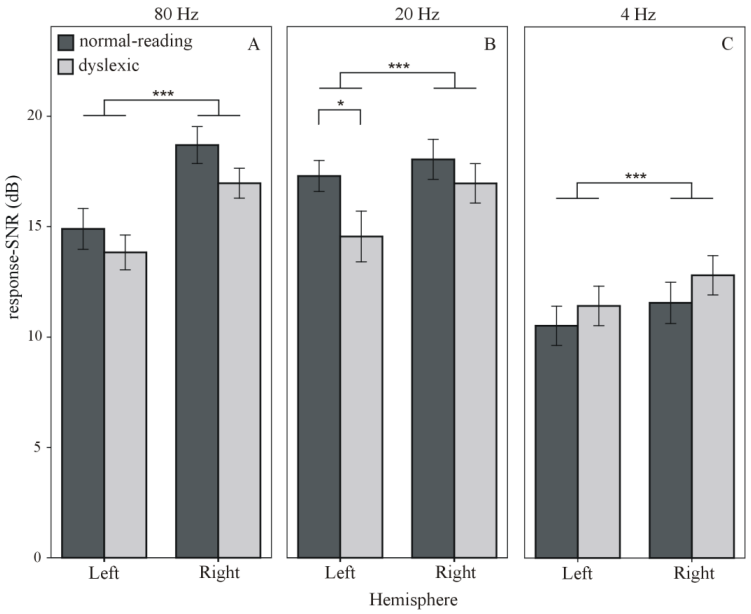


Figure 2.2 Average response-strengths for normal-reading (dark grey) and dyslexic (light grey) adults, averaged over mastoid and parietal electrodes, for three modulation frequencies. Bargraphs for (A) brainstem processing (80 Hz AM), (B) cortical phonemic-rate processing (20 Hz AM) and (C) cortical syllabic-rate processing (4 Hz AM). Bars represent the average response-SNRs for left and right hemisphere electrodes. Error bars indicate ± 1 SE. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$

2.3.2. Coherence

Interhemispheric coherence was analyzed by a RM-ANOVA with factors Group (normal-reading vs. dyslexic) and Position (mastoid (M1M2) vs. parietal (P3P4)).

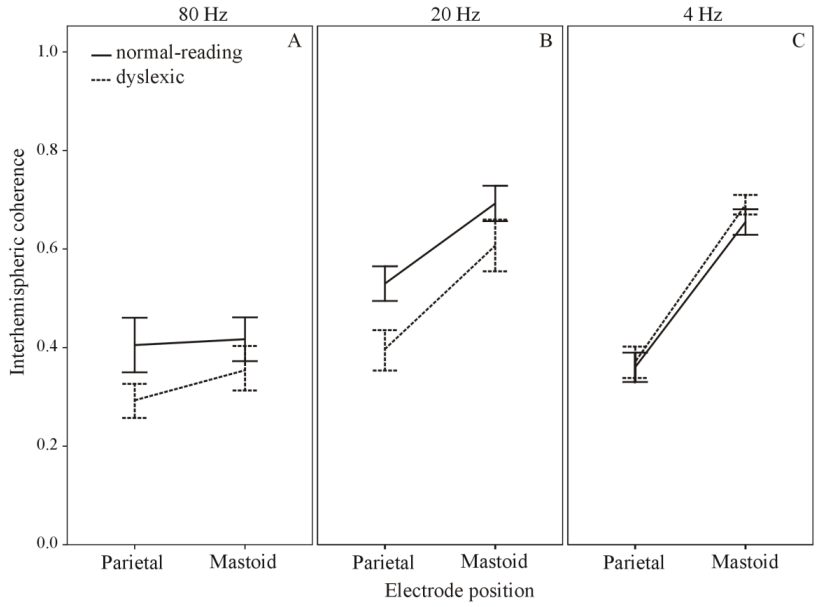


Figure 2.3 Interhemispheric phase coherence. Interhemispheric phase coherence for normal-reading (full lines) and dyslexic (dashed lines) adults for parietal and mastoid electrodes for (A) 80 Hz AM, (B) 20 Hz AM and (C) 4 Hz AM. Error bars indicate ± 1 SE.

For 80 Hz, no main effects of Group ($F(1,58) = 2.85$, $p = 0.097$, $\eta_p^2 = 0.05$) or Position ($F(1,58) = 1.01$, $p = 0.319$, $\eta_p^2 = 0.02$), nor a significant Group x Position interaction ($F(1,58) = 0.49$, $p = 0.486$, $\eta_p^2 = 0.01$) was found, indicating no group differences for the 80 Hz ASSR (Figure 2.3A). On the other hand for 20 Hz, a significant main effect of Group ($F(1,58) = 4.42$, $p = 0.040$, $\eta_p^2 = 0.07$), and Position ($F(1,58) = 52.03$, $p < 0.001$, $\eta_p^2 = 0.47$), but no significant Group x Position interaction ($F(1,58) = 0.87$, $p = 0.356$, $\eta_p^2 = 0.02$) was found. Overall, interhemispheric coherence at mastoid electrodes was larger than coherence at parietal electrodes (mean difference: 0.19, SE: 0.03). Additionally, normal-reading adults demonstrated higher interhemispheric coherence compared to adults with dyslexia (mean difference: 0.11, SE: 0.05) (Figure 2.3B). For 4 Hz, a main effect of Position ($F(1,58) = 310.24$, $p < 0.001$, $\eta_p^2 = 0.84$) was found. However, no main effect of Group ($F(1,58) = 0.43$, $p = 0.516$, $\eta_p^2 = 0.01$) nor a Group x Position interaction ($F(1,58) = 0.51$, $p = 0.480$, $\eta_p^2 = 0.01$) was found, indicating no group differences for the 4 Hz ASSR (Figure 2.3C). Overall, coherence at mastoid

electrodes was larger than coherence at parietal electrodes (mean difference: 0.31, SE: 0.02).

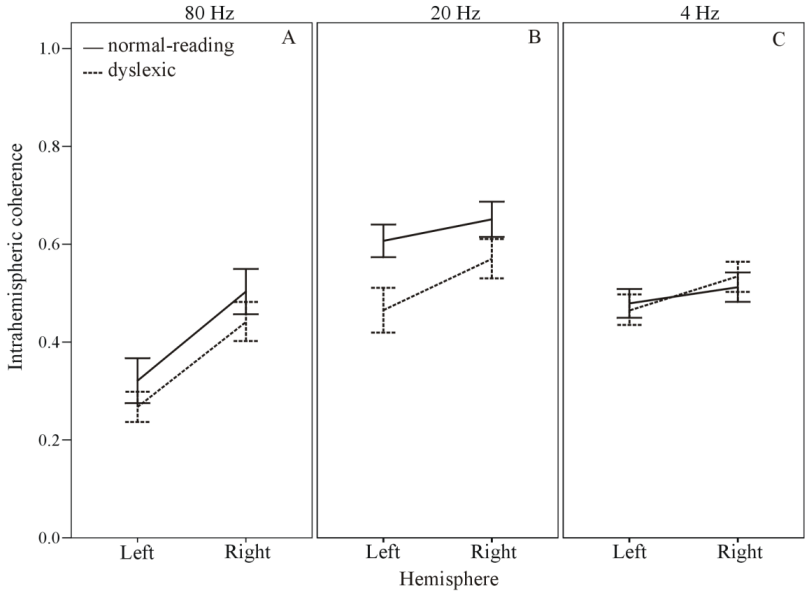


Figure 2.4 Intrahemispheric phase coherence. Intrahemispheric phase coherence for normal-reading (full lines) and dyslexic (dashed lines) adults for left and right hemisphere electrodes for (A) 80 Hz AM, (B) 20 Hz AM and (C) 4 Hz AM. Error bars indicate ± 1 SE.

Additionally, intrahemispheric coherence was analyzed by RM-ANOVA with the factors Group (normal-reading vs. dyslexic) and Laterality (right (P4M2) vs. left (P3M1) hemisphere). For 80 Hz, a main effect of Laterality was found ($F(1,58) = 39.50$, $p < 0.001$, $\eta_p^2 = 0.41$). No main effect of Group ($F(1,58) = 1.27$, $p = 0.265$, $\eta_p^2 = 0.02$), nor a Group x Laterality interaction was observed ($F(1,58) = 0.02$, $p = 0.893$, $\eta_p^2 < 0.01$), indicating no group differences for this modulation frequency (Figure 2.4A). In general, right hemisphere coherence was higher than left hemisphere coherence (mean difference: 0.18, SE: 0.03). For 20 Hz, a main effect of Group ($F(1,58) = 4.42$, $p = 0.040$, $\eta_p^2 = 0.07$) and Laterality ($F(1,58) = 20.91$, $p < 0.001$, $\eta_p^2 = 0.27$), but no Group x Laterality interaction $F(1,58) = 3.53$, $p = 0.065$, $\eta_p^2 = 0.06$) was found. Coherence in the right hemisphere was higher than coherence in the left hemisphere (mean difference: 0.08, SE: 0.02). Additionally, adults with dyslexia demonstrated lower intrahemispheric coherence than normal-reading adults (mean difference: 0.11, SE: 0.05) (Figure 2.4B). For 4 Hz, a main effect of

Laterality ($F(1,58) = 7.23$, $p = 0.009$, $\eta_p^2 = 0.11$) was observed. No main effect of Group ($F(1,58) = 0.01$, $p = 0.913$, $\eta_p^2 < 0.01$), nor a significant Group x Laterality interaction ($F(1,58) = 0.84$, $p = 0.364$, $\eta_p^2 = 0.01$) was found, indicating no group differences for this modulation frequency (Figure 2.4C). Overall, coherence in the right hemisphere was higher than coherence in the left hemisphere (mean difference: 0.05, SE: 0.02).

2.3.3. Correlations

Pearson correlations were calculated to examine relations between ASSR coherence and psychophysical measures of speech-in-noise intelligibility and phonological awareness (Table 2.3). Better phonological awareness skills related to higher coherence at 20 Hz but not at 4 Hz or 80 Hz. Furthermore, sentence speech-in-noise intelligibility correlated significantly with 4 Hz, but not with 20 Hz ASSR coherence. Additionally, phoneme-level speech-in-noise intelligibility correlated with ASSR coherence at 20 Hz but not with coherence at 4 Hz. For speech-in-noise perception, higher phonemic-rate coherence results in better phoneme-level speech-in-noise intelligibility, whereas higher syllabic-rate coherence results in better sentence-level speech-in-noise intelligibility. This was not the case for 80 Hz, where only right intrahemispheric coherence correlated with speech-in-noise perception for sentences. Comparable results were also obtained for correlations between response-SNRs and psychophysical measures for speech-in-noise intelligibility and phonological awareness. However, these correlations, especially those with phonological awareness, were smaller and often failed to reach significance.

Table 2.3 Whole-sample correlations between ASSR coherence at 80, 20 and 4 Hz, and phonological awareness (PA) and speech-in-noise intelligibility (SPIN)

	80 Hz				**20 Hz**				**4 Hz**			
	INTER		**INTRA**		**INTER**		**INTRA**		**INTER**		**INTRA**	
	P3P4	**M1M2**	**LH**	**RH**	**P3P4**	**M1M2**	**LH**	**RH**	**P3P4**	**M1M2**	**LH**	**RH**
PA[a]	-0.22	-0.06	-0.16	-0.16	**-0.36****	-0.18	**-0.33****	**-0.27***	0.13	0.22	0.10	0.02
SPIN[b] (phonemes)	0.07	-0.18	-0.01	0.01	**-0.36****	**-0.29***	**-0.38****	**-0.27***	0.06	0.13	-0.02	0.22
SPIN[b] (sentences)	-0.15	-0.15	-0.18	**-0.26***	0.09	-0.04	0.03	0.07	**-0.26***	-0.11	**-0.27***	-0.10

[a]Composite phonological awareness score of response times
[b]Speech-Reception-Threshold (SRT)
*$p < 0.05$; **$p < 0.01$

2.4. Discussion

Identifying the neural foundations of reading and spelling problems in dyslexia is an important aspect for early detection and appropriate intervention of children with this disability. It has been hypothesized that the literacy problems in dyslexia can be allocated to deviant mechanisms for auditory temporal modulation processing that are critical for accurate speech perception and subsequently also for precise development of phonological representations. The present study demonstrated with objective measures that adults with dyslexia have difficulties processing phonemic-rate modulations and that these difficulties are related to reduced speech perception and phonological skills. The present study recorded ASSRs in a population of adults with dyslexia. ASSRs provide an objective measure for auditory temporal modulation processing in that they are elicited automatically without cognitive demand, given that the subject is in a state of alertness (Picton et al., 2003). More importantly, the presentation of modulated steady state stimuli allows objective response detection in the EEG frequency spectrum, exactly at the presented modulation frequency. By comparing responses to several modulation frequencies, we were able to map phase-locking efficiency at important levels of the auditory system and at several modulation frequencies that are critical for phonological development.

Adults with dyslexia demonstrated normal temporal modulation processing for the 80 Hz amplitude modulation for response-strength, coherence and lateralization. A number of studies investigated the neural origin of this ASSR. As one ascends the auditory pathway from auditory nerve until the cortex, neurons become less sensitive in following high modulation rates (Picton et al., 2003). Magnetoencephalography (MEG) studies identified 80 Hz ASSR sources in the brainstem (Herdman et al., 2002). Additionally, EEG studies found latencies between 10-30 ms for the 80 Hz ASSR, corresponding to neural sources in the higher brainstem that may in part be accompanied with early cortical sources (e.g., John & Picton, 2000a; Picton et al., 2003). Yet, the finding that 80 Hz ASSRs are not influenced by sleep or anesthesia (Aoyagi et al., 1993; Cohen et al., 1991) argues indirectly for minimal cortical contribution in the generation of this response. The present results suggest that in adults with dyslexia sensitivity to those temporal modulations that are generated in the brainstem is normal. These results seem to contradict studies demonstrating deviant speech-evoked ABRs in children with reading disabilities (e.g., Wible et al., 2004; Banai et al., 2005; Wible et al., 2005; Banai et al., 2009; Hornickel et al., 2009; Hornickel et al., 2011). However, most

studies demonstrating the link between speech-evoked ABRs and reading abilities included a broad variety of language disorders other than dyslexia (e.g., poor readers, specific language disorder). As poor reading abilities can result from a variety of underlying cognitive and neurological problems, it would be incorrect to generalize findings of atypical speech-evoked ABRs to a specific population of individuals with dyslexia. Additionally, speech-evoked ABRs and ASSRs are evoked by distinct acoustic features. Whereas speech-evoked ABRs encode the onset/offset and the fine structure of an auditory signal (e.g., Skoe & Kraus, 2010), ASSRs follow the ongoing modulation envelope of the signal (e.g., Picton et al., 2003). Both measures are therefore rather complementary than contradictory.

Normal-reading adults and adults with dyslexia differed in their ability to phase-lock to the phonemic processing rate (20 Hz). This difference was observed in response-strengths as well as in intrahemispheric and interhemispheric coherence. Neurophysiologically, the strength of an ASSR depends on the phase-locking ability of neural populations to the temporal envelope of a stimulus. Decreased response-strengths could therefore result from either a reduced number of neurons that phase-lock to modulations or alternatively from asynchronicity of neuronal firing within a neural generator. On the other hand, reduced phase coherence between electrodes implies decreased or imprecise synchronization between distant neuronal ensembles, suggesting decreased information transfer between distant brain regions involved in the same process. Even though the present study cannot make conclusions about impairments at the neuronal level, it is reasonable to conclude that the observed 20 Hz results reflect a general neurological deviance in processing these speech envelope cues in adults with dyslexia. Decreased brain activity and reduced functional connectivity in dyslexia has previously been reported, however this has never been directly linked to speech envelope processing. During word and pseudoword reading tasks, a number of studies found decreased brain activity in individuals with dyslexia, especially in the left hemisphere (e.g., Shaywitz, 1998; Pugh et al., 2000). Additionally, Diffusion Tensor Imaging (DTI) studies have provided evidence for a decreased white matter integrity (i.e., less efficient neural communication) in the left temporo-parietal cortex in dyslexic individuals (Horwitz et al., 1998; Pugh et al., 2000), and more specifically in the left arcuate fasciculus (AF) and superior longitudinal fasciculus (SLF) (e.g., Klingberg et al., 2000; Rimrodt et al., 2010). Both white matter tracts are part of a left hemisphere dorsal pathway, responsible for mapping phonological representations onto articulatory representations. If the functional integrity of dorsal sound-to-articulation pathway in the left hemisphere indeed underlies the reading problems in dyslexia, it is possible

that this deficit stems from an earlier problem at the acoustic-phonological level, i.e., in the processing of the speech envelope. Moreover, to accurately map sounds to articulatory units, acoustic signals need to be clustered into phonological sound units.

Group differences were observed for the phonemic processing rate (20 Hz), but not for the syllabic-rate (4 Hz). Comparable to the present findings, previous studies demonstrated reduced AM sensitivity at the phonemic-rate (McAnally & Stein, 1997; Menell et al., 1999) but not at the syllabic-rate in adults with dyslexia (Witton et al., 2002). However, in children with dyslexia, both syllabic and phonemic-rate processing difficulties have been evidenced (Lorenzi et al., 2000; Abrams et al., 2009; Rocheron et al., 2002). These studies suggest that temporal processing difficulties in individuals with dyslexia occur at the same level of the individual's phonological development. Assuming that phonological awareness builds upon accurate encoding of spoken language, which in turn is influenced by the ability to phase-lock to temporal modulations, it is possible that sensitivity for specific modulations develops in a similar way as phonological development. Indeed, in the present study, phonological awareness related significantly to the 20 Hz ASSR and not to the 4 Hz ASSR. Additionally, ASSRs to 20 and 4 Hz AM related significantly to phoneme and sentence in noise perception respectively, indicating the link between sensitivity for these modulations and speech perception. If sensitivity to syllabic-rate and phonemic-rate modulations indeed relates to the grain size of phonological awareness, one may expect that children that later develop dyslexia demonstrate AM processing difficulties at the syllabic-rate prior to reading instruction, whereas phonemic-rate difficulties rather appear for experienced readers. However, this hypothesis has never been investigated directly. If a developmental syllabic-to-phonemic-rate shift truly exists, one may expect that in children a syllabic-rate deficiency will be more pronounced compared to adults. To clarify this hypothesis, studies investigating syllabic and phonemic-rate processing in children of different age groups are necessary. Moreover, to enlighten the development of these temporal modulations and to clarify their influence on literacy development, longitudinal studies including children at-risk for dyslexia are required.

The present results bring new light on the discussion as to whether an auditory temporal processing deficit, causing phonological and literacy problems, exists in dyslexia. Dyslexic adults seem to have a general neurological disability to process phonemic-rate modulations in speech, whereas syllabic-rate modulation processing

seems to be intact. Even though we cannot make conclusions about causality of phonemic-rate phase-locking and speech perception, phonological and literacy skills, we found evidence for a relation between these abilities. Further research in a population of children with dyslexia is necessary to unravel this causal relationship and to validate whether the hypothesized developmental shift from syllabic-rate to phonemic-rate sensitivity actually occurs.

Chapter 3
Auditory steady-state response asymmetry: the influence of stimulation side on response-strengths

The content of this chapter is in second revision for Journal of the Association for Research in Otolaryngology. Poelmans, H., Luts, H., Vandermosten, M., Ghesquière, P., Wouters, J. Hemispheric asymmetry of auditory steady-state responses to monaural and diotic stimulation.

Abstract
Hemispheric lateralization of speech perception has been under debate for many years. Originally, it was suggested that speech is lateralized to the left hemisphere. However, it becomes more clear that both hemispheres closely interact during speech perception. One theory hypothesizes that fast, phonemic-rate modulations of the speech envelope lateralize to the left hemisphere whereas right lateralization occurs for slow, syllabic-rate modulations.
In the present study, neural processing of phonemic- and syllabic-rate modulations was investigated with auditory steady-state responses (ASSRs). ASSRs to speech-weighted noise stimuli, amplitude modulated at 4, 20 and 80 Hz were recorded in 30 normal-hearing adults. The 80 Hz ASSR is primarily generated by the brainstem, whereas 20 and 4 Hz ASSRs are mainly cortically evoked and relate to phonemic- and syllabic- modulation rates of the speech envelope. Stimuli were presented diotically (same signal to both ears) and monaurally (one signal to the left or right ear). For 80 Hz, diotic ASSRs were larger than monaural responses. This binaural advantage decreased with decreasing modulation frequency. For 20 Hz, diotic ASSRs were equal to monaural responses while for 4 Hz diotic responses were smaller than monaural responses. Comparison of left and right ear stimulation demonstrated that with decreasing modulation rate a gradual change from ipsilateral to right lateralization occurred, with the strongest lateralization for the 4 Hz, syllabic-rate modulation. Together these results (*i*) suggest that ASSR enhancement to binaural stimulation decreases in the ascending auditory system and (*ii*) indicate that right lateralization is more prominent at low-frequency ASSRs, with the most pronounced lateralization for 4 Hz.

3.1. Introduction

Spoken language consists of a continuous stream of acoustic information. Temporal envelope information plays an important role for accurate speech intelligibility (Shannon et al., 1995). The temporal envelope of speech contains multiple rates of amplitude modulations (AM), ranging between 2-50 Hz (Rosen, 1992; Drullman et al., 1994). Particularly, modulations near 4 and 20 Hz are important because they comprise the syllabic- and phonemic-rate of speech (Pöppel, 2003).

The ability of the brain to detect these modulations can be assessed by auditory steady-state responses (ASSRs). ASSRs are oscillatory potentials that synchronize to the rate of a rhythmic auditory signal (Picton et al., 2003). Depending on the modulation frequency, ASSRs are generated at different levels of the auditory system. That is, ASSRs to 80-100 Hz modulations are primarily generated in the brainstem (John & Picton, 2000a), whereas ASSRs near 40 Hz have important cortical and subcortical sources (Herdman et al., 2002) and ASSRs below 25 Hz are thought to have cortical generators (Alaerts et al., 2009). Previous studies have shown that ASSRs relate to word recognition scores in adults (Alaerts et al., 2009; Dimitrijevic et al., 2001; Dimitrijevic et al., 2004). However, most studies focused on ASSRs in the 80 and 40 Hz frequency regions. Yet, ASSRs to lower frequencies may be more closely related to speech envelope processing and thus may provide important higher-level information about speech perception and central auditory functioning.

Indeed, recently evidence was found that syllabic-rate (4 Hz) ASSRs related to sentence-in-noise perception, whereas phonemic-rate (20 Hz) ASSRs related to phoneme-in-noise perception. Additionally, both modulation rates were found to be more prominently recorded over the right hemisphere (Poelmans et al., 2012a). Similarly, Ross et al. (2005) demonstrated a right hemispheric laterality for 40 Hz ASSRs. However, it is assumed that low-frequency modulations are processed asymmetrically in the brain (Pöppel et al., 2008; Goswami, 2011), with a right hemispheric preference for processing syllabic-rate modulations (~3-7 Hz) (Hämäläinen et al., 2012a; Millman et al., 2010; Abrams et al., 2008) and a bilateral (Hämäläinen et al., 2012a; Herdman et al., 2003) or left hemispheric (Johnsrude et al., 1997; Jamison et al., 2006; Belin et al., 1998) preference for phonemic-rate modulations (~12-50 Hz).

