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Neurophysiological and clinical investigation of phonological input processing in non-brain damaged individuals and patients with aphasia // Annelies Aerts

NEUROPHYSIOLOGICAL AND CLINICAL INVESTIGATION OF PHONOLOGICAL INPUT PROCESSING IN NON-BRAIN DAMAGED INDIVIDUALS AND PATIENTS WITH APHASIA

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UNIVERSITEIT GENT

FACULTY OF **MEDICINE AND HEALTH SCIENCES**

Department of Internal Medicine

Neurophysiological and clinical investigation of phonological input processing in non-brain damaged individuals and patients with aphasia

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Thesis submitted in fulfilment of the requirements for the degree of Doctor in Social Health Sciences: Logopaedics and Audiology

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I remember when,
I remember, I remember when I lost my mind
There was something so special about that place
Even your emotions have an echo in so much space

And when you're out there without care
Yeah, I was out of touch
But it wasn't because I didn't know enough
I just knew too much

Does that make me crazy?
Does that make me crazy?
Does that make me crazy?
Possibly

And I hope that you are
Having the time of your life
But think twice
That's my only advice

Come on now, who do you
Who do you, who do you, who do you think you are?
Ha ha ha, bless your soul
You really think you're in control?

Well, I think you're crazy
I think you're crazy
I think you're crazy
Just like me

My heroes had the heart
To live their lives out on a limb
And all I remember
Is thinking, I want to be like them

Ever since I was little
Ever since I was little
It looked like fun
And it's no coincidence I've come
And I can die when I'm done

But maybe I'm crazy
Maybe you're crazy
Maybe we're crazy
Probably

Gnarls Barkley | Crazy | 3 april 2006 |
Voor Simon, omdat je me nog elke dag doet beseffen wat echt belangrijk is in 't leven... (juli '82 - juni '06)

Dit werk draag ik op aan Tim …

… mijn steun en toeverlaat in alle mogelijke omstandigheden!

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LIST OF PUBLICATIONS

This doctoral thesis is based on studies reported in or submitted to the following journals:

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Hallez, H., Santens, P. & De Letter, M. (2013). **Neurophysiological investigation of phonological input: Aging effects and development of normative data**. *Brain and Language, 125* (3), 253-263. (impact factor 2013: 3.31)

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Aerts, A., Strobbe, G., van Mierlo, P., Hartsuiker, R.J., Corthals, P., Santens, P. & De Letter, M. (submitted). **Spatio-temporal differentiation of neural activity in auditory and motor regions during pre-attentive and attentive phoneme discrimination**. *Behavioural Brain Research*. (impact factor 2013: 3.39)

LIST OF ABBREVIATIONS

µV	microvolt
AAT	Aachen Aphasia Test
AL	anterior left
AM	anterior midline
ANOVA	Analysis of Variance
APD	auditory phoneme discrimination
AR	anterior right
AWR	auditory word recognition
BA	Brodmann area
BEM	boundary element model
CL	central left
CM	central midline
CR	central right
CoR	cognitive reserve
CVA	cerebrovasculair accident
CVC	consonant-vowel-consonant
d	standardized mean difference
dB SPL	decibel sound pressure level
dB	decibel
DHI	Dutch Handedness Inventory
ECFS	extreme capsule fibre system
EEG	electroencephalography
ERP	event-related potential
FEW(R)	family-wise error (rate)
fMRI	functional magnetic resonance imaging
FOP	frontal operculum
GA	grand average
GG	Greenhouse-Geisser
Hz	Hertz
ICA	independent component analysis

IFC	inferior frontal cortex
IFOF	inferior frontal-occipital fascicle
IPC	inferior parietal cortex
ISI	interstimulus interval
kHz	kilohertz
kΩ	kilo-ohm
LI	laterality indices
log10freq	logarithmic frequency per million
MEG	magnetoencephalography
MIP	maximum intensity projection
MMN	Mismatch Negativity
MMSE	Mini Mental State Examination
MNI	Montreal Neurological Institute
MoA	manner of articulation
MRI	magnetic resonance imaging
ms	milliseconds
MSP	multiple sparse priors
MTG	middle temporal gyrus
NeXTeNS	Nederlandse Extensie voor Tekst naar Spraak
oct	octave
PAC	primary auditory cortex
PALPA	Psycholinguistic Assessment of Language Processing in Aphasia
PC	phonemic contrast
PD	phoneme discrimination
PET	positron emission tomography
PL	posterior left
PM	posterior midline
PoA	place of articulation
PR	posterior right
PvA	plaats van articulatie
PW	pseudowords
R	correlation coefficient
R^2	coefficient of determination
RCT	randomized controlled trial
RW	real words

SAS	Statistical Analysis Software
SAT	Semantische Associatie Test/Semantic Association Test
SD	standard deviation
SLP	speech and language pathologist
SMC	sensorimotor cortex
SPM	Statistical Parametric Mapping
SPSS	Statistical Package for Social Sciences
STC	superior temporal cortex
STG	superior temporal gyrus
STS	superior temporal sulcus
SUBTLEX-NL	subtitle word frequencies based on Dutch subtitles
VAST	Verb and Sentence Test
VOT	voice-onset time
WEZT	Werkwoord en Zinnen Test
WR	word recognition
WvA	wijze van articulatie

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SUMMARY

Aphasia is an acquired language disorder affecting one or more language modalities (production and/or comprehension) and occurs in approximately 30-45 % of all stroke patients. Aphasia has a major impact on a person's communication abilities and even has the most negative impact on the quality of life, followed by disorders like cancer and Alzheimer disease. Phonological and lexical input processes form part of the first processing steps of language comprehension and deficits of these processes can cause a destabilization in the consecutive language process. Unfortunately, in the acute stage of stroke, it is not always possible to evaluate these input processes objectively with behavioural tests, as some patients cannot be instructed due to severely impaired comprehension, reduced consciousness or confusion. The implementation of neurophysiological measures, i.e. event-related potentials (ERPS), can circumvent such problems as they have already demonstrated their sensitivity and usefulness in measuring certain language processes in both a healthy and clinical population. However, there is still a lack of standardized normative data for ERPs in order to be used in clinical practice.

The main objective of this doctoral thesis was to develop Flemish normative data for specific ERPs related to phonological input processes (N100-P200 complex, Mismatch Negativity (MMN), P300, and N400) and to gauge them as an objective diagnostic and therapeutic evaluation method in a population of patients with aphasia in the acute stage of stroke. A first and second study investigated the effects of age and sex on the amplitudes and latencies of the neurophysiological correlates of pre-attentive (MMN) and attentive (P300) phoneme discrimination and pre-attentive (N100, P200 and N400) word recognition in healthy, non-brain damaged individuals. A third study explored whether the phoneme discrimination and word recognition tasks were feasible to administer in patients with aphasia in the acute stage of stroke and to what extent the ERPs deviate from the newly developed Flemish normative data. In a fourth study the effect of therapy after intensive and conventional language treatment in a patient with aphasia was measured by implementing both behavioural and neurophysiological measures. Finally, a fifth study aimed to disentangle the temporal organization of auditory and motor regions during the phoneme discrimination task in healthy individuals, using a recent source reconstruction technique.

Aging influenced auditory phoneme discrimination in a hierarchical way, in which the phonemic contrast place of articulation (PoA) demonstrated the most robust ERPs and voicing the most

vulnerable. Moreover, phoneme discrimination based on PoA, and not voicing or manner of articulation (MoA), revealed higher neurophysiological responses (MMN and P300) in women compared to men. During word recognition, advancing age did not affect the P200 and N400 elicited by pseudowords, yet did so with the P200 and N400 elicited by real words. Sex-related differences in terms of information processing speed at the level of the P200 and N400 in response to real words and pseudowords were revealed as well. Earlier ERPs such as the P50 and N100 were not affected by increasing age, neither during phoneme discrimination nor during word recognition. Neurophysiological normative data were developed according to the aging effects (different age categories), though to make a justified distinction between men and women these data need to be complemented with more subjects.

Patients with post-stroke aphasia demonstrated roughly the same pattern during phoneme discrimination, namely PoA being the most spared and voicing together with MoA the most vulnerable, arguing for a qualitative pattern of phonemic contrast discrimination after stroke. The attentive task had an adverse effect on the performance of the patients with aphasia and the P300 response, due to the increased processing load. During word recognition, patients with aphasia mainly suffered from a delayed processing, which did not impair the response to pseudowords. Early language intervention after stroke improved these phonological input processes in a patient with aphasia, as evidenced by behavioural and neurophysiological measures. The combination of an intensive and impairment-based approach appeared to play an important role throughout the therapy periods. Moreover, ERPs have proven to be sensitive enough to be used in the clinical evaluation of phoneme and word processing in patients with aphasia in the acute stage of stroke and definitely provided an added value during the therapy follow-up.

Finally, the source reconstruction unravelled that phoneme discrimination depends on an early, anticipatory activation of auditory-acoustic properties in superior temporal auditory regions, more perpetuated for MoA/voicing, and a later auditory-to-motor and motor-to-auditory interaction in sensorimotor (frontal and parietal) areas, more perpetuated for PoA. Such a spatiotemporal integration of the different phonemic contrasts is important for successful phoneme discrimination and future research should investigate whether, to what degree and how this integration pattern is disturbed in aphasia entailing phonological input disorders.

SAMENVATTING

Afasie is een verworven taalstoornis waarbij één of meerdere taalmodaliteiten (productie en/of begrip) aangetast zijn en treft ongeveer 30-45 % van alle patiënten die lijden aan een cerebrovasculair accident (CVA). Afasie heeft een grote impact op de communicatieve mogelijkheden van de patiënt en blijkt zelfs de grootste negatieve impact te hebben op de levenskwaliteit, gevolgd door aandoeningen zoals kanker en de ziekte van Alzheimer. Fonologische en lexicale inputprocessen vormen de initiële fases binnen het begrijpen van taal, waardoor een verstoring van deze processen kan leiden tot een destabilisatie van het daaropvolgende taalproces. In de acute fase van een CVA is het echter niet steeds mogelijk om deze inputprocessen te evalueren aan de hand van gedragsmatige testen, aangezien sommige patiënten moeilijk geïnstrueerd kunnen worden door ernstige begripsproblemen, beperkt bewustzijn of verwardheid. Het implementeren van neurofysiologische maten, zoals event-related potentialen (ERPs), kan dergelijke problemen opvangen aangezien het reeds is aangetoond dat ERPs gevoelig genoeg zijn om bepaalde taalprocessen te meten in zowel een gezonde populatie als bij patiënten. Er zijn echter tot op heden nog geen gestandaardiseerde neurofysiologische normatieve data ontwikkeld voor gebruik in de klinische praktijk.

De belangrijkste doelstelling van dit proefschrift behelsde het ontwikkelen van Vlaamse normatieve data voor specifieke ERPs gerelateerd aan fonologische inputprocessen (N100-P200 complex, Mismatch Negativity (MMN), P300 en N400) en het testen van deze ERPs als een potentiële diagnostische en therapeutische evaluatiemethode in een populatie van afasiepatiënten in het kader van een acuut CVA. Een eerste en tweede studie onderzochten de effecten van leeftijd en geslacht op de amplitudes en latenties van de neurofysiologische correlaten van pre-attentieve (MMN) en attentieve (P300) foneemdiscriminatie en pre-attentieve (N100, P200 en N400) woordherkenning bij gezonde personen. Een derde studie ging na of het haalbaar was om de foneemdiscriminatie- en woordherkenningstaken af te nemen bij afasiepatiënten in de acute fase van een CVA en in welke mate de ERPs afwijken van de nieuw ontwikkelde Vlaamse normatieve data. In een vierde studie werden de effecten van taalstimulatie gemeten na een intensieve en conventionele therapie door het implementeren van zowel gedragsmatige als neurofysiologische maten. Ten slotte werd in een vijfde studie getracht de temporele organisatie van auditieve en motorische regio's tijdens foneemdiscriminatie te ontrafelen bij gezonde personen, aan de hand van bronreconstructie.

Leeftijd beïnvloedde auditieve foneemdiscriminatie op een hiërarchische manier, waarbij het foneemcontrast plaats van articulatie (PvA) de meest robuuste ERPs vertoonde en stemhebbendheid de meest kwetsbare. Bovendien lokte foneemdiscriminatie gebaseerd op PvA, en niet stemhebbendheid of wijze van articulatie (WvA), grotere neurofysiologische responsen (MMN en P300) uit bij vrouwen in vergelijking met mannen. Tijdens woordherkenning leek gevorderde leeftijd geen effect te hebben op de P200 en N400 uitgelokt door pseudowoorden, wat echter wel het geval was bij de P200 en N400 uitgelokt door bestaande woorden. Verschillen tussen mannen en vrouwen waren aanwezig op het vlak van verwerkingssnelheid van de P200 en N400 als reactie op bestaande woorden en pseudowoorden. Vroege ERPs zoals de P50 en N100 waren noch tijdens foneemdiscriminatie noch tijdens woordherkenning aangetast door stijgende leeftijd. Neurofysiologische normatieve data werden ontwikkeld rekening houdende met de leeftijdseffecten (opdeling in verschillende leeftijdscategorieën), doch niettemin moeten deze data aangevuld worden met meer subjecten om een juist onderscheid te kunnen maken tussen mannen en vrouwen.

Afasiepatiënten demonstreerden zo goed als hetzelfde patroon tijdens foneemdiscriminatie, waarbij PvA het meest gespaard bleef en stemhebbendheid en WvA het meest kwetsbaar bleek, wat pleit voor een kwalitatief patroon van foneemdiscriminatie na een CVA. De attentieve taak had door een verhoogde verwerkingslast een nadelig effect op de prestatie van de afasiepatiënten en de P300 potentiaal. Tijdens woordherkenning vertoonden de afasiepatiënten voornamelijk een vertraagde verwerking wat echter de uitgelokte respons op pseudowoorden niet benadeelde. Vroege taaltherapie na een CVA verbeterde deze fonologische inputprocessen bij een afasiepatiënt, zoals werd aangetoond met gedragsmatige en neurofysiologische maten. De combinatie van een intensieve en stoornisgerichte aanpak leek een belangrijke factor te zijn doorheen de verschillende therapieperiodes. Daarenboven bewezen de ERPs sensitief genoeg te zijn om gebruikt te worden in de klinische evaluatie van foneem- en woordverwerking bij afasiepatiënten in de acute fase na een CVA en betekenden ze zeker een meerwaarde tijdens de therapeutische follow-up.

Ten slotte toonde de bronreconstructie aan dat foneemdiscriminatie afhankelijk is van enerzijds vroege, anticipatoire activiteit van auditief-akoestische eigenschappen in de superieur temporale auditieve regio's, meer bestendigd voor WvA en stemhebbendheid, en anderzijds een late auditief-motorische interactie in sensomotorische area's (frontaal en pariëtaal), meer bestendigd voor PvA. Dergelijke spatiotemporele integratie van de verschillende foneemcontrasten is belangrijk voor een succesvolle foneemdiscriminatie en toekomstig onderzoek moet focussen op hoe, of en in welke mate dit integratiepatroon verstoord is bij afasie met onderliggende gestoorde fonologische inputprocessen.

GENERAL INTRODUCTION

CHAPTER 1

Auditory speech perception and comprehension in non-brain damaged individuals and patients with aphasia

1.1 Auditory speech perception and comprehension

During the comprehension of a spoken word, multiple, distinct stages have to be completed successfully before a listener can give a correct meaning to the heard word. Several models of single word processing try to explain the trajectory from an incoming speech sound wave to the understanding of that incoming speech sound wave (Basso, 2003; Ellis & Young, 1986, 1996; Gaskell & Marslen-Wilson, 2002; McClelland & Elman, 1986). Some form of dichotomy exists among these different language models, assuming either a distributed representation of words (connectionist models) (Gaskell & Marslen-Wilson, 2002; McClelland & Elman, 1986) or a local representation of words (localist models) (Basso, 2003; Bormann & Weiller, 2012; Ellis & Young, 1986, 1996). The most important difference between these two views is the proposition of "mental lexicons" by the localist models, which implies the existence of a repository for local mental representations acquired and stored throughout life. A separate mental lexicon is supposed to be present for every language modality (auditory, orthographic, visual and environmental) and is called the *phonological input lexicon* in the case of spoken word processing. The current doctoral thesis is based on the localist model posed by Ellis and Young (1996), thus also assumes the presence of a mental lexicon for spoken words, considering the lack of evidence supporting the opposite (Coltheart, 2004).

For a complete and correct comprehension of a spoken word, several phases have to be passed successfully before a definite match can be made with conceptual, meaningful information in the semantic system (see Figure 1.1). According to the model put forward by Ellis and Young (1996), these are the phonological input phases **(1)** phonological analysis, **(2)** phonological input lexicon and **(3)** access to the semantic system, which eventually leads to **(4)** semantic processing of the word.

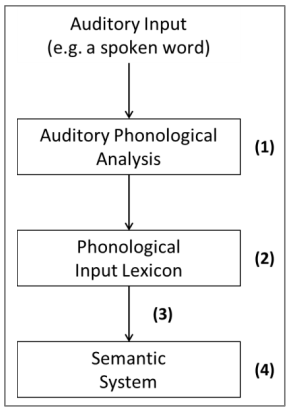

Figure 1.1: Outline of the single word processing model by Ellis and Young (1996). Terminology is different from the one used in the original model.