The present study aimed to systematically examine response-strengths and response asymmetry of phonemic- (20 Hz) and syllabic-rate (4 Hz) modulations with ASSRs.

As a control condition, 80 Hz ASSRs were included for two reasons. First, this modulation frequency is thought to be generated in the brainstem and therefore less affected by functional laterality (John & Picton, 2000a). Second, this modulation frequency is generally assessed in clinical measurements of hearing thresholds and may therefore provide important information to optimize recordings (e.g. Luts et al., 2006). In a within-subject design, we assessed the influence of monaural (one signal to the left or right ear) versus diotic (same signal to both ears) auditory input. Additionally, response asymmetry along the auditory pathway was investigated.

3.2. Methods

3.2.1. Participants

Thirty adults[1] participated (mean age: 22 years 3 months, SD: 2 years 1 month; 21 female participants) in the present study. All participants were native Dutch speakers, without a history of brain damage, language problems, psychiatric symptoms, visual problems or hearing loss. They were right-handed, assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), and were required to have normal audiometric pure-tone hearing thresholds (i.e., 25 dB HL or less for all octave frequencies from 0.25-8.0 kHz) at both ears.

3.2.2. Stimulus parameters

Continuous amplitude modulated speech-weighted noise stimuli were created. The noise carriers were derived from the speech-weighted masking noise of the "Leuven Intelligibility Sentence Test" (LIST) (van Wieringen & Wouters, 2008). This noise represents the long-term average speech spectrum of 730 sentences of a female speaker. Noises were 100% amplitude modulated at modulation frequencies near 4, 20 and 80 Hz. These modulation frequencies were adjusted to ensure an integer number of modulation cycles occurred within each data block of 1.024 s (i.e. epoch) (John & Picton, 2000b), resulting in exact modulation frequencies of 3.91 Hz, 19.53 Hz and 80.08 Hz respectively. For simplicity, these modulation frequencies will be further referred to as the rounded frequencies: 4, 20 and 80 Hz respectively. Stimuli were generated in Matlab R14 (The MathWorks Inc., 2005).

[1] Five of these participants also participated in the study presented in Chapter 2.

3.2.3. Experimental protocol

Stimuli were presented with Etymotic Research ER-3A insert earphones at 70 dB SPL, in three ways: (*i*) monaurally to the left ear (LE), (*ii*) monaurally to the right ear (RE), and (*iii*) bilaterally, diotic to both ears (BE). The EEG was recorded in a double-walled and soundproof booth with a Faraday cage. Participants were asked to lie down on a bed and to watch a soundless movie to stay alert. Two ASSR recordings were carried out for each stimulus within the same session.

3.2.4. ASSR recording parameters

The continuous EEG was recorded by 10 surface Ag/AgCl electrodes on the scalp, placed in accordance with the international 10-20 system for electrode placement (Malmivuo & Plonsey, 1995). EEG was recorded from two central electrodes, Oz[2] and Fpz, three left hemispheric electrodes, P3, F3 and M1 (left mastoid) and three corresponding right hemispheric electrodes, P4, F4 and M2 (right mastoid). The reference electrode was placed at Cz and the ground electrode at the right clavicle. Inter-electrode impedances were kept below 5 kOhm at 30 Hz. The electrodes were connected to a low-noise Jaeger-Toennies multichannel amplifier. Each EEG channel was amplified with a gain of 50000 and band-pass filtered between 0.2 Hz and 100 Hz (6 dB/octave), 2 Hz and 100 Hz (6 dB/octave) and 20 Hz and 300 Hz (6 dB/octave), for the 4 Hz, 20 Hz and 80 Hz modulation frequencies respectively. The amplified EEG signals were recorded and stimuli were presented by a RME Hammerfall DSP Multiface multichannel soundcard in combination with the experimental Setup ORL for Multichannel ASSR (SOMA) (Van Dun et al., 2008) at a sampling rate of 32 kHz and downsampled to 1 kHz. The continuous EEG was recorded in epochs. Each epoch consisted of 1024 samples (corresponding to 1.024 seconds). Sixteen successive artifact-free epochs were linked into a sweep (corresponding to 16.384 seconds). Online artifact rejection was set to 100 µV, to exclude muscle artifacts. For each stimulus, 18 sweeps were recorded.

[2] It is important to note that despite the lying position of the participant, electrode Oz did not measure higher noise levels than other electrodes. Artifact rejection criteria were thus equal for all electrodes.

3.2.5. ASSR data analysis

Data analyses were performed by means of Matlab R14 (The MathWorks Inc., 2005). Ten percent of the recorded epochs, i.e., those with the largest noise values, in each recording were rejected to exclude artifacts. Sweeps were reconstructed by linking 16 consecutive low-noise epochs. For each recording, the remaining 16 sweeps of EEG were weighted-averaged in the time domain and transformed into the frequency domain using a Fast Fourier Transform (FFT). The signal-to-noise ratio (SNR), as a measure of response-strength, was calculated by the log-transformation of the ratio between the response power at the stimulated modulation frequency and the power estimate of 40 neighbouring frequency bins on each side of the response-frequency bin (corresponding to approximately 2.44 Hz to the left and right side of the modulation frequency). A response was considered significant when the F-ratio statistic showed a significant difference ($p < 0.05$) between the response-power and the mean noise-power (John & Picton, 2000a), corresponding to a response-SNR of 4.85 dB. In the analyses, the baseline level of the response-SNRs was placed at 0 dB because this indicates that no response can be detected in the EEG noise. Negative response-SNRs were then transformed to the baseline level of 0 dB.

For the three modulation frequencies the highest response-SNRs were found at mastoid (M1, M2), parietal (P3, P4) and occipital (Oz) electrodes, whereas the smallest responses were recorded at frontal electrodes (F3, F4, Fpz). These frontal electrodes were less sensitive to record significant responses as evidenced by the higher number of participants with non-significant responses (Table 3.1) and were excluded for further analyses. Additionally, the midline occipital electrode (Oz) was excluded, to allow the comparison of right and left hemispheric responses. Response-SNRs of parietal and mastoid electrodes over the same hemisphere were averaged into a measure for right hemispheric (P4, M2) and a measure for left hemispheric (P3, M1) processing.

Table 3.1 Percentage of participants with non-significant responses for frontal, mastoid and parietal electrodes for modulation frequencies of 80 Hz, 20 Hz and 4 Hz and for diotic (BE), left ear (LE) and right ear (RE) stimulation.

Percentage non-significant responses (%)									
	80 Hz			**20 Hz**			**4 Hz**		
	parietal	**mastoid**	**frontal**	**parietal**	**mastoid**	**frontal**	**parietal**	**mastoid**	**frontal**
BE	2	0	11	9	5	11	21	17	32
LE	11	5	16	7	3	21	17	10	30
RE	9	3	28	4	3	22	7	5	19
Mean	**7**	**3**	**18**	**7**	**4**	**18**	**15**	**11**	**27**

Furthermore, individual laterality indices (LI) were calculated. The LI was based on the response power, i.e., the difference between the amplitude power at the modulation frequency and the average noise power over 80 neighbouring frequency bins (40 on each side). Subsequently, the response power was Root-Mean-Square averaged over electrodes over the right (R) and the left hemisphere (L). The LI was then calculated as the difference between R and L normalized by the sum of R and L:

$$\mathrm{LI} = \frac{\mathrm{R} - \mathrm{L}}{\mathrm{R} + \mathrm{L}}$$

Thus, the LI was +1 for a response completely asymmetrical to the right hemisphere, zero for a symmetrical response, and –1 for a response completely asymmetrical to the left hemisphere. For the calculation of these indices, negative ratios between response-amplitudes and the average noise-amplitudes were converted to zero, indicating that signal and noise were equally high.

3.2.6. Statistical analyses

Statistical analyses were performed with SPSS 16 (SPSS, 2007). For each stimulus, a test and retest were recorded. Test-retest differences in response-SNR were investigated separately for each modulation frequency by a RM-ANOVA with the factors Test (test, retest), Stimulation (BE, LE, RE) and Electrode (all 8 electrodes)

as within-subject factors. Results showed no main effect of Test or any interaction with this factor for any of the tested modulation frequencies (all $F < 2.15$, $p > 0.127$). Because there were no significant differences in response-SNR between the test and retest, both recordings were linked together and FFT statistics were carried out over the linked data, i.e., after 32 sweeps. This prolonged duration resulted in better averaging of the data and higher response-SNRs.

Normality of the response-SNRs and LIs was tested by a Kolmogorov-Smirnov test separately for all stimulations, modulation frequencies and electrodes. The significance level was set at $p < 0.01$, to adjust for multiple comparisons. All response-SNRs and LIs were normally distributed according to this criterion.

Response-SNRs were analyzed by a series of repeated measures analyses of variance (RM-ANOVA). Reported p-values of the RM-ANOVA were Greenhouse-Geisser corrected and post-hoc analyses were Bonferroni corrected for multiple comparisons. LIs were analyzed with a one-sample t-test to test whether lateralization was significantly different from zero. All statistical analyses were two-tailed ($\alpha = 0.05$).

3.3. Results

3.3.1. Response-strength

Data are shown in Figure 3.1. To examine the influence of stimulation side on the response-strength of ASSRs, a RM-ANOVA with the factors Stimulation (BE, LE, RE) and Hemisphere (left hemisphere (LH), right hemisphere (RH)) as within-subject factors was tested separately for each modulation frequency.

For 80 Hz, a main effect of Stimulation ($F(2,58) = 85.18$, $p < 0.001$) and a Stimulation x Hemisphere interaction ($F(2,58) = 15.00$, $p < 0.001$) was found. For both hemispheres, BE elicited larger responses than LE and RE (all mean differences ≥ 4.6 dB, all $t(29) \geq 4.57$, $p \leq 0.001$). Additionally in the RH, ipsilateral RE elicited larger responses than LE (mean difference: 2.0 dB, SE: 0.6 dB, $t(29) = 3.34$, $p = 0.007$). This difference was not observed at LH electrodes (mean difference: 1.7 dB, SE: 0.8 dB, $t(29) = 2.23$, $p = 0.100$).

For 20 Hz, a main effect of Hemisphere ($F(2,58) = 8.47$, $p = 0.007$) and a Stimulation x Hemisphere interaction ($F(2,58) = 13.09$, $p < 0.001$) was found. At RH electrodes, responses to RE were larger than responses to LE (mean difference:

2.3 dB, SE: 0.6 dB, $t(29) = 3.70$, $p = 0.003$). This difference was not observed at LH electrodes (mean difference: 0.4 dB, SE: 0.5 dB, $t(29) = 0.73$, $p = 1.000$). Additionally, this interaction revealed that responses were larger in the RH compared to the LH for BE (mean difference: 2.0 dB, SE: 0.5 dB, $t(29) = 4.10$, $p < 0.001$) and RE (mean difference: 2.3 dB, SE: 0.7 dB, $t(29) = 3.44$, $p = 0.002$) but not for LE (mean difference: 0.3 dB, SE: 0.5 dB, $t(29) = 0.67$, $p = 0.509$). Moreover, the difference between LE and RE was characterized by decreased RH activation for LE compared to RE (mean difference: 2.3 dB, SE: 0.6 dB, $t(29) = 3.70$, $p = 0.003$).

Finally for 4 Hz, significant main effects of Stimulation ($F(2,58) = 8.09$, $p = 0.002$), and Hemisphere ($F(2,58) = 11.69$, $p = 0.002$) were found. Overall, BE elicited smaller responses compared to monaural LE (mean difference: 2.7 dB, SE: 1.0 dB, $t(29) = 2.62$, $p = 0.042$) and RE (mean difference: 3.2 dB, SE: 0.9 dB, $t(29) = 3.57$, $p = 0.004$). In contrast, LE and RE did not differ from each other (mean difference: 0.5 dB, SE: 0.6 dB, $t(29) = 0.93$, $p = 1.000$). Additionally, RH responses were larger than LH responses (mean difference: 0.9 dB, SE: 0.3 dB).

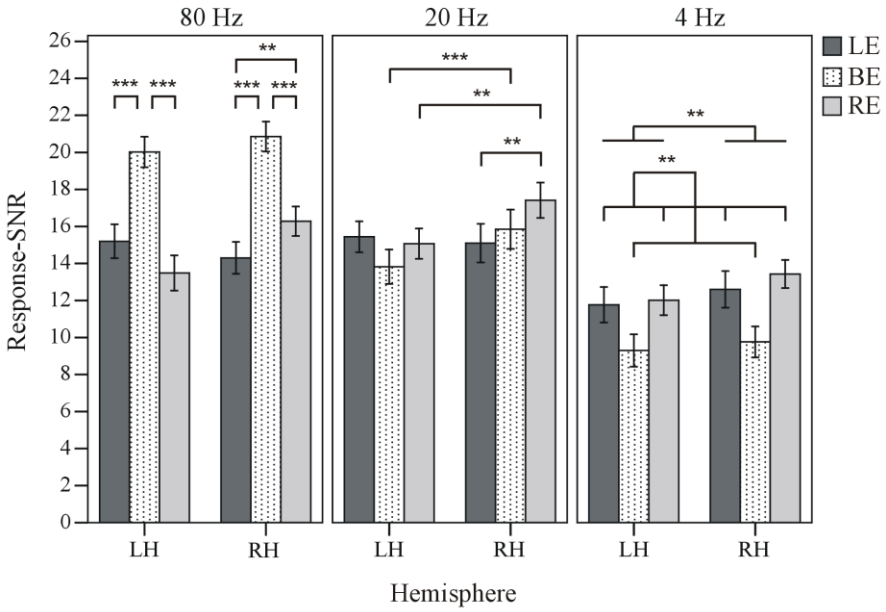


Figure 3.1 Average response-strengths for left ear (LE: left, dark grey bars), diotic (BE: middle, dotted bars) and right ear (RE: right, light grey bars) stimulation, for 80 Hz AM, 20 Hz AM and 4 Hz AM. Bars represent the average response-SNRs for left (LH) and right hemisphere (RH) electrodes. Error bars indicate ± 1 SE **p ≤ 0.01, ***p ≤ 0.001

3.3.2. Laterality

Hemispheric asymmetry of the ASSRs was investigated with laterality indices, shown in Figure 3.2. Individual LIs were evaluated separately for each modulation frequency and stimulus presentation manner.

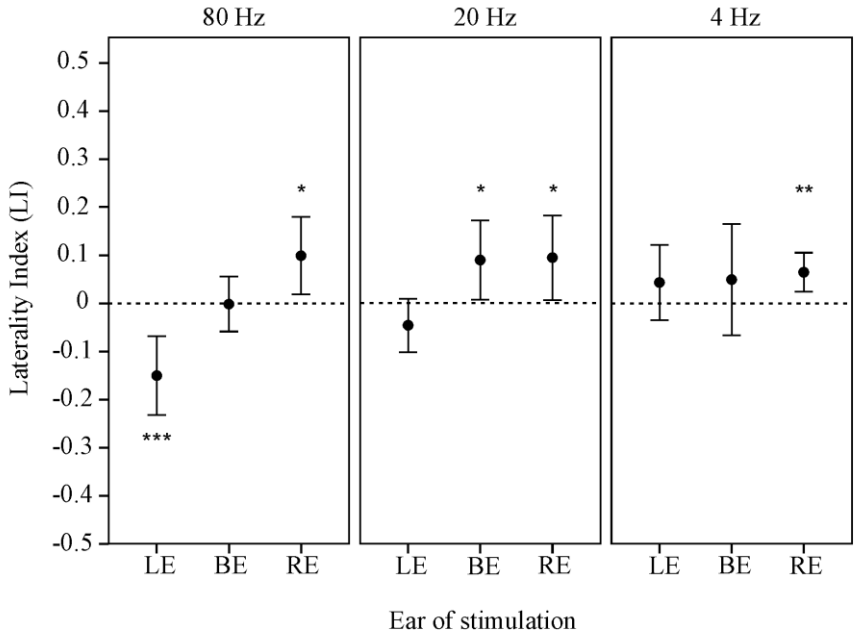


Figure 3.2 Mean laterality indices (LI) for 80 Hz, 20 Hz and 4 Hz AM, for left ear (LE), diotic (BE) and right ear (RE) stimulation. Error bars represent the 95% confidence interval of the mean $*p \leq 0.05$, $**p \leq 0.01$, $***p \leq 0.001$

A significant ipsilateral asymmetry was found for 80 Hz ASSRs. LE led to clear leftward asymmetry (LI = -0.15, $t(29) = -3.738$, $p = 0.001$), whereas RE led to rightward asymmetry (LI = 0.10, $t(29) = 2.518$, $p = 0.018$). Responses were symmetrical for BE (LI = -0.002, $t(29) = -0.060$, $p = 0.953$). For 20 Hz ASSRs, asymmetry to the right hemisphere was found for RE (LI = 0.10, $t(29) = 2.211$, $p = 0.035$) and BE (LI = 0.09, $t(29) = 2.243$, $p = 0.033$). For LE, the absolute LI was substantially negative, however, this apparent asymmetry to the left hemisphere did not reach significance (LI = -0.05, $t(29) = -1.686$, $p = 0.102$). For 4 Hz ASSRs, RE led to right hemispheric asymmetry (LI = 0.06, $t(29) = 3.271$, $p = 0.003$), whereas no

significant asymmetry was found for LE (LI = 0.04, $t(29) = 1.138$, $p = 0.265$). Symmetrical responses were also found for BE (LI = 0.05, $t(29) = 0.871$, $p = 0.391$).

These results were confirmed by an individual subject analysis. Analogous to Abrams et al. (2008), participants were categorized as having left (LI < 0) or right (LI > 0) asymmetric ASSRs. Table 3.2 shows the number of participants demonstrating left- or right ASSR asymmetry for the three modulation frequencies and stimulus presentation sides. A binomial test confirmed the ipsilateral, left asymmetry to LE for 80 Hz. Left asymmetry was present in 83% of participants ($z = 3.65$, $p < 0.001$). Also for 20 Hz, right hemispheric asymmetry was confirmed by asymmetry observed in 80% ($z = 3.29$, $p = 0.001$) and 90% ($z = 4.38$, $p < 0.001$) of participants for BE and RE respectively. Finally, for 4 Hz the significant right asymmetry to RE was confirmed by asymmetry observed in 70% ($z = 2.19$, $p = 0.043$) of participants. However, even though right asymmetry to LE was not significant, right asymmetry was observed in 70% ($z = 2.19$, $p = 0.043$) of participants.

Table 3.2 Number of participants (N = 30) demonstrating left (LH) or right (RH) ASSR asymmetry to left ear (LE), diotic (BE) and right ear (RE) stimulation and for 80 Hz, 20 Hz and 4 Hz AM.

		LH	**RH**
LE	80 Hz	25 *(83%)*	5 *(17%)*
	20 Hz	19 *(63%)*	11 *(37%)*
	4 Hz	9 *(30%)*	21 *(70%)*
BE	80 Hz	18 *(60%)*	12 *(40%)*
	20 Hz	6 *(20%)*	24 *(80%)*
	4 Hz	15 *(50%)*	15 *(50%)*
RE	80 Hz	10 *(33%)*	20 *(67%)*
	20 Hz	3 *(10%)*	27 *(90%)*
	4 Hz	9 *(30%)*	21 *(70%)*

3.4. Discussion

The present study investigated ASSRs to AM stimuli presented diotically or monaurally to the left or right ear. Results revealed that 80 Hz ASSRs to diotic stimulation were larger than to monaural stimulation and that this binaural advantage decreased with decreasing modulation frequency. Additionally, the comparison of both monaural conditions revealed a gradual change from ipsilateral to rightward asymmetry along the auditory pathway, with the strongest right asymmetry for 4 Hz ASSRs.

Hierarchical processing of binaural cues in the auditory system

Given that with decreasing modulation frequency ASSRs are generated at higher levels of the auditory system, the present results suggest that diotic information is encoded differently along the ascending auditory pathway. Whereas diotic 80 Hz responses were up to 6.6 dB larger than monaural responses, the diotic advantage decreased strongly for 20 and 4 Hz ASSRs. For 20 Hz, diotic ASSRs were equal to monaural responses while for 4 Hz diotic responses were even smaller than monaural responses.

Previous ASSR studies reported enhanced binaural compared to monaural ASSRs at 80 Hz (Lins & Picton, 1995) but only slightly higher binaural than monaural responses at 40 Hz (Picton et al., 2003). This was, however, never explored for ASSRs lower than 40 Hz. Together with the present results, this suggests that the bihemispheric interactions along the auditory pathway differ in their contribution to binaural responses. It seems that at early levels of the auditory system excitatory processes underlie enhanced binaural responses whereas inhibitory influences operate at higher levels of the auditory system, resulting in attenuated diotic compared to monaural responses in the auditory cortex. This change from enhanced to attenuated diotic ASSRs along the auditory pathway may relate to binaural integration (Gelfand, 2001), i.e. the integration of input from the left and right ears into a binaural construct. It is known that binaural integration takes place in the auditory brainstem and that at higher levels of the auditory system, binaural processing continues on an integrated construct (Colburn et al., 2006). The present results may indicate that diotic 80 Hz ASSRs relate to the combination of left and right ear inputs, whereas monaural 80 Hz ASSRs only encode input from one ear. The weakened diotic relative to monaural responses for 20 and 4 Hz may then reflect a processing difference at higher levels of the auditory system. If after

binaural integration differences between left and right ear inputs disappear and binaural processing continues on a integrated construct (Picton, 2011), then at the cortical level differences between monaural and diotic ASSRs may decrease as well.

Perceptually, binaural hearing serves an important role in separating speech from environmental noise or in the spatial localization of sounds (Colburn et al., 2006). If 80 Hz ASSRs are sensitive to binaural integration, they may be valuable to measure related binaural perceptual processes. For instance, 80 Hz ASSRs have previously been shown to be responsive to binaural cues related to sound localization (i.e. interaural time/loudness differences) (Zhang & Boettcher, 2008). In this context, diotic stimulation agrees with a sound source located in front of the listener whereas monaural stimulation reflects a sound source located laterally to the listener. The difference between diotic and monaural 80 Hz ASSRs in the present study may then reflect encoding differences between sources.

Alternatively, diotic stimulus presentation is known to result in binaural summation, the percept of greater loudness to binaural compared to monaural stimulation at the same supra-threshold SPL. Given that ASSR amplitudes increase with increasing stimulus intensity (Picton et al., 2003), it seems that binaural summation can be measured with 80 Hz ASSRs and not with 20 and 4 Hz ASSRs.

Nonetheless, 80 Hz ASSRs do not reflect all binaural processes. Binaural masking level differences (BMLD), reflecting the benefit from using both ears instead of one when detecting signals in noise, were only found for cortically-evoked, 7 Hz ASSRs (Wong & Stapells, 2004) and not for 80 Hz (Wong & Stapells, 2004), or even 40 Hz (Ishida & Stapells, 2009) ASSRs.

Clinically, 80 Hz ASSRs (or higher) are typically used in hearing screening and diagnosis of infants. The present results may imply that for 80 Hz ASSRs stimuli presented simultaneously to both ears still reflect the input from both ears, whereas for lower modulations responses may be mediated by the listener's ability to integrate binaural cues into a construct. These slow-rate ASSRs are therefore less suitable for measuring stimulus sensitivity, e.g. in screening protocols involving multi-stimulus presentation, but can rather contribute to the evaluation of higher-order auditory processes such as temporal envelope processing.

Hemispheric asymmetry

From a bottom-up perspective, response asymmetry of subcortical structures is mainly directed by anatomical constraints, whereas at the cortical level asymmetry may additionally be influenced by functional specializations of the central auditory system. Anatomically, information is transferred from each ear to both ipsilateral and contralateral auditory cortices. Although evidence exists for a dominant contralateral pathway, a reasonable amount of auditory information is transferred via the ipsilateral pathway (Jäncke et al., 2002).

The present results demonstrate that the influence of which ear was stimulated on response asymmetry changed along the auditory pathway. At 80 Hz, monaural stimulus presentation clearly led to ipsilateral response asymmetry. This is consistent with previous ASSR studies reporting smaller or even absent 80 Hz ASSRs contralateral to the stimulus (Small & Stapells, 2008; van der Reijden et al., 2005; Poelmans et al., 2012a). Given that both the generation of 80 Hz ASSRs and the crossover to the contralateral side takes place in the brainstem, it is possible that neural generators of 80 Hz ASSRs are located earlier in the auditory pathway than the contralateral crossover. Alternatively, it may also be possible that 80 Hz ASSRs are generated by a single, medial source in the brainstem and that the orientation of this source depends on which ear is stimulated. To clarify these hypotheses, high-density ASSR recordings and source localization analyses are necessary.

At higher levels of the auditory system, laterality was less clear. To right ear stimulation, ipsilateral right asymmetry was found for all modulation rates. In contrast, to left ear stimulation, the observed ipsilateral left asymmetry at 80 Hz seemed to gradually decrease with decreasing modulation frequency and change towards right hemispheric processing, with the most pronounced asymmetry for 4 Hz ASSRs. That is, even though laterality for 20 Hz and 4 Hz was statistically not significant to left ear stimulation, 63% of the participants demonstrated *ipsilateral left* asymmetry for 20 Hz and 70% of the participants demonstrated *contralateral right* asymmetry for 4 Hz.

The present results support temporal sampling models (Pöppel, 2003; 2008; Goswami, 2011), claiming that syllabic- and phonemic-rate modulations are processed asymmetrically in the brain. Consistent with these models, the present 4 Hz results support a large amount of studies reporting right lateralization of slow, syllabic-rate modulations (Abrams et al., 2008; Millman et al., 2010; Boemio et al., 2005; Hämäläinen et al., 2012a). However, lateralization of phonemic-rate modulations is still under debate. Whereas temporal sampling models predict left

lateralization of phonemic-rate modulations (Johnsrude et al., 1997; Jamison et al., 2006; Belin et al., 1998), evidence also exists in favour of bilateral activation to phonemic-rate modulations (Hämäläinen et al., 2012a; Herdman et al., 2003). The present 20 Hz results favour bilateral sensitivity to phonemic-rate modulations. Given that ipsilateral asymmetry was found for 20 Hz ASSRs, it seems unlikely that a single left hemispheric source underlies 20 Hz ASSR generation.

The present study was the first to systematically investigate ASSR asymmetry for speech-related, phonemic- and syllabic-rate modulations by comparing different stimulation sides. Previously, ASSR asymmetry was only investigated for 40 Hz AM, representing the higher end of phonemic-rate modulations, and results were rather contradictory. Whereas Ross et al. (2005) demonstrated right asymmetry of 40 Hz ASSRs, Yamasaki et al. (2005) suggested a left hemispheric specialization for this modulation rate. An important factor contributing to contradicting results is the methodological difference between studies. First, studies assessed asymmetry with different techniques (MEG: Ross et al., 2005; EEG: Yamasaki et al., 2005), implying different sensitivity to subcortical sources. Second, stimulus factors such as duration (short stimuli: Yamasaki et al., 2005; Hämäläinen et al., 2012a; longer stimuli: Abrams et al., 2008; Ross et al., 2005) or complexity (modulated pure tones: Ross et al., 2005; modulated noise: Hämäläinen et al., 2012a; real speech: Abrams et al., 2008; Yamasaki et al., 2005) may have influenced hemispheric asymmetry. The present results were obtained with a relatively simple stimulus, a steady-state speech-weighted noise, 100% amplitude modulated at one modulation frequency. The use of a speech-weighted noise carrier, containing the important frequencies of real speech, allowed examining temporal modulation asymmetry without the top-down influence of semantics in real speech.

The present results about the influence of monaural versus diotic stimulation on the one hand and left ear versus right ear stimulation on the other hand, on slow-rate ASSRs, may clinically be important, given that slow-rate ASSRs are related to sensitivity to speech-related modulations. The finding that hemispheric activation depends on which ear is stimulated and differs for syllabic- and phonemic modulations, may have important consequences for clinical populations which have monaural hearing aids, deviant hemispheric asymmetries or interhemispheric transfer dysfunction.

Chapter 4
The relation between auditory steady-state responses and structural white matter density in adults with dyslexia

The content of this chapter has been submitted for publication to Neuroimage. Vandermosten, M., Poelmans, H., Sunaert, S., Ghesquière, P., Wouters, J. White matter lateralization and interhemispheric synchronization to auditory modulations in normal reading and dyslexic adults. (Vandermosten, M. and Poelmans, H. are joint first authors).

Abstract
Adequate speech perception depends on how acoustic elements are integrated into meaningful phonological units, such as syllables or phonemes. Assembling phonological information takes place at multiple timescales, and it is hypothesized that these timescales play a role in hemispheric dominance for speech processing in the brain. Fast acoustic variations are thought to be lateralized to the left hemisphere whereas right lateralization occurs for slow acoustic variations. It has been suggested that this complementary function at different hemispheres is rooted in a different degree of myelination in the left versus right hemisphere. In the present study, structural white matter lateralization and functional phonemic- and syllabic-rate phase locking was investigated in a sample of normal reading and dyslexic adults. White matter integrity and lateralization, measured with diffusion tensor imaging (DTI), was examined in cortical auditory and language regions (i.e. posterior region of the superior temporal gyrus, the inferior frontal gyrus and the arcuate fasciculus) and in the interhemispheric connection between them (splenium of the corpus callosum). Additionally, neural processing of slow, syllabic-rate (i.e. 4 Hz) and fast, phonemic-rate (i.e. 20 Hz) modulations was examined with auditory steady-state responses (ASSR). ASSRs were evaluated based on their interhemispheric coherence, a measure for functional connectivity between distant brain regions involved in the same process. We also investigated the relation between interhemispheric coherence during auditory temporal processing and white matter properties of the dorsal fiber tract, its projection points and the splenium of the corpus callosum. Results demonstrated reduced white matter lateralization in the posterior region of the superior temporal gyrus and the arcuate fasciculus as well as reduced

interhemispheric coherence to phonemic-rate modulations in dyslexic relative to normal readers. Additionally, we found that the degree of white matter lateralization in the posterior region of the superior temporal gyrus and white matter integrity in splenium of the corpus callosum was related to the synchrony between neural ensembles in both hemispheres. Moreover, this relation was specifically observed for phonemic-rate information and was different for normal reading and dyslexic adults. These results indicate that in dyslexic adults, phonemic-rate acoustic information is insufficiently integrated in the dorsal phonological system, and that this may be due to reduced white matter lateralization in posterior region of the superior temporal gyrus and arcuate fasciculus.

4.1. Introduction

Spoken language comprehension depends on the recognition and interpretation of meaningful units, such as words, phrases or sentences. These high-level perceptual constructs are assembled from pre-lexical, acoustic-phonetic cues that are integrated and categorized along multiple timescales. That is, in time windows of ± 20-80 ms, segmental information about for example phoneme identity is clustered, whereas in longer time windows of ± 150-300 ms, important suprasegmental information about speech prosody and stress, is processed (Obrig et al., 2010; Pöppel et al., 2008). Continuous extraction of segmental and suprasegmental information from the speech stream is supported by acoustic cues in the temporal envelope of speech, which consists of amplitude fluctuations (i.e., amplitude modulations, AM) between 2 and 50 Hz (Shannon et al., 1995; Drullman et al., 1994; Rosen, 1992). Of particular interest are modulations near 4 Hz (± 250 ms) and 20 Hz (± 50 ms) because they comprise the time windows in which, respectively, suprasegmental (syllabic) and segmental (phonemic) acoustic cues appear in speech (Pöppel, 2003).

Imprecise processing of syllabic- and/or phonemic-rate cues in speech can negatively affect the perception of spoken language and can influence the development of well-specified phonological representations (Nittrouer, 2006). The development of these phonological representations is characterized by a change in grain size. That is, preschool children manipulate speech mainly at the syllable level, and it is only during reading acquisition, when children learn that every speech sound (phoneme) corresponds to a written symbol (grapheme), that explicit representations develop at the phoneme level (Anthony et al., 2003; Ziegler & Goswami, 2005). Given the predictive influence of phonological processing on reading development, the accuracy by which acoustic information is clustered into phonological representations is crucial for the development of adequate reading skills (Boets et al., 2011a; Leppänen et al., 2010; Corriveau et al., 2010).

Within this context, it has been suggested that a fundamental deficit in auditory temporal processing indirectly underlies the reading and spelling problems in individuals with dyslexia (e.g., Tallal & Gaab, 2006; for a review, Farmer & Klein, 1995). Developmental dyslexia refers to a neurological disorder that manifests itself as a failure to acquire adequate reading and spelling skills despite normal intelligence, education and intense remedial effort and is thought to affect 5 to 10% of the children (Vellutino et al., 2004). Evidence exists that the reading and writing problems in dyslexia are caused by a deficit in the development and the use of

phonological representations (e.g., Snowling, 2000; but see Ramus & Szenkovits, 2008). Whether phonological representations are only impaired at the phoneme- or also at the syllable-level remains largely unknown. Whereas most studies indicate a phoneme-level deficit (de Gelder & Vroomen, 1991; Swan & Goswami, 1997; Snowling, 2000; Goswami & East, 2000), others favour a deficit at both levels (Goswami, 2002; Lambrecht Smith et al., 2010; Maionchi-Pino et al., 2010). According to the original auditory temporal processing theory, auditory problems in dyslexic readers are believed to be specific to rapid modulations (Tallal, 1980), implying the phoneme level. Yet, several psychophysical studies have demonstrated decreased sensitivity to temporal modulations over a wide range of modulation frequencies in individuals with dyslexia (adults: McAnally & Stein, 1997; Menell et al., 1999; Witton et al., 1998; Witton et al., 2002; Stuart et al., 2006; children: Lorenzi et al., 2000; Rocheron et al., 2002).

4.1.1. Cortical auditory and phonological processing in normal readers

According to the hierarchical model of speech processing (Hickok & Pöppel, 2007), early cortical structures such as Heschl's gyrus and the supratemporal plane are sensitive to unstructured and simple time-structured acoustic signals respectively, whereas higher level structures such as the superior temporal gyrus are best responsive to complex sublexical spectrotemporal signals and are thought to be involved in the construction of sound-based representations of speech (Hickok & Pöppel, 2004). Next, at the level of the anterior and posterior superior temporal sulcus an abstract representation of speech units, insensitive to acoustic variances, is obtained (Okada et al., 2010; Peelle et al., 2010). From the superior temporal cortex, speech signals are processed in two parallel streams. In particular, a *ventral sound-to-meaning stream*, which engages areas in the left anterior superior temporal sulcus and middle temporal gyrus, maps sound-based representations of speech to conceptual representations (Pöppel et al., 2008; Rauschecker & Scott, 2009). It is evidenced that the ventral anatomical counterpart of this sound-to-meaning stream is the extreme capsule fiber system or inferior fronto-occipital fasciculus (Frey et al., 2008; Wong et al., 2011). In addition, starting from the posterior temporal cortex, a *dorsal auditory-to-motor stream* projects towards inferior parietal and frontal (Broca's and premotor) regions and is functionally responsible for mapping phonemic representations onto motor representations, necessary for articulation.

This pathway consists of two functionally different components, i.e. the left temporoparietal component that is involved in phonological processing and grapheme-to-phoneme mapping, and the frontal component (i.e. regions in and around Broca's area) that is among others involved in the active analysis of phonological elements within words (Fiez & Petersen, 1998; Poldrack et al., 1999). Saur et al. (2010) demonstrated that the functional connection between these two components is mediated via the arcuate fasciculus (AF, often used interchangeably with the Superior Longitudinal Fasciculus (Brauer et al., 2011) or as one of its subdivision (Makris et al., 2005)). Thus, phonological processing during speech perception depends both on acoustically-based processes in the posterior temporal areas but also on a dorsal interaction with frontal regions.

A large body of evidence exists that these areas are mainly lateralized to the left hemisphere during speech processing (for a review see Tervaniemi & Hugdahl, 2003), however, it is still unclear as to which speech characteristics drive this lateralization. According to the domain-driven hypothesis, left dominance is rooted in the linguistic aspects of speech (Dehaene-Lambertz et al., 2005; Dehaene-Lambertz et al., 2010; Rosen et al., 2011). Yet, Pöppel et al. (2008) and Zattore & Gandour (2008) independently proposed that functional specialization relates to a hemispheric difference in the sensitivity of the auditory cortex to process particular spectrotemporal features. More specifically, spectral aspects and slow acoustic modulations are preferentially processed in the right auditory cortex, whereas temporal aspects like duration and faster modulations are more left lateralized (Zatorre & Gandour, 2008). According to Pöppel and colleagues (2003; 2008), this functional specialization is situated in the non-primary auditory cortex and rooted in the length of integration windows, being between 20-50 ms (i.e. 12-50 Hz) in the left and between 150-300 ms (i.e. 3-7 Hz) in the right hemisphere. This view is supported by fMRI and EEG studies that demonstrate either an enhanced left hemispheric response to rapidly-changing stimuli (Zaehle et al., 2004), an enhanced right hemispheric response to slowly-changing signals (Abrams et al., 2008; Boemio et al., 2005; Britton et al., 2009; Belin et al., 1998; Luo & Pöppel, 2007; Telkemeyer et al., 2009) or both simultaneously (Liégeois-Chauvel et al., 1999; Giraud et al., 2007; Schonwiesner et al., 2005; Jamison et al., 2006; Warrier et al., 2009; Zatorre & Belin, 2001). This signal-driven approach explains a left lateralization for phoneme identification (e.g. Jäncke et al., 2002; Dehaene-Lambertz & Gliga, 2004; Zatorre et al., 1996) and a right lateralization for prosody and syllable identification (Meyer et al., 2002; Zatorre et al., 1992; Zatorre, 1988) based on the length of the integration windows of important acoustic cues instead of their linguistic content

(like domain-driven models). Despite evidence that not linguistic but rather acoustic-temporal characteristics drive the leftward asymmetry (Boemio et al., 2005; Husain et al., 2006; Joanisse & Gati, 2003; Zaehle et al., 2004), experience and familiarity with phonetic categories can modulate the pattern of hemispheric specialization for rapid versus slow changes (see reviews of Zatorre & Gandour, 2008; Minagawa-Kawai et al., 2011).

In addition to their functional specialization, the left and right primary auditory and superior temporal cortices also differ in volume (e.g. review Shapleske et al., 1999). This volumetric asymmetry is mainly present in white rather than grey matter (Penhune et al., 1996; Warrier et al., 2009), which fits the assumption of Zatorre and colleagues (2001; 2002) that the functional hemispheric asymmetry for spectrotemporal information is specifically related to hemispheric asymmetry of white matter myelination, rather than to volume *per se*. A more myelinated left auditory cortex can thus lead to faster neural processing and this could underlie the left specialization for handling fast temporal information. Direct evidence for white matter lateralization is provided by a post-mortem analysis of the posterior superior temporal lobe in 16 men (Anderson et al., 1999). Results of this study confirmed the greater white matter volume on the left than on the right and showed that this was due to greater myelin sheath thickness on the left (Anderson et al., 1999). A non-invasive MRI-technique that is relatively sensitive to white matter microstructure *in vivo* is diffusion tensor imaging (DTI). DTI provides parameters, such as fractional anisotropy (FA) which indirectly measures the degree of myelination and/or axon density (Beaulieu, 2002), and is adept to virtually reconstruct white matter pathways in vivo, via tractography (Basser et al., 2000). Evidence is lacking on white matter lateralization, measured by DTI, in the auditory regions, though it has repetitively been demonstrated that the dorsal white matter tract departing from them, the arcuate fasciculus, has a leftward asymmetry in fractional anisotropy (Thiebaut de Schotten et al., 2011; Rodrigo et al., 2007; Büchel et al., 2004; Catani et al., 2007; Barrick et al., 2007; Eluvathingal et al., 2007; Hagmann et al., 2006; Matsumoto et al., 2008; Makris et al., 2005; Nucifora et al., 2005; Powell et al., 2006; Parker et al., 2005; Vernooij et al., 2007).

The above-cited studies demonstrate that there is concordant evidence for a functional hemispheric specialization for slow versus rapid modulations as well as for a structural asymmetry in the volume of the auditory regions and white matter integrity of the dorsal tract departing from them. A link between these asymmetries is often assumed but is rarely explicitly tested. In a fMRI study, Warrier et al. (2009)

investigated this hypothesis by linking anatomical variability of the primary auditory cortex to individual differences in BOLD-signal to temporal and spectral acoustic stimuli. They reported that a larger volume in the left hemisphere was associated with temporal processing whereas a larger right hemispheric volume was associated with spectral processing. Additionally, Golestani et al. (2002) found in a fMRI study a significant correlation between the rate of learning to identify a new and unknown speech contrast (a non-native Hindi speech contrast) and the amount of white matter in the parietal cortex, especially in the left hemisphere. Intriguingly, this relation was exclusively found for rapidly changing speech and non-speech stimuli, but not for steady-state sounds. Though these two studies support a link between structural lateralization and spectrotemporal processing, they used volumetric measures, which impedes firm conclusions on the importance of white matter structural characteristics (such as myelination) in processing temporal acoustic features.

4.1.2. Cortical auditory and phonological processing in dyslexic readers

A large body of evidence allocates the well-known phonological problems in dyslexia to a functional and structural deficit in left temporoparietal areas (reviews by: Eden & Zeffiro, 1998; Shaywitz, 1998; Shaywitz et al., 2002; meta-analysis: Richlan et al., 2009) and in the AF (Vandermosten et al., 2012a). Less is known however about the neural correlate of the auditory processing problems that are often observed in dyslexic readers (Tallal, 1980). Several studies assign the auditory problems in dyslexia to deviant hemispheric specialization of the auditory system to process rapidly versus slowly changing cues. Functional imaging studies demonstrated a leftward bias for rapid versus slow transitions in normal readers, whereas this lateralization was not present in their dyslexic peers (in children: Gaab et al., 2007; in adults: Ruff et al., 2002). In addition, several EEG and MEG studies provide evidence that dyslexic readers do not present the typical left hemispheric dominance in response to speech or rapidly changing signals (for a review see Lyytinen et al., 2005). Especially acoustic changes at the phonemic-rate, important for speech perception, were found to be less lateralized to (Lehongre et al., 2011) or reduced within (Poelmans et al., 2012a) the left hemisphere in dyslexic compared to normal readers, and this related to phonological performance. However, evidence also exists in favour of reduced right hemispheric lateralization to syllabic-rate modulations. In normal readers, these modulations were consistently found to be

more prominently processed in the right hemisphere, whereas dyslexic readers rather showed a symmetrical organization (Abrams et al., 2008; Abrams et al., 2009; Hämäläinen et al., 2012a). These studies indicate that a disturbance in hemispheric lateralization of syllabic- and phonemic-rate modulations is present in dyslexia and raises the possibility that the connection of the auditory system with the phonological system is not optimal in dyslexia.

Concerning structural asymmetry in normal versus dyslexic readers, there is no evidence for a group difference in the size of the primary auditory cortex (Leonard et al., 1993; 2002), and mixed evidence exists for a decreased left asymmetry in the adjacent planum temporale (for reviews see, Beaton, 1997; Eckert & Leonard, 2000; Morgan & Hynd, 1998) and IFG (Robichon et al., 2000). Though volume measures are a valuable index for asymmetry, we expect that especially the microstructural properties of white matter explain the functional left asymmetry for processing rapidly changing acoustic information, and that a reduced left dominance of these microstructural properties might be at the basis of the temporal processing problems in dyslexic readers. In general, DTI-studies provide only indirect evidence for this hypothesis by showing lower white matter integrity (i.e. FA) in the left, and only to a lesser extent in the right, temporoparietal regions (Klingberg et al., 2000; Deutsch et al., 2005; Hoeft et al., 2006; Rimrodt et al., 2010; Richards et al., 2008; Niogi & McCandliss, 2006; Steinbrink et al., 2008; Carter et al., 2009; Keller & Just, 2009; Odegard et al., 2009), IFG (Deutsch et al., 2005; Richards et al., 2008; Rimrodt et al., 2010) and AF (Vandermosten et al., 2012a). Niogi & McCandliss (2006) assessed a reduced lateralization in white matter integrity more directly by calculating a lateralization index for segments of several white matter tracts. Result showed a significantly lesser degree of left lateralization in the temporoparietal region (i.e. superior corona radiata) in dyslexic relative to normal readers. However, no evidence is available on group differences in laterality concerning the full AF and its two projection points (STGp and IFG). Additionally, no study has been undertaken among dyslexics to investigate the relation between white matter and auditory temporal processing.

Given that dyslexics (*i*) display a reduced functional left hemispheric specialization in response to rapidly changing stimuli, (*ii*) tend to present a reduced volumetric leftward asymmetry of the superior temporal cortex and, to a lesser extent, the IFG, and (*iii*) demonstrate white matter anomalies mainly in the left but not in the right temporoparietal region, IFG and AF, it might be that the auditory temporal processing problems in dyslexic readers are a consequence of reduced lateralization

of myelination in brain areas responsible for detailed spectrotemporal pattern analysis.