(1) One of the first phases of spoken word comprehension is the ***auditory phonological analysis*** during which individual speech sounds are extracted from the incoming speech sound wave (segmentation). These individual speech sounds are phonemes, which are the smallest segmental units used to obtain meaningful contrasts between utterances, e.g. two spoken words (International Phonetic Association, 1999). These segmental units are defined by phonemic contrasts that characterize and distinguish between each phoneme. First of all, any constriction of the air flow in the mouth-throat canal distinguishes consonants (turbulent flow) from vowels, which are realised without any form of obstacle in the mouth (laminar flow) (Rietveld & van Heuven, 2009). The degree of constriction in consonants is called "manner of articulation" (MoA), the place of constriction is called "place of articulation" (PoA). For **PoA**, eight different places of constriction exist based on the positioning of the tongue and the lips and can vary from anterior placement in the mouth, as with bilabial (e.g. /b/) or alveolar phonemes (e.g., /t/), to posterior placement in the mouth, as with velar (e.g., /k/) or uvular (e.g. /R/) phonemes (Rietveld & van Heuven, 2009). For **MoA**, five different manners of constriction can be identified: (1) plosives are marked by a short interruption of the air flow followed by a short explosion, e.g. /p/; (2) fricatives are characterised by a turbulent flow of air, e.g. /f/; (3) liquidae are marked by a minimal obstruction of the air flow, e.g. /l/; (4) nasals are produced with an obstruction in the oral cavity while the air runs through the nasal cavity because of a lowered soft palate (velum) (e.g. /m/); (5) semi-vowels are realised with a minimal obstruction of the air flow and when the obstruction becomes wider, a real vowel arises (e.g. /j/)(Rietveld & van Heuven, 2009). Besides PoA and MoA, a third phonemic contrast regards the presence or absence of vibration of the vocal cords during phoneme production and is called "phonation of the phonemes" (voicing). More specifically, **voicing** can be defined by the length of time between the release of a phoneme and the onset of the vibration of the vocal cords, which is called the voice-onset time (VOT). The VOT for voiced phonemes (e.g., /d/) is shorter than the VOT for voiceless phonemes (e.g., /t/), because the vibration of the vocal cords in /d/ starts before the release of the phoneme. Voiced phonemes in Dutch often have a negative VOT (voice lead), whereas voiceless phonemes always have a positive VOT of 0 ms or more (voice lag) (Rietveld & van Heuven, 2009). Each phoneme is composed of a unique combination of these three phonemic contrasts and two phonemes can differ in one, two or all three phonemic contrasts. Therefore, an essential part of an intact auditory phonological analysis process is the ability to identify a speech sound as a phoneme and to discriminate between two phonemes. Phonemes differing in three phonemic contrasts (e.g. /b/ and /X/) are automatically more easily discriminated than phonemes differing in two (e.g. /b/ and /k/) or one (e.g. /b/ and /p/) phonemic contrast (Blumstein & Cooper, 1972; Blumstein, Baker & Goodglass, 1977). Moreover, a study by Hessler, Jonkers, Stowe and Bastiaanse (2013) even demonstrated (in

the Dutch language) that within one phonemic contrast (PoA) more attention is required to process a smaller difference (/p/-/t/) than a larger difference (/p/-/k/).

(2) From the moment the speech sound wave is segmented into its different phonemes, a phonological representation is reconstructed and in the case of a correct reconstruction, access can be provided to the ***phonological input lexicon***. The phonological input lexicon constitutes the repository of all known phonological representations or word forms ever acquired and stored. It indicates that a certain spoken word form has been heard before, forms part of a person's mental lexicon and therefore is a genuine, existing word. Word forms with similar phonological structures, such as [la:kən] and [ma:kən], are stored closely together (i.e., lexical neighbours). So, when an incorrect phoneme is extracted during the phonological analysis stage, due to poor identification and/or discrimination abilities, it is possible that a certain word form cannot be recognized and is identified as an existing word. For example, correctly discriminating between /w/ and /m/ comprises a differentiation in MoA and is important for distinguishing between a Dutch, real word, e.g. [wa:pən], and a pseudoword, e.g. [ma:pən].

(3) When a correct phonological structure is formed and eventually matched with stored, known word forms, ***access*** must be granted to the meaning of the heard word in the ***semantic system***. In this way matching between heard word forms and word meanings is allowed in the semantic system. This phase, together with the phonological analysis and phonological input lexicon phase, is modality-specific. Printed words (orthographic) or objects (visual) will be processed in separate orthographic and visual analysis phases and orthographic and visual input lexicons.

(4) Finally, when the word form selected in the phonological input lexicon gained access to the semantic system, the actual meaning of a word can be retrieved from the ***semantic system***. The semantic system is a long-term repository for the meaning of words. According to Ellis and Young (1996), one semantic system exists for all language modalities and receives input from auditory, orthographic, visual as well as environmental stimuli. Word meanings are ordered in semantic categories, meaning that all word meanings related to "fruits" are stored closely together (e.g. "apple" and "pear"). Word meanings from different semantic categories are stored further away from each other (e.g. "apple" and "truck"), although certain categories will be more closely stored (e.g. "fruits" and "vegetables") compared to other categories (e.g. "fruits" and "vehicles"). An example of how a semantic network can look like schematically is represented in Figure 1.2.

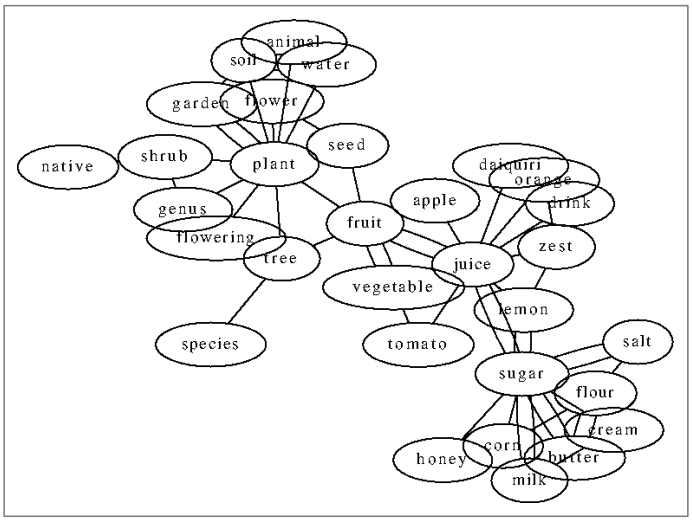

Figure 1.2: A simplified schematic representation of a part of the semantic network (adopted from Iosif, 2013 with permission)

Based on the above outlined neurocognitive language processing model (Ellis & Young, 1996), a set of 52 language tests has been developed by Kay, Lesser and Coltheart (1992), namely the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA). Each test is designed to cover a certain phase of the model, making it possible to investigate each relevant step in spoken word comprehension and production. The possibility of selecting certain subtests based on observed symptoms in an aphasic patient, makes the PALPA are very useful clinical tool. Consequently, this was an important motivation for choosing this model to strengthen the current doctoral thesis.

1.2 Impaired auditory speech perception and comprehension in aphasia

Aphasia is an acquired language disorder caused by brain damage, most often an ischemic stroke or a haemorrhage, and occurs in approximately 30-45 % of all stroke patients (Dickey et al., 2010; Kauhanen et al., 2000). Aphasia has a major impact on communication abilities of patients and even showed to have the most negative impact on the quality of life, followed by diseases like cancer and Alzheimer disease (Lam & Wodchis, 2010). Both comprehension and production of language can be disturbed, with either one of them discrepantly more affected. Auditory comprehension disorders can be caused by deficient phonological, lexical or semantic processing or a combination of multiple impaired phases. In case of a defect in phonological input phases, such as phonological analysis or

the phonological input lexicon, a destabilization of consecutive language processing can impair further language comprehension (Robson, Keidel, Lambon Ralph & Sage, 2012).

A ***deficit*** in the ***phonological analysis*** system is characterized by difficulties with identifying phonemes from the incoming speech sound wave and/or discriminating between two phonemes. In its isolated form this is called "word-sound deafness" (Coltheart, 2004; Franklin, 1989; Stefanatos, Gershkoff & Madigan, 2005). Aphasic patients with this kind of deficit are unable to understand or repeat existing or non-existing spoken words with a sparing of other language modalities and spoken word production. Important at this point is to exclude the possibility of attributing the auditory analysis deficiencies to hearing loss and dissociate them from pure "auditory agnosia", which is the inability to recognize and interpret environmental sounds (Coltheart, 2004). A discrimination task using minimal word pairs (e.g. [kɑt] and [bɑt]) can be used to uncover word-sound deafness, in which aphasic patients have to decide if two spoken words (or pseudowords) are the same or different. Obviously, phonemic contrasts play an important role here. Blumstein et al. (1977) demonstrated that aphasic patients have more difficulty with discriminating PoA compared to voicing. Klitsch (2008) found that MoA is the most easily processed whereas PoA the most difficult, leaving voicing in between. However, Saffran, Marin and Yeni-Komshian (1976) and Caplan and Aydelott-Utman (1994) posed that voicing reveals the most problems. Finally, in a comparison of all three phonemic contrasts, voicing also appeared the most difficult contrast, yet no clear difference was found between PoA and MoA (Hessler, Jonkers & Bastiaanse, 2010). It seems that until now no consensus has been reached regarding the presence of some form of hierarchy in the (disturbed) processing of phonemic contrasts.

When phonological analysis is intact, as indicated by normal discrimination abilities, selective ***impairment*** of the ***phonological input lexicon*** can explain why certain aphasic patients are not capable of recognizing heard words, despite being able to repeat them correctly. In its pure, isolated form, this is called "word-form deafness" (Coltheart, 2004; Franklin, 1989). With a deficit at this phase, aphasic patients cannot decide whether a particular word has been heard before, hence forms part of the mental lexicon, which can lead to two possible error patterns. When a real word is presented, it is possible that a competing, related word form with a similar phonological structure as the heard word is selected from the phonological input lexicon. For example, presenting a real word like [bɑl] can lead to the selection of another, highly similar real word [bɑt]. Word frequency plays an important role at this point, as high frequency words carry more "lexical weight" and will be more easily chosen than low frequency words with less "lexical weight". When a pseudoword is presented, it is possible that the phonological structure of a real word is recognized and selected from the input

lexicon. Pseudowords with a high similarity to real words, such as pseudowords derived from real words, will be more easily designated as real words and are therefore more difficult to process. For example, presenting a pseudoword like [ɑpəm] can lead to the selection of the highly similar real word [ɑpəl]. A lexical decision task can reveal such a deficit, where aphasic patients are asked whether a particular spoken real word or pseudoword sounds familiar or not, by answering either YES or NO, which immediately gives an impression about the impairment.

It is possible that aphasic patients demonstrate intact phonemic perception during the phonological analysis, hence show correct repetition, but also intact semantic processing as indicated by spared comprehension of written words or pictures. When these aphasic patients are also capable of making correct decisions on the lexical status of a heard word and recognize real words as being part of their phonological input lexicon, there is an isolated ***deficit*** in the ***access to the semantic system***. This is called "word-meaning deafness" (Bormann & Weiller, 2012; Franklin, 1989). Such aphasic patients are not able to match a retrieved word form from the input lexicon with a corresponding meaningful semantic representation. The semantic system itself is NOT affected, as shown by a dissociation between the auditory modality and the other language modalities. Therefore, a comparison between auditory stimuli and orthographic, visual and even environmental stimuli are necessary. An aphasic patient not able to match a spoken word (e.g. [kɑt]) with a picture must be able to match the same, written word (e.g. KAT) with the same picture. Only then it can be guaranteed that it concerns a disrupted access to the semantic system and not an impaired semantic system itself.

Aphasic patients with a ***pure, generic semantic deficit*** will have problems with understanding words when presented with spoken words (e.g. [kɑt]), written words (e.g. KAT), objects or pictures of objects (e.g. picture of a cat or a real cat) or environmental sounds (e.g. the miaow of a cat). The absence of any language impairment in other modalities (e.g. orthographic or visual) is an important factor to distinguish auditory phonological analysis or input lexicon deficits from higher-level semantic impairments. Repetition, reading and naming is characterized by semantic errors (called semantic paraphasias), within the same semantic category (e.g. naming an "apple" as "orange") as well as between semantic categories (e.g. naming an "apple" as "ball"). Other classic semantic tasks are impaired, such as auditory and written synonym-judgement tasks and word-picture matching tasks. An important factor at this stage is the degree of concreteness and imageability, in which concrete and highly imageable words (e.g. "table") are processed more easily than abstract and less imageable words (e.g. "envy").

In reality, the above described isolated disorders of phonological input processes and semantic impairments are rare and instead a combination of disorders mostly occurs, in language

comprehension as well as production. In addition, the presence of other aphasic symptoms, such as naming difficulties in case of anomia, contributes to specific aphasic syndromes (e.g. the well-known Broca and Wernicke's aphasias). Moreover, language goes beyond single word processing, showing additional effects of sentence context, morphosyntactic rules and pragmatic abilities when narrative language is considered. Using the well-defined PALPA tasks (Kay et al., 1992) all the above mentioned disorders of phonological input processes can be assessed and filtered from a larger language comprehension or production deficit.

1.3 References

Basso, A. (2003). *Aphasia and its therapy* (1st ed). New York: Oxford University Press.

Blumstein, S., & Cooper, W. (1972). Identification versus discrimination of distinctive features in speech perception. *Quarterly Journal of Experimental Psychology, 24* (2), 207-214.

Blumstein, S. E., Baker, E., & Goodglass, H. (1977). Phonological factors in auditory comprehension in aphasia. *Neuropsychologia, 15*, 19-30.

Bormann, T., & Weiller, C. (2012). "Are there lexicons?" A study of lexical and semantic processing in word-meaning deafness suggests "yes". *Cortex, 48*, 294-307.

Caplan, D. & Aydelott-Utman, J. (1994). Selective acoustic phonetic impairment and lexical access in an aphasic patient. *The Journal of the Acoustical Society of America, 95* (1), 512-517.

Coltheart, M. (2004). Are there lexicons? *The Quarterly Journal of Experimental Psychology, 57A* (7), 1153–1171.

Dickey, L., Kagan, A., Lindsay, P., Fang, J., Rowland, A., & Black, S. (2010). Incidence and Profile of Inpatient Stroke-Induced Aphasia in Ontario, Canada. *Archives of Physical Medicine and Rehabilitation, 91*, 196-202.

Ellis, A.W., & Young, A.W (1986). *Human Cognitive Neuropsychology*. Hove, UK: Psychology Press.

Ellis, A.W., & Young, A.W (1996). *Human Cognitive Neuropsychology: A Textbook with Readings* (augmented edition). Hove, UK: Psychology Press.

Franklin, S. (1989). Dissociations in auditory word comprehension: Evidence from nine fluent aphasic patients. *Aphasiology, 3*(3), 189-207.

Gaskell, M.G., & Marslen-Wilson, W.D. (2002). Representation and competition in the perception of spoken words. *Cognitive Psychology, 45*, 220–266.

Hessler, D., Jonkers, R., & Bastiaanse, R. (2010). The influence of phonetic dimensions on aphasic speech perception. *Clinical Linguistics & Phonetics, 24* (12), 980-996.

Hessler, D., Jonkers, R., Stowe, L., & Bastiaanse, R. (2013). The whole is more than the sum of its parts: Audiovisual processing of phonemes investigated with ERPs. *Brain and Language, 124*, 213-224.

International Phonetic Association (1999). *Handbook of the International Phonetic Association: a guide to the use of the international phonetic alphabet*. Cambridge University Press.

Iosif, E. (2013). Network-Based Distributional Semantic Models, PhD thesis, Technical University of Crete.

Kauhanena, M.-L., Korpelainena, J.T., Hiltunenb, P., Määttäa, R., Mononena, H., Brusinc, E. et al. (2000). Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. *Cerebrovascular Diseases, 10*, 455–461.

Kay, J., Lesser, R., & Coltheart, M. (1992). *PALPA: Psycholinguistic Assessments of Language Processing in Aphasia*. Hove, UK: Psychology Press.

Klitsch, J. (2008). Open your eyes and listen carefully. Auditory and audiovisual speech perception and the McGurk effect in Dutch speakers with and without aphasia (doctoral dissertation, University of Groningen). *Groningen Dissertations in Linguistics (GRODIL), 67*.

Lam, J. M. C., & Wodchis, W. P. (2010). The relationship of 60 disease diagnoses and 15 conditions to preference-based health-related quality of life in Ontario hospital-based long-term care residents. *Medical Care, 48*, 380–387.

McClelland, J. L., & Elman, J. L. (1986). The TRACE model of speech perception. Cognitive Psychology, 18, 1–86.

Rietveld, A. C. M., & van Heuven, V. J. (2009). *Algemene fonetiek* (3rd ed). Bussum: Uitgeverij Coutinho.

Robson, H., Keidel, J.L., Lambon Ralph, M.A., & Sage, K. (2012). Revealing and quantifying the impaired phonological analysis underpinning impaired comprehension in Wernicke's aphasia. *Neuropsychologia, 50*, 276– 288.

Saffran, E. M., Marin, O. S. M., & Yeni-Komshian, G. H. (1976). An analysis of speech perception in word deafness. *Brain and Language, 3*, 209-228.

Stefanatos, G.A., Gershkoff, A., & Madigan, S. (2005). On pure word deafness, temporal processing, and the left hemisphere. *Journal of the International Neuropsychological Society, 11*, 456–470.

CHAPTER 2

Neuroanatomical and neurophysiological organization of auditory speech perception and comprehension in non-brain damaged individuals

2.1 Neuroanatomy of auditory speech perception and comprehension

Auditory speech perception and comprehension as outlined above is supported by distributed networks in separate parts of the brain (see Figure 2.1), which are interconnected by distinct pathways. These pathways substantiate the information transfer between the different brain regions. The main language-sensitive areas are organized in dorsal and ventral processing streams and each subserve distinct stages of auditory speech perception and comprehension (Friederici & Gierhan, 2013; Gierhan, 2012; Hickok & Poeppel, 2004, 2007; Saur et al., 2008). In what follows, the functional neuroanatomy of auditory speech perception and comprehension will be discussed.

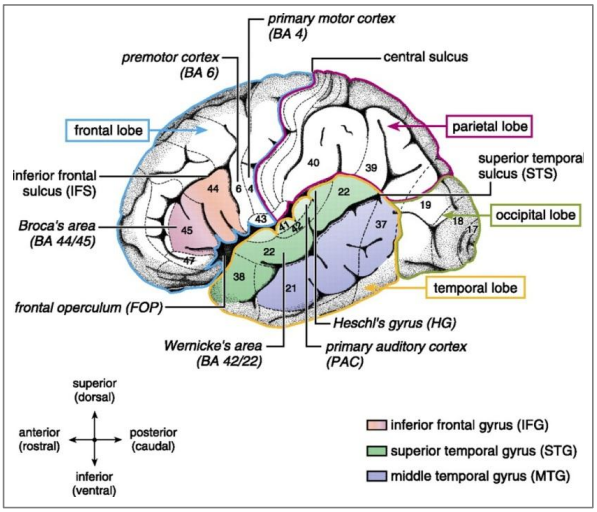

Figure 2.1: Neuroanatomical organization of the language network in the left hemisphere (adopted from Friederici, 2011 with permission).

Primary, acoustic-phonetic analysis is carried out in the middle and posterior part of the superior temporal gyrus (STG) and sulcus (STS) bilaterally (Binder et al., 2000; DeWitt & Rauschecker, 2012; Friederici, 2011, 2012; Hickok & Poeppel, 2004, 2007). An important structure in these areas is Heschl's gyrus, which consists of the primary auditory cortex (PAC), a part anterolateral to Heschl's gyrus (planum polare) and a part posterior to Heschl's gyrus (planum temporale) (Friederici, 2011; Jäncke, Wüstenberg, Scheich & Heinze, 2002). Processing starts in the PAC, where a first, acoustic, spectrotemporal analysis of auditory, both simple and complex, sounds occurs and subsequently diverges to anterior and posterior parts of Heschl's gyrus. The planum polare, anterolateral of Heschl's gyrus, has shown to be sensitive to phonemes and able to differentiate between speech and

non-speech sounds (Friederici, 2011; Obleser, Zimmermann, Van Meter & Rauschecker, 2007). On the other hand, the planum temporale posterior of Heschl's gyrus serves a more non-specialized function, showing involvement in different kinds of complex sound processing, irrespective of the nature of the sound, and is important for gating information to higher-order cortical regions (Griffiths & Warren, 2002; Obleser et al., 2007). Despite the preponderant bilateral organization of this early language process, hemispheric asymmetries do occur with respect to spectrotemporal cues. In the case of rapid temporal cues (25-30 ms), as with phonemic contrasts like PoA and voicing, there is more left-hemispheric overweight, whereas a right-hemispheric overweight emerges with slower temporal (150-300 ms) and spectral cues (prosodic features) (Boemio, Fromm, Braun & Poeppel, 2005; Trébuchon-Da Fonseca, Giraud, Badier, Chauvel & Liégeois-Chauvel, 2005; Zatorre & Belin, 2001).

From here on, the cortical network diverges into a ventral and dorsal processing stream, dependent on the language function (see Figure 2.2). The left-laterized dorsal pathway projects from the posterior STG via the inferior parietal cortex to frontal areas along the arcuate and superior longitudinal fascicle (Burton, 2009; Friederici, 2009; Saur et al., 2008). The bilaterally organized ventral pathway runs from posterior STG to middle and inferior temporal regions, through short-range fibre tracts within the temporal cortex, and via the anterior temporal cortex to inferior frontal areas via uncinate fascicle, extreme capsule, extreme capsule fibre system (ECFS) and inferior frontal-occipital fascicle (IFOF) (Friederici, 2011; Hickok and Poeppel, 2004, 2007; Upadhyay et al., 2012).

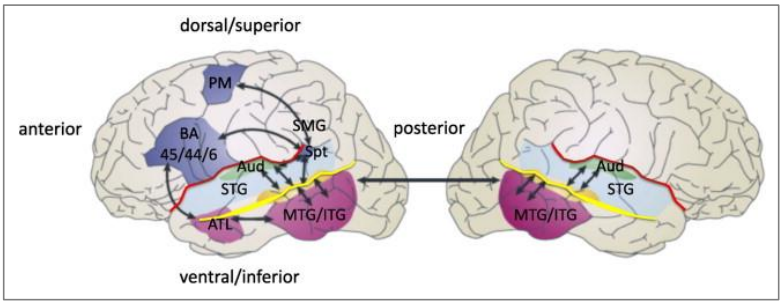

Figure 2.2: Dual stream model first posed by Hickok and Poeppel in 2000 (adopted from Hickok, 2009 with permission)

It has been claimed that at least two different dorsal pathways and two ventral pathways exist (see Figure 2.3) (Friederici, 2009, 2011, 2013; Gierhan, 2012).

A first dorsal stream *(dorsal pathway I)* has end points in motor and premotor areas and corresponds to the superior longitudinal fascicle (Friederici, 2011; Gierhan, 2012). This pathway connects with the inferior parietal cortex, which serves as an auditory-motor interface where auditory features are integrated with articulatory-based representations (Hickok, Buchsbaum, Humphries & Muftuler, 2003; Hickok, Okada & Serences, 2009; Turkeltaub & Branch Coslett, 2010). The involvement of motor cortex in speech perception, including both premotor and primary motor regions, has been well established and is somatotopically driven by articulatory characteristics of the phonemic contrasts (D'Ausilio et al., 2009; Pulvermüller et al., 2006; Wilson, Saygin, Sereno & Iacoboni, 2004).

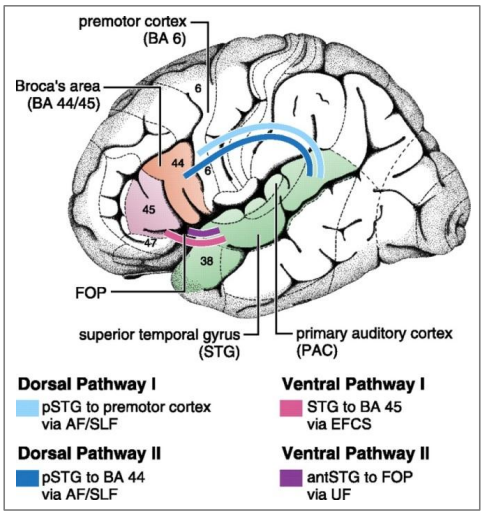

Figure 2.3: Ventral and dorsal pathways of auditory language processing (adopted from Friederici, 2011 with permission).

Dorsal pathway I plays only a limited, more modulatory role in speech perception and recognition and is addressed during sublexical tasks, such as phoneme discrimination, where auditory features of speech sounds are linked to articulatory features to achieve an accurate detection of phonetic-phonological categories (Celsis et al., 2002; Turkeltaub & Branch Coslett, 2010). In general, *dorsal pathway I* has a more prominent role during speech production processes, mainly in the context of speech development and speech repetition, where the mapping of auditory features to motor features is essential (Friederici, 2009; Hickok & Poeppel, 2007). When a new word or a non-familiar word is encountered, higher level of activation can be expected in *dorsal pathway I*, as there will be a higher reliance on articulatory-based representations of the different word segments (i.e. phonemes) (Burton, 2001; Burton, 2009; Londei et al., 2010; Zaehle et al., 2008). A second dorsal stream *(dorsal*

pathway II), has end points in inferior frontal regions, such as Brodmann areas (BA) 44 and the frontal operculum (FOP), and corresponds to the arcuate fascicle (Friederici 2011; Gierhan, 2012). *Dorsal pathway II* is more involved in higher-level syntactic processing, such as processing of syntactically complex sentences (Friederici, 2012). Considering that syntactic processing falls outside the scope of the current doctoral thesis and covers a wide range of separate literature, this will not be further discussed.

Acoustic-phonological analysis in terms of speech recognition (making connection with the phonological input lexicon) does not necessarily depend on the dorsal pathway, but projects from superior temporal regions to more ventrally located regions (Hickok & Poeppel, 2004, 2007; Hickok, 2009). Further phonological processing as a function of spoken word recognition has been linked to areas in the superior temporal sulcus, in both anterior and posterior directions (Hickok, 2009). Other studies have also denoted anterior superior temporal regions as sensitive for a spoken word's phonological form (Binder et al., 2000; Cohen et al., 2004; DeWitt & Rauschecker, 2012; Friederici, 2012). Superior temporal regions are connected with posterior middle and inferior temporal regions through short range fibre tracts and are responsible for lexico-semantic processing during speech comprehension (Hickok & Poeppel, 2004, 2007). Posterior middle and inferior temporal regions, including angular gyrus, have been designated as a form of conceptual integration centre, supporting sound-to-meaning mapping (Binder, Desai, Graves & Conant, 2009; Hickok & Poeppel, 2004, 2007; Specht et al., 2008; Vigneau et al., 2006). However, anterior temporal regions are also involved in semantic processing, a finding based on the specific semantic deficits seen in patients with semantic dementia who typically show an atrophy and degeneration of the anterior temporal poles bilaterally (Patterson, Nestor & Rogers, 2007). The anterior temporal poles function as an amodal "semantic hub" in which attributes of distinct modality-specific association regions are integrated (e.g. shape, colour, use, names, ...) (Hoffman & Lambon Ralph, 2011; Pobric, Jefferies & Lambon Ralph, 2010). Posterior temporal regions are supposed to be more involved in accessing semantic knowledge from auditory input whereas the anterior temporal poles are more involved in integrating semantic knowledge across modalities (Hickok, 2009). On the one hand a first long-range ventral pathway *(ventral pathway I)* forms part of the IFOF, which is mediated by the ECFS, and connects posterior temporal regions, via anterior temporal areas, with anterior inferior frontal regions (BA 45/47). This pathway is responsible for aspects of controlled retrieval and selection of single-word meanings and semantic, contextual integration in higher-level structures, such as sentences (Friederici 2011; Gierhan, 2012; Saur et al., 2010; Turken & Dronkers, 2011). On the other hand, a second ventral pathway *(ventral pathway II)* connects anterior temporal regions with posterior inferior frontal

regions (FOP) via the uncinate fascicle and is associated with more simple syntactic computations, such as syntactic phrase structure building (Friederici, 2011, 2012).

2.2 Neurophysiology of auditory speech perception and comprehension

Language comprehension entails a multistage process that is supported by a widely-distributed neuronal network in the brain. Consequently, processes occurring at earlier stages of speech perception and comprehension (i.e., operations at the basis of language processing, such as phonology) can influence the whole consecutive language process (Pulvermüller, Shtyrov & Hauk, 2009). Furthermore, fast computation of a phonological representation from the speech input can even facilitate access to the phonological input lexicon (Dehaene-Lambertz, Dupoux & Gout, 2000). Clearly, besides structure and function, another factor must be taken into account when investigating speech perception and comprehension, which is timing.

By means of event-related potentials (ERPs) it is possible to investigate specific language processes with respect to timing. ERPs are an electrical reaction of the brain to a certain stimulus and can be extracted from the basic electrical signal in the brain (as measured with an electroencephalogram or EEG). ERPs reflect postsynaptic potentials originating from the neuronal dendrites and cell body. Each neuron forms a dipole (a pair of positive and negative electrical charges separated by a small distance) and in order to obtain a recordable ERP, thousands of neuronal dipoles must be spatially aligned, hence voltages can be added to each other. Every single response of the brain to a stimulus is constant, though very small and co-occurring with random noise of higher amplitude. For an ERP to be clearly registered, enough stimuli have to be presented of which the activation then can be averaged and noise can be cancelled out (Luck, 2005).
Amplitude, latency and scalp distribution are three measurable and informative aspects of ERPs (Friedman & Johnson, 2000). First, the ERP amplitude provides an index of the degree of neural activation (i.e., extent of allocation of neural resources to specific cognitive processes). Second, the ERP latency represents the point in time when the peak occurs and therefore provides key information about timing of activation. Finally, the ERP's scalp distribution (related to electrode positions on the scalp) reveals basic information on possible location of activated brain areas. The polarity of the ERP (positive or negative) is determined by the relation between electrode position and the orientation of the neural, intracranial dipole, which always has a positive and negative pole.

The time course of primary acoustic-phonetic perception during detection and identification of phonemes (i.e. subprocess of the auditory phonological analysis stage) can be examined with the ***P50***, a positive potential around 50 ms (sometimes called P1), and the ***N100***, a negative potential

around 100 ms (see Figure 2.4). They typically represent sensory-perceptual processes and intermediate stages of auditory feature analysis, detection and identification (Cooper, Todd, McGill & Michie, 2006; Tavabi, Obleser, Dobel & Pantev, 2007). The P50 and N100 are elicited with an oddball paradigm, a task in which a deviant, to be detected, stimulus is interspersed with a string of identical, standard stimuli (e.g. with a 0.20-0.80 probability, respectively). Early ERPs like the P50 and N100 typically represent detection and identification processes of the standard phoneme in the oddball paradigm and can be seen as an intermediate stage of auditory analysis (Näätänen & Winkler, 1999). They have already revealed an interesting differentiation with respect to the phonemic contrasts during phoneme detection and identification, showing distinct P50 and N100 responses in the place of articulation (anterior-posterior), voicing (voiced-voiceless) and manner of articulation (plosives-fricatives; orals-nasals) continuums (Digeser, Wohlberedt & Hoppe, 2009; Horev, Most & Pratt, 2007; Kaukoranta, Hari & Lounasmaa, 1987; Lawson & Gaillard, 1981b; Obleser, Lahiri & Eulitz, 2003, 2004; Ostroff, Martin & Boothroyd, 1998; Sharma & Dorman, 1999; Tavabi et al., 2007).

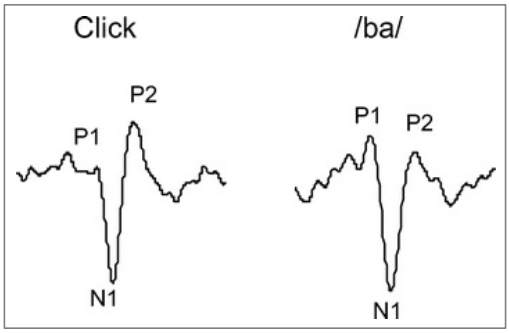

Figure 2.4: The P50-N100-P200 ERP complex in response to a click and syllable [bɑ], with positive polarity upwards (adopted from Martin, Tremblay & Korczak, 2008 with permission)

Immediately after the N100 potential emerges the ***P200***, a positive stimulus-locked deflection around 200 ms (see Figure 2.4). The P200 is actually kind of a "forgotten" or "neglected" ERP, most often seen as the "tail-end" of the N100 in a P50-N100-P200 ERP complex (Crowley & Colrain, 2004). However, research into different cognitive domains, such as attention, maturation and aging, provides evidence for the P200 being an independent ERP component (Crowley & Colrain, 2004). Unfortunately, it has been only rarely looked at from a language-related perspective, which prevents a thorough understanding of this component (Cooper et al., 2006). At phoneme perception level, it is most likely also associated with automatic registration of a stimulus and detection and identification processes (Bertoli, Smurzynski & Probst, 2002; Brunellière, Dufour, Nguyen & Frauenfelder, 2009;

Digeser et al., 2009). At word level, the P200 has been related to preparatory phases prior to lexico-semantic processes, such as form-based phonological analyses with respect to neighbourhood density, phonotactic probability and the legality of spoken or written (pseudo)words (Hunter, 2013; Laszlo, Stites & Federmeier, 2012; Liu, Jin, Qing & Wang, 2011). Together with the P50 and the N100, the P200 is an obligatory response to any auditory presented transient sound, most clearly seen in response to the standard stimulus in an oddball paradigm (Bertoli et al., 2002).

The time course of actual discrimination between different phonemes is represented by the ***Mismatch Negativity (MMN)***, a negative potential around 100-200 ms after stimulus presentation (see Figure 2.5) (Näätänen, Gaillard & Mäntysalo, 1978). The MMN is preceded by the earlier P50 and N100 components and is also elicited with an oddball paradigm. It reflects an automatic, pre-attentive change detection process of the brain when a difference between two stimuli is perceived (Kujala & Näätänen, 2010), making it a unique measure of auditory discrimination accuracy of acoustic and phonemic categories (Näätänen, 2001). During the discrimination process the listener disregards irrelevant within-category acoustic differences and retains only the linguistic, categorical information (Tampas, Harkrider & Hedrick, 2005). The neural basis of the MMN is based on a sensory memory representation, more specifically the activation of different short-term and long-term phoneme-memory traces (Dehaene-Lambertz, 1997; Kujala & Näätänen, 2010; Näätänen et al., 1997). These traces are based on recognition patterns of phonemic contrasts that mature throughout language development and are specific to one's native language. It has even been demonstrated that the MMN is influenced by the number of phonemic contrasts during a phoneme discrimination task, showing shorter latencies and larger amplitudes when phonemes differ in three phonemic contrasts compared to one or two phonemic contrasts (Lawson & Gaillard, 1981a). The neural sources of the MMN to linguistic sounds, in this case phonemes, are strongly left-lateralized, in contrast with right-lateralized MMN to pure tones, clicks or sine wave bursts, and are located in or in the vicinity of the auditory cortex and frontal areas (Kujala & Näätänen, 2010; Rinne et al., 1999; Shtyrov & Pulvermüller, 2007).