4.1.3. Hypotheses

In sum, concordant evidence has indicated that the original view of left hemispheric specialization for speech perception is actually driven by its spectrotemporal characteristics. More specifically, the left auditory regions preferentially respond to fast changes in acoustic information whereas slowly changing signals are predominantly processed in the right hemisphere. This signal-driven hemispheric specialization explains why phonemes, for which identification depends on fast acoustic changes, are lateralized to the left, and suprasegmental information such as syllables, depending on slow acoustic changes, is lateralized to the right hemisphere. It has been suggested that this complementary function of each hemisphere is rooted in a different degree of myelination in the left versus right hemisphere, however, evidence is lacking on three crucial points.

First, more evidence is required on hemispheric differences in myelination. Second, evidence is lacking on the direct relationship between functional neural specialization for slowly and rapidly changing signals, and structural measures, such as the lateralization of myelination. Only one study investigated the spectrotemporal specialization of each hemisphere in relation to the anatomy of the auditory regions (Warrier et al., 2009), yet, they focused on the volume parameters (instead of myelination) and on primary auditory regions (whereas hemispheric specialization is primarily expected in secondary auditory regions and the dorsal tract (Pöppel et al., 2008; Zaehle et al., 2008)). Third, no evidence is available on the relationship between functional hemispheric specialization for processing spectrotemporal cues and structural lateralization measures in dyslexic readers. Given that dyslexic readers are impaired in processing rapidly changing signals and that they tend to demonstrate decreased volumetric and functional lateralization, it is interesting to investigate whether lateralization of white matter integrity in the auditory regions and dorsal tract is also reduced in dyslexic readers, and whether the relation between these structural lateralization indices and functional specialization of each hemisphere is different.

Therefore, a first aim of the present study is to investigate microstructural white matter lateralization in auditory and language regions in normal reading and dyslexic

adults by means of DTI. We are particularly interested in the posterior region of STG (STGp), because this region is involved in acoustic spectrotemporal analysis, but also in its dorsal projections towards IFG via AF, since the integration into phonological representation takes place here. Additionally, myelination of the callosal projections via the splenium may be important, since these may underlie hemispheric asymmetry in STGp (Westerhausen et al., 2009). DTI is a structural MRI technique that provides a quantitative index of the degree of anisotropy, i.e. FA, which is partly and indirectly determined by microstructural white matter properties such as myelination and/or axon density. We calculated a FA-lateralization index for STGp, IFGop and AF and we also extracted FA-values for the splenium of the corpus callosum which constitutes the interhemispheric connection between these structures. Second, the central aim is to investigate whether FA-lateralization in the dorsal fiber tract and its projections points and FA in the splenium of the corpus callosum is related to neural processing slow, syllabic-rate (i.e. 4 Hz) and faster, phonemic-rate (i.e. 20 Hz) modulations. The latter is measured by means of auditory steady-state responses (ASSRs) in the EEG. The ASSR is a neural oscillatory activity that is evoked by a rhythmic auditory stimulus (Picton et al., 2003; 2011). ASSRs measure how well the auditory system phase locks to the stimulus rhythm and are considered as an objective measure to evaluate neural processing of acoustic modulations. Of particular interest, in the context of the present study, is how well brain regions in both hemispheres synchronize to syllabic- and phonemic-rate modulations. Given that the integration of auditory information into the dorsal phonological system depends on a large network of intra- and interhemispheric connections, interhemispheric synchrony provides a global measure of syllabic- and phonemic-rate processing. Thus, we aim to investigate whether interhemispheric coherence during auditory temporal processing was associated with FA-lateralization of the dorsal fiber tract and its projection points and with FA in the splenium of the corpus callosum. By also including dyslexic readers, it will be possible to examine whether this correlational pattern was different for both reading groups.

4.2. Methods

4.2.1. Participants

Twenty dyslexic and 20 normal reading adults (age range 19-32 years), recruited from the student population of the University of Leuven, participated. All were native Dutch speakers, without a history of brain damage, language problems, psychiatric symptoms, visual problems or hearing loss. All participants were predominantly right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), had adequate nonverbal intelligence (standard score > 90 on the Matrices subtest of WAIS-III (Wechsler, 1992)), and adequate audiometric pure-tone hearing thresholds (< 25 dB HL on all octave audiometric frequencies). The study was approved by the local Ethical Board and informed consent was obtained from all participants according to the Declaration of Helsinki.

The 40 participants of the present study were identical to the sample described in Vandermosten et al. (2012a) and were selected from the sample described in Poelmans et al. (2012a) and Vandermosten et al. (2010). The selection of the 40 participants was based on a composite score of three standardized literacy tests (word and pseudoword reading and spelling) (Brus & Voeten, 1973; Van den Bos et al., 1994): the 20 best and 20 poorest performers of the original sample were selected[3]. All individuals with dyslexia had a formal diagnosis of developmental dyslexia and scored below percentile 3 of a university norm group (Depessemier & Andries, 2009) on both standardized reading tests. The 20 normal reading individuals reported no history of reading difficulties and scored above percentile 20 of the university norm group on both reading tests. Both groups were matched for gender, age and nonverbal intelligence. As defined, performance on word and pseudoword reading and spelling was significantly poorer in the dyslexic compared to the normal reading group. Table 4.1 displays descriptive statistics for the two groups.

[3] Because in the total group, literacy performance was rather a continuous than a categorical variable, the control and dyslexic group were made more dichotomous on literacy by selecting 20 controls with the best literacy scores and 20 dyslexics with the worst literacy scores. This dichotomy was made to ensure a clear comparison between very good readers and severely impaired readers.

Table 4.1 Participant characteristics (M ± SD)

	Dyslexic readers (N = 20)	Normal readers (N = 20)	Test statistics
Subject characteristics			
Gender (male/female)	7/13	8/12	$\chi^2(1) = 0.11$, $p = 0.744$
Age (years)	22.1 ± 3.1	21.4 ± 3.0	$t(38) = -0.66$, $p = 0.514$
Non-verbal IQ	108 ± 10	106 ± 10	$t(38) = -0.54$, $p = 0.592$
Defining literacy measures			
Word reading[a]	66.1 ± 1.9	99.8 ± 11.4	$t(38) = 13.10$, $p < 0.0001$
Pseudoword reading[a]	66.0 ± 1.8	107.9 ± 9.8	$t(38) = 18.75$, $p < 0.0001$
Spelling[a]	69.3 ± 6.5	105.8 ± 9.6	$t(38) = 14.04$, $p < 0.0001$

[a] = Standardized scores with population average M = 100 and SD = 15

4.2.2. Structural measures: DTI

4.2.2.1. Data acquisition

All participants underwent MRI examination on a 3T system (Philips, Best, The Netherlands). The DTI data were acquired using a single spin shot EPI with SENSE acquisition. DTI images covering the entire brain and the brainstem were acquired with the following parameters: matrix size = 112 x 109; field of view (FOV) = 220 x 220 mm²; repetition time (TR) = 11043 ms, echo time (TE) = 55 ms, 68 contiguous sagittal slices (slice thickness = 2.2 mm; voxel size = 1.96 x 1.96 x 2.2 mm³), acquisition time = 10 min 34 s. A pair of diffusion gradients was applied along 45 non-collinear directions with a b-value of 800 s/mm². Additionally, one set of images with no diffusion weighting (b = 0 s/mm²) was acquired. Two identical DTI datasets were consecutively acquired for each subject to increase the signal-to-noise ratio, bringing the total acquisition time to 21 min and 8 s.

4.2.2.2. Data processing

DTI images were first visually checked for possible artifacts. DTI post-processing involved correcting for eddy-current and motion-induced artifacts using CATNAP with the required reorientation of the b-matrix (Landman et al., 2007; Leemans & Jones, 2009). Fractional anisotropy (FA) was extracted from three left and right brain regions: the posterior part of the Superior Temporal gyrus (STGp), the opercular part of the inferior frontal gyrus (IFGop), and the white matter tract which connects these two language regions, i.e. the arcuate fasciculus (AF). In addition, we delineated the fibers passing through the splenium of the corpus callosum (CCsplenium) (Figure 4.1). This posterior part of the CC was chosen as it is demonstrated that it connects the bilateral STGp (Westerhausen et al., 2009). Concerning fibertracking for the AF and CCsplenium, a whole brain tractography was first calculated for each concatenated DTI dataset using a seed point of [2 2 2], fractional anisotropy (FA) threshold of 0.2 to seed and end tracking, angle threshold of 40°, and fiber length range of 50-500 mm. Fibertracking of AF and CCsplenium was done in native space and an average FA was obtained per tract. To reconstruct the AF, we defined the regions of interest in line with the protocol of Wakana et al. (2007), there referred to as 'SLF', and for CCsplenium, the splenium was delineated on the midsagittal slice in line with the protocol of Witelson (1989). Concerning the two bilateral cortical areas, STGp and IFGop, the individual concatenated datasets were nonrigidly normalized to MNI (Montreal Neurological Institute) space using the software ExploreDTI (Leemans & Jones, 2009). In addition, FA-data were smoothed with a 6mm kernel. Each participant's DTI data were masked based on their individual FA map at a threshold of 0.2 in order to restrict the analyses to white matter. Subsequently, the region of interest of STGp and IFGop was defined based on the Harvard-Oxford atlas in MNI space at 25% probability threshold. The region of interest of the STGp and IFGop were placed on the smoothed masked normalized FA-maps of each individual, and FA-values were extracted for the bilateral STGp and IFGop.

Next, given our focus on structural asymmetry in white matter integrity, we calculated a lateralization index (LAT) for the AF, STGp and IFGop according to the following formula:

$$\text{LAT (FA)} = \frac{\text{right (FA)} - \text{left (FA)}}{\text{right (FA)} + \text{left(FA)}} \times 100$$

A negative lateralization score indicates the FA is relatively left lateralized across two regions of interest while a positive lateralization score reflects relative right FA-lateralization. Values close to zero indicate no lateralization.

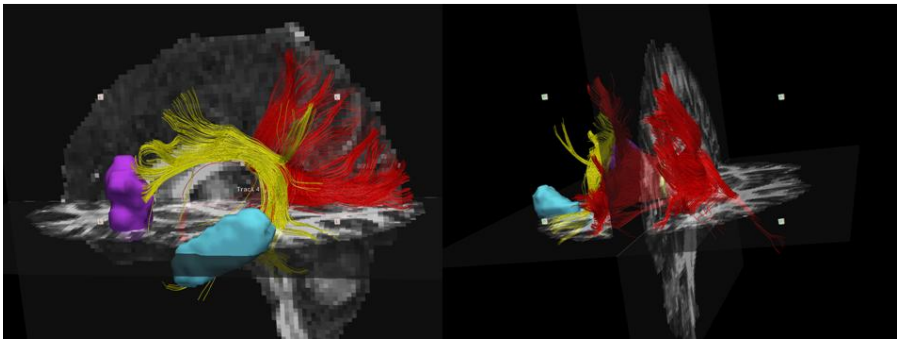


Figure 4.1 Left AF (depicted in yellow), STGp (depicted in light blue), IFGop (depicted in purple) and CCsplenium (depicted in red). Left panel: sagittal view from the left. Right panel: coronal view from posterior.

4.2.3. Electrophysiological measures: ASSR

4.2.3.1. Stimuli

ASSRs were recorded to continuous amplitude modulated speech-weighted noise stimuli. The noise carriers were derived from the speech-weighted masking noise of the "Leuven Intelligibility Sentence Test" (LIST: van Wieringen & Wouters, 2008). This noise represents the long-term average speech spectrum of 730 sentences of a female speaker. Noises were 100% amplitude modulated at 3.91 Hz and 19.53 Hz. For simplicity, these modulation frequencies will be further referred to as the rounded frequencies: 4 Hz and 20 Hz respectively. These modulation frequencies were selected because of their importance in speech intelligibility (Shannon et al., 1995), representing the syllabic- and phonemic-rate respectively. Stimuli were generated in Matlab R14. In the experiment, all stimuli were presented monaurally to the right ear with ER-3A insert phones, at 70 dB SPL.

4.2.3.2. Data acquisition

The continuous EEG was recorded by 10 surface Ag/AgCl electrodes on the scalp, placed in accordance with the international 10-20 system for electrode placement (Malmivuo & Plonsey, 1995). EEG was recorded from two central electrodes, Oz and Fpz, three left hemispheric electrodes, P3, F3 and M1 (left mastoid) and three corresponding right hemispheric electrodes, P4, F4 and M2 (right mastoid). The reference electrode was placed at Cz and the ground electrode at the right clavicle. Inter-electrode impedances were kept below 5 kOhm at 30 Hz. The electrodes were connected to a low-noise Jaeger-Toennies multichannel amplifier. Each EEG channel was amplified with a gain of 50000 and band-pass filtered between 0.2 and 100 Hz (6 dB/octave) for 4 Hz and between 2 and 100 Hz (6 dB/octave) for the 20 Hz modulation. Because the ASSR is a frequency-specific response, these filter settings only served to minimize the number of artifacts in the EEG. The amplified EEG signals were recorded and stimuli were presented by a RME Hammerfall DSP Multiface multichannel soundcard in combination with the experimental Setup ORL for Multichannel ASSR (SOMA) (Van Dun et al., 2008) at a sampling rate of 32 kHz and downsampled to 1 kHz. The continuous EEG was recorded in epochs. Each epoch consisted of 1024 samples (corresponding to 1.024 seconds). Sixteen successive epochs were clustered into a sweep. Online artifact rejection was set to 100 µV, to exclude muscle artifacts. For each stimulus, 18 artifact-free sweeps were recorded. The EEG was recorded in a double-walled and soundproof booth with a Faraday cage. Participants were asked to lie down on a bed and to watch a soundless movie to stay alert. Two ASSR recordings were carried out for each stimulus within the same session.

4.2.3.3. Data processing

Data analyses were performed by means of Matlab R14. Ten percent of the recorded epochs, i.e., those with the largest noise values, in each recording were rejected to exclude artifacts. Sweeps were reconstructed by clustering 16 consecutive noise-free epochs. For each recording, the remaining 16 sweeps of EEG were weighted-averaged in the time domain and transformed into the frequency domain using a Fast Fourier Transform (FFT). Because the test and retest did not differ significantly, both recordings were linked together and FFT statistics were carried out over the linked data, i.e., after 32 sweeps. Data-analyses was performed on response-SNRs of

parietal (P3, P4) and mastoid electrodes (M1, M2) (for a detailed description of the data analysis see: Poelmans et al., 2012a). For these electrode pairs interhemispheric phase coherence was calculated, according to the following formula:

$$C_{12}(f) = \frac{|W_{12}(f)|^2}{(W_{11}(f) \times W_{22}(f))}$$

Phase coherence is based on the degree of synchronicity between neuronal networks in both hemispheres and is a sensitive marker of functional connectivity between distant brain regions involved in the same process. It is calculated as a correlation in the time domain between two signals, recorded simultaneously at different scalp electrodes at a given frequency or frequency band. The coherence at frequency f between signals 1 and 2 indicated as C12(f) is calculated as the squared magnitude of the cross-spectral density of the signal pair W12(f), normalized by dividing with the product of the power spectra of the two signals, respectively W11(f) and W22(f) (Nunez & Srinivasan, 2006). Coherence values range between zero and one. Low interhemispheric coherence indicates no synchronization between active brain regions in the left and the right hemispheres, whereas high coherence indicates a high degree of synchronized neuronal activity between both hemispheres. For 4 Hz and for 20 Hz, interhemispheric phase coherence was calculated separately for parietal and mastoid electrodes and averaged into one measure for interhemispheric coherence for each modulation rate.

4.2.4. Statistical analyses

In the group analyses and the correlations, the quality of the DTI data acquisition (indexed by mean chi square) and IQ were used as a covariate. In the ASSR-group analyses only IQ was included. All correlational analyses were checked for possible outliers, defined as a standardized residual > 3. One normal reading subject had an outlying value, and was therefore excluded from the correlational analysis.

4.3. Results

4.3.1. DTI-measures in dyslexic versus normal readers

A lateralization index based on the left and right FA-values in STGp, AF and IFGop was calculated and compared between dyslexic and normal readers. In addition, FA

of CCsplenium was extracted and compared between both reading groups. Concerning the STGp, normal readers demonstrated a significant left FA-lateralization ($t(19) = -4.53$, $p < 0.001$), whereas dyslexic readers rather showed a symmetric FA-distribution ($t(19) = -0.26$, $p = 0.801$). Group comparison confirmed that dyslexic readers had a significantly lower degree of left lateralization than normal readers ($F(1, 36) = 5.79$, $p = 0.021$) (Figure 4.2, left panel).

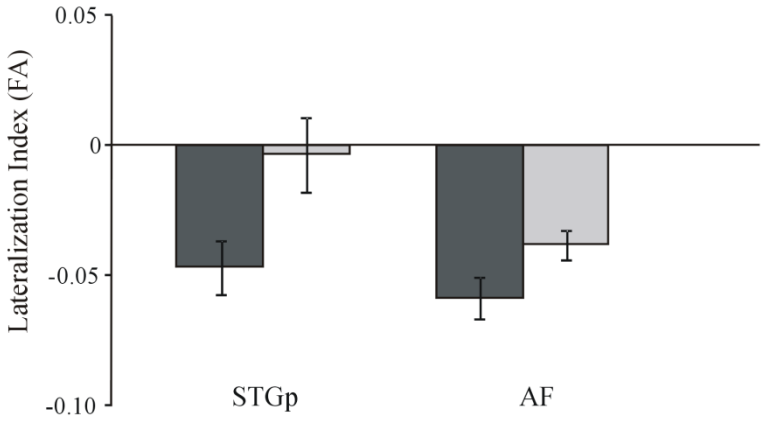


Figure 4.2 Average FA-lateralization indices of STGp and AF, which showed a significant difference between normal (dark bars) and dyslexic (light bars) readers. Error bars indicate ± 1 SE.

This group difference in STGp lateralization was rooted in a non-significant tendency of a lower FA in the left and a higher FA in the right STGp in dyslexic relative to normal readers ($p > 0.17$). The individual distribution of lateralization indices is displayed in the left panel of Figure 4.3, and indicates that dyslexic readers have a lower lateralization index than normal readers, and additionally, a lower number of dyslexic individuals have a left lateralization (i.e. a negative lateralization index in 17 of the 20 normal readers versus 12 of the 20 dyslexic readers).

Concerning the AF, we described in a previous paper (Vandermosten et al., 2012a) that dyslexic readers showed a significant lower FA in the left AF but not in the right compared to normal readers. This could suggest a group difference in the lateralization index, which we calculated in the present study. Results indicated a significant left lateralization for both normal reading ($t(19) = -7.34$, $p < 0.001$) and dyslexic ($t(19) = -6.51$, $p < 0.001$) readers, but this left FA-lateralization was again less prominent in dyslexic than in normal readers ($F(1,36) = 4.39$, $p = 0.043$) (Figure

4.2, right panel). The individual lateralization distribution (Figure 4.3, right panel) demonstrates that almost every normal and dyslexic reader exhibits a left lateralization (i.e. negative lateralization index), but that dyslexic readers show this to a lesser extent.

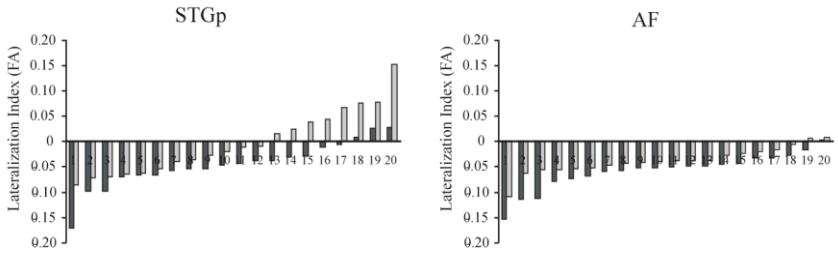


Figure 4.3 Individual distribution of the lateralization indices of the STGp and AF for normal (dark bars) and dyslexic (light bars) readers.

For the IFGop, a significant left FA-lateralization was found for both normal reading ($t(19) = -7.49$, $p < 0.001$) and dyslexic adults ($t(19) = -7.22$, $p < 0.001$). Group comparison of the IFGop lateralization, however, did not reveal a group difference in this structure ($F(1, 36) = 0.78$, $p = 0.383$). Similarly, for the CCsplenium no group differences in FA were found between normal reading and dyslexic adults ($F(1, 36) = 0.19$, $p = 0.668$).

To conclude, while the CCsplenium and IFGop did not demonstrate any difference between normal reading and dyslexic adults, group differences were found in the lateralization of STGp and AF. More specifically, STGp and AF display a left FA-lateralization in normal readers, whereas in dyslexic readers a symmetric FA-pattern in STGp and a less pronounced left FA-lateralization in AF is observed.

4.3.2. ASSRs to phonemic- and syllabic-rate modulations in dyslexic versus normal readers

In a previous study, we described that adults with dyslexia demonstrated reduced phase coherence between the left and the right hemisphere for phonemic-rate but not for syllabic-rate responses (Poelmans et al., 2012a). In the present study, this group

difference was still present in a subgroup of this sample (N = 40 instead of N = 60), however, effects were only approaching significance, probably due to diminished statistical power. As shown in Figure 4.4, normal reading adults demonstrated higher interhemispheric coherence than dyslexic adults for 20 Hz (mean difference: 0.10, SE: 0.06, $F(1, 37) = 2.75$; $p = 0.105$) (for N = 60: mean difference: 0.11, SE: 0.05, p = 0.040). For 4 Hz, on the other hand, interhemispheric coherence did not differ between groups (mean difference: -0.02, SE: 0.04, $F(1, 37) = 0.19$, $p = 0.664$) (for N = 60: mean difference: -0.02, SE: 0.03, p = 0.516).

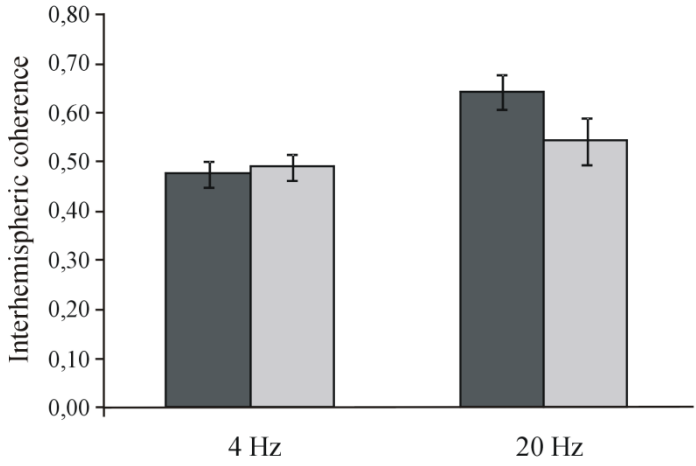


Figure 4.4 Interhemispheric coherence for 4 and 20 Hz, for normal reading (dark bars) and dyslexic (light bars) adults. Error bars indicate ± 1 SE.