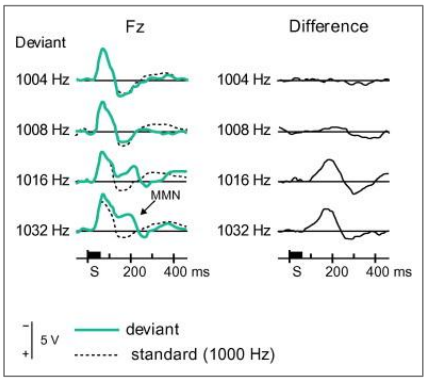

Figure 2.5: The MMN as a function of frequency change (adopted from Näätänen, Paavilainen, Rinne & Alho, 2007 with permission).

The theory of neuronal memory traces for phonemes could be extended to the lexical word form level, when a word-specific MMN enhancement, evoked by deviant meaningful words among standard meaningless word-like stimuli in an oddball task, was demonstrated (Endrass, Mohr & Pulvermüller, 2004; Korpilathi, Krause, Holopainen & Lang, 2001; Pulvermüller et al., 2001; Pulvermüller, Shtyrov, Kujala & Näätänen, 2004). This MMN enhancement occurs in the same time window as the phoneme-related MMN (100-200 ms) and is related to activation of long-term cortical memory traces for words realized as distributed, strongly connected populations of neurons (Shtyrov & Pulvermüller, 2007). The existence of such pre-existing, long-term memory traces for spoken words is supported by the finding that an enhanced word-related MMN occurs independent of lexical status of the standard stimulus, and shows that the brain is capable of very early pre-attentive lexical classification of incoming speech signals (Shtyrov & Pulvermüller, 2002).

Auditory phoneme discrimination can also be investigated at a higher cognitive level, by explicitly requesting to focus attention to the discriminating phonemes and push a button whenever a subject hears a deviant stimulus. Such task demands typically elicit a later, stimulus-locked positive deflection between 300-600 ms, namely the ***P300*** (Sutton, Braren, Zubin & John, 1965) (see Figure 2.6). Especially relevant in this case is the response to the deviant stimulus in the oddball paradigm, whereas with the MMN it is necessary to make a difference ERP by subtracting the response to the standard stimulus from the response to the deviant stimulus (deviant – standard). An important distinction exists between two P300 components, namely the P3a and the P3b. The earlier P3a is related to detection of novel stimuli in a train of standard and deviant stimuli (some form of orienting response), whereas the later P3b (corresponding to the P300 of interest for the current

doctoral thesis) refers to the actual task-relevant deviance detection and discrimination abilities (Linden, 2005).

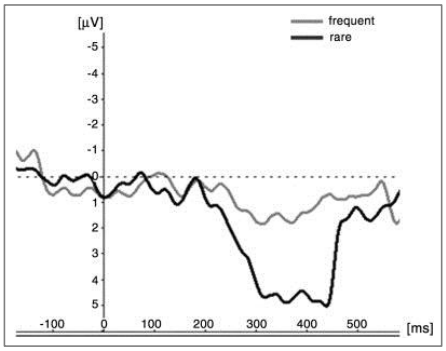

Figure 2.6: The P300 potential in response to the deviant (named "rare" in this picture) stimulus (adopted from Juckel et al., 2012 with permission).

The P300 (i.e., the P3b) is generated more posterior in the brain at centroparietal areas, including mainly inferior parietal cortices such as the supramarginal gyrus (Celsis et al., 2002; Picton, 1992; Linden, 2005). With respect to phoneme categorization, it has been suggested that the MMN may represent the first, acoustic level of processing and the P300 the second, phonetic level of processing (Dalebout & Stack, 1999). However, cross-linguistic studies emasculated this hypothesis by proving that the MMN is already involved in phonemic categorization and not merely reflective for acoustic processing (Näätänen et al., 1997; Sharma & Dorman, 1999, 2000). So, the P300 ERP also represents phoneme discrimination processes, though related to behavioural performance and effect of cognitive processing load (Tampas et al., 2005). For example, within one phonemic contrast larger P300 amplitudes are found with smaller differences between phonemes compared to larger differences, probably related to a higher amount of attention needed to process a smaller difference (Hessler, Jonkers, Stowe & Bastiaanse, 2013). Also, processing of subtle within-category, between-speakers variability is only perceived through an attention-dependent detection process reflected in the P300 response (Deguchi et al., 2010).

All the above described ERPs are not specific to language and can be elicited by different kinds of auditory stimuli, such as clicks, sine waves, pure tones and phonemes. A specific language-related ERP is the ***N400***, a centroparietal negative stimulus-locked potential emerging around 300-500 ms (Kutas & Hillyard, 1980). Its significance ranges from lexical and semantic integration at word level to integration of semantic features in a sentence context (Friederici, 2011; Kutas & Federmeier, 2011). As briefly but succinctly summarized by Friederici (2011, p. 1380), N400 amplitude increases have

been demonstrated in word-level situations (1) when a word does not have a lexical status (i.e., a pseudoword compared to a real word); (2) when the second word of a word pair does not match the first word semantically; and in sentence-level situations (3) when semantic features violate the relation between the verb and its noun argument in verb-argument structure; (4) when a word does not fit the preceding sentence context with respect to semantic knowledge and is simply unexpected; and (5) its amplitude is known to decrease for words as the sentence unrolls due to increased predictability of the upcoming word. Particularly relevant for the present doctoral thesis, is the N400 as an indicator for lexical processing, namely the N400 pseudoword effect (see Figure 2.7). The N400 pseudoword effect is characterized by larger and longer lasting N400 amplitudes in response to pseudowords compared to real words and is linked to an enhanced search for pseudowords (without lexical representation) in the lexico-semantic memory (Friedrich, Eulitz & Lahiri, 2006; Garagnani, Wennekers & Pulvermüller, 2008; Sinai & Pratt, 2002).

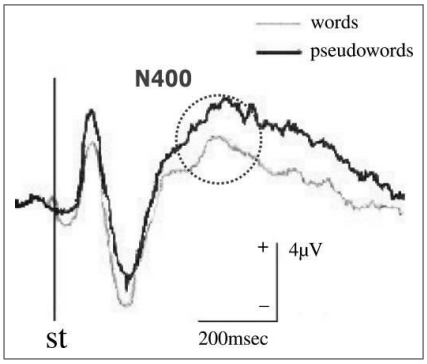

Figure 2.7: The N400 pseudoword effect; st = stimulus (adopted from Garagnani, Wennekers & Pulvermüller, 2008 with permission).

Actually, the N400 pseudoword effect is the reverse pattern of the MMN enhancement in response to real words, which has been related to the level of attention devoted to the stimuli. Lower levels of attention are related to stronger inhibition of coactive lexical representations leading to a stronger and earlier MMN response to words, while higher levels of attention should be related to reduced inhibition of coactive lexical representations leading to a stronger and later N400 response to pseudowords (Garagnani et al., 2008).

Considering the importance of temporal synchronization between consecutive language processes and the specialized neuronal network supporting these language processes, it is of great relevance to unravel the organization of language in terms of structure and time (spatiotemporal properties of

language process). By implementing non-invasive source imaging techniques, which estimate the source of the electrical or magnetic brain activity, it is possible to explore neuroanatomical activation patterns of language processes on a millisecond time basis (considering the high temporal resolution inherent to ERP research). A major drawback of neuroimaging studies, such as fMRI and PET technique, is the very weak temporal resolution (up to multiple seconds), which can lead to a summation of activity over several, distinct language processes (Obleser et al., 2003). EEG and MEG source imaging studies, ranging from 37 to 275 channels, investigating certain language processes already revealed some interesting outcomes. Diesch and Luce (1997) and later Obleser, Lahiri and Eulitz (2003, 2004) and Obleser, Scott and Eulitz (2006) demonstrated that the auditory association cortices are spatially mapped along an anterior-posterior dimension determined by mutually exclusive place of articulation features based on N100m and Mismatch Field topography (see Figure 2.8).

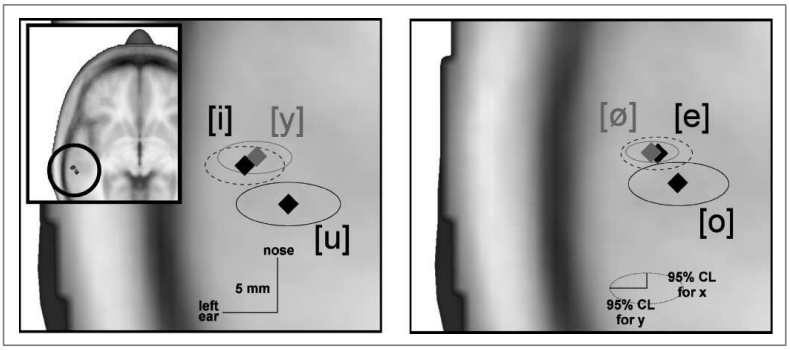

Figure 2.8: Spatial mapping along the anterior-posterior dimension for /i/ and /y/ (adopted from Obleser, Lahiri & Eulitz, 2004 with permission).

Tavabi et al. (2007) confirmed this finding and added that the P50m is topographically aligned along a medial-lateral dimension in more primary auditory regions, like Heschl's gyrus. A study by Pulvermüller, Shtyrov and Ilmoniemi (2003) focused on source imaging during word processing and found a delay of ≈20 ms between left-lateralized superior temporal and inferior frontal activation associated with the word-related MMN which peaked around 130 ms. Other studies have shown the involvement of superior temporal cortices as well (MacGregor, Pulvermüller, van Casteren & Shtyrov, 2012; Pulvermüller et al., 2004), in which preliminary evidence was provided for the existence of distinct neurophysiological topographies for 2 individual words (Pulvermüller et al., 2004). These studies clearly evidence the validity of source imaging techniques and how they can contribute to unveiling the spatiotemporal processing of language.

2.3 References

Bertoli, S., Smurzynski, J. & Probst, R. (2002). Temporal resolution in young and elderly subjects as measured by mismatch negativity and a psychoacoustic gap detection task. *Clinical Neurophysiology, 113*, 396-406.

Binder, J., Frost, J., Hammeke, T., Bellgowan, P., Springer, J., Kaufman, J., et al. (2000). Human temporal lobe activation by speech and nonspeech sounds. *Cerebral Cortex, 10*, 512-528.

Binder,J.R., Desai, R.H., Graves, W.W. & Conant, L.L. (2009). Where Is the Semantic System? A Critical Review and Meta-Analysis of 120 Functional Neuroimaging Studies. *Cerebral Cortex, 19*, 2767-2796.

Boemio, A., Fromm, S., Braun, A. & Poeppel, D. (2005). Hierarchical and asymmetric temporal sensitivity in human auditory cortices. *Nature Neuroscience, 8*(3), 389-395.

Brunellière, A., Dufour, S., Nguyen, N. & Frauenfelder, U.H. (2009). Behavioral and electrophysiological evidence for the impact of regional variation on phoneme perception. *Cognition, 111*, 390-396.

Burton, M.W. (2001). The role of inferior frontal cortex in phonological processing. *Cognitive Science, 25*, 695-709.

Burton, M.W. (2009). Understanding the role of the prefrontal cortex in phonological processing. *Clinical Linguistics & Phonetics, 23*, 180-195.

Celsis, P., Boulanouar, K., Doyon, B., Ranjeva, J., Berry, I., Nespoulous, J., et al. (1999). Differential fMRI responses in the left posterior superior temporal gyrus and left supramarginal gyrus to habituation and change detection in syllables and tones. *Neuroimage, 9*, 135-144.

Cohen, L., Jobert, A., Le Bihan, D. & Dehaene, S. (2004). Distinct unimodal and multimodal regions for word processing in the left temporal cortex. *Neuroimage, 23*, 1256-1270.

Cooper, R. J., Todd, J., McGill, K. & Michie, P. (2006). Auditory sensory memory and the aging brain: A mismatch negativity study. *Neurobiology of Aging, 27*, 752-762.

Crowley, K.E. & Colrain, I.M. (2004). A review of the evidence for P2 being an independent component process: Age, sleep and modality. *Clinical Neurophysiology, 115*, 732-744.

D'Ausilio, A., Pulvermüller, F., Salmas, P., Bufalari, I., Begliomini, C. & Fadiga, L. (2009). The motor somatotopy of speech perception. *Current Biology, 19*, 381-385.

Dalebout, S.D. & Stack, J.W. (1999). Mismatch negativity to acoustic differences not differentiated behaviorally. *Journal of the American Academy of Audiology, 10*, 388-399.

Deguchi, C., Chobert, J., Brunellière, A., Nguyen, N., Colombo, L. & Besson, M. (2010). Pre-attentive and attentive processing of French vowels. *Brain Research, 1366*, 149-161.

Dehaene-Lambertz, G. (1997). Electrophysiological correlates of categorical phoneme perception in adults. *NeuroReport, 8*, 919-924.

Dehaene-Lambertz, G., Dupoux, E. & Gout, A. (2000). Electrophysiological correlates of phonological processing: A cross-linguistic study. *Journal of Cognitive Neuroscience, 12*(4), 635-647.

DeWitt, I. & Rauschecker, J.P. (2012). Phoneme and word recognition in the auditory ventral stream. *Proceedings of the National Academy of Sciences, 109*, 505-514.

Diesch, E. & Luce, T. (1997). Magnetic fields elicited by tones and vowel formants reveal tonotopy and nonlinear summation of cortical activation. *Psychophysiology, 34*, 501-510.

Digeser, F.M., Wohlberedt, T. & Hoppe, U. (2009). Contribution of spectrotemporal features on auditory event-related potentials elicited by consonant-vowel syllables. *Ear & Hearing, 30*, 704-712.

Endrass, T., Mohr, B. & Pulvermüller, F. (2004). Enhanced mismatch negativity brain response after binaural word presentation. *European Journal of Neuroscience, 19*, 1653-1660.

Friederici, A.D. & Gierhan, S.M.E. (2013). The language network. *Current Opinion in Neurobiology, 23*, 250-254.

Friederici, A.D. (2009). Pathways to language: fiber tracts in the human brain. Trends in Cognitive Sciences, 13(4), 175-181.

Friederici, A.D. (2011). The brain basis of language processing: from structure to function. *Physiological reviews, 91*, 1357-1392.

Friederici, A.D. (2012). The cortical language circuit: from auditory perception to sentence comprehension. *Trends in Cognitive Sciences, 16*, 262-268.

Friedman, D. & Johnson, R. (2000). Event-Related Potential (ERP) studies of memory encoding and retrieval: A selective review. *Microscopy Research and Technique, 51*, 6-28.

Friedrich, C.K., Eulitz, C. & Lahiri, A. (2006). Not every pseudoword disrupts word recognition: an ERP study. *Behavioral and Brain Functions, 2*(36), doi: 10.1186/1744-9081-1182-1136.

Garagnani, M., Wennekers, T. & Pulvermüller, F. (2008). A neuroanatomically grounded Hebbian-learning model of attention–language interactions in the human brain. *European Journal of Neuroscience, 27*, 492-513.

Gierhan, S.M.E. (2012). Connections for auditory language in the human brain. *Brain and Language, 127*(2), 205-221.

Griffiths, T.D. & Warren, J.D. (2002). The planum temporale as a computational hub. *Trends in Neurosciences, 25*(7), 348-353.

Hessler, D., Jonkers, R., Stowe, L., & Bastiaanse, R. (2013). The whole is more than the sum of its parts: Audiovisual processing of phonemes investigated with ERPs. *Brain and Language, 124*, 213-224.

Hickok, G. & Poeppel, D. (2004). Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. *Cognition, 92*, 67-99.

Hickok, G. & Poeppel, D. (2007). The cortical organization of speech processing. *Nature Reviews Neuroscience, 8*, 393-402.

Hickok, G. (2009). The functional neuroanatomy of language. *Physics of Life Reviews, 6*, 121-143.

Hickok, G., Buchsbaum, B., Humphries, C. & Muftuler, T. (2003). Auditory–motor interaction revealed by fMRI: Speech, music, and working memory in area Spt. *Journal of Cognitive Neuroscience, 15*, 673-682.

Hickok, G., Okada, K. & Serences, J.T. (2009). Area Spt in the human planum temporale supports sensory-motor integration for speech processing. *Journal of Neurophysiology, 101*, 2725-2732.

Hoffman, P. & Lambon Ralph, M.A. (2011). Reverse Concreteness Effects Are Not a Typical Feature of Semantic Dementia: Evidence for the Hub-and-Spoke Model of Conceptual Representation. *Cerebral Cortex, 21*(9), 2103-2112.

Horev, N., Most, T. & Pratt, H. (2007). Categorical perception of speech (VOT) and analogous non-speech (FOT) signals: Behavioral and electrophysiological correlates. *Ear & Hearing, 28*, 111-128.

Hunter, C.R. (2013). Early effects of neighborhood density and phonotactic probability of spoken words on event-related potentials. *Brain & Language, 127*, 463-474.

Jäncke, L., Wüstenberg, T., Scheich, H. & Heinze, H.-J. (2002). Phonetic perception and the temporal cortex. *Neuroimage, 15*, 733-746.

Kaukoranta, E., Hari, R. & Lounasmaa, O.V. (1987). Responses of the human auditory cortex to vowel onset after fricative consonants. *Experimental Brain Research, 69*, 19-23.

Korpilathi, P., Krause, C.M., Holopainen, I. & Lang, A.H. (2001). Early and Late Mismatch Negativity Elicited by Words and Speech-Like Stimuli in Children. *Brain and Language, 76*, 332-339.

Kujala, T. & Näätänen, R. (2010). The adaptive brain: A neurophysiological perspective. *Progress in Neurobiology, 91*, 55-67.

Kutas, M. & Federmeier, K.D. (2011). Thirty years and counting: Finding meaning in the N400 component of the event-related brain potential (ERP). *Annual Review of Psychology, 62*, 621-647.