4.3.3. Correlations of DTI- with ASSR-measures

The left panel of Table 4.2 presents correlations between the FA-lateralization in STGp and interhemispheric coherence for 4 and 20 Hz ASSRs in normal and dyslexic readers. In normal readers, a negative correlation between FA-lateralization in STGp and interhemispheric coherence for 20 Hz was found, suggesting that stronger interhemispheric coherence for 20 Hz ASSRs coheres with left FA-lateralization in STGp (r = -0.57, p = 0.016). In contrast, a positive (i.e. right lateralization), though not significant, correlation was found in dyslexic readers. This apparent reversed correlation pattern between normal and dyslexic readers was indeed significant (z = 2.44, p = 0.015). Regarding interhemispheric coherence for 4

Hz, there was no clear correlation with FA-lateralization of STGp in normal or dyslexic readers, as well as no difference in correlations between normal reading and dyslexic adults.

Table 4.2 Correlations between FA-lateralization of STGp and FA of the CCsplenium, and interhemispheric coherence for 4 and 20 Hz in normal (NR) and dyslexic readers (DR)

	STGp		**Fisher z**	**CCsplenium**		**Fisher z**
	NR	*DR*	NR vs. DR	*NR*	*DR*	NR vs. DR
4 Hz	0.10	-0.26	*p = 0.285*	*-0.11*	*0.19*	*p = 0.379*
20 Hz	**-0.57 ***	0.35	***p* = 0.015**	**-0.41 (*)**	**0.47***	***p* = 0.006**

(*) $p < 0.10$, * $p < 0.05$

Concerning the FA-lateralization in AF and IFGop, no significant correlations were found with interhemispheric coherence for 4 Hz and 20 Hz in normal, nor in dyslexic readers (all $|r| < 0.28$; $p > 0.259$).

Similar to STGp, normal reading and dyslexic adults demonstrated a reversed correlation pattern between interhemispheric coherence for 20 Hz and FA in CCsplenium. In normal reading adults, a negative correlation was found between FA in CCsplenium and interhemispheric coherence for 20 Hz whereas in dyslexic adults FA in CCsplenium correlated positively with interhemispheric coherence for 20 Hz (Table 4.2, right panel). This indicates that in normal readers, stronger interhemispheric coherence for 20 Hz is related to decreased FA in CCsplenium, whereas stronger interhemispheric coherence for 20 Hz related to higher CCsplenium FA in dyslexic readers. This correlational pattern was statistically different between normal and dyslexic readers ($z = -2.76$, $p = 0.006$). For 4 Hz, correlations between FA in CCsplenium and interhemispheric coherence were not significant, and did not differ between normal reading and dyslexic adults ($z = -0.88$, $p = 0.378$).

4.4. Discussion

In this study, we examined structural FA-lateralization of the dorsal white matter tract (i.e. AF) and its endpoints (i.e. STGp and IFGop) in a sample of normal

reading and dyslexic adults for whom group differences in functional interhemispheric connectivity at 20 Hz AM have been reported previously (Poelmans et al., 2012a). The unique contribution of the present study is that we investigated the association between interhemispheric coherence (using ASSR) and white matter lateralization (using DTI). Moreover, we examined whether this relation is different for interhemispheric coherence of 4 and 20 Hz AM, representing phonological information at the syllable- and phoneme-level, respectively. The combination of ASSR and DTI revealed that the degree of white matter lateralization in STGp and white matter integrity in CCsplenium was related to the amount of synchrony between neural ensembles in both hemispheres. Moreover, this association was specifically found for phonemic-rate envelope information and was different for normal reading and dyslexic adults.

4.4.1. Structural lateralization in normal and dyslexic readers

Concerning our DTI-results, normal readers demonstrated a leftwards FA-lateralization of important structures on the dorsal phonological pathway, i.e. STGp, IFGop and their connection via AF. Numerous studies have reported leftward volumetric asymmetries in the planum temporale and its surrounding areas (e.g. review Shapleske et al., 1999) and to a certain extent also in IFG (Falzi et al., 1982; Foundas et al., 1998; Amunts et al., 1999). Yet limited evidence is available on lateralization of the microstructural properties of white matter, besides a post-mortem study showing more myelination in left versus right superior temporal cortex (Anderson et al., 1999) and DTI-studies showing higher FA in left versus right AF (Thiebaut de Schotten et al., 2011; Catani et al., 2007; Büchel et al., 2004; Hagmann et al., 2006; Lebel & Beaulieu, 2009; Nucifora et al., 2005; Powell et al., 2006). Our results extend these findings by showing left dominance of FA not only in the AF and its posterior connection point (i.e. STGp), but also in its frontal projection point (i.e. IFGop). In addition, we demonstrate that in dyslexic readers this left FA-asymmetry is not found in STGp, and only to a smaller extent in AF.

An abnormal lateralization in dyslexic readers is supported by early post-mortem and imaging studies finding a reduced volumetric asymmetry in the planum temporale, though more recent studies could not replicate this (Eckert & Leonard, 2000). Concerning lateralization of microstructural white matter properties, only one DTI-study in dyslexic readers explicitly investigated FA-asymmetry in a dyslexic sample (Niogi & McCandliss, 2006). In line with our results, they reported a

decreased left FA-lateralization in the temporoparietal region for dyslexic readers, though this region was located medially to the STGp and AF where we identified lateralization differences. It thus seems that left FA-lateralization in posterior language areas is important for an adequate reading performance, and this questions whether there is also a link with the underlying processes of reading, such as auditory and phonological processing. Given the hierarchical model of auditory processing (Hickok & Pöppel, 2004), asymmetry of STGp is expected to be more important for spectrotemporal acoustic analysis whereas asymmetry of AF is more important for high-level phonological processing. The latter was indeed supported by a recent DTI-study, which showed a link between good cognitive performance on a phonological test and leftward asymmetry of the AF in a large group of typical developing children and adults (Lebel & Beaulieu, 2009). The role of spectrotemporal processing in relation to FA-lateralization, especially of the superior temporal cortex, was however still unexplored, though it could assist in disentangling the neural basis of auditory processing problems in dyslexic readers.

4.4.2. Functional phonemic- and syllabic-rate processing in normal and dyslexic readers

In the light of the auditory temporal processing deficit in dyslexia, neural auditory processing was evaluated for phonemic- and syllabic-rate (i.e. 20 Hz and 4 Hz modulation respectively) with ASSRs. The present study only found a trend towards lower interhemispheric phase coherence at 20 Hz for dyslexic compared to normal reading adults. However, we assume that this non-significant group difference is due to reduced statistical power for two reasons. First, dyslexic adults demonstrated significantly lower interhemispheric coherence than normal readers in an expanded sample of the present study (Poelmans et al., 2012a). Second, whereas the sample size is reduced by one third, the average group difference (0.10 in the present sample, 0.11 in Poelmans et al., 2012a) and standard error (SE: 0.06 in the present sample, SE: 0.05 in Poelmans et al., 2012a) remained comparable. The lack of a significant group difference in the present study can thus most likely be attributed to the lower number of participants. We therefore conclude that dyslexic readers display phonemic-rate processing difficulties. Whereas reduced phase coherence in individuals with a reading disability (although not necessarily dyslexia) has previously been found during an active visuo-spatial attention task (Dhar et al., 2010) or during rest (Marosi et al., 1995; Shiota et al., 2000; Barry et al., 2009), it

was never investigated in the auditory domain in a dyslexic population. Until recently, only evidence existed for lowered phase-locking strengths in individuals with dyslexia. While some studies associated this with a syllabic-rate phase locking reduction in the right hemisphere (Hämäläinen et al., 2012a; Abrams et al., 2009), others found evidence for reduced phonemic-rate phase locking in the left hemisphere in adults with dyslexia (Lehongre et al., 2011; Poelmans et al., 2012a).

Our results extended these findings by showing that this left hemispheric phase locking reduction is accompanied with reduced intra- and interhemispheric coherence (Poelmans et al., 2012a). Interestingly, phonemic-rate phase locking related to phonological processing (Lehongre et al., 2011; Poelmans et al., 2012a), suggesting that the quality by which phonemic-rate information is processed in superior temporal cortex influences further phonological processing, presumably in the AF (Vandermosten et al., 2012a). Given that these modulations may not be directly generated in the superior temporal cortex (Giraud et al., 2000; Liégeois-Chauvel et al., 1999; Liégeois-Chauvel et al., 2004), a wide network of intra- and interhemispheric connections may be necessary for the integration of phonemic-rate acoustic information in the left hemispheric phonological system. Consequently, if phonemic-rate information is insufficiently maintained throughout this network, it may be inadequate to build well-defined phonological representations in the dorsal phonological system. Given that functional connectivity is largely supported by white matter tracts (Greicius et al., 2009), a central focus of the present study is the link between interhemispheric connectivity for temporal processing (via ASSR) and lateralization and integrity of white matter (via DTI). Despite its relevance, the link between neurophysiologic and DTI measures is - besides a few exceptions (Teipel et al., 2009; Whitford et al., 2011) - still unexplored. Furthermore, by including dyslexic readers we can examine the link between the functional and structural neural basis of their auditory processing problems.

4.4.3. Does FA-lateralization in STGp relate to functional phonemic- and syllabic-rate processing in normal and dyslexic readers?

In normal readers, better phonemic-rate interhemispheric coherence related to leftwards FA-lateralization of STGp, whereas syllabic-rate coherence did not. Previous studies found substantial evidence that white matter integrity in the left

hemisphere related to reading (Nagy et al., 2004; Beaulieu et al., 2005; Gold et al., 2007; Dougherty et al., 2005) and to phonological awareness (Deutsch et al., 2005; Dougherty et al., 2005; Vandermosten et al., 2012a). However, the link between FA and temporal auditory processing has not been made. Given that the degree of myelination relates to nerve conduction velocity (Jack et al., 1983), it is suggested that left dominance in myelination underlies the left hemispheric preference for processing rapidly changing cues (Zatorre & Belin, 2001; Zatorre et al., 2002). The study of Warrier et al. (2009) partly supports this hypothesis by demonstrating that more white matter volume in the left auditory cortex coheres with neural activity of temporal - and not of spectral - processing, however, they used volumetric measures which are generally too gross to specifically examine the microstructural properties of white matter, such as myelination. Given the positive relationship between FA and myelination (Hüppi et al., 1998; Werring et al., 1999; Wimberger et al., 1995), our study provides, for the first time, indirect evidence that more myelination (i.e. a higher FA) in the left relative to the right STGp is related to better neural processing of fast modulations (such as 20 Hz), and not to slow modulations (4 Hz). This finding supports multi-time resolution models of speech processing (Hickok & Pöppel, 2007; Pöppel, 2003; Ghitza & Greenberg, 2009), which predict that faster, phonemic-rate modulations are lateralized to the left hemisphere. We note however that in infants this functional left asymmetry for fast acoustic information is not consistently found, which leaves open the possibility that the left asymmetry we observed in adults is a reflection of particular learning mechanisms (for a review see Minagawa-Kawai et al., 2011). Alternatively, these models predict right hemispheric activation for slow, syllabic-rate modulations. This prediction was indeed confirmed in a large number of functional neuroimaging (Boemio et al., 2005; Belin et al., 1998; Telkemeyer et al., 2009), as well as EEG/MEG (Abrams et al., 2008; Britton et al., 2009; Luo & Pöppel, 2007) studies, both in adults and in infants (Minagawa-Kawai et al., 2011). However, we did not find a relation between white matter lateralization measures and interhemispheric coherence for the syllabic rate in STGp, neither in IFGop and AF. Although we do not have a final explanation for the lack of correlations in the present study, it may be that this functional right hemispheric lateralization for slow modulation rates is not rooted in microstructural white matter properties such as myelination, or alternatively, in other brain regions than those we investigated. The latter is supported by studies demonstrating a different cortical locus for processing syllables and phonemes (Siok et al., 2003; Peeva et al., 2010). That is, phoneme-level processes were found in the left supplementary motor area, pallidum, posterior superior temporal gyrus, and superior

lateral cerebellum (Peeva et al., 2010) or in the left inferior prefrontal gyri (Siok et al., 2003), whereas syllable-level processes were rather found in the left ventral premotor cortex (Peeva et al., 2010), or in the left middle frontal cortex (Siok et al., 2003).

Another possible explanation is related to the age of the participants (i.e. adult participants). Given that adults' phonological awareness is more tuned to the phoneme level, it might be that -in parallel to their phonological development- adults only display correlations for phonemic-rate acoustic modulations, whereas infants or young children who are more tuned to the syllable level, might also display correlations for the syllabic-rate modulations. The latter is indeed confirmed by previous studies in children (e.g. Abrams et al., 2009)

In dyslexic readers, no significant relation between FA-lateralization of STGp and interhemispheric coherence for 20 Hz, or for 4 Hz was found. However, assuming the absolute correlation values, in dyslexic readers better phonemic-rate phase locking tends to relate to right lateralization of STGp. This reversed correlational pattern was confirmed by a significant group difference in correlations between dyslexic and typical readers. It is possible that poor readers implement a compensatory mechanism for a less effective left hemispheric network. If phonemic-rate acoustic information is insufficiently maintained to be integrated in the left dorsal pathway, it may be that dyslexic readers compensate this by depending more than normal readers on a right hemispheric network. Indeed, Hoeft et al. (2011) found that dyslexic readers use the right AF to compensate their literacy problems. Compensation by activation in the right hemisphere is also commonly reported in a large variety of language deficits, including dyslexia. However, it rarely compensates all aspects of the behavioural profile (Kell et al., 2009; Lehongre et al., 2011; Preibisch et al., 2003). Second, it is possible that the formation of phonological representations of dyslexic readers relies on acoustic information of larger or smaller time chunks than the phonemic rate. Indeed, studies have shown that dyslexic readers phase locked better than normal readers to rates higher (50 - 70 Hz: Lehongre et al., 2011) or lower (10 Hz: Hämäläinen et al., 2012a) than the phonemic-rate. If phonological representations were based on acoustic information on a different timescale, they would be over- or underspecified and may be linked to the reading problems in dyslexia.

4.4.4. Does FA in CCsplenium relate to functional phonemic- and syllabic-rate processing in normal and dyslexic readers?

Given that dyslexic readers displayed a symmetric FA-pattern in STGp, which in turn did not display the typical correlation with interhemispheric coherence of 20 Hz, we examined whether this was rooted in abnormalities of the white matter fibers underlying this interhemispheric connection. A limitation of conventional DTI is that fibertracking is hindered by crossing fibers (Mori, 2007), which impedes the direct reconstruction of the fibers connecting the left and right STGp. Nevertheless, from post mortem research it is known that the fibers maintaining this connection run through the splenium of the CC (Westerhausen et al., 2009), and we therefore delineated the fibers passing through that region. Our data showed a significant correlation between interhemispheric coherence for 20 Hz and FA in CCsplenium for both normal and dyslexic readers, which agrees with independent evidence that the integrity of the corpus callosum influences interhemispheric coherence (Teipel et al., 2009; Pogarell et al., 2005). Given that fMRI (Shaywitz et al., 2003; 2007), DTI (Hoeft et al., 2011) and EEG (Dujardin et al., 2011) studies have suggested that dyslexic readers recruit right hemisphere areas to compensate for poor left hemisphere functioning, interhemispheric connectivity, both structurally and functionally, is especially important in dyslexia. Macrostructure studies of the CC in dyslexia are inconsistent, but several studies have shown a difference in the posterior CC, particularly in the splenium (Duara et al., 1991; Rumsey et al., 1996). Also at the microstructural level, two recent DTI-studies have pointed out group differences in the posterior part of the CC, with dyslexic readers having a higher FA than typical readers (Odegard et al., 2009; Frey et al., 2008). Under the assumption that the CC plays an integrative role in hemispheric lateralization, it might be that a better structural connectivity of the splenium in dyslexic readers (as reflected by a higher FA) coheres with an atypical hemispheric asymmetry. Previous studies in a typical population have indeed shown an inverse relation between indices of lateralization and colossal size (Witelson & Goldsmith, 1991) and colossal FA (Westerhausen et al., 2004; 2006; but see Putnam et al., 2008 for a positive relation). Given that the splenium region is crucial in connecting the left and right STGp (Westerhausen et al., 2009), it might thus be that the better structural connection of the splenium in dyslexic readers, as shown in previous DTI-studies, underlies the lower asymmetry we observed in STGp for our dyslexic readers. Although our results could not

confirm FA group differences in CCsplenium, we did find an opposite correlational pattern between both reading groups. In dyslexic readers FA in CCsplenium related positively with 20 Hz interhemispheric transfer, whereas this was negative in typical readers. Furthermore, we know from our ASSR-results that our dyslexic participants had lower interhemispheric coherence for 20 Hz than typical readers (Poelmans et al., 2012a). Our present results might indicate that those dyslexic readers that have a more synchronized neural network for 20 Hz also have a higher structural connectivity in the splenium of the CC as well as a more symmetric FA-pattern in STGp. Based on the present results, we therefore hypothesize that, relative to normal readers, dyslexic readers compensate their phase locking reduction to the phonemic rate by relying more on the right STGp via a better structural connection in the splenium of the CC.

4.4.5. An integrative model for dyslexia?

By the combination of the present results together with those of previous studies in largely the same sample (Vandermosten et al., 2012a; Poelmans et al., 2012a) we suggest a speculative model on acoustic and phonological processing. First, the present study shows that neural interhemispheric synchrony to the phonemic rate depends in a typical population on a structural left dominance of white matter integrity in STGp (analogue to a functional leftward dominance for fast modulations (Zatorre & Gandour, 2008). Second, in a previous ASSR study, in which the present sample was extended up to 60 subjects, a link has been demonstrated between interhemispheric synchrony to the phonemic rate and speech-in-noise perception (Poelmans et al., 2012a). Third, in a previous DTI-report involving the same sample as the present study (Vandermosten et al., 2012a), it was demonstrated that speech-in-noise perception was positively correlated with the left and negatively with the right AF, which suggests that optimal processing of the phonological aspects of speech perception depends on a structural left dominance of white matter integrity in the AF. Based on these three findings, we hypothesize that optimal left asymmetry of white matter integrity in STGp is crucial for an adequate neural transfer of phonemic-rate information, and that the quality by which these acoustic modulations are processed will reflect on further phonological processing.

Anatomically, these phonological processes seem to take place in the AF (which connects with STGp). This might imply that, analogue to the importance of left FA-lateralization in STGp to optimally process phonemic-rate acoustic modulations, left

FA-lateralization of the AF might mediate processes depending on phonological representations, such as the perception of speech in noise. In contrast to this pattern, the present study shows that dyslexic readers are unable to develop sufficient FA-asymmetry in STGp, which corroborates their difficulties in neural transfer of phonemic-rate information. Given that left asymmetry in STGp is not related to slow modulations, such as syllabic-rate information, the decreased left dominance in dyslexic readers does not affect auditory transfer of syllabic modulations and therefore no group differences are observed in neural interhemispheric synchrony to syllabic-rate information. However, the decreased asymmetry in STGp and inadequate synchrony to phonemic-rate information can reflect on the further phonological analysis and on building well specified phonological representations at the phoneme level. This might be evidenced by a decreased left asymmetry in the AF and by their deviant performance on phonological tasks reported in Vandermosten et al. (2012a). Thus, the consistent decreased left dominance demonstrated with the present results as well as a decreased functional (Poelmans et al., 2012a) and structural (Vandermosten et al., 2012a) *intra*hemispheric connectivity in the left hemisphere, might indicate that dyslexic readers tend to rely on a less developed network. Friederici (2011) has demonstrated that during typical development the functional language network evolves from reliance on interhemispheric towards left intrahemispheric connections. At the structural level, this finding is supported by developmental DTI-studies showing an early maturation of the CC and a late maturation of the AF (Lebel & Beaulieu, 2009). Though there is some evidence available in literature that the posterior part of the CC is more developed in dyslexic relative to typical readers, reflected by a higher FA (Odegard et al., 2009; Frey et al., 2008), the present study could not replicate this result. Nevertheless, our results do suggest a compensatory role of the CCsplenium in interhemispheric transfer of phonemic-rate modulation, possibly being more processed in the right STGp than in normal readers.

Although our study was able to demonstrate significant group differences (normal versus dyslexic readers) and correlations between FA-lateralization and functional coherence at phonemic-rate modulations, we acknowledge that the obtained effects are only modest and some effects close to be significant. Nevertheless, we believe that our results provide valuable and unique information on the interaction between structural white matter lateralization and processing of rapidly changing auditory information, which is of particular interest to aetiology theories of dyslexia. Further development of the neurological techniques (e.g. ASSRs with high-density recordings and coherence analyses at the source level, or the possibility to

reconstruct crossing fibers with DTI) might be necessary to reduce variability in the data and to further unravel the hypotheses we postulated here.

4.4.6. Conclusion

The present study reveals that dyslexic readers have a decreased left lateralization of white matter integrity in auditory and dorsal language regions as well as a decreased neural synchronization for phonemic- but not for syllabic- modulations. Given that previous studies indicate that neural processing of phonemic versus syllabic modulations is rooted in interhemispheric functional differences, the central aim of the present study was to investigate whether this lateralization pattern is also present at the structural level, specifically in white matter properties, and whether dyslexic readers display a deviant lateralization pattern. Our results reveal that normal readers display a link between neural interhemispheric response for phonemic modulations and left FA-lateralization in STGp, in line with functional lateralization studies, whereas dyslexic readers display a trend towards the opposite pattern, with a tendency to relate more to right lateralization. Additionally, interhemispheric coherence for fast modulations related differently to FA in CCsplenium for normal than for dyslexic readers. We conclude that we find a trend that deficient neural synchronization for fast modulations coheres with dyslexic's decreased left lateralization in STGp. This might in its turn affect further phonological processing, which seems to be reflected in a decreased left lateralization of AF and IFGop. Possibly, dyslexic readers compensate their lack of left lateralization, necessary for fast acoustic cues and phonological processing, by more interhemispheric white matter connections.

Chapter 5
Auditory temporal processing in children with dyslexia

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Abstract
The aetiology of developmental dyslexia remains widely debated. An appealing theory postulates that the reading and spelling problems in individuals with dyslexia originate from reduced sensitivity to slow-rate dynamic auditory cues. This low-level auditory deficit is thought to provoke a cascade of effects, including inaccurate speech perception and eventually unspecified phoneme representations. The present study investigated sensitivity to frequency modulation and amplitude rise time, speech-in-noise perception and phonological awareness in 11-year-old children with dyslexia and a matched normal-reading control children. Group comparisons demonstrated that children with dyslexia were less sensitive than normal-reading children to slow-rate dynamic auditory processing, speech-in-noise perception, phonological awareness and literacy abilities. Correlations were found between slow-rate dynamic auditory processing and phonological awareness, and speech-in-noise perception and reading. Yet, no significant correlation between slow-rate dynamic auditory processing and speech-in-noise perception was obtained. Together, these results indicate that children with dyslexia have difficulties with slow-rate dynamic auditory processing and speech-in-noise perception and that these problems persist until sixth grade.