Kutas, M. & Hillyard, S.A. (1980). Reading senseless sentences: Brain potentials reflect semantic incongruity. *Science, 207*, 203-205.

Laszlo, S., Stites, M. & Federmeier, K.D. (2012). Won't get fooled again: An event-related potential study of task and repetition effects on the semantic processing of items without semantics. *Language and Cognitive Processes, 27*(2), 257-274.

Lawson, E. A., & Gaillard, A. W. K. (1981a). Mismatch negativity in a phonetic discrimination task. *Biological Psychology, 13*, 281-288.

Lawson, E. A., & Gaillard, A. W. K. (1981b). Evoked potentials to consonant-vowel syllables. *Acta Psychologica, 49*, 17-25.

Linden, D.E.J. (2005). The P300: Where in the brain is it produced and what does it tell us? *The Neuroscientist, 11*(6), 563-576.

Liu, B., Jin, Z., Qing, Z. & Wang, Z. (2011). The processing of phonological, orthographical, and lexical information of Chinese characters in sentence contexts: An ERP study. *Brain Research, 137*(2), 81-91.

Londei, A., D'Ausilio, A., Basso, D., Sestieri, C., Gratta, C.D., Romani, G.L., et al. (2010). Sensory-motor brain network connectivity for speech comprehension. Human Brain Mapping, 31, 567-580.

Luck, S. (2005). *An introduction to the event-related potential technique* (1st ed.). Cambridge, UK: MIT Press.

MacGregor, L.J., Pulvermüller, F., van Casteren, M. & Shtyrov, Y. (2012). Ultra-rapid access to words in the brain. *Nature Communications, 3*, 711.

Näätänen, R. & Winkler, I. (1999). The concept of auditory stimulus representation in cognitive neuroscience. *Psychological bulletin, 125*(6), 826-59.

Näätänen, R., Lehtokoski, A., Lennes, M., Cheour, M., Huotilainen, M., Iivonen, A., et al. (1997). Language-specific phoneme representations revealed by electric and magnetic brain responses. *Nature, 385*, 432-434.

Näätänen, R. (2001). The perception of speech sounds by the human brain as reflected by the mismatch negativity (MMN) and its magnetic equivalent (MMNm). *Psychophysiology, 38*, 1-21.

Näätänen, R., Gaillard, A. W., & Mäntysalo, S. (1978). Early selective-attention effect on evoked potential reinterpreted. *Acta Psychologica (Amsterdam), 42*, 313-329.

Obleser, J., Lahiri, A. & Eulitz, C. (2003). Auditory-evoked magnetic field codes place of articulation in timing and topography around 100 milliseconds post syllable onset. *NeuroImage, 20*, 1839-1847.

Obleser, J., Lahiri, A. & Eulitz, C. (2004). Magnetic brain response mirrors extraction of phonological features from spoken vowels. *Journal of Cognitive Neuroscience, 16*, 31-39.

Obleser, J., Scott, S.K. & Eulitz, C. (2006). Now you hear it, now you don't: transient traces of consonants and their nonspeech analogues in the human brain. *Cerebral Cortex, 16*, 1069-1076.

Obleser, J., Zimmermann, J., Van Meter, J. & Rauschecker, J.P. (2007). Multiple Stages of Auditory Speech Perception Reflected in Event-Related fMRI. *Cerebral Cortex, 17*, 2251-2257.

Ostroff, J.M., Martin, B.A. & Boothroyd, A. (1998). Cortical evoked response to acoustic change within a syllable. *Ear & Hearing, 19*, 290-297.

Patterson, K., Nestor, P.J. & Rogers, T.T. (2007). Where do you know what you know? The representation of semantic knowledge in the human brain. *Nature Reviews Neuroscience, 8*(12), 976-987

Picton, T.W. (1992). The P300 wave of the human event-related potential. *Journal of Clinical Neurophysiology, 9*(4), 456-479.

Pobric, G., Jefferies, E. & Lambon Ralph, M.A. (2010). Category-specific versus category-general semantic impairment induced by transcranial magnetic stimulation. *Current Biology, 20*, 964-968.

Pulvermüller, F., Kujala, T., Shtyrov, Y., Simola, J., Tiitinen, H., Alku, P., et al. (2001). Memory traces for words as revealed by the mismatch negativity. *NeuroImage, 14*(3), 607-616.

Pulvermüller, F., Huss, M., Kherif, F., del Prado Martin, F.M., Hauk, O. & Shtyrov, Y. (2006). Motor cortex maps articulatory features of speech sounds. *Proceedings of the National Academy of Science, 103*(20), 7865-7870.

Pulvermüller, F., Shtyrov, Y. & Hauk, O. (2009). Understanding in an instant: Neurophysiological evidence for mechanistic language circuits in the brain. Brain and Language, 110, 81-94.

Pulvermüller, F., Shtyrov, Y. & Ilmoniemi, R. (2003). Spatiotemporal dynamics of neural language processing: an MEG study using minimum-norm current estimates. *NeuroImage, 20*, 1020-1025.

Pulvermüller, F., Shtyrov, Y., Kujala, T. & Näätänen, R. (2004). Word-specific cortical activity as revealed by the mismatch negativity. *Psychophysiology, 41*, 106-112.

Rinne, T., Alho, K., Alku, P., Holi, M., Sinkkonen, J., Virtanen, J., et al. (1999). Analysis of speech sounds is left-hemisphere predominant at 100-150 ms after sound-onset. *NeuroReport, 10*, 1113-1117.

Saur, D., Kreher, B.W., Schnell, S., Kümmerer, D., Kellmeyer, P., Vry, M.-S., et al. (2008). Ventral and dorsal pathways for language. *Proceedings of the National Academy of Sciences, 105*, 18035-18040.

Saur, D., Schelter, B., Schnell, S., Kratochvil, D., Küpper, H., Kellmeyer, P., et al. (2010). Combining functional and anatomical connectivity reveals brain networks for auditory language comprehension. *NeuroImage, 49*, 3187-3197.

Sharma, A. & Dorman, M.F. (1999). Cortical auditory evoked potential correlates of categorical perception of voice-onset time. *Journal of the Acoustical Society of America, 106*, 1078-1083.

Sharma, A. & Dorman, M.F. (2000). Neurophysiologic correlates of cross-language phonetic perception. *Journal of the Acoustical Society of America, 107*, 2697-2703.

Shtyrov, Y. & Pulvermüller, F. (2002). Neurophysiological evidence of memory traces for words in the human brain. *NeuroReport, 13*, 521–525.

Shtyrov, Y. & Pulvermüller, F. (2007). Language in the Mismatch Negativity Design: Motivations, Benefits, and Prospects. *Journal of Psychophysiology, 21*(3-4), 176-187.

Sinai, A. & Pratt, H. (2000). Electrophysiological evidence for priming in response to words and pseudowords in first and second language. *Brain and Language, 80*, 240-252.

Specht, K., Huber, W., Willmes, K., Shah, N.J. & Jäncke, L. (2008). Tracing the ventral stream for auditory speech processing in the temporal lobe by using a combined time series and independent component analysis. *Neuroscience letters, 442*, 180-185.

Sutton, S., Braren, M., Zubin, J. & John, E.R. (1965). Evoked-potential correlates of stimulus uncertainty. *Science, 150*(3700), 1187-1188.

Tampas, J.W., Harkrider, A.W. & Hedrick, M.S. (2005). Neurophysiological indices of speech and nonspeech stimulus processing. *Journal of Speech Language and Hearing Research, 48*, 1147-1164.

Tavabi, K., Obleser, J., Dobel, C. & Pantev, C. (2007). Auditory evoked fields differentially encode speech features: An MEG investigation of the P50m and N100m time courses during syllable processing. *European Journal of Neuroscience, 25*, 3155-3162.

Trébuchon-Da Fonseca, A., Giraud, K., Badier, J.-M., Chauvel, P. & Liégeois-Chauvel, C. (2005). Hemispheric lateralization of voice onset time (VOT) comparison between depth and scalp EEG recordings. *NeuroImage, 27*, 1-14.

Turkeltaub, P.E. & Branch Coslett, H. (2010). Localization of sublexical speech perception components. *Brain and language, 114*, 1-15.

Turken, A.U. & Dronkers, N.F. (2011). The neural architecture of the language comprehension network: converging evidence from lesion and connectivity analyses. *Frontiers in Systems Neuroscience, 5*, 1-20.

Upadhyay, J., Silver, A., Knaus, T.A., Lindgren, K.A., Ducros, M., Kim, D.-S., et al. (2012). Effective and Structural Connectivity in the Human Auditory Cortex. The Journal of Neuroscience, 28(13), 3341-3349.

Vigneau, M., Beaucousin, V., Hervé, P.Y., Duffau, H., Crivello, F., Houdé, O., et al. (2006). Meta-analyzing left hemisphere language areas: Phonology, semantics, and sentence processing. NeuroImage, 30, 1414-1432.

Wilson, S.M., Saygin, A.P., Sereno, M.I. & Iacoboni, M. (2004). Listening to speech activates motor areas involved in speech production. *Nature Neuroscience, 7*, 701-702.

Zaehle, T., Geiser, E., Alter, K., Jancke, L. & Meyer, M., (2008). Segmental processing in the human auditory dorsal stream. *Brain Research, 1220*, 179-190.

Zatorre, R.J. & Belin, P. (2001). Spectral and temporal processing in human auditory cortex. *Cerebral Cortex, 11*, 946-953.

CHAPTER 3

Neuroanatomical and neurophysiological organization of auditory speech perception and comprehension in aphasia

3.1 Impaired neuronal network in post-stroke aphasia

Lesions at various locations in the neuronal language network induce a variety and mostly combination of aphasic symptoms, some of which have already been discussed above. For example, ***conduction aphasia***, characterized by phonologically-based repetition disorders and otherwise spared comprehension and fluent production, is typically linked to lesions of the grey matter in the inferior parietal cortex, where auditory-motor integration processes occur, such as the temporoparietal junction and supramarginal gyrus (Hickok & Poeppel, 2004). Another well-known aphasia syndrome is ***Broca's aphasia***, caused by brain lesions in inferior frontal regions, more specifically the anterior part of the arcuate fasciculus (Fridriksson, Guo, Fillmore, Holland & Rorden, 2013). However, such lesions mainly lead to impaired language *production* as manifested by non-fluent, agrammatical speech due to word finding problems and syntactical disintegration with overall spared language comprehension. ***Word-sound deafness***, a language disorder with impaired phonemic perception and understanding with sparing of other language modalities and spoken word production, is caused by lesions in the posterior superior temporal gyrus. In general there must be a bilateral impairment (cfr. the early acoustic-phonetic analysis is processed bilateral in posterior STG), although cases with unilateral damage are reported (Stefanatos et al., 2005). Deficits involving inferior areas of the posterior temporal gyrus lead to ***transcortical sensory aphasia***, which is characterized by poor comprehension, semantically-based production errors and spared repetition. This means that the mapping of auditory speech representations onto meaning is disrupted (Hickok & Poeppel, 2004). When, on top of the language impairments just mentioned, repetition is also disturbed, brain damage usually involves large portions of left posterior temporal and parietal cortex including STG, MTG, supramarginal and angular gyri, and encompasses ***Wernicke's aphasia*** (Hickok & Poeppel, 2004). So in terms of auditory speech perception and comprehension, brain lesions in superior posterior temporal and inferior parietal areas mainly lead to phonologically-based disorders, whereas lesions to anterior and posterior middle and inferior temporal regions mainly induce semantically-based disorders. Syntactic processing disorders originate from inferior frontal lesions.

Almost immediately after stroke, mechanisms of (spontaneous) recovery, neuronal plasticity and reorganization processes are initiated as a form of compensation and can persist for years after stroke. Different mechanisms can occur throughout the years post-stroke, such as restitution of damaged, premorbid language regions (a in Figure 3.1), recruitment of perilesional areas directly surrounding the damaged area (a in Figure 3.1) or functional (b in Figure 3.1) or dysfunctional (c in Figure 3.1) activation of homotopic language areas in the right hemisphere (Breier et al., 2004; Hamilton, Chrysikou & Coslett, 2011). Right hemisphere recruitment might be beneficial when it is

related to a decreased left-to-right inhibition (b in Figure 3.1), whereas a more detrimental role is attributed to an increased right-to-left inhibition (c in Figure 3.1) (Hamilton et al., 2011).

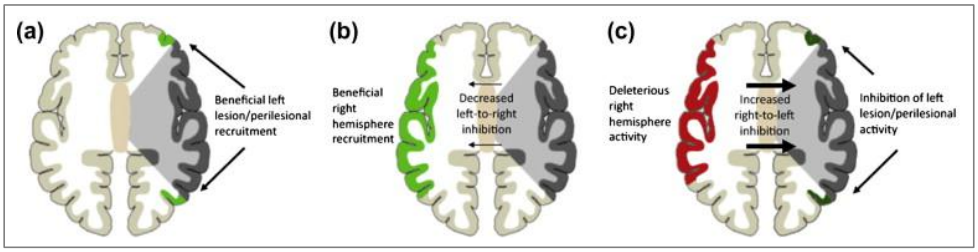

Figure 3.1: Possible (dys)functional reorganization patterns in chronic aphasic patients (adopted from Hamilton, Chrysikou & Coslett, 2011 with permission).

Whether or not a particular reorganization pattern is favourable, also depends on size and location of lesion, impaired language function and time post-stroke (Heiss & Thiel, 2006; Saur et al., 2006; Tyler, Wright, Randall, Marslen-Wilson & Stamatakis, 2010). For example, increased right-hemisphere involvement is not necessarily disadvantageous in the case of language functions that are already more bilaterally organized, such as primary acoustic-phonemic analyses and semantics (Tyler et al., 2010). Rather, this might reflect an asymmetric shift towards greater right hemisphere participation in a bi-hemispheric contribution to language. On the other hand, increased right-hemisphere involvement during strongly left-laterized language functions, such as phonology and syntax, might point towards genuine (dys)functional reorganization. Regarding time post-stroke, the highest dynamic of language recovery is observed in the first 2 weeks after stroke (Pedersen, Jørgensen, Nakayama, Raaschou & Olsen, 1995). Using a language comprehension task, Saur et al. (2006) found little left hemisphere activation within the first days after stroke which co-occurred with mild language recovery, whereas after 2 weeks, increased right-hemisphere activation contributed to functional language improvement. Clearly, brain lesion-related reorganization and plasticity processes in the acute stage of stroke relative to functional language improvement deserve clinical attention and require more investigation.

3.2 Language-related neurophysiological alterations in post-stroke aphasia

Neuronal plasticity and reorganization processes also become evident at a neurophysiological level and can be identified by measuring the electrical activity of the brain during a particular language process, using the three parameters of the previously discussed ERPs (see section 2.2). In general,

aphasic patients show reduced ERP amplitudes, most likely due to smaller or absent postsynaptic potentials in the same neurons, less activation of fewer neurons in a population and/or less temporal synchronization among the generating neurons related to the brain damage (Ilvonen et al., 2003; Kutas & Federmeier, 2011). Moreover, due to the neuronal damage, the information transfer between different neuron populations is disturbed which leads to prolonged ERP latencies. As such, it has already been demonstrated in aphasic patients that the MMN to speech sound stimuli (vowels, phonemes) is more attenuated compared to tone stimuli differing in frequency or duration (Aaltonen, Tuomainen, Laine, & Niemi, 1993; Ilvonen et al., 2004; Wertz et al., 1998). Moreover, within speech sound discrimination, consonant contrasts seem to be more vulnerable than vowel contrasts and within consonant contrasts some form of hierarchical pattern exists (Csépe, Osman-Sági, Molnár, & Gósy, 2001). Finally, dependent on the location of the lesions, the topographical scalp distribution of ERPs related to a certain language task can be altered, which provides information about potential compensation mechanisms as described in section 3.1. Higher MMN amplitudes at contralesional right-hemispheric or perilesional electrodes and/or attenuated amplitudes over electrodes positioned at lesions sites can reveal information about (dys)functional recovery patterns during sound discrimination (Becker & Reinvang, 2007; Ilvonen et al., 2003).

It is remarkable though that only a few ERP studies have investigated aphasic patients in the acute stage of stroke (e.g. within 2 weeks after stroke) (Ilvonen et al., 2003; Nolfe, Cobianchi, Mossuto-Agatiello & Giaquinto, 2006). In the early stages of stroke it is possible that extensive behavioural evaluation is problematic or even impossible in aphasic patients and ERPs can provide a way of counteracting this practical problem. Moreover, only a few studies have implemented ERPs as a measure of treatment-related language improvement (Pulvermüller, Hauk, Zohsel, Neininger & Mohr, 2005; Wilson et al., 2012). Nonetheless, the added value is promising, as an ERP amplitude re-enhancement can accompany improvement of language functions over time (Ilvonen et al., 2003; Nolfe et al., 2006; Pulvermüller, Mohr & Lutzenberger, 2004). For instance, increased amplitudes of the P300 potential in response to meaningful words (“aphasia recovery potential”) after therapy (Pulvermüller, Hauk, Zohsel, Neininger & Mohr, 2005) or a shift from a more right-lateralized scalp distribution of the N400 potential before therapy to a more left-lateralized distribution after therapy (Wilson et al., 2012) has already been associated with an improvement in behavioural language performance. Clearly, ERPs can provide a complementary instrument in the diagnostic and therapeutic evaluation of patients with aphasia and make it possible to connect neurological findings with clinical observations. This would not only support clinical practice (overcome possible bottom or ceiling effects of behavioural measures), but can enhance understanding of the neurophysiological mechanisms involved in language processing and its evolution after stroke (Kim & Tomaino, 2008).

3.3 References

Aaltonen, O., Tuomainen, J., Laine, M., & Niemi, P. (1993). Cortical differences in tonal versus vowel processing as revealed by an ERP component called mismatch negativity (MMN). *Brain and Language, 44*(2), 139-152.

Becker, F., & Reinvang, I. (2007). Successful syllable detection in aphasia despite processing impairments as revealed by event-related potentials. *Behavioral and Brain Functions, 3*(1).

Breier, J.I., Castillo, E.M., Boake, C., Billingsley, R., Maher, L., Francisco, G., et al. (2004). Spatiotemporal patterns of language-specific brain activity in patients with chronic aphasia after stroke using magnetoencephalography. *NeuroImage, 23*, 1308-1316.

Csépe, V., Osman-Sági, J., Molnár, M., & Gósy, M. (2001). Impaired speech perception in aphasic patients: event-related potential and neuropsychological assessment. *Neuropsychologia, 39*(11), 1194-1208.

Fridriksson, J., Guo, D., Fillmore, P., Holland, A. & Rorden, C. (2013). Damage to the anterior arcuate fasciculus predicts non-fluent speech production in aphasia. *Brain, 136*, 3451-3460.

Hamilton, R.H., Chrysikou, E.G. & Coslett, B. (2011). Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. *Brain and Language, 118*, 40-50.

Heiss, W.-D. & Thiel, A. (2006). A proposed regional hierarchy in recovery of post-stroke aphasia. *Brain and Language, 98*, 118-123.

Hickok, G. & Poeppel, D. (2004). Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. *Cognition, 92*, 67-99.

Ilvonen, T.-M., Kujala, T., Kiesiläinen, A., Salonen, O., Kozou, H., Pekkonen, E., et al. (2003). Auditory Discrimination After Left-Hemisphere Stroke A Mismatch Negativity Follow-Up Study. *Stroke, 34(7)*, 1746-1751.

Ilvonen, T., Kujala, T., Kozou, H., Kiesiläinen, A., Salonen, O., Alku, P., et al. (2004). The processing of speech and non-speech sounds in aphasic patients as reflected by the mismatch negativity (MMN). *Neuroscience letters, 366*(3), 235-240.

Kim, M., & Tomaino, C. A. (2008). Protocol Evaluation for Effective Music Therapy for Persons with Nonfluent Aphasia. *Topics in Stroke Rehabilitation, 15* (6), 555-569.

Nolfe, G., Cobianchi, A., Mossuto-Agatiello, L., & Giaquinto, S. (2006). The role of P300 in the recovery of post-stroke global aphasia. *European Journal of Neurology, 13*(4), 377-384.

Pedersen, P.M., Jørgensen, H.S., Nakayama, H., Raaschou, H.O. & Olsen, T.S. (1995). Aphasia in acute stroke: incidence, determinants, and recovery. *Annals of Neurology, 38*(4), 659-66.

Pulvermüller, F., Mohr, B., & Lutzenberger, W. (2004). Neurophysiological correlates of word and pseudo-word processing in well-recovered aphasics and patients with right-hemispheric stroke. *Psychophysiology, 41* (4), 584-591.

Pulvermüller, F., Hauk, O., Zohsel, K., Neininger, B., & Mohr, B. (2005). Therapy-related reorganization of language in both hemispheres of patients with chronic aphasia. *NeuroImage, 28*(2), 481-489.

Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., et al. (2006). Dynamics of language reorganization after stroke. *Brain, 129*(6), 1371-1384.

Stefanatos, G.A., Gershkoff, A., & Madigan, S. (2005). On pure word deafness, temporal processing, and the left hemisphere. *Journal of the International Neuropsychological Society, 11*, 456-470.

Tyler, L.K., Wright, P., Randall, B., Marslen-Wilson, W.D. & Stamatakis, E.A. (2010). Reorganization of syntactic processing following left-hemisphere brain damage: does right-hemisphere activity preserve function? *Brain, 133*, 3396-3408.

Wertz, R. T., Auther, L. L., Burch-Sims, G. P., Abou-Khalil, R., Kirshner, H. S., & Duncan, G. W. (1998). A comparison of the mismatch negativity (MMN) event-related potential to tone and speech stimuli in normal and aphasic adults. *Aphasiology, 12*(7-8), 499-507.

Wilson, K. R., O'Rourke, H., Wozniak, L. A., Kostopoulos, E., Marchand, Y., & Newman, A. J. (2012). Changes in N400 topography following intensive speech language therapy for individuals with aphasia. *Brain and Language, 123*(2), 94-103.

CHAPTER 4

Research aims

Although ERPs already proved to be sensitive and effective for investigating functional (re)organization and time course of language processes in both healthy individuals and aphasic patients, there is still a lack of standardized normative data for ERPs to be used in a clinical setting. The main objective of this doctoral thesis was to develop normative data for specific ERPs related to phonological input processes (N100-P200 complex, MMN, P300, and N400) and to gauge them as a diagnostic and therapeutic evaluation method in a population of aphasic patients in the acute stage of stroke. To achieve this objective, the following four research aims were formulated.

A **FIRST AIM** was to investigate the effects of age and sex on the amplitudes and latencies of the neurophysiological correlates of pre-attentive (MMN) and attentive (P300) phoneme discrimination and pre-attentive (N400) word recognition, in the framework of developing preliminary Flemish normative data. For phoneme discrimination, all three phonemic contrasts present in the Dutch language were implemented to search for a possible qualitative pattern of phonemic contrast sensitivity. The ability to discriminate between real words and pseudowords was measured during the word recognition task. The effects of age together with the normative data are described in ***chapter five***. The effects of sex are discussed in ***chapter six***.

A **SECOND AIM** was to measure whether the phoneme discrimination and word recognition paradigms were feasible to administer in aphasic patients in the acute stage of stroke. Additionally, it was investigated to what extent the qualitative pattern of phonemic contrast sensitivity and the ability to discriminate between real words and pseudowords deviates from the normative data. These results are discussed in ***chapter seven***.

A **THIRD AIM** was to measure effects of therapy after intensive and conventional language treatment in a single-subject study by implementing both behavioural and neurophysiological measures. In this way, the added value of ERPs in the clinical evaluation of aphasic patients in the acute and subacute stage was assessed. These results are discussed in ***chapter eight***.

A **FOURTH AIM** was to disentangle the temporal organization of the sensorimotor neuronal network during the phoneme discrimination task in healthy, non-brain damaged individuals. For this, a recent source reconstruction technique was used to evaluate if it would be sensitive enough for future implementation in a clinical setting. These results are discussed in ***chapter nine***.

PUBLICATIONS

CHAPTER 5

Neurophysiological investigation of phonological input: Aging effects and development of normative data

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Hallez, H., Santens, P. & De Letter, M. (2013). **Neurophysiological investigation of phonological input: Aging effects and development of normative data**. Brain and Language, 125 (3), 253-263.

Abstract

The current study investigated attended and unattended auditory phoneme discrimination using the P300 and Mismatch Negativity event-related potentials (ERPs). Three phonemic contrasts present in the Dutch language were compared. Additionally, auditory word recognition was investigated by presenting rare pseudowords among frequent words. Two main goals were: (1) obtain normative data for ERP latencies (ms) and amplitudes (μV) and (2) examine aging influences. Seventy-one healthy subjects (21-83 years) were included. During phoneme discrimination aging was associated with increased latencies and decreased amplitudes. However, a discrepancy between attended and unattended processing, as well as between phonemic contrasts, was found. During word recognition aging only had an impact on ERPs elicited by real words, indicating that mainly semantic processes were altered leaving lexical processes unharmed. Early sensory-perceptual processes, reflected by N100 and P50, were free from aging influences. In future, neurophysiological normative data can be applied in the evaluation of acquired language disorders.

Keywords

Mismatch Negativity (MMN); P300; phonology; input; auditory discrimination; word recognition; aging; neurophysiology; aphasia

1. Introduction

In order to understand spoken language, it is necessary to complete several phonological stages successfully before proceeding with semantic processing. Phonological stages comprise detection, identification and discrimination of spoken phonemes followed by the recognition of a spoken word as being part of a person's mental lexicon (McClelland & Elman, 1986; Poeppel, Idsardi & van Wassenhove, 2008). A spoken phoneme is considered as the smallest segmental unit used to obtain meaningful contrasts between utterances (International Phonetic Association, 1999). These units are defined by phonemic contrasts that characterize and distinguish between each phoneme. The three main contrasts that can be identified in Dutch consonants are place of articulation (PoA), manner of articulation (MoA) and phonation of the consonants (voicing).

How are these phonemes and words represented in the brain? The discrimination of spoken phonemes has been linked to the activation of different long-term phoneme-memory traces (Dehaene-Lambertz, 1997; Näätänen et al., 1997). These traces are based on recognition patterns of phonemic contrasts that mature throughout language development and are specific to one's native language. Taking into account that spoken words consist of fixed sequences of spoken phonemes and syllables, it can be assumed that the cerebral representation of spoken words is a hierarchically organized structure of simultaneously activated phoneme memory traces. In turn, they can form specific cortical memory traces for words (Näätänen, 2001; Pulvermüller et al., 2001; Shtyrov & Pulvermüller, 2002). These cortical memory traces, both for phonemes and for words, are physically dependent on neuronal cell assemblies which consist of simultaneously firing nerve cells and create an associative network through Hebbian learning. These networks have specifically been located in the language dominant left temporal lobe, with the possibility that distinct topographical patterns exist for individual words (Näätänen, 2001; Pulvermüller, 1999; Pulvermüller, Shtyrov, Kujala, & Näätänen, 2004b). Additionally, aging has been associated with a loss of grey matter density (Sowell et al., 2003). This can lead to weakened internal connections within the memory traces, leading to impaired discriminatory abilities (Alexandrov, Boricheva, Pulvermüller & Shtyrov, 2011). Although, on a behavioural level poorer phoneme discrimination skills in older subjects are not always expressed (Holmes, Kricos & Kessler, 1988). However, auditory comprehension abilities in elderly people are very often disturbed. Problems with complex language stimuli arise and more contextual information during word recognition is needed due to a decline in auditory sensitivity, deficits in temporal processing and/or general cognitive slowing (e.g. disturbed semantic memory recruitment) (Benichov, Cox, Tun & Wingfield, 2012; Schneider, Daneman & Pichora-Fuller, 2002; Sommers et al., 2011).

The neurophysiological correlates of phoneme discrimination and word recognition can be investigated by means of event-related potentials (ERPs). For phoneme discrimination the pre-attentive Mismatch Negativity (MMN; Näätänen, Gaillard & Mäntysalo, 1978) and the attentive P300 potential (Sutton, Braren, Zubin & John, 1965) can be applied. In addition, the lexical/semantic N400 potential is considered as a measure for both word recognition and word comprehension (Kutas & Hillyard, 1980). The MMN and P300 are typically elicited by dedicated oddball paradigms in which a frequent stimulus is interspersed by an infrequent, target stimulus. The N400 can also be elicited by such a task although it is more common in priming and violation paradigms (Kutas & Federmeier, 2011). The MMN is a relatively small negative potential, which occurs between 150 and 250 ms after stimulus onset even when the subject is not attending to the stimulus. This ERP is associated with the outcome of an automatic and preconscious auditory discrimination process (Näätänen, Paavilainen, Rinne & Alho, 2007). The positive P300 potential, on the other hand, is quite large, appears approximately 300 ms after infrequent stimulus presentation and is more related to working memory, context updating, attention resources and stimulus classification and categorization (Linden, 2005; Polich, 2004). Finally, the N400 is a negative deflection around 400 ms after stimulus presentation and is mostly linked to processes such as lexical access and semantic or contextual priming and integration (Giaquinto, Ranghi & Butler, 2007; Kutas & Federmeier, 2000). Event-related potentials emerging as a response to the frequent stimulus both in attended and unattended conditions are the negative N100 potential around 100 ms and the positive P200 potential around 200 ms (often called the N100-P200 complex). They are associated with sensory-perceptual processes and intermediate stages of auditory feature analysis, detection and identification and are fully separable from the MMN, P300 or N400 (Cooper, Todd, McGill & Michie, 2006; Näätänen, Kujala & Winkler, 2011).

Several studies have been conducted to unravel the effects of aging on the potentials mentioned above. Generally, non-linguistic stimuli (pure tones differing in frequency and/or duration) have been used and it seems that the pre-attentive MMN has been less affected by age than the attentive P300 potential (Schiff et al., 2008). P300 studies have found decreased amplitudes and prolonged latencies in older individuals compared to younger individuals (Juckel et al., 2012; Kok, 2000; Polich, 2004; Schiff et al., 2008). This pattern was attributed to more difficult and less efficient auditory processing in the elderly (Bertoli, Smurzynski & Probst, 2005). However, in a study with only small changes between contrasting pure tones equal amplitudes of the P300 across ages have been found, but in combination with fading of the MMN in the older age group (Alain, Mcdonald, Ostroff & Schneider, 2004). This was interpreted as a greater reliance on controlled processes in elderly people. Amplitude attenuations and peak latency delays of the MMN with increasing age have repeatedly

but not consistently been demonstrated in several studies (Cooper et al., 2006; Czigler, Csibra & Csontos, 1992; Gaeta, Friedman, Ritter & Hunt, 2002; Kiang, Braff, Sprock & Light, 2009; Pekkonen et al., 1996). Moreover, a study that has used linguistic stimuli (phonemes differing in voicing and PoA) even indicates that the MMN can be affected in a different way depending on the phonemic contrasts (Csèpe, Osman-Sági, Molnár & Gósy, 2001). However, this has been established in aphasic patients and has to our knowledge never been confirmed in the context of aging influences. The N400 in the context of lexical access and word recognition has indicated to be unaffected by age, showing no differences in latencies and amplitudes between young and elderly age groups (Giaquinto et al., 2007; Karayanidis, Andrews, Ward & McConaghy, 1993). Early ERP components, such as the N100 and P200, have displayed distinct effects of aging. The P200 has been one of the very few potentials that more often displays large amplitude increases in the elderly and has been related to inhibition during auditory processing (Crowley, Trinder & Colrain, 2002). Regarding P200 latencies, conflicting results have described both prolongations and stability through aging (Crowley & Colrain, 2004). The N100 has been less subject to aging effects, although interstimulus interval (ISI) can be an influencing factor with mainly amplitude increases at longer stimulus intervals (Bertoli et al., 2005; Cooper et al., 2006; Czigler et al., 1992; Kisley, Davalos, Engleman, Guinthera & Davis, 2005).

Combined with behavioural data, ERPs can be of great value in clinical and diagnostic situations. In view of the distinct disturbances of phonemic contrast perception in patients with brain lesions (Csèpe et al., 2001), it is necessary to figure out which kind of phonological input stimuli are the most susceptible to aging and which trends can be observed for phoneme discrimination and word recognition during aging. This is essential before implementing cognitive event-related brain potentials in the evaluation of language-impaired individuals of variable ages.

The current study has two main objectives. Primarily, we want to provide neurophysiological normative data for different age categories for phoneme discrimination and word recognition processes for the evaluation of language disorders and the monitoring of language rehabilitation in aphasia. On that account, it is important to study the effects of the healthy aging brain on these language processes. So, a second aim is to qualitatively map influences of aging 1) on consonant contrast sensitivity of the three different phonemic contrasts naturally present in Dutch, namely PoA, voicing and MoA and 2) on word recognition. It is examined whether there exists a discrepancy between unattended (MMN) and attended (P300) discrimination of phonemic contrasts and whether there is a correlation between neurophysiological and behavioural task results.

2. Methods

2.1 Subjects

Seventy-one healthy subjects, who were mainly recruited from hospital staff and senior club houses, participated in the study. All persons investigated were right-handed, as verified with the Dutch Handedness Inventory (DHI; Van Strien, 1992), except for 1 person who was left handed (score of -10 on DHI). All the participants had Dutch as native language and had normal hearing. None of them had neurological or psychiatric disorders. Prior logopaedic problems, such as speech and language developmental disorders, were excluded by history. At time of testing, none of the participants was on medication. The age of the participants (48 females, 23 males) ranged from 21 to 83 years with an average of 50.18 years (SD: $\pm$ 14.96) and their mean level of education was 13.94 years (SD: $\pm$ 2.93). In order to generate normative tables six age categories were created per decade: 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years and 70+ category. The Mini Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975) was performed in participants above the age of 70 to ascertain the absence of underlying cognitive decline. Table 5.1 gives a summary of the number of subjects per age category with MMSE results for the 70+ category. The study was approved by the Ethics Committee of the University Hospital Ghent and an informed consent was obtained from all the subjects.

Table 5.1: Summary of general information of the normative group.

Age category (y)	Number of subjects	Gender distribution per age category (m/f)	Mean years of education per age category (y)	MMSE results
20-29	9	3/6	14.44	N/A
30-39	9	4/5	14.78	N/A
40-49	12	3/9	14.00	N/A
50-59	17	5/12	14.35	N/A
60-69	18	8/10	13.00	N/A
70 +	6	0/6	11.50	All subjects 30/30
Mean age = 50.18	Total = 71	Total = 23/48	Mean years of education = 13.94	Mean = 30

Legend: y = years; m = male; f = female; N/A = not applicable; MMSE = Mini-Mental State Examination.

2.2 Materials and stimuli

Two types of oddball paradigms were administered: an auditory phoneme discrimination and word recognition paradigm. The first paradigm was further subdivided in six parts, three of which were attended (P300) and three unattended (MMN). The word recognition paradigm was also an

unattended oddball paradigm. All the tasks were administered during one session that lasted for about 30 min. During the unattended MMN paradigms, the subjects were instructed to ignore the stimuli and to focus their attention on a silent movie. On the other hand, during the attended P300 paradigms, the subjects were asked to push a button every time they heard the infrequent stimulus, consequently focussing their attention to the stimuli. The sequence of the individual tasks was counterbalanced across subjects, meaning that every subject started with another task. All the stimuli were presented binaurally with Apple Inc. earphones, placed directly into the external ear, at a comfortable listening level of ca. 70 dB.