5.1. Introduction

Developmental dyslexia is characterized by a specific disability in learning to read and write despite adequate intelligence, education and intense remedial effort (Vellutino et al., 2004). It is well established that the majority of individuals with dyslexia demonstrate difficulties in the use and representation of phonological information (Snowling, 2000). A crucial step in the development of phonological representations is the awareness that every speech sound corresponds to a written symbol. Consequently if individuals with dyslexia perceive speech differently than normal-reading individuals, mapping speech sounds onto their corresponding symbols will become more challenging.

The most commonly used measure to assess speech sound processing in individuals with dyslexia is categorical perception. Categorical perception tasks demonstrated that the phoneme categories of individuals with dyslexia are less defined compared to normal-reading individuals (e.g. Vandermosten et al., 2010; for a review, see Vandermosten et al., 2011). However, reported effects were often subtle in that a deficit was only found in a subset of participants with dyslexia (e.g. Adlard & Hazan, 1998; Manis et al., 1997) or group differences were restricted to a specific task (e.g. Maassen et al., 2001) or to specific speech conditions (e.g. Blomert & Mitterer, 2004; Cornelissen et al., 1996).

Yet, the finding of only a subtle categorical perception deficit in individuals with dyslexia may be attributed to the fact that categorical perception is typically evaluated in quiet listening conditions. Given that speech signals contain redundant auditory information, speech identification performance in quiet can be achieved based on several auditory cues. By presenting speech signals in adverse listening conditions, auditory information becomes less reliable, resulting in speech sound identification based on a reduced amount of auditory cues. It is therefore possible that speech perception in noise is a more sensitive condition to provoke a deficit in individuals with dyslexia. Speech-in-noise perception has previously been investigated in individuals with dyslexia, but results are rather diverse. A number of studies found impaired speech-in-noise perception abilities in individuals with dyslexia (e.g. Bradlow et al., 2003; Chandrasekaran et al., 2009; Wible et al., 2002; Ziegler et al., 2009), suggesting that a core deficit in dyslexia is the inability to extract crucial auditory information from a complex or noisy signal. However, not all studies were able to support this hypothesis (Hazan et al., 2009).

The question is now whether this speech perception deficit is specific to processing speech sounds or whether it stems from deviant perception of low-level auditory cues that constitute speech sounds. Originally, it was proposed that individuals with dyslexia have difficulties processing brief and rapidly successive acoustic cues (Tallal, 1980). Though more recently, the importance of "dynamic" (i.e. "changing over time") auditory information processing in relation to dyslexia has received more attention (for a review, see McArthur & Bishop, 2001). Dynamic auditory cues such as amplitude- (AM) and frequency modulations (FM) are extensively present in speech signals. In particular slowly-varying auditory cues, with modulations between 2 and 20 Hz, provide important information about phonemic and syllabic transitions, and contribute largely to speech intelligibility (Drullman et al., 1994; Shannon et al., 1995). Consequently, imprecise processing of these slow-rate modulations can negatively affect the perception of spoken language and can withhold the development of precise phonological representations (Nittrouer, 2006).

Detection of slow-rate modulations was often found impaired in individuals with dyslexia (McAnally & Stein, 1997; Witton et al., 1998; Menell et al., 1999; e.g. Lorenzi et al., 2000; Rocheron et al., 2002; Witton et al., 2002; Stuart et al., 2006). Yet, not all studies were able to replicate these findings (Hill et al., 1999; e.g. Edwards et al., 2004). Nevertheless, a strong relation between slow-rate modulation detection performance and phonological abilities has been found in school-aged children (Witton et al., 1998; Witton et al., 2002; Stuart et al., 2006; Talcott et al., 1999) as well as in preschoolers (Boets et al., 2008; Boets et al., 2011a). Another important slow-rate auditory cue for speech perception is sound rise time (i.e. the rate of change of the amplitude envelope at the onset of a syllable) (Goswami et al., 2002). In natural speech, sound rise times comprise a combination of dynamic cues, such as changes in intensity, duration, and fundamental frequency, which are important for analyzing prosodic patterns in speech (Goswami et al., 2010) but also for phoneme discrimination (Goswami et al., 2011b). Atypical processing of sound rise time results in the distorted perception of syllable boundaries. Given that infants process spoken language based on its syllable structure, an inability to extract syllable-level information from the speech signal would result in the deficient representation of onset-rime and phoneme information, which both are crucial for literacy acquisition (e.g. Goswami et al., 2002; Ziegler & Goswami, 2005; Pasquini et al., 2007). Studies investigating sound rise time perception found indeed significantly poorer performance of individuals with dyslexia compared to normal-reading individuals (children: Richardson et al., 2004; adults: Hämäläinen et al.,

2005; Pasquini et al., 2007). Additionally, rise time detection tasks were found to relate to reading, spelling, and phonological awareness abilities.

In sum, studies investigating slow-rate dynamic processing and speech-in-noise perception in individuals with dyslexia favour a deficit in both domains. However, only an isolated study assessed both kinds of signals in the same population. Boets et al. (2011a) showed retrospectively that preschool children who later on develop dyslexia were already impaired in slow-rate FM sensitivity and speech perception. These kindergarten measures were related to each other and uniquely predicted later growth in reading. In line with this study, the present study explored slow-rate dynamic auditory processing and speech-in-noise perception abilities in a group of sixth grade children.

The aim of this study was twofold. First, we aimed to investigate the nature of the speech-in-noise perception deficit in children with dyslexia. By presenting sentences in stationary and in temporally fluctuating noise, we were able to explore the influence of the dynamic nature of masking noise on speech perception. If individuals with dyslexia are less sensitive to dynamic variations in auditory signals, reduced sentence intelligibility in the fluctuating noise can be expected. However, if inferior speech-in-noise perception in individuals with dyslexia is the result of an inability to extract relevant auditory information from noisy signals, reduced speech-in-noise perception is expected independent of which kind of noise is presented. Furthermore, as sentences-in-noise perception can be facilitated by top-down influences of semantic information, it can be assumed that a potential speech-in-noise perception deficit is more pronounced in a words-in-noise test. It can therefore be hypothesized that the reduction of possible top-down influences does not affect the presence (or absence) of a speech-in-noise perception deficit but may rather expose the magnitude of the deficit.

Second, in order to investigate the presence of a slow-rate dynamic processing deficit in individuals with dyslexia, a 2 Hz FM-detection task and a rise time discrimination task were conducted. Both tasks tap aspects of slow-rate dynamic processing mechanisms and have repeatedly been proven to be among the most sensitive auditory tasks to identify dyslexia. However, thus far they have never been assessed in the same participants. If both tasks indeed measure the same process, we hypothesize deviant performance on both tasks in individuals with dyslexia.

5.2. Methods

5.2.1. Participants

Fifty-eight 11-year-old children, attending sixth grade of primary school, participated in the study. Children were selected from the sample of Boets et al. (2006) that was longitudinally followed-up. Children were originally divided based on their family risk for dyslexia (i.e. a high-risk group with at least one first degree relative with a formal diagnosis of dyslexia, and a low-risk group with no dyslexic relatives) (Boets et al., 2010).

Literacy achievement was assessed by a standardized word-reading (EMT: Brus & Voeten, 1973) and pseudoword-reading test (Klepel: Van den Bos et al., 1994), and a spelling test (Dudal, 1997), administered in first, third and sixth grade of primary school, resulting in nine literacy scores for each participant (3 literacy tests x 3 test moments). In line with current practice in Belgium and the Netherlands (Gersons-Wolfensberger & Ruijssenaars, 1997), the criterion to diagnose dyslexia took into account both the severity and the persistence of children's literacy problems. In sixth grade, thirteen of the children demonstrated severe literacy problems, defined as performance below the 10^{th} percentile of the norm group on the same standardized literacy task on at least two consecutive test moments. Additionally, they performed below the 50^{th} percentile on all literacy tasks at all test points. These children constitute the dyslexic group. The remaining 45 normal-reading children did not show any reading or spelling difficulties throughout primary school. Based on their family risk for dyslexia, these normal-reading children constitute two separate groups: a group of low-risk normal-reading children (N=25) and a group of high-risk normal-reading children (N=20).

All children were native Dutch speakers, without a history of brain damage, psychiatric symptoms or visual problems. Additionally, all participants had adequate nonverbal intelligence, defined by a standard score above 85 on Raven's progressive matrices (Raven et al., 1984) and adequate audiometric pure-tone hearing thresholds (i.e., 25 dB HL or less from 0.25 – 8.0 kHz) at the test ear.

Table 5.1 shows participant characteristics for the three groups in sixth grade. Groups did not differ in age, gender and nonverbal IQ (all $p > 0.224$). As defined, groups differed in sixth grade word-reading ($F(2, 55) = 22.60$; $p < 0.001$), pseudoword reading ($F(2, 55) = 27.23$; $p < 0.001$) and spelling abilities ($F(2,$

55) = 29.66; $p < 0.001$). Children with dyslexia performed significantly poorer than both normal-reading groups, who themselves did not differ from each other on any of the sixth grade literacy tasks.

Table 5.1 Sixth grade participant characteristics (M ± SD)

	Low-risk normal-reading (*N* = 25)	**High-risk normal-reading** (*N* = 20)	**Dyslexic** (*N* = 13)
Gender (f/m)	11/14	9/11	5/8
Age (years)	11.7 ± 0.3	11.6 ± 0.2	11.6 ± 0.3
Non-verbal IQ	111.9 ± 13.5	104.7 ± 16.6	108.1 ± 8.2
Word-reading[a]	99.2 ± 11.8	88.3 ± 17.0	67.3 ± 15.4
Pseudoword-reading[a]	108.0 ± 11.3	102.3 ± 10.9	79.2 ± 15.0
Spelling[a]	100.4 ± 10.9	93.8 ± 8.4	79.4 ± 9.0

[a] Scores are standardized with population average (M = 100, SD = 15)

5.2.2. Experimental setup

All tasks were performed on a Dell Latitude E6500. The phonological awareness tasks were controlled by E-Prime (Schneider et al., 2002). The auditory and speech perception tasks were controlled by APEX software (Laneau et al., 2005; Francart et al., 2008). Stimuli were presented using an integrated audio PC-card and routed to an audiometer (Madsen OB622), in order to control the presentation level. The stimuli were presented monaurally to the right ear over calibrated TDH-39 headphones at 70 dB sound pressure level (SPL). All tests were administered individually in a quiet room in the children's school. The study was approved by the Committee of Medical Ethics of Clinical Research of KU Leuven. Parents of all children gave a written informed consent.

5.2.3. Tasks

5.2.3.1. Auditory processing tasks

Auditory processing was measured by tasks assessing FM-detection, rise time discrimination and intensity discrimination. Stimuli were generated in MATLAB R14 and saved as 16-bit wav-files (sample frequency 44100 Hz). Thresholds were estimated by means of a one-up, two-down adaptive staircase procedure, which targets the threshold corresponding to 70.7 % correct responses (Levitt, 1971). In all tasks, a threshold run was terminated after eight reversals and the threshold was calculated as the average of the last four reversals. Each participant completed three threshold runs for every experiment and the average of the best two runs was calculated for each task. Prior to data collection, participants were given a short period of practice, comprising supra-threshold trials, to familiarize them with the stimuli and the tasks.

FM-detection

Participants were required to detect a 2 Hz sinusoidal frequency modulation of a 1 kHz carrier tone with varying modulation depth in an adaptive three-alternative forced-choice "odd-one-out" paradigm. Participants were asked to determine which of the three stimuli sounded different from the other two. The detection threshold was defined as the minimum depth of frequency deviation (in Hz) required to detect the modulation. Modulation depth of the target stimulus decreased with a factor 1.2 from 100 Hz towards 11 Hz. From a frequency deviation of 11 Hz, a step size of 1 Hz was used. The reference stimulus was a pure tone of 1 kHz. The length of both the reference and the target stimulus was 1000 ms including 50 ms cosine-gated onset and offset. The inter-stimulus-interval (ISI) was 350 ms.

Sound rise time discrimination

Rise time sensitivity was measured by an adaptive two-alternative forced-choice AXB paradigm. In each trial three stimuli were presented. The middle stimulus was used as a fixed reference stimulus. Children were asked to identify the stimulus that differed from the reference stimulus. Stimuli consisted of speech-weighted noises with linear amplitude rise times. The stationary speech-weighted noise was identical to the stationary noise used in the speech-in-noise tests for sentences. Rise times

varied logarithmically between 15 ms and 300 ms in 40 steps. The total duration of the stimuli was fixed to 800 ms, including a linear fall time of 75 ms. The stimulus with the shortest rise time (15 ms) was used as the reference stimulus in every trial. The ISI was 350 ms. Discrimination thresholds were defined as the minimal difference in rise time required to discriminate between the reference and the target stimulus.

Intensity discrimination

The intensity discrimination task was identical to the rise time discrimination task. A two-alternative forced-choice AXB paradigm was used to measure intensity discrimination thresholds. In each trial, the middle of three stimuli was used as a fixed reference stimulus. Children were asked to identify the stimulus that was different from the reference stimulus. Stimuli consisted of speech-weighted noise with a total duration of 800 ms, including a linear rise time and fall time of 75 ms each. The most silent stimulus (70 dB SPL) was used as the reference stimulus in every trial. Intensity varied linearly between 70 dB SPL and 80 dB SPL in 40 steps of 0.25 dB SPL each. The ISI was 350 ms. Discrimination thresholds were defined as the minimal intensity difference (in dB SPL) required to discriminate between the reference and the target stimulus. The intensity discrimination task was designed as a control task for two reasons. First, this task controls for cognitive demands related to the experimental task procedure. Second, the intensity discrimination task controls for the possible influence of intensity discrimination ability on the performance of the rise time discrimination task.

5.2.3.2. Speech-in-noise perception

Speech-in-noise intelligibility was assessed for phonemes and sentences. In both tests, the level of the background noise was fixed at 70 dB SPL, whereas the speech level varied. Speech and noise were presented through Sennheiser HDA 200 headphones to the right ear.

Words-in-noise perception

This test assessed the perception of CVC words presented in noise. The CVC words were obtained from Flemish recordings of the NVA list, consisting of 15 sublists of 33 target phonemes spoken by a male speaker (Wouters et al., 1994). The stationary

speech-weighted noise of the NVA was used as masking noise. Before administering the six experimental word lists, a practice list was conducted at 0 dB signal-to-noise ratio (SNR). Subsequently, 3 x 2 lists were presented at SNRs of -4 dB, -7 dB and -10 dB. Participants were instructed to repeat every perceived phoneme when the entire word was not perceived. The percentage of correctly perceived phonemes was then calculated for each list and averaged over the two lists presented at identical SNRs. For every participant, a logistic function relating the percentage correct responses to SNR level was fitted to the data and the Speech Reception Threshold (SRT, i.e. the signal-to-noise ratio at which 50% of phonemes is correctly perceived) was calculated.

Sentences-in-noise perception

Speech-in-noise intelligibility for sentences was assessed for a stationary speech-weighted noise and for a fluctuating ICRA noise (Dreschler et al., 2001). Speech material for both conditions consisted of Flemish sentences, available as the Leuven Intelligibility Sentence Test (LIST), spoken by a female speaker (van Wieringen & Wouters, 2008). In the stationary noise condition, sentences were presented in a stationary speech-weighted noise, derived from white noise that was spectrally weighted to the average spectrum of the spoken LIST-sentences. In the fluctuating noise condition, LIST-sentences were presented in a fluctuating ICRA5-250 noise. This noise was a modified version of the ICRA5 noise with a maximum pause length of 250 ms (Wagener et al., 2006). For both conditions, three lists of 10 sentences were presented. SRTs were determined adaptively by means of a one-up, one-down paradigm with a step size of 2 dB. A response was considered correct if all the key words of the sentence were repeated correctly. After determining the level of the (imaginary) 11^{th} item, the SRT was calculated on the basis of the last six levels (see van Wieringen & Wouters, 2008, for details). The two best SRTs out of the three lists of the same noise condition were averaged to compute a mean SRT for each noise condition.

5.2.3.3. Phonological Awareness

Phonological awareness (PA) was assessed by a phoneme deletion and a spoonerisms task.

Phoneme deletion

The phoneme deletion task consisted of three blocks of eight pseudowords. Every trial contained a spoken pseudoword followed by a single phoneme. Participants had to name the remaining pseudoword after omission of this target phoneme. Before every block, two practice items were present. The first block involved the deletion of the second phoneme of a one-syllable pseudoword with onset cluster. The second block required the deletion of the penultimate phoneme of a one-syllable pseudoword with offset cluster. In the last block, the middle phoneme of a two-syllable pseudoword had to be deleted. Performance on this task was assessed by the number of correct responses (max: 24).

Spoonerisms

The spoonerisms task also consisted of three blocks of eight (pseudo)word pairs. In every trial two (pseudo)words were presented. Participants were asked to exchange the initial letters of both (pseudo)words. Each block was preceded by two practice items. The first block involved two words with a single consonant onset. The second block comprised two words with a consonant cluster onset. In the last block, two pseudowords with a single consonant onset were presented. Performance was assessed by the number of correct responded (pseudo)words (max: 48).

5.2.4. Statistical analyses

Statistical analyses were performed with SPSS. Only on the words-in-noise test did one normal-reading child show outlying performance (> 3 SD of its group mean). Data from this participant were left out of the words-in-noise analyses. All statistical tests were two-tailed ($\alpha = 0.05$). Reported p-values were Bonferroni corrected when necessary.

5.3. Results

5.3.1. No differences between low-risk and high-risk normal-reading children

We first investigated the presence of any differences in performance between the normal-reading children at high versus low family risk. A univariate ANOVA

showed that groups did not differ for phoneme deletion ($F(1, 43) = 0.06$; $p = 0.808$), spoonerisms ($F(1, 43) = 0.27$; $p = 0.607$), FM sensitivity ($F(1, 43) = 0.21$; $p = 0.646$), rise time discrimination ($F(1, 43) = 0.17$; $p = 0.680$) or intensity discrimination ($F(1, 43) = 0.05$; $p = 0.827$). A repeated measures ANOVA for speech-in-noise intelligibility, with stimulus type (sentences fluctuating versus sentences stationary versus words stationary) as within-subject factor and group (low-risk normal-reading versus high-risk normal-reading) as between-subject factor, revealed no main effect of group ($F(1, 42) = 1.24$; $p = 0.272$), nor a significant noise type x group interaction ($F(2, 84) = 0.07$; $p = 0.926$). Since the normal-reading children at high versus low family risk did not differ from each other on any of the measures for literacy, phonology, auditory processing and speech perception, both groups were collapsed into one normal-reading group, in order to compare performance with those of children with dyslexia.

5.3.2. Performance of dyslexic versus normal-reading children

Table 5.2 provides summary statistics for phonological processing, auditory processing and speech perception in the normal reading and dyslexic reading children. Children with dyslexia demonstrated significantly poorer performance on phoneme deletion ($F(1, 56) = 29.47$; $p < 0.001$) and spoonerisms ($F(1, 56) = 33.06$; $p < 0.001$). Significantly poorer performance was also observed for FM-detection ($F(1, 56) = 9.92$; $p = 0.003$) and rise time discrimination ($F(1, 56) = 5.80$; $p = 0.019$). In contrast, no group difference was found for the intensity discrimination task ($F(1, 56) = 2.68$; $p = 0.107$).

Table 5.2 Average performance on low-level auditory processing and speech-in-noise perception tasks

	Normal-reading *(N=45)*		**Dyslexic** *(N=13)*	
	M	***SD***	**M**	***SD***
Phoneme deletion	19.5	*2.7*	13.6	*5.4*
Spoonerisms	38.0	*6.2*	24.1	*11.6*
FM-detection (Hz)	5.2	*1.9*	7.5	*3.2*
Rise time discrimination[a] (step)	22.4	*7.9*	16.6	*6.9*
Rise time discrimination[b] (ms)	70.1	*50.1*	104.0	*61.8*
Intensity discrimination[a] (step)	32.7	*3.4*	30.8	*4.4*
Intensity discrimination[c] (dB)	1.8	*0.8*	2.3	*1.1*
Sentences in stationary noise (SRT)	-7.3	*1.1*	-6.7	*0.8*
Sentences in fluctuating noise (SRT)	-12.1	*1.8*	-11.3	*1.8*
Words in stationary noise[d] (SRT)	-8.6	*1.6*	-7.9	*1.1*

[a] Stimulus number (max: 40)
[b] Rise times reliably distinguished from the standard stimulus (15 ms rise time)
[c] Just noticeable difference (JND) in dB SPL
[d] $N = 57$; data of one normal-reading child were excluded because of outlying performance

A repeated measures ANOVA for speech-in-noise intelligibility revealed a main effect of group ($F(1, 55) = 5.87$; $p = 0.019$), a main effect of stimulus type ($F(2, 110) = 108.62$; $p < 0.001$), but no stimulus type x group interaction ($F(2, 110) = 0.12$; $p = 0.892$). As shown in Figure 5.1, children with dyslexia performed significantly slightly poorer than normal-reading children (mean difference: 0.7 dB, SE: 0.3 dB), independent of the dynamic nature of the added noise or the used speech material. As expected for sentences-in-noise perception, SRTs for the fluctuating noise condition were better than SRTs for the stationary noise condition (mean difference: 4.7 dB, SE: 0.3 dB, $p < 0.001$). This effect was equal for both groups.

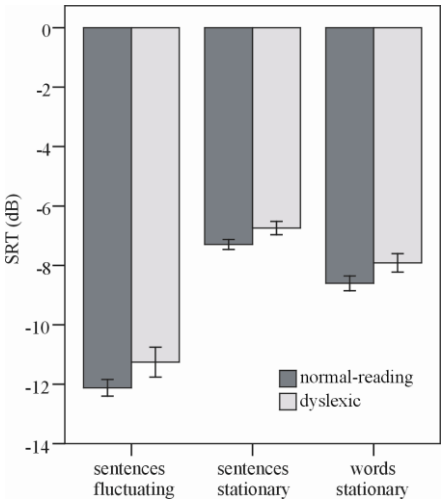


Figure 5.1 Average speech-in-noise intelligibility performance for sentences and words for normal-reading children (dark bars) and children with dyslexia (light bars). Error bars indicate ± 1 standard error of the mean.

5.3.3. Relations between slow-rate auditory processing, speech perception, phonological awareness and literacy measures

Because group differences were found on measures for slow-rate auditory processing, speech-in-noise perception, phonological awareness and reading, correlations between these measures was examined. Comparable to Hazan, Messaoud-Galusi, Rosen, Nouwens, and Shakespeare (2009), composite z-scores were calculated by converting performance measures of all tasks to whole-group z-scores. Z-scores for FM-detection and SRTs of speech-in-noise perception for words and sentences were multiplied by -1 to obtain comparable performance. Composite scores were then calculated to compare performance on reading tasks, phonological awareness, speech-in-noise perception and slow-rate dynamic auditory processing. For each participant, a READING score was calculated by averaging z-scores for word-reading and pseudoword-reading tasks, a PHONOLOGY score was calculated by averaging z-scores for phoneme deletion and spoonerisms tasks, a SPEECH-IN-NOISE score was calculated as the mean of the z-scores of words in stationary, sentences in stationary and sentences in fluctuating noise and a DYNAMIC score was calculated by averaging z-scores for FM-detection and rise time discrimination

tasks. As expected, normal-reading children and children with dyslexia also differed on the READING ($F(1, 56) = 49.39$; $p < 0.001$), PHONOLOGY ($F(1, 56) = 43.51$; $p < 0.001$), SPEECH-IN-NOISE ($F(1, 56) = 6.00$; $p = 0.017$) and DYNAMIC ($F(1, 56) = 11.05$; $p = 0.002$) composite scores.