Regarding the phoneme discrimination task, the participants were presented twice with three different auditory oddball paradigms, delivered in separate blocks, both in the unattended (MMN) and attended (P300) condition. Within the MMN and P300 paradigm each block consisted of 250 stimuli and 150 stimuli, respectively. The standard phoneme was /b/ and the deviant phonemes were /g/, /p/ and /m/ in order to cover the phonemic contrasts PoA, voicing and MoA, respectively. The stimuli were chosen in such a way that the standard and deviant stimulus only differed in one phonemic contrast. In order to control for noise during stimulus creation, phonemes were generated using the website NeXTeNS where text could be converted to speech (http://nextens.uvt.nl/demo.html). To obtain an unstressed phonetically pronounced phoneme, e.g. /p/, a word such as [ɦɛlpən] (“to help” in Dutch) was put into the textbox and then converted into a WAV-file. Subsequently this file was manipulated by means of the software PRAAT (Boersma & Weenink, 2010) so that the unstressed syllable /p/ in [ɦɛlpən] was isolated as a separate stimulus. In all stimulus blocks, the standard phoneme and the deviant appeared with a probability of 0.80 and 0.20, respectively. The stimuli were given in a random order in which two deviants could not follow each other without having a standard in between, thus two or more deviants never occurred in succession. All the spoken phonemes had a duration of 150 ms. The interstimulus interval (ISI) was set at 500 ms in the MMN paradigm and 2000 ms in the P300 paradigm.

An unattended MMN paradigm, where pseudowords were implemented as deviant stimuli and real words as standard stimuli, was developed to cover the word recognition task. Stimuli were spoken by a 24 year old female Dutch native speaker with a flat intonation and digitally recorded with a sampling frequency of 44.1 kHz. The recordings were performed in a sound attenuated room using a Samson C01U microphone, an Apple MacBook Pro laptop and PRAAT. The standard stimuli and deviant stimuli appeared with a probability of 0.80 and 0.20, respectively. A total of 125 stimuli were presented, including 100 real words (all nouns) and 25 pseudowords. The stimuli were given in a random order in which two pseudowords could not follow each other without having a real word in between. The real words were controlled for lexical frequency (mean: 3.15 log10freq) using the

SUBTLEX-NL (Keuleers, Brysbaert & New, 2010), age of acquisition (mean: 6.0 years) (Ghyselinck, Custers, & Brysbaert, 2003) and length (all stimuli consisted of 5 phonemes and 1 or 2 syllables). Pseudowords were derived from the real words by replacing one vowel and one consonant in 25 real words randomly selected from the list of 100 existing words. As such legal and pronounceable stimuli were created. The stimuli were presented with an interstimulus interval (ISI) of 1000 ms.

2.3 EEG recording and analysis

For organizational reasons, registration always took place in the afternoon (2 p.m.) or in the early evening (5 p.m.). The electroencephalogram (EEG) was recorded with the Neuron-Spectrum-5 (4EPM) registration software (Neurosoft, Moscow, Russia). An universal electrode cap (Haube-S2) was used and included the following 20 electrode sites: Cz, Fz, Fpz, Pz, Oz, C3, C4, T3, T4, F3, F4, F7, F8, P3, P4, T5, T6, Fp1, Fp2 and O1. The electrodes were placed on the scalp according to the international 10-20 system. An impedance-reducing gel was used which eliminated the need for skin abrasion (Electro-Gel TM, Electro-Cap International, Inc.). The EEG was acquired using a linked ears reference and an extra electrode placed on the forehead was used as ground. The impedance of the electrodes was kept below 5 kΩ. Data was collected using a 32 channel SynAmp (Neuroscan) amplifier and was continuously digitized with a sampling frequency of 500 Hz. During registration, a 0.5 – 75 Hz band-pass filter was used, with the notch filter switched off. Off-line EEG analysis was performed using BrainVision Analyzer 2 (Brain Products, Munich, Germany). Firstly, additional filtering was applied with high-pass filter of 0.5 Hz (slope 12 dB/oct), low-pass filter of 30 Hz (slope 48 dB/oct) and notch filter enabled at 50 Hz. Independent component analysis (ICA) was used to remove artefacts caused by eye blinks and eye movements. The standard and deviant trials were evaluated separately during segmentation. For the three P300 paradigms the EEG was segmented into 1100 ms long epochs from 100 ms pre-stimulus to 1000 ms post-stimulus. For the three phoneme discrimination MMN paradigms the EEG was segmented into 500 ms long epochs from 100 ms pre-stimulus to 400 ms post-stimulus. Finally, for the word recognition MMN paradigm the EEG was segmented into 1000 ms long epochs from 100 ms pre-stimulus to 900 ms post-stimulus. The epochs were baseline corrected using a pre-stimulus window of 100 ms. All epochs containing data exceeding ± 100 µV in electrodes of interest (see below) were manually rejected from further analysis. This was done separately for the standard trials and the deviant trials. Within the attended P300 condition wrong trials (no button-press with deviant trials and button-press with standard trials) were also rejected from further analysis. The data was converted to an average reference and for every participant all the standard trials were averaged together and all the deviant trials were averaged together. Finally, to compute the Mismatch Negativity in the unattended conditions the

standard trials were subtracted from the deviant trials, creating a difference waveform. Ultimately, grand average waveforms (GA) of all the averaged deviant, standard or difference waveforms of all 71 participants together were generated for all seven conditions. Peak detection was carried out semi-automatically. Latencies and amplitudes were measured in every individual in the midline electrodes Fz, Cz and Pz depending on which ERP was examined. Additionally, F3 and F4 were included for the word recognition task. The focus on midline electrodes was based on the magnitude and clarity of the ERPs in these electrodes in the GA waveforms.

2.4 Behavioural linguistic evaluation

In order to investigate possible correlations of ERP results with behavioural testing, three different subtests of the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA; Kay, Lesser & Coltheart, 1992) – Dutch edition (Bastiaanse, Bosje & Visch-Brink, 1995) were administered. All the subtests were counterbalanced across subjects. Firstly, the phoneme discrimination tests PALPA 1 and PALPA 2 were performed. These consisted of a same-different judgement task in which the participants had to judge whether pairs of pseudowords (PALPA 1) or minimal pairs of real words (PALPA 2) were the same or not. The participants were instructed to say “yes” as a response to a similar word pair and to say “no” to a dissimilar word pair. The aurally presented stimuli were monosyllabic (pseudo)words of consonant/vowel/consonant (CVC)-structure. They all differed in phonemic contrasts voicing, PoA or MoA which were either initial, final or based on metathesis (i.e. an altered sequence of phonemes). Finally, the lexical decision task in the subtest PALPA 5 contained 80 real words and 80 pseudowords. The pseudowords were derived from the real words by changing one or multiple phonemes, making them legal pseudowords. The participants were asked to decide after each spoken word whether the stimulus was a real word or not, by saying “yes” to a real word or “no” to a pseudoword. In both tests, the answers of the participants were written down on a score sheet, giving 1 for correct answers and 0 for wrong answers.

2.5 Statistical analysis

A regression analysis was carried out for age and the ERP results in every condition, namely the phoneme discrimination task with its three phonemic contrasts in the attended and unattended condition and the unattended word recognition task. Secondly, non-parametric Spearman correlation analyses were performed between age and behavioural results on the one hand and between neurophysiological results and behavioural results on the other hand. Due to multiple comparisons, the probability of making a Type I error increased. Usually, a Bonferroni correction is applied, but this involves some restrictions. Firstly, statistical power drops to 33% while the probability of making a Type II error remains very high (Nakagawa, 2004). Secondly, there is no

consensus among statisticians for when this statistical procedure should be used (Perneger, 1998). Thirdly, the more measures are evaluated, the less probable it becomes to find significant results (Moran, 2003). For these reasons, Bonferroni corrections were not implemented in the present study. Instead the significance level was reduced to ≤ 0.01. Results between 0.01 and 0.05 were considered as trends. All the statistical analyses were performed by means of IBM SPSS Statistics 19.

3. Results

3.1 Event-related potentials in the GA waveforms

In the phoneme discrimination task an MMN in the unattended condition and a P300 in the attended condition could be elicited for every phonemic contrast used in every age group. Therefore, only grand average waveforms of all 71 participants are displayed in figure 5.1. No clear differences in ERP morphology were detected between the phonemic contrasts in the attended condition (figure 5.1D-5.1F). However, in the unattended condition each phonemic contrast elicited a different MMN wave (figure 5.1A-5.1C). For the word recognition task, no MMN could be identified in the difference waveform between real words and pseudowords. When analysing the response to the real words and pseudowords separately it became clear that the neuronal reactions to both stimuli were nearly identical in the time window between 0 ms and 400 ms (figure 5.1G-5.1I), explaining the inability to elicit a MMN. Starting from 400 ms onwards, a negative component between 400 and 600 ms was evoked in response to pseudowords whereas in response to real words the same component was observed but with a positive shift. This appeared as a very small, less well distinguishable ERP in the difference wave around 500 ms. Consequently, we executed a paired samples t-test on N400 amplitudes to real words and to pseudowords which showed that the N400 to pseudowords was significantly greater than the N400 to real words [$t(69) = 4.41$, $p < 0.001$]. When discussing the effects of aging on word recognition in more detail, we will only focus on the ERPs to the real words and pseudowords separately.

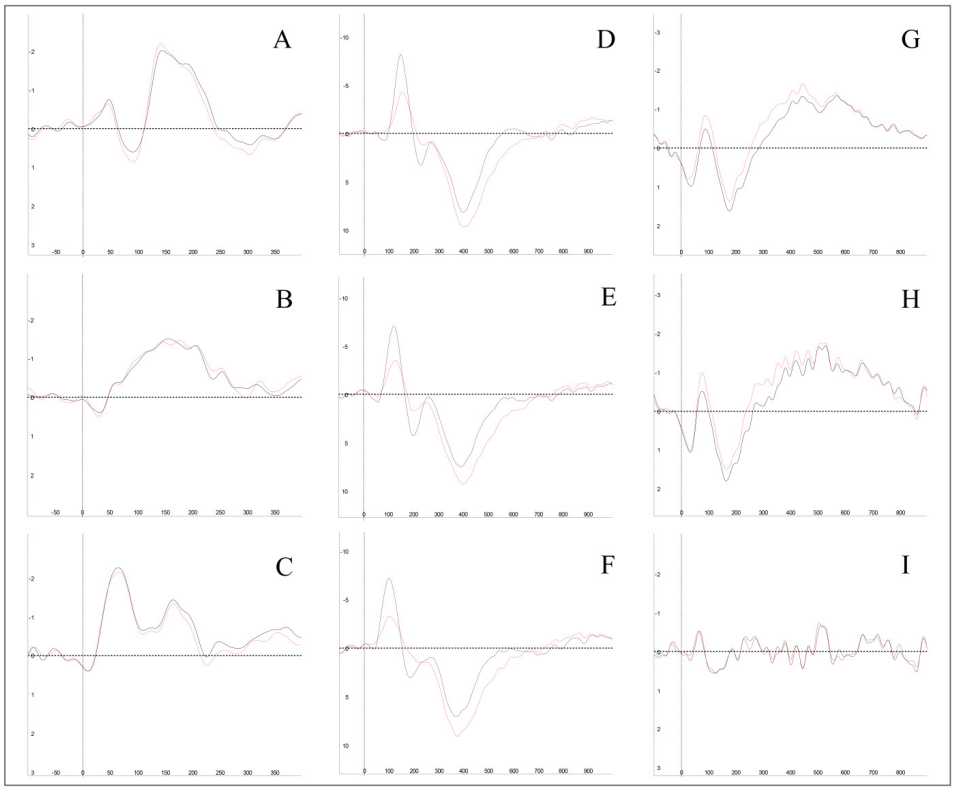

Figure 5.1: Grand average waveforms of the normative group for every task. Latency (x-axis) is represented in milliseconds (ms) and amplitude (y-axis) in microvolts (µV). Negative values are plotted upwards. From A to C: Grand average waveforms of the MMN in electrodes Cz (red) and Fz (black) in the unattended phoneme discrimination task for the phonemic contrasts PoA (A), Voicing (B) and MoA (C). From D to F: Grand average waveforms of the P300 in electrodes Pz (red) and Cz (black) in the attended phoneme discrimination task for the phonemic contrasts PoA (D), Voicing (E) and MoA (F). From G to I: Grand average waveforms in electrodes Cz (red) and Fz (black) in the unattended word recognition task for response to real words (G), pseudowords (H) and the difference wave (I).

3.2 Correlation between age and behavioural results

Age did not correlate with the subscores of the PALPA except for a trend for pseudowords on PALPA 5 (R = -0.284, p = 0.02). This means that older subjects tend to obtain lower scores on identifying pseudowords as such (responding "no" to pseudowords).

3.3 Regression between age and neurophysiological results – Phoneme discrimination

Pearson's correlation and R square values together with their p-values can be found in Table 5.2. The normative data for the amplitudes and latencies per ERP subdivided in age categories can be found in Appendices 5A.1 and 5A.4, respectively.

Concerning the actual phoneme discrimination processes reflected by the P300 potential in the attended condition and the MMN potential in the unattended condition, the regression analysis revealed that age significantly predicted several ERP amplitudes and latencies.

Phonemic contrast PoA. The P300 potential at Pz showed significantly increased latencies and a trend towards decreased amplitudes in older subjects compared to younger subjects with respect to PoA. No significant correlations were found for the MMN potential.

Phonemic contrast MoA. The P300 potential at Pz showed significantly increased latencies in older subjects compared to younger subjects with respect to MoA. The MMN potential at Fz and Cz displayed significantly increased latencies and a trend towards decreased amplitudes in older subjects.

Phonemic contrast voicing. The P300 potential at Pz showed significantly increased latencies (see figure 5.2A) and decreased amplitudes (see figure 5.2B) in older subjects compared to younger subjects with respect to voicing. The MMN potential at Fz and Cz displayed significantly decreased amplitudes in older subjects.

Table 5.2: *R*-values, R^2-values and *p*-values for the regression analysis of age and neurophysiological correlates of attended and unattended auditory primary analysis and phoneme discrimination and unattended auditory word recognition.

		ATTENDED						UNATTENDED					
		LATENCY			AMPLITUDE			LATENCY			AMPLITUDE		
APD		**N100**	**P200**	**P300**	**N100**	**P200**	**P300**	**P50**	**P200**	**MMN**	**P50**	**P200**	**MMN**
PoA	*R*	-0.013	0.415	0.294	-0.071	-0.084	-0.216	-0.040	0.277	0.074	0.125	0.062	-0.017
	R^2	<0.001	0.172	0.086	0.005	0.007	0.047	0.002	0.077	0.005	0.016	0.004	<0.001
	p	*0.457*	*<0.001*	*0.006*	*0.278*	*0.242*	*0.035*	*0.371*	*0.01*	*0.271*	*0.150*	*0.304*	*0.443*
Voicing	*R*	0.061	0.318	0.520	-0.092	-0.181	-0.361	-0.066	0.212	0.178	0.157	-0.031	-0.270
	R^2	0.004	0.101	0.270	0.009	0.033	0.131	0.004	0.045	0.032	0.025	0.001	0.073
	p	*0.306*	*0.003*	*<0.001*	*0.222*	*0.065*	*0.001*	*0.291*	*0.038*	*0.068*	*0.096*	*0.398*	*0.01*
MoA	*R*	0.017	0.396	0.281	-0.043	-0.217	-0.175	0.027	0.309	0.306	0.109	-0.044	-0.228
	R^2	<0.001	0.157	0.079	0.002	0.047	0.031	0.001	0.095	0.094	0.012	0.002	0.052
	p	*0.445*	*<0.001*	*0.009*	*0.363*	*0.035*	*0.074*	*0.413*	*0.004*	*0.005*	*0.184*	*0.359*	*0.028*
AWR								**N100**	**P200**	**N400**	**N100**	**P200**	**N400**
Words	*R*							0.147	0.171	0.076	-0.057	0.349	-0.287
	R^2	N/A	N/A	N/A	N/A	N/A	N/A	0.022	0.029	0.006	0.003	0.122	0.082
	p							*0.112*	*0.078*	*0.267*	*0.320*	*0.002*	*0.008*
Pseudowords	*R*							0.026	0.145	-0.016	0.080	0.155	-0.119
	R^2	N/A	N/A	N/A	N/A	N/A	N/A	0.001	0.021	<0.001	0.006	0.024	0.014
	p							*0.417*	*0.115*	*0.447*	*0.256*	*0.100*	*0.164*

Legend: APD = auditory phoneme discrimination; AWR = auditory word recognition; PoA = place of articulation; MoA = manner of articulation; N/A = not applicable; dark grey = significant result (≤ 0.01); light grey = trend (0.01 < x ≤ 0.05)

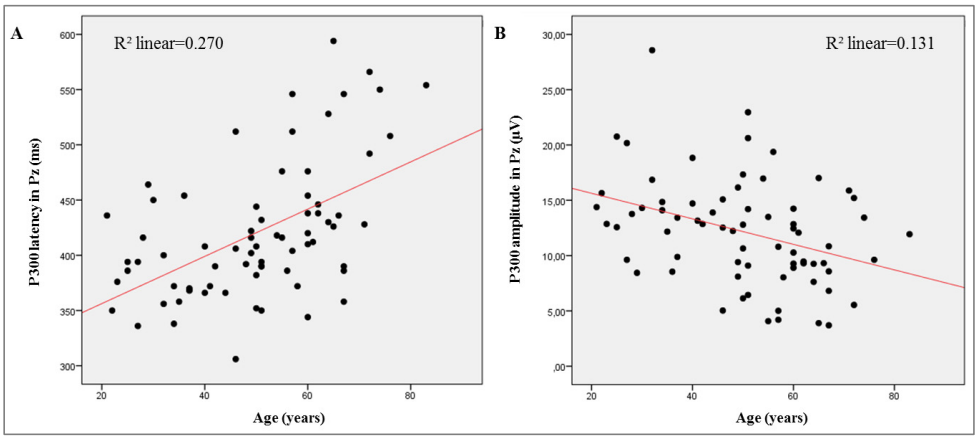

Figure 5.2: Regression analysis between P300 latencies (A) and amplitudes (B) (voicing) at Pz electrode.