Table 5.3 Whole-sample Pearson correlations between slow-rate auditory processing, speech-in-noise perception, phonological awareness and reading (N=58)

	DYNAMIC	READING	PHONOLOGY
DYNAMIC		0.22	**0.38****
SPEECH-IN-NOISE[a]	0.24	**0.38****	0.22

[a] $N = 57$; data of one normal-reading child were excluded because of outlying performance
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

Pearson correlation coefficients were calculated to investigate the interrelations between the studied variables. Table 5.3 shows that speech-in-noise perception correlates with reading abilities, but not with phonological awareness. The reverse pattern can be seen for slow-rate dynamic processing, correlating significantly with phonological abilities, but not with reading. Finally, no significant correlation between speech-in-noise perception and slow-rate dynamic processing was found. To verify inflation of correlations due to extreme samples, these relations were also investigated for the normal-reading group alone. Even within this subsample, the correlation between speech-in-noise perception and reading ($r = 0.30$, $p = 0.050$, $N = 44$) and between slow-rate dynamic processing and phonology ($r = 0.29$, $p = 0.051$, $N = 45$) were close to significance. Comparable to the whole-sample correlations, no significant correlations between speech-in-noise perception and slow-rate dynamic processing ($r = 0.17$, $p = 0.278$, $N = 44$), reading and slow-rate dynamic processing ($r = 0.09$, $p = 0.544$, $N = 45$) and between speech-in-noise perception and phonology ($r = 0.05$, $p = 0.731$, $N = 44$) were found in the normal-reading group alone.

5.4. Discussion

It is well established that phonological processing abilities are related to literacy development and that individuals with dyslexia show a phonological processing deficit (Snowling, 2000). Currently it is under debate whether this phonological processing deficit stems from a specific deficit in processing speech sounds or whether it originates from reduced sensitivity to slow-rate dynamic auditory

information. The present study investigated sensitivity to several slow-rate dynamic cues and speech perception measures in relation to skills characterizing developmental dyslexia (i.e. phonological processing, reading and spelling). Performance of sixth grade children was examined to study to what extent auditory processing and speech perception difficulties are still manifest in children with dyslexia at the end of primary school.

The present study demonstrated that children with dyslexia are less sensitive to slow-rate dynamic information, investigated by sound rise time perception and FM sensitivity, than normal-reading children, whereas sensitivity to intensity did not differ between groups. Sound rise time sensitivity has been shown to be a sensitive measure to discriminate between individuals with and without dyslexia. Studies found atypical sound rise time processing in adults (Hämäläinen et al., 2005; Corriveau et al., 2007) and children with dyslexia (Goswami et al., 2002; Richardson et al., 2004; Muneaux et al., 2004; Georgiou et al., 2010) and demonstrated associations between rise time sensitivity and a variety of phonological awareness tasks. Furthermore, sound rise time has been shown to discriminate between normal-reading children and children with dyslexia in several languages (English, Spanish, Chinese: Goswami et al., 2011a; Greek: Georgiou et al., 2010; Finnish: Hämäläinen et al., 2009; Hungarian: Suranyi et al., 2009; French: Muneaux et al., 2004). The present study is the first to demonstrate this effect in Dutch-speaking children, supporting the assumption that decreased sound rise time sensitivity is a language-universal characteristic of dyslexia (Goswami et al., 2011a). Additionally, sensitivity to sound rise time was evaluated in the simplest but most realistic conditions. Whereas all other rise time studies used a pure tone carrier signal, the present study applied a speech-weighted noise signal as carrier signal. The benefit of this complex carrier noise is that it contains important frequencies of real speech and therefore activates a broader frequency region in the auditory system compared to pure tones. While pilot tests demonstrated floor performance in some children for pure tone rise time stimuli, the application of a speech-weighted noise carrier resulted in reliable performance for all children (excluding ceiling or floor effects). This ensured that all children were able to perform the task and allowed to make a qualitative comparison of rise time sensitivity in both participant groups.

The present findings reinforce previous studies in that findings are consistent across age, stimuli and language. In addition to rise time perception difficulties, children with dyslexia also demonstrated reduced sensitivity to slow-rate FM. Comparable to studies investigating sound rise time, FM detection performance previously

discriminated between individuals with and without dyslexia. Group differences have been reported in adults (Witton et al., 2000) and children (Talcott et al., 2000; Boets et al., 2006) and FM has been shown to be related to pseudoword-reading and phonological awareness (Witton et al., 1998; Boets et al., 2008; Boets et al., 2011a; Witton et al., 2002; Stuart et al., 2006; Talcott et al., 1999). Studies investigating sound rise time and FM sensitivity independently demonstrated poorer performance in individuals with dyslexia. The present study extends previous research in that rise time and FM sensitivity were examined in the same group of children with and without dyslexia. This within-group comparison demonstrated that individuals with dyslexia performed poorer on slow-rate dynamic auditory tasks, independent of whether stimuli comprised a change in frequency (FM) or a change in amplitude (sound rise time) over time. Moreover, as no group difference was found for the intensity discrimination task, these results indicate that the auditory processing problems in dyslexia arise from a specific impairment in the ability to process slowly-varying auditory information, independent of the nature of the variation.

Because accurate processing of slow-rate auditory cues is an important aspect of speech perception, impaired processing of these cues would inevitably lead to speech intelligibility problems. Indeed, previous studies demonstrated a speech-in-noise perception deficit in reading-disabled individuals (Chermak et al., 1989; Ramirez & Mann, 2005; Cornelissen et al., 1996), however results were not always clear (Hazan et al., 2009). The present study found evidence in favour of a (subtle) speech-in-noise perception deficit in children with dyslexia. Contrary to our expectations, this deficit occurred independent of the dynamic nature of the noise or semantic influence of the speech material. Based on the hypothesis that individuals with dyslexia are less sensitive to slow-rate dynamic variations, we expected a larger difference between normal-reading children and children with dyslexia for sentences presented in fluctuating noise compared to sentences presented in stationary noise. However, children with dyslexia benefited equally as normal-reading children from the dips in the background noise.

Comparable to the present results, Ziegler, Pech-Georgel, George, and Lorenzi (2009) demonstrated with a variety of amplitude-modulated noise conditions that children with dyslexia have a normal masking-release (i.e. better performance in fluctuating than in stationary noise), but that they are in general impaired in identifying speech in the presence of noise. Similarly, they demonstrated inferior performance of children with dyslexia when speech was degraded by eliminating temporal fine-structure cues without using external noise. From these results, the

authors suggested that children with dyslexia have normal sensitivity to dynamic information but that their speech-in-noise perception problems are rather characterized by a lack of speech robustness in adverse situations. The present results partly confirmed this hypothesis. Indeed, children with dyslexia demonstrated poorer speech-in-noise perception performance, favouring the hypothesis that they suffer a lack of speech robustness in adverse situations. However, the fact that normal-reading children and children with dyslexia benefitted equally from the dynamic nature of fluctuating noise does not necessarily imply that children with dyslexia are unimpaired in processing slow-rate dynamic information. Speech is a complex signal containing several auditory cues that can lead to speech identification. It is possible that the presence of dips in the fluctuating noise still allowed a significant degree of speech recovery based on unimpaired auditory cues. Therefore, the possibility that the speech-in-noise perception problem stems from decreased sensitivity to slow-rate dynamic auditory cues cannot be confirmed nor excluded based on these data.

The finding of poorer performance of children with dyslexia on tasks assessing slow-rate dynamic sensitivity and speech-in-noise perception favour the hypothesis of a low-level auditory processing deficit as the cause of impaired phonological awareness in individuals with dyslexia. However, the present study could not provide clear evidence for this hypothesis.

First, correlational analyses could not demonstrate a link between slow-rate dynamic processing and speech-in-noise perception. Yet, both measures correlated respectively with phonological awareness and reading ability, supporting the possibility that both deficits independently relate to reading-related measures. However, this seems unlikely considering that slow-rate dynamic cues are prominent features of speech signals. A more likely explanation is that in 11-year old children the link between these variables is simply not evident (or even not present) anymore. Infants are born with a certain auditory sensitivity based on which they fine-tune their sensitivity to important acoustic cues in their native language (Kuhl, 2004). If in some children auditory development is impaired, speech perception abilities can be affected already early in life. It is possible that by the time these children learn to read, the original relation between auditory sensitivity and speech perception is already concealed because of different developmental influences on both levels.

Alternatively, after formal reading instruction, top-down processes can also influence perception at all these domains (Mayo et al., 2003). Therefore, to make strong conclusions about the relation between slow-rate dynamic auditory

processing abilities, speech perception, phonological awareness and literacy development a longitudinal design, starting at an early, pre-reading age is necessary. Indeed, longitudinal evidence for a causal, bottom-up influence of auditory processing and speech perception on later literacy skills has previously been obtained in preschool children. Recently, Boets et al. (2011a) found that FM-detection and speech-in-noise perception in kindergarten contributed to subsequent growth in reading ability, even after controlling for phonological abilities and letter knowledge. Additionally, Corriveau, Goswami, and Thomson (2010) found that both sound rise time perception and sensitivity to a frequency change over time predicted phonological awareness abilities in a normally developing sample, suggesting that a general sensitivity to dynamic auditory cues is important for literacy development.

Even though the present study could not obtain clear evidence supporting relations between slow-rate dynamic auditory processing and speech perception, it was demonstrated that after six years of reading education, children with dyslexia displayed atypical performance on both measures. Additionally, slow-rate dynamic auditory processing and speech perception correlated to phonological awareness and literacy abilities, confirming their link to reading-related abilities. These results indicate that the low-level auditory processing problems of children with dyslexia are persistent and possibly not entirely susceptible to remediation or compensation.

Chapter 6
General conclusions and future research directions

6.1. General discussion of research findings

This project aimed at investigating the nature of the temporal envelope processing deficit in dyslexia. In Chapter 2, we investigated the possibility to assess low-frequency ASSR as a objective neurophysiological correlate for a temporal envelope processing deficit in adults with dyslexia. The response characteristics of these low-frequency ASSRs in relation to monaural and diotic stimulus presentation were characterized in Chapter 3. In Chapter 4, the relation between ASSR coherence and structural white matter tracts in the brain was described. In Chapter 5, we assessed the nature of the auditory temporal processing deficit in normal-reading and dyslexic children with several psychophysical tasks assessing different aspects of auditory temporal processing, speech-in-noise perception, phonological processing and reading. In this final chapter, the implications of assessing low-frequency ASSRs as an objective neurophysiological tool to measure sensitivity to auditory temporal information will be discussed, together with its limitations and questions that remain to be answered (6.1.1). In a second section, the implications of comparing syllabic- and phonemic-rate processing are discussed in the context of speech perception (6.1.2). Subsequently, the neurophysiological underpinnings of auditory temporal sensitivity in normal reading and dyslexic adults are described (6.1.3). In 6.1.4, the exploration of auditory temporal sensitivity is described in the context of the causal model underlying dyslexia. In 6.1.5, other possible explanations for auditory processing problems in dyslexia are discussed. The clinical implications of this research project are discussed in 6.1.6. Finally, this chapter will be concluded with a discussion about the general limitations of this project (6.2) and suggestions for future research (6.3).

6.1.1. Low-frequency ASSRs as a tool to measure neurophysiological responsiveness to auditory temporal information

ASSRs are a powerful tool to evaluate several aspects in auditory neuroscience. Until now, their application has already proven their value in the objective estimation of hearing thresholds (e.g. Luts et al., 2004). A relatively new application of ASSRs is in the context of estimating speech perception abilities by assessing responses to suprathreshold auditory temporal modulations (e.g. Alaerts et al., 2009; Dimitrijevic et al., 2004). Whereas most ASSR studies focused on ASSRs in the 40 and 80 Hz domain, ASSRs to low modulation rates (below 40 Hz) have the potential of being more strongly linked to speech understanding performance, because these slow modulations comprise the most essential variations in the temporal envelope of speech (Rosen, 1992) and are crucial for speech understanding (Drullman et al., 1994; Shannon et al., 1995). However, a certain amount of questions regarding the response characteristics of these ASSR and their relation to psychophysical measures of temporal envelope processing remain unanswered. This project aimed to elucidate certain response characteristics of ASSRs to low modulation rates and to apply them as a measure to evaluate temporal envelope sensitivity in a sample of adults with dyslexia (Chapter 2 and Chapter 4). Whereas most results are already discussed in each chapter, some global findings are discussed here to highlight the core findings in this doctoral project.

First, we demonstrated that syllabic- (4 Hz) and phonemic-rate (20 Hz) ASSRs relate to psychophysical measures of speech-in-noise perception and phonological awareness (Chapter 2). Psychophysical speech-in-noise perception was assessed with a phoneme-in-noise and a sentence-in-noise perception task. Phonological awareness performance was based on a phoneme deletion and a spoonerism task. Phonemic-rate ASSRs correlated with phoneme-in-noise perception and phonological awareness, whereas syllabic-rate ASSRs only correlated to sentence-in-noise perception. This correlational pattern was in the expected direction because sentence-in-noise perception was the only task that made appeal up on syllable-level information. Whereas previous studies already demonstrated the relation between 80 and 40 Hz ASSRs and speech perception (Dimitrijevic et al., 2004), or observed a global relation between low-frequency ASSRs and speech intelligibility (Alaerts et al., 2009), this study was the first to demonstrate that phonemic- and syllabic-rate

ASSRs are independently sensitive to objectively evaluate different grain-sizes in speech perception and phonological processing.

Second, we found that the low-frequency ASSRs are influenced by the way stimuli are presented and that this effect differs for different modulation rates (Chapter 3). Based on the comparison between diotic and monaural stimulus presentation, we demonstrated that stimulus presentation does not influence the response-strength of phonemic-rate (20 Hz) ASSRs but that there is an influence on syllabic-rate (4 Hz) ASSRs, for which the largest response-strengths can be recorded to monaural stimulus presentation. Alternatively, based on the comparison of the two monaural conditions, we observed that while 4 Hz ASSRs were more prominently recorded at electrodes over the right hemisphere, independent of which ear was stimulated, 20 Hz ASSRs were larger over electrodes ipsilateral to the stimulated ear. These findings converge with the data presented in Chapter 2, which demonstrated larger responses over the ipsilateral right hemisphere to right ear stimulus presentation. Whether these differences between syllabic- and phonemic-rate ASSRs are characteristic for neurons tapped by these ASSRs or whether they also generally apply for processing syllabic- and phonemic-rate modulation has yet to be shown. Nonetheless, this study shows that a critical factor in the evaluation of lateralization of low modulation rates is the side to which stimuli are presented.

Third, these data partially confirm the "Asymmetrical Sampling in Time" theory of Pöppel and colleagues (2003; 2008), that phonemic- and syllabic-rate modulations are processed asymmetrically in the brain, with a right hemispheric preference for syllabic-rate modulations and a left hemispheric preference for phonemic-rate modulations. Whereas a left hemispheric preference for phonemic-rate modulations was only found to ipsilateral left ear stimulation, syllabic-rate modulations were consistently more prominent at electrodes over the right hemisphere. Lateralization research is however characterized by a wide variety of measurement techniques, stimuli, and stimulus presentation manners and only a few studies systematically investigated these parameters. Investigating lateralization of temporal auditory information requires a good temporal resolution of the measurement technique in order to accurately measure temporal variation. However, techniques with a high temporal resolution (EEG/MEG) often depend on scalp-recorded responses, which lack spatial sensitivity about underlying neural sources. A good balance between temporal and spatial resolution is found in high-density EEG and MEG recordings, evaluating lateralization with source analyses methods.

Only a few studies investigated Pöppel's AST theory with these techniques. With a 151 channel MEG system, Schoonhoven (2003) recorded ASSRs to 40 and 80 Hz AM stimuli, presented to the left ear. They demonstrated that both 40 and 80 Hz responses were larger at electrodes over the contralateral (right) than over the ipsilateral (left) hemisphere. Accordingly, Ross et al. (2005) demonstrated that 40 Hz ASSRs were lateralized to the right hemisphere for left ear and binaural (diotic) stimulus presentation but that no lateralization occurred for right ear stimulation. Similarly, Lehongre et al. (2011) demonstrated a right hemispheric dominance for modulation rates near 40 Hz to binaural stimulus presentation, but also found that phonemic-rate modulations (25-35 Hz) were left-dominant, suggesting that a left dominance occurs for modulation rates close to the phonemic-rate. However, Hämäläinen et al. (2012a) could not find evidence for this left dominance. In their study, binaural stimulation resulted in bilateral responses for modulation rates of 4, 10 and 20 Hz. In line with the AST theory, they did find evidence for a right hemispheric preference for the 2 Hz modulation rate. A possible reason for the discrepancy between this study and the present result may be the difference in the recording techniques. Whereas the present project made use of EEG recordings, Hämäläinen et al. (2012a) recorded ASSRs with MEG. Given that both methods differ in their sensitivity to radially oriented neural sources, a difference in the measured neural activity may underlie the deviating results of both studies. Future studies will be necessary to enlighten these results.

Comparable with the study presented in Chapter 3, Herdman et al. (2002) recorded ASSRs in the EEG, to 12, 39 and 88 Hz AM stimuli presented either to the left or the right ear. For 88 Hz, scalp-recorded ASSRs were larger at electrodes ipsilateral to the stimulated ear and source analyses demonstrated that this response was generated by an ear-specific underlying source with a contralateral orientation. However, no clear asymmetry was found for 39 and 12 Hz ASSRs. The results of the present project (Chapter 3) confirm the 88 Hz response pattern of Herdman and colleagues (2002). However, for modulation rates below 40 Hz, the response pattern amongst EEG studies (Herdman et al., 2002 versus the results in Chapter 3), and between EEG and MEG studies is unclear. An important factor contributing to this is the difference in sensitivity to underlying sources between EEG and MEG. MEG is mainly sensitive to tangentially oriented sources that lay mostly along the sulcal walls and is thus less receptive to sources along the gyral surface of the cortex. Additionally, MEG tends to be less sensitive to sources located deeper in the brain (Nunez & Srinivasan, 2006). In contrast, EEG is thought to be more sensitive to sources in cortical gyri and less sensitive to cortical sulci (Nunez & Srinivasan,

2006). The benefits of either MEG or EEG thus depend on the orientation of the underlying sources. Unfortunately, such source information is not generally available. Generally, these findings highlight the versatility of research to the lateralization of temporal auditory processing. Future studies investigating response asymmetry for a broad range of modulation rates are necessary to unravel the underlying pattern.

6.1.2. Phonemic- versus syllabic-rate processes in speech perception

In the present dissertation, phonemic- and syllabic-rate processes are treated as dichotomous variables underlying speech perception. In reality however, when we listen to speech we are confronted with a continuous acoustic stream, containing information at rates between 2 and 50 Hz (Rosen, 1992). In continuous speech, information thus occurs at rates important for syllable and phoneme perception, as well as on rates higher and lower than the rates used in this project. In this context, a more realistic view of syllabic- and phonemic-rate processing may be in a continuous instead of a dichotomous manner (e.g. Obrig et al., 2010). We can therefore hypothesize that the observed 20 Hz group differences in the ASSR study (Chapter 2) are not specific to the 20 Hz modulation rate, but may rather span over a wider range of modulations. This hypothesis is supported by the study of Lehongre et al. (2011), observing deviant neural responses in dyslexic adults at modulation rates near 30 Hz rather than near 20 Hz.

However, due to methodological and theoretical considerations, phonemic- and syllabic-rate processes are often treated as dichotomous in literature. Pöppel and colleagues (e.g. Boemio et al., 2005; Giraud & Pöppel, 2012; Pöppel, 2003; 2008; 2008) compared processing of phonemic- and syllabic-rate modulations in terms of hemispheric specialization. In addition, this dichotomy has been made to examine hemispheric development in relation to phonemic- and syllabic-rate processing (e.g. Telkemeyer et al., 2009; 2011), and in relation to dyslexia (e.g. Hämäläinen et al., 2012a; Lehongre et al., 2011). Nonetheless, it is important to note that the selection of certain modulation rates as representing syllabic- and/or phonemic-rate information may be relatively arbitrary and oversimplified.

6.1.3. Auditory temporal processing in normal-reading and dyslexic adults

One of the main objectives of this project was to acquire neurophysiological evidence for an auditory temporal processing deficit in adults with dyslexia and to specifically examine whether adults with dyslexia would demonstrate different responses to phonemic- and/or syllabic-rate modulations (Chapter 2). We found a neurophysiological phase-locking reduction in individuals with dyslexia, specifically to phonemic-rate modulations. In contrast, normal-reading and dyslexic adults did not differ in their neural sensitivity to phase-lock to syllabic-rate amplitude modulations.

In the framework of the auditory temporal processing deficit theory of dyslexia, these results may suggest a bottom-up neural deviance in processing phonemic-rate temporal modulations underlies the reading and spelling problems in dyslexia. That is, as temporal modulations designate the timeframe in which sublexical acoustic-phonetic information in the speech stream is sampled into relevant phonological units, imprecise processing of phonemic-rate modulations may cause that phonological representations are assembled in a disadvantageous temporal format. This low-level acoustic sampling problem may have serious consequences for phonological processes at a higher cognitive level, where cognitions such as phonological awareness, phoneme-grapheme associations and phonological memory depend on the precision of phonological representations. However, in contrast to this bottom-up explanation for the auditory deviances found in adults with dyslexia, a top-down explanation for auditory processing difficulties in adults with dyslexia may also apply. From a top-down point of view, auditory processing problems are the result of altered perceptual mechanisms due to years of reading impairment. This view is described from a developmental perspective in 6.1.5.

Whereas the impaired temporal sampling theory of dyslexia is most commonly assessed with AM stimuli (e.g. Hämäläinen et al., 2012a; Lehongre et al., 2011), it may also underlie impairments found with other auditory temporal cues, such as sound onset time (e.g. Muneaux et al., 2004; Pasquini et al., 2007; Richardson et al., 2004) and frequency modulation detection (e.g. Boets et al., 2006; Talcott et al., 1999; 2003; Witton et al., 2000; 2002). Tasks relying on the detection of onset time, amplitude or frequency modulation converge in that they all require the same underlying ability, the detection of a change within a certain time window. Hence, if

the information in this time window is sampled differently, results on psychophysical tasks will most probably deviate from those of normal readers.

As described in Chapter 4, a possible neural origin for this auditory temporal processing deficit in dyslexia is the STGp. In normal readers, global interhemispheric synchrony to phonemic-rate modulations related to left lateralization of white matter density in STGp, whereas this relation was not evident in dyslexic adults, suggesting that deficient phonemic-rate sampling in individuals with dyslexia relates to a neural deviance (functional and/or anatomical) in STGp. These results are indirectly confirmed by studies with intracerebral recordings demonstrating that the left SAC and STGp are more sensitive to higher modulation rates than their right hemispheric counterparts (Liégeois-Chauvel et al., 2004; Gourevitch et al., 2008; Giraud et al., 2000). The neural architecture of these regions is thought to be crucial for conceptualizing auditory-phonological representations, necessary for speech perception (Hickok & Pöppel, 2004; 2007). However, it is also clear that processing temporal modulations is not limited to one specific structure in the auditory cortex but rather depends on a distributed network of intra- and interhemispheric connections (e.g. Gourevitch et al., 2008). Measures of connectivity, such as the FA of white matter tracts or the phase coherence of electrophysiological responses may thus provide crucial information about the anatomical and functional architecture underlying temporal modulation processing. In sum, the results of the present project suggest that the complex network involved in phonemic-rate temporal modulation processing is disrupted in individuals with dyslexia (possibly in the left hemisphere), and that this results in an insufficient integration of phonemic-rate acoustic information in the dorsal phonological system.

Based on the results of this project, adults with dyslexia demonstrate difficulties on tasks that require analyses within phonemic-rate time windows. No generalization can however be made as to whether this deficit is also present in children because (*i*) we did not investigate neural phase-locking to phonemic- and syllabic-rate modulations in children, (*ii*) neither did we systematically assess psychophysical sensitivity to phonemic- and syllabic-rate modulations in children. Suggestions for future studies in this domain are described in section 6.3.2.

6.1.4. Auditory temporal processing in normal reading and dyslexic children

As described in Chapter 5, we examined low-level auditory processing, speech perception, phonological processing and reading skills in a group of normal-reading and dyslexic sixth grade children. These children participated in a longitudinal study that started in last year of kindergarten (Boets et al., 2006; 2010; 2011a). The primary goal of this study was to perform a follow-up of their auditory perception skills at the end of primary school. This follow-up consisted of those tasks that discriminated between normal-reading children and children (at risk for) dyslexia during earlier test moments (reading, phonological awareness, categorical perception (see Vandermosten et al., 2011), words-in-noise perception, FM-detection). In addition, an onset time discrimination task was included because of the temporal nature of this task and because of the growing amount of evidence for the sensitivity of this task to discriminate between normal-reading and dyslexic individuals (e.g. Goswami et al., 2002; Suranyi et al., 2009; Muneaux et al., 2004; Pasquini et al., 2007; Richardson et al., 2004). Finally, in the light of the noise-exclusion deficit theory (e.g. Ziegler et al., 2009), a sentence-in-noise perception task was included to evaluate speech perception performance in "natural" conditions where speech is redundant and perception is be facilitated with top-down information.

We found that sixth grade children with dyslexia performed less well than normal-reading children on psychophysical tasks assessing auditory temporal sensitivity, whereas no group differences were found for the non-temporal control task (intensity discrimination), suggesting that children with dyslexia may not suffer from a general auditory processing deficit but may have difficulties processing auditory information with temporal variations. This is in line with the auditory temporal processing deficit theory for dyslexia. Whereas literature reports evidence for an auditory processing deficit in dyslexia with temporal as well as non-temporal stimuli, only a scarce number of studies examined both types of the stimuli with the same tasks and within the same participants (for a review see Hämäläinen et al., 2012b). More studies that systematically investigate auditory sensitivity to temporal as well as non-temporal cues are thus necessary.

Auditory temporal sensitivity was assessed with an FM-detection and an onset time discrimination task. Both tasks measure different aspects of temporal processing. FM-detection is based on the detection of a change in frequency over time, whereas onset time discrimination depends on analyzing an amplitude change over time.

Both tasks however converge in that they both require analyzing an acoustic change within a certain time window. Lower performance of children with dyslexia on both tasks thus suggests that the auditory temporal processing problems in dyslexia are independent of the nature of the change detection, but rather relates to the timeframe in which temporal fluctuation takes place. In this context, reduced performance on the 2 Hz FM-detection task indicates that children with dyslexia are less sensitive to process temporal variations in the syllabic-rate timeframe. However, the fact that these children also performed worse on the onset time discrimination task, measuring sensitivity to discriminate between the 15 ms onset (corresponding to a hypothetical temporal rate of ± 66 Hz) of the reference sound and the stimulus sound with a longer onset, may suggest that children with dyslexia were also less sensitive to process temporal variation in the phonemic-rate timeframe. As already mentioned in 6.1.2, this would be an interesting research question to answer in future studies.

In addition to auditory temporal processing problems, these children with dyslexia also exhibited (subtle) problems perceiving speech in noise. These speech perception problems were general and independent of the nature of the stimulus (words or sentences) or the nature of the masking noise (stationary or fluctuating). Additionally, groups differed in their performance on phonological awareness tasks and reading. The presence of processing problems at all these levels is in line with the predictions made by the auditory temporal processing deficit theory for dyslexia. However, correlations between these variables were unclear, probably due to mechanisms related to compensation or reading intervention. This study does however add cross-sectional evidence to the few studies that did find causal relations between auditory temporal processing and reading abilities (Boets et al., 2011a; Stefanics et al., 2011; Corriveau et al., 2010).

Convincing evidence for the existence of a causal relation between low-level auditory processing, speech perception and phonological development comes from longitudinal studies. In the Jyväskylä Longitudinal study of Dyslexia (JLD), neurocognitive processes related to auditory processing, speech perception and phonology were longitudinally assessed with auditory ERPs in children at risk for dyslexia, from birth until the second year of primary school (e.g. Guttorm et al., 2005; 2010; Leppänen et al., 2010; 2012). This unique project demonstrated direct associations between newborn responses to auditory and speech stimuli, and later reading-related skills. Newborns at risk for dyslexia showed at birth diminished pitch change detection compared to newborns without risk for dyslexia (Leppänen et al., 2010). Additionally, newborn ERPs were associated with phonological skills and

letter knowledge prior to school age and with speech perception (phoneme duration perception), reading speed and spelling in the 2nd grade of primary school. These data provide direct evidence that auditory processing problems in dyslexia are already present at birth and have a causal influence on pre-reading speech perception and phonological processing.

6.1.5. Alternative explanations for auditory processing problems in dyslexia

The auditory temporal processing deficit theory of dyslexia, as described in the previous sections, is based on the idea that auditory processing abilities affect phonological and literacy development in a bottom-up manner. However, the present data cannot provide conclusive evidence for this bottom-up mechanism. Given that the examined samples in this research project consisted of children and adults with at least 6 years of reading experience, it may also be that observed difficulties of individuals with dyslexia are the result of their reading impairment. That is, lower neural responses to phonemic-rate modulations in dyslexic readers may result from their impaired reading abilities. If the phonological development of individuals with dyslexia is impaired, it may be that top-down mechanisms influence the way phonological representations are assembled and thus how acoustic information is perceived. In this context, it may just as well be that slow rate temporal processing difficulties in childhood result in poorer phonological development. This poor phonemic learning during reading acquisition is then reflected in atypical adult performance with fast rate temporal stimuli.

Evidence for this hypothesis comes from studies examining hemispheric lateralization to syllabic- and phonemic-rate modulations (e.g. Telkemeyer et al., 2009; 2011). These studies show that right lateralization of slow, syllabic-rate modulations is present from birth, whereas this is not the case for faster, phonemic-rate modulations. Given that dyslexia is a developmental disorder, it could be that phonemic-rate processing difficulties in adulthood represent the developmental consequences of poorer reading abilities.

Furthermore, data from the present research project support the idea that the reading and spelling problems in dyslexia are probably the result of a multidimensional disorder instead of a specific auditory temporal processing deficit (e.g. Pennington, 2006; Ramus et al., 2003; Snowling, 2008). Data from Chapter 2, Chapter 4 and

Chapter 5 suggest that auditory temporal processing problems are indeed present at a group level, but are probably not present in all individual participants with dyslexia. Basic auditory processing problems could be one of the possible risk factors underlying dyslexia. In this context, auditory processing problems could be in a causal relationship with dyslexia in a sub-group of individuals, or act as a moderator together with other risk factors determining the severity of the dyslexia phenotype (Pennington, 2006). Future longitudinal studies are necessary to disentangle these matters.

6.1.6. Clinical implications

The findings of the present project may also have some clinical implications for future diagnostic and remediating purposes. First, the finding of deviant performance of children and adults with dyslexia on tasks involving the perception of temporal auditory information may provide an important tool to diagnose children with dyslexia. If auditory processing problems are indeed causal to dyslexia, assessing these abilities may serve as an early marker to detect children with dyslexia, already before they learn to read. Although the present findings only reflect group level differences, they may provide an important first step towards finding a behavioural (Chapter 5) or a neural (Chapter 2, Chapter 4) marker for dyslexia. Future studies, with improved EEG recording and analysis techniques, may be able to determine a neural correlate for an auditory temporal processing deviance in dyslexia that is sensitive to discriminate between normal-reading and dyslexic persons at the individual level. This sensitive biomarker can then be applied to determine whether children at risk for dyslexia will later develop dyslexia. Although the current data are not sensitive enough for these purposes, it may provide a necessary first step for future developments.

Second, if reduced auditory temporal processing abilities are causal to dyslexia, training auditory temporal processing skills in children at risk for dyslexia may improve their future reading and spelling skills. Future studies are necessary to determine which auditory cues are processed differently in individuals with dyslexia and whether training the perception of these cues has a beneficial influence on reading skills. The next step will then be to assess auditory temporal perception skills in preschool children at risk for dyslexia and to determine whether preschool training programs can prevent children at risk for dyslexia to develop reading and spelling problems.

6.2. General limitations

There are, however, a number of limitations in this project. One limitation is that the results of the ASSR studies are based on scalp-recorded data from 8 electrodes. Compared to ERP studies that are often recorded with high-density (64, 128, 256 channel) recording systems, EEG analyses based on 8 electrodes may seem very restricted. However, commercial ASSR recording systems evaluate ASSRs based on only one or two active electrodes (e.g. John & Picton, 2000b). The main reason for this difference lies within the magnitude of the recorded responses. Whereas ERPs have amplitudes in the order of microVolts, ASSRs are much smaller (in the order of nanoVolts), implying that recording ASSRs requires a higher level of amplification in combination with a low amount of noise imposed by these amplifiers. The use of high-end low-noise amplifiers increases recorded signal-to-noise ratios and thus improve ASSR detection in the background EEG noise. Particularly for recording ASSRs to low modulation rates, which are embedded in a high level of background EEG noise, and for recording ASSRs at threshold level, when amplitudes are very low, this factor plays an essential role. Therefore, within this context, EEG-recorded ASSR studies only report data recorded from a limited set of electrodes (e.g. Alaerts et al., 2009; Choi et al., 2011; Tlumak et al., 2011; Wilding et al., 2012). The disadvantage of this limited amount of electrodes is that statistical analyses can only be performed on responses recorded at the scalp. High-density EEG recordings are absolutely necessary for EEG analyses, to determine the underlying activity of the scalp-recorded potentials at the source level (e.g. Herdman et al., 2002). Accordingly, the results presented in Chapter 2, Chapter 3 and Chapter 4 are solely based on scalp-recorded ASSRs. The terms, such as lateralization, asymmetry, and hemisphere refer in this context to the electrodes where ASSRs are recorded and do not directly assess the underlying neural sources. Additionally, the link between structural white matter pathways and functional neural synchrony to syllabic- and phonemic-rate modulations (Chapter 4) may have been underestimated by the electrode-level analyses. It is possible that high-density ASSR recordings, analyzing coherence between neural sources provide a clearer image of this structure-function relation in the brain.

A second limitation of this project is related to the fact that we assessed auditory temporal sensitivity in adults and 6th grade children with dyslexia that can be considered as experienced readers because of their trajectory in reading education, and possibly also reading intervention. Given the diversity in reading methods and interventions, the influence of these factors could not be controlled for. Because of

brain plasticity, reading intervention could have had a top-down influence on the anatomical (Chapter 4) and functional (Chapter 2) neural differences between normal-reading and dyslexic adults, as well as on the psychophysical performance of the sixth grade children. Nonetheless, the strict selection of participants with (*i*) a diagnosis of dyslexia, (*ii*) that still demonstrate severe reading difficulties (below percentile 10) in sixth grade (Chapter 5) or adulthood (Chapter 2 and Chapter 4) suggests that these participants did not completely compensate for their deficit.

Third, the results of the present project are based on group-level analyses. Due to the large amount of inter-individual variability in the electrophysiological recordings, individual level analyses were not sensitive enough to discriminate between normal-reading and dyslexic individuals. Similarly, psychophysical data was only analysed at the group level. Because of the large amount of variability and the large difference in the number of participants within groups (due to the longitudinal character of the participant sample), no reliable individual level analyses were performed. Future studies investigating auditory temporal processing in children should target a larger sample of children with dyslexia and aim to reduce individual variability of the response measures (for example by including training).

6.3. Future research directions

It is clear that (at least some) individuals with dyslexia differ in the way they process auditory temporal information and that this dysfunction can be evaluated at the psychophysical as well as at the objective electrophysiological level. However, a number of questions remain unanswered and require further investigation.

6.3.1. Optimizing ASSR recordings and analyses

In this project, ASSR analyses were done at a group level. Because of the between-subject variability of ASSR recordings, analyses at the level of the individual remain challenging. Yet, individual analyses may be important for diagnostic purposes. Research is therefore needed to increase the experimental precision of ASSR recordings.

Alternatively, given the relation between ASSRs to low modulation rates and psychophysical measures of speech perception and phonological processing (e.g. Lehongre et al., 2011; Poelmans et al., 2012a), more evidence is needed on the exact

neural origin of these modulations to determine the exact locus of the auditory processing deviance in individuals with dyslexia. A possible method to enable this is to record ASSRs with a high-density EEG recording system that allows analyses at the source level. Analyzing amplitudes and latencies of ASSR sources may be more sensitive to discriminate between normal-reading and dyslexic individuals. Additionally, beside amplitude and latency information, source coherence measures can provide information about the neural synchrony between active ASSR sources and may be directly linked to white matter trajectories (e.g. Teipel et al., 2009), as proposed in Chapter 4.

6.3.2. Neurophysiological syllabic- and phonemic-rate processing in normal-reading and dyslexic individuals

In the light of the temporal sampling framework (Goswami, 2011), more information is needed on the relation between ASSRs and the brain's intrinsic oscillatory activity. Given that syllabic- and phonemic-rate ASSRs coincide with important frequency bands in the EEG, it may be that ASSRs build upon these spontaneous oscillations. The phase-locking deficit in dyslexia can then either be reduced to a deficit to engage intrinsic EEG bands to follow an externally imposed rhythm or to a reduction in EEG power within certain EEG bands. Accordingly, based on findings that slower oscillations (delta, theta) modulate faster oscillations (gamma) in cortex via hierarchical nesting of activity (e.g. Lakatos et al., 2005), the mutual relation between syllabic- and phonemic-rate ASSRs in individuals with dyslexia should be further explored.

In the context of dyslexia, these questions should be regarded in a developmental perspective. As discussed in Chapter 2, phonemic- and/or syllabic-rate modulations may provide crucial information about how sublexical auditory information is sampled from the speech stream and is integrated in the phonological system. The question however remains whether the observed phonemic-rate processing problem is already present in children, or whether it develops along with phonological awareness. It is reasonable to assume that the brain's inefficiency to accurately sample phonemic information is most strongly expressed in phoneme awareness problems at the time that a child learns to read and depends on phoneme-sized segments to process language. However, it is well known that during childhood phonological awareness develops from syllable- to phoneme-level units (e.g. Ziegler

& Goswami, 2005) and that children with dyslexia demonstrate syllable-level phonological processing problems before phoneme awareness can be assessed (e.g. Boets et al., 2007; Goswami et al., 2000; Goswami, 2002). Hence, it may be that preschool syllable-level phonological processing problems are underpinned by a syllabic-rate phase-locking reduction. This would imply that in individuals with dyslexia, phase-locking deviances are evident at the most appropriate level of phonological processing. This hypothesis is indirectly supported by the maturation of spontaneous neural oscillations. If, as hypothesized by Goswami (2011), stimulus-evoked phase-locking depends on spontaneous neural oscillations in the theta/delta band for syllabic-rate modulations and beta/gamma band for phonemic-rate modulations, then the developmental pattern of these oscillations may provide unique information about the development of phase-locking abilities to syllabic- and phonemic-rate modulations. Only a few studies have investigated the maturation of inherent EEG bands. These studies showed that in children delta band oscillations are higher than in adults and that they are typically even higher in children with dyslexia (Penolazzi et al., 2008). Additionally, a progressive increase in beta power in individuals aged from 7 to 60 years was associated with the parallel decrease in alpha and theta power (Anokhin et al., 1996; Yordanova & Kolev, 1997a; 1997b). In either scenario, assessing the neural phase-locking strength to phonemic- and/or syllabic-rate modulations in preschool may provide sensitive predictive information about children who may later develop dyslexia. To validate this hypothesis, it may also be necessary to expand the examination of modulation sensitivity to a wider range of modulation rates and to link neurophysiological responses to relevant psychophysical measures. As suggested by Lehongre et al. (2011), sensitivity to modulations in children with dyslexia may be shifted towards higher or lower modulation rates and may relate to important aspects of phonological processing and literacy. To answer these open questions, a *longitudinal* study, starting in preschool and including children with and without family *risk for dyslexia*, investigating sensitivity to a wide range of *modulation rates* and linking neurophysiological activity to *psychophysical* measures would be very interesting.

6.3.3. Elucidating the relation between functional and structural brain measures during reading development

In this project, we assessed the relation between neural synchrony to syllabic- and phonemic-rate modulations and white matter density in normal-reading and dyslexic

adults (Chapter 4). Besides assessing functional syllabic- and phonemic-rate processing at the source level (6.3.1), future studies should directly assess this relation in a longitudinal design to explore the causal nature of the functional and anatomical differences between normal-reading and dyslexic children. Moreover, this design would elucidate whether functional processing of temporal modulations is different in individuals with dyslexia because of structural white matter deviances or whether structural white matter tracts adapt or compensate because of a dysfunction in processing temporal modulations.

6.4. General conclusions

In this research project, we aimed to examine the auditory temporal processing deficit in dyslexia with objective electrophysiological as well as with psychophysical measures. By means of ASSRs, we found that (*i*) individuals with dyslexia demonstrated a specific phonemic-rate phase-locking deviance compared to normal-reading adults, that (*ii*) this phase-locking deviance reflected in reduced phase-locking in the left hemisphere as well as in lower inter- and intrahemispheric coherence, and that (*iii*) phonemic-rate ASSRs correlated with psychophysical measures of phonological awareness and speech-in-noise perception. Additionally, we evidenced that (*iv)* the response characteristics of these slow-rate ASSRs were influenced by the stimulus presentation side, in that phonemic-rate modulations demonstrated a ipsilateral response asymmetry, whereas syllabic-rate modulations rather showed a functional right hemispheric bias. Finally, (*v*) functional interhemispheric synchrony to phonemic-rate modulations related to structural white matter measures in structures involved in speech perception, and (*vi*) this relation was different for normal-reading than in dyslexic adults. These results provide new evidence for the neurophysiological underpinnings of the auditory temporal processing theory of dyslexia.

Additionally, this project aimed to examine the nature of the auditory temporal processing deficit and its relation to speech perception, phonological awareness and reading in children with dyslexia. We demonstrated that children with dyslexia were impaired in two temporal tasks differing in the nature of the temporal change, whereas no impairment was found for the non-temporal control task. These results suggest that the temporal processing problem in dyslexia is specific to the time window in which a temporal change needs to be analyzed, instead of processing the temporal information per se. Additionally, group differences were found for speech-

in-noise perception, phonological awareness and reading. However, correlations between auditory temporal processing, speech perception and phonological awareness were not clear, suggesting that reading development changes the causal relation between these processing levels. Overall, these findings suggest that individuals with dyslexia are impaired in processing temporal acoustic information occurring within certain timeframes that are important for phonological processing.

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Vandermosten, M., **Poelmans, H.**, Sunaert, S., Ghesquière, P., Wouters, J. White matter lateralization and interhemispheric synchronization to auditory modulations in normal reading and dyslexic adults. Neuroimage, *submitted*.

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Conference contributions

Poelmans, H., Luts, H., Vandermosten, M., Ghesquière, P., Wouters, J. Auditory steady-state responses as a measure to evaluate sensitivity to speech-related modulations in adults with dyslexia. Oral presentation at 1st International Workshop on Segregation and Integration in Music and Language, Tubingen, 24-25 February 2012.

Wouters, J., Hofmann, M., Luts, H., **Poelmans, H.**, Van Deun, L., Vanvooren, S., Van Wieringen, A. Applications of auditory steady-state responses in the study of neural processing and auditory prostheses. Oral

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Vandermosten, M., Boets, B., **Poelmans, H.**, Sunaert, S., Wouters, J., Ghesquière, P. Diffusion Tensor Imaging in adults with dyslexia demonstrates left superior longitudinal fasciculus involvement in reading, phonology and speech perception. Poster presentation at 11th International Conference on Cognitive Neuroscience (ICON), Mallorca, Spain, 25-29 September 2011.

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Froyen, D., Bonte, M., van Atteveldt, N., **Poelmans, H.**, Blomert, L. The long road to automation: Neurocognitive development of letter/speech-sound processing. Poster presentation at 9th International Multisensory Research Forum (IMRF), Hamburg, Germany, July 2008.

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Curriculum vitae

Hanne Poelmans was born in Tongeren, Belgium on 25 November 1982. She received her secondary education (Mathematics-Sciences) at the Onze-Lieve-Vrouwe Humaniora in Tongeren and graduated in 2000. In 2004, she obtained a Masters degree in Biological Psychology (doctorandus in Psychologie) from Maastricht University, the Netherlands. Her master's thesis was entitled "Phonotactic processing in dyslexic children: an ERP study." In 2005, she obtained a Masters degree in Clinical Psychology (Licentiaat Psychologie) with distinction from Ghent University, Belgium. Between 2005 and 2008, she was a researcher at Maastricht University (the Netherlands) and at the University of Jyväskylä (Finland), studying psychophysical and electrophysiological correlates of dyslexia. From 2008, she has been a research member of the group Experimental Oto-Rhino-Laryngology at the Department of Neurosciences of KU Leuven, under the supervision of Prof. Jan Wouters and Prof. Pol Ghesquière. Her main research interests are in the domain of auditory evoked potentials and more specifically in the context of auditory processing, speech perception and dyslexia.