Response to the standard phoneme. Regarding the ERPs associated with the standard wave reflecting primary auditory analysis, such as phoneme detection and identification, the regression analysis revealed that age significantly predicted a few ERP amplitudes and latencies.

Significantly higher P200 latencies at Cz were found in older subjects compared to the younger subjects with respect to PoA in the attended and unattended condition, MoA in the attended and unattended condition and voicing only in the attended condition with a tendency towards higher P200 latencies in the unattended condition. For P200 amplitudes at Cz, only a trend towards lower amplitudes in older subjects was found with respect to MoA in the attended condition. Latencies and amplitudes associated with earlier processes reflected by the N100 at Cz in the attended condition and P50 at Fz in the unattended condition were not significantly correlated with age.

3.4 Regression between age and neurophysiological results – Word recognition

Pearson's correlation and *R* square values together with their significant *p*-values can be found in Table 5.2. The normative data for the amplitudes and latencies per ERP subdivided in age categories can be found in Appendices 5A.5 and 5A.8, respectively.

N100. No significant correlations between age and latency or amplitude of the N100 measured at Cz in response to real words and pseudowords were found.

P200. For the P200 wave measured at F3/Fz/F4 in response to real words significantly increased amplitudes were observed in older subjects compared to younger subjects.

N400. A significant negative correlation between the amplitude and age of the subjects was established for the N400 measured at Cz in response to real words.

3.5 Correlation between neurophysiological and behavioural results

The most consistent correlations between neurophysiological results and scores on PALPA subtests were found in the attended phoneme discrimination paradigm between the P300 latencies for PoA (R = -0.286, p = 0.01), voicing (R = -0.296, p = 0.01) and MoA (R = -0.306, p = 0.01) and the total score on PALPA 5 (lexical decision test). The P300 amplitude only showed a correlational trend with the total score on PALPA 5 for the condition with MoA as phonemic contrast (R = 0.248, p = 0.039).

4. Discussion

This study investigated aging influences on phoneme discrimination and word recognition in the context of developing normative ERP data. Significant, but distinct aging influences were found for every phonemic contrast examined and for word recognition. Additionally, significant correlations were found between neurophysiological correlates of phoneme discrimination and behavioural lexical decision.

4.1 Auditory phoneme discrimination

Phonemic contrast PoA. The latency of the phonemic contrast PoA was influenced by age when attentional resources were required. This pattern of increased processing speed with age for PoA in the present study confirms earlier findings in the literature (Juckel et al., 2012; Schiff et al., 2008). Although there was a trend towards smaller amplitudes in older adults, no significant influences of age on P300 amplitude could be detected. This is consistent with previous research which found that the magnitude of the electrocortical responses was the same in young and old adults when attention was focussed on the auditory stimuli (Alain et al., 2004). Furthermore, no significant influences of age occurred on preconscious, automatic discrimination of the phonemic contrast PoA, reflected by stable MMN latencies and amplitudes across all ages. The hypothesis that elderly subjects successfully rely more on controlled processes as a compensatory mechanism for deficient early and automatic discrimination processes does not seem feasible in this case (Alain et al., 2004). On the contrary, because of the prolonged P300 latencies and unaffected MMN latencies and amplitudes our results suggest that the timing of attention allocation during PoA discrimination is not completely free from aging influences. Besides, the unchanging MMN latencies and amplitudes are in agreement with a study that did not find age effects on the MMN but did so for the P300 latency when using subtle frequency contrasts (Bertoli et al., 2005). Taking into account the wide frequency range between /b/ and /g/, it is possible that the automatic deviance detection of PoA was made based on its large frequency contrast. Consequently this may mean that the consonant contrast PoA is more resistant against age related changes in the brain, as aging only leads to deficient temporal processing of attentional stimulus categorization while preserving preconscious abilities.

Phonemic contrast MoA. When the phonemic contrast MoA was used, in addition to the P300 latency the MMN latency was also influenced by age. This indicates that not only cognitive resources engaged in attentional processing of this phonemic contrast decline with age, but even pre-attentive deviance discrimination processes are affected. This might be due to the fact that this phonemic contrast is processed in brain areas that are more subject to age-related neuronal changes, such as reduced neuronal density and atrophic volume reduction (Schiff et al., 2008; Sowell et al., 2003), making MoA more vulnerable to aging processes than PoA. Moreover, there was a trend towards attenuated MMN amplitudes in elderly subjects. It is possible that MMN amplitude decreases were not significantly established because a short ISI of 500 ms was used in the present study. By using longer ISIs (4500 ms) a study by Pekkonen et al. (1996) demonstrated that the duration of the sensory-memory stimulus trace deteriorated faster in elderly subjects. So, it is thinkable that a longer ISI in the present study would have led to genuine significant MMN amplitude attenuations. However, the longer ISI of 2000 ms in the attentive discrimination of MoA did not provoke age-related amplitude decreases. With the phonemic contrast PoA this led to a tendency towards reduced amplitudes, but for MoA this was not the case. Taking into account that only latencies were affected and that accurate consonant processing is dependent on correctly perceiving rapidly changing speech sound patterns (Näätänen et al., 2012), it can be presumed that aging primarily influences processing speed of phonemic contrast MoA.

Phonemic contrast voicing. The strongest relationship was found between age and processing speed and electrocortical responsiveness of the phonemic contrast voicing in the attended condition. According to the regression analysis, this was predicted by aging influences for 27% and 13%, respectively. It has already been established that various brain areas are differently affected by aging processes (Sowell et al., 2003). Moreover, every phoneme inherent to a certain language has a specific representation and location in the brain based on its phonemic and acoustic characteristics, forming language-specific phoneme memory traces (Dehaene-Lambertz, 1997; Näätänen et al., 1997). As has been shown by Obleser, Scott and Eulitz (2006), phonemic features are organized in a somatotopic way, such that consonants with a frontal articulation and consonants with a backwards articulation represent more anterior and posterior sources in the supratemporal gyrus, respectively. Likewise, it has been cautiously suggested that word memory traces carrying relevant lexical and semantic information may display distinct neuronal distributions throughout the cortex (Pulvermüller et al., 2004b). As such, it is expectable that each phonemic contrast is subject to aging processes in a different and phonemic-specific way. A possible explanation might be that the neuronal assemblies representing the phonemic contrast voicing are less “hard-wired” in the brain, which can be ascribed to the narrow frequency band in which /b/ and /p/ are located and the similar duration of both

phonemes, increasing the complexity of the phonemic contrast. Therefore, supported by the current aging influences on attentive discrimination of voicing and the significant relation between the MMN amplitude reduction and aging, it is plausible that voicing is even more vulnerable to age-related brain changes than PoA and MoA.

Response to the standard phoneme – N100/P50. In the unattended condition the N100 potential was absent and instead a positive potential at earlier latencies around 50 ms (P50) emerged. However, in the attended condition, a clear N100 potential was elicited (see figure 5.3).

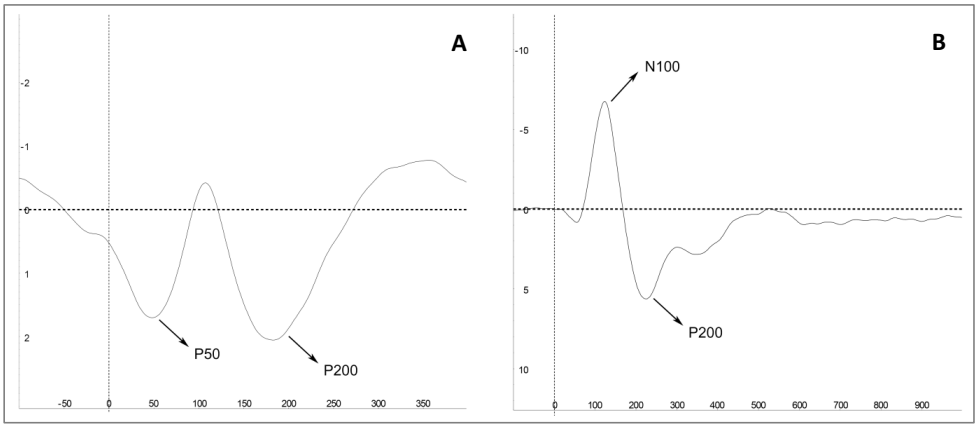

Figure 5.3: Standard wave ERPs of MMN paradigm in electrode Cz displaying P50 and P200 potentials (A) and standard wave ERPs of P300 paradigm in electrode Cz displaying N100 and P200 potentials (B) during phoneme discrimination of the phonemic contrast PoA. Latency (x-axis) is represented in milliseconds (ms) and amplitude (y-axis) in microvolts (µV). Negative values are plotted upwards.

Potentially, an altered pattern of electrical brain activity was evoked, leading to the emergence of more positive electrical activity in an earlier time window. This can be due to the ISI, since it has been established before that the N100 amplitude increases as a function of longer ISI and vice versa (Cooper et al., 2006; Czigler et al., 1992). This is further supported by the present results where a clear N100 potential was evoked when larger ISIs were used in the attended condition (2000 ms). So, attention can also be a co-occurring factor, such that N100 amplitudes become larger in attended conditions than in unattended conditions (Schiff et al., 2008). A P50 has also been observed in addition to a clear N100 potential when very short ISIs are employed (350 ms) (Gaeta et al., 2002) and even when language stimuli are used (Tavabi, Obleser, Dobel & Pantev, 2007). Given that in the present study a P50 was elicited with more complex language stimuli at an ISI of 500 ms in the unattended condition, indicates that sensory-perceptual auditory detection processes start earlier

than the time window of N100. No significant age effects were revealed for N100 or P50 latencies and amplitudes. This is in line with previous research which postulates that N100 potential can remain rather stable across life span with respect to its latency and amplitude, although attention can be an influencing factor (Bertoli et al., 2005; Czigler et al., 1992; Schiff et al., 2008). The P50 showed not to be influenced by age, which is in line with other literature findings (Gaeta et al., 2002) and indicates a resistance of sensory-perceptual detection processes against aging influences.

Response to the standard phoneme – P200. An increase in P200 latencies with age in all the attended and unattended conditions confirms earlier literature findings (Bertoli et al., 2002, 2005; Cooper et al., 2006). Moreover, it demonstrates the presence of dissimilar age effects in the N100/P50 and P200 time window. Actually, the P200 potential is often not recognized as an independent component (Crowley & Colrain, 2004) and its cognitive correlate has remained unclear up to now. Nonetheless, distinct effects of aging and attention on P200 latency and/or amplitude have been established, even when embedded in an ERP-complex with the N100 (Bertoli et al., 2002, 2005; Crowley & Colrain, 2004; Czigler et al., 1992). This suggests that different neuronal generators and cognitive functions can be involved. Taken together with the notion that genuine sensory-perceptual processes might be less influenced by age (Bertoli et al., 2005) and the current outcomes, it can be carefully assumed that the P200 is more related to higher cognitive language processes, such as identification and preparatory classification of sound stimuli (e.g. phonemes). By contrast, the N100 and P50 are more likely linked to brain areas accountable for regular acoustical feature detection and analysis processes.

To our knowledge, this is the first time that actual phonemes are used as stimuli with respect to electrocortical aging influences. Therefore, the present study has revealed influences of aging on proper neurophysiological correlates of phoneme discrimination with a clear discrepancy between different phonemic contrasts and a dissociation between attended and unattended processing.

4.2 Auditory word recognition

N400 time window. As mentioned earlier in Section 1, the N400 potential is a neurophysiological correlate for lexical-semantic retrieval processes (Kotz & Friederici, 2003). However, the cognitive correlate of the N400 has been rather dubious as it might represent pure lexical processes or already more semantically related integration processes (Brown & Hagoort, 1993). When pseudowords are derived from real words in a lexical decision task, the semantic representation of the pseudoword's root word becomes active (Deacon, Dynowska, Ritter & Grose-Fifer, 2004). Therefore, the N400 to derived pseudowords has been labeled as a "sensitivity" to semantic information, but in itself reflective for lexical processes as it is highly unlikely that the pseudoword itself causes semantic

activation. Hence, the N400 to pseudowords in the current auditory word recognition task, in which derived pseudowords were used, can be interpreted as reflective for lexical processes during word recognition (Giaquinto et al., 2007). As can be seen in figure 5.4, there were morphological differences between the N400 as response to real words and N400 as response to pseudowords. This can be due to the variance in imageability and frequency between both word types, given that the more predictable a word becomes at word level the more the N400 amplitude will be reduced (Kotz & Friederici, 2003). Moreover, within slow wave potentials, such as N400, negativity is associated with cortical excitability and positivity with diminished cortical activity (Angrilli, Elbert, Cusumano, Stegagno & Rockstroh, 2000; Karayanidis et al., 1993). This means that the processing of real words probably can proceed with less "cortical effort", as they form part of our mental lexicon and are much more imaginable and frequent than pseudowords, ultimately resulting in a positivity shift in the present real word N400.

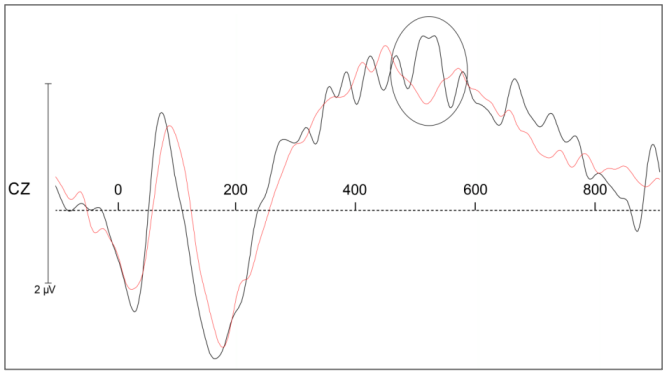

Figure 5.4: Overlay of responses to real words (red) and pseudowords (black) in the Cz electrode during the word recognition task. N400 mismatch between real words and pseudowords is indicated by a circle.

The real word N400 but not the pseudoword N400 exhibited decreasing amplitudes with age without significant changes in its latency values. The real word N400 presumably represents more than only lexical processes since it cannot be ruled out that semantic connotations become active when real words are perceived (Federmeier, Van Petten, Schwartz & Kutas, 2003; Kutas & Federmeier, 2000; Stern, Prather, Swinney & Zurif, 1991). Taken together with the present observation that no aging influences were detected on the pseudoword N400, it can be concluded that advancing age mainly has an impact on semantic information processing, leaving lexical processes relatively unharmed.

These findings are consistent with previous, behavioural and neurophysiological, research outcomes (Giaquinto et al., 2007; Karayanidis et al., 1993).

N100-P200 time window. Influences of advancing age during word recognition were already established earlier, around 200 ms, with a P200 amplitude enhancement in response to real words. The actual function of the P200 in the context of lexical-semantic processes has been related to preparatory phases prior to lexical processes, such as form-based analyses with respect to the legality of the (pseudo)words presented (Laszlo, Stites & Federmeier, 2012). By the time the N400 potential has initiated, the decision on the legal status of the phonemes must be determined (Deacon et al., 2004), thereby suggesting the possibility that the P200 is reflective for the analysis of the different phonemes and their sequence. Consequently, the N400 onset marks the end stage of this analysis process. Therefore, the higher P200 amplitudes observed in elderly people can indicate that they are more susceptible to task-irrelevant stimuli due to diminished inhibition, which interferes with the form-based processes and causes the N400 amplitude decrease. This is in correspondence with other studies reporting amplitude increases of the P200 (Crowley & Colrain, 2004; Crowley et al., 2002). However, the preservation of P200 latency is in disagreement with what has been observed before (Federmeier et al., 2003; Giaquinto et al., 2007). Sensory-perceptual processes during word and pseudoword processing were relatively spared in elderly people, reflected by an absence of aging influences on the N100 potential. This has also been reported by Giaquinto et al. (2007) and is in agreement with the general finding that sensory-perceptual processes reflected by the N100 are largely free from aging influences (Bertoli et al., 2005).

Behavioural performance and ERP results. The association between reduced speed of attended phoneme discrimination and the ability to distinguish behaviourally between real words and pseudowords is suggestive for a substantial impact of phoneme perception and discrimination on word recognition. This can be further supported by the finding that deficient phoneme processing in aphasic patients is decisive for lexical decision abilities (Csépe et al., 2001). The fact that no relationship was found between behavioural phoneme discrimination and its neurophysiological correlates can potentially be explained by the maximum scores obtained by almost every individual on the behavioural discrimination tests. Therefore, it can be questioned whether the behavioural phoneme discrimination tasks presently used are sensitive enough to detect phonological input impairments. Perhaps other, more powerful tests are able to reveal the neurophysiological established phonological input disorders in the older subjects. Notwithstanding, this demonstrates the possibility that age-related electrocortical changes in the brain can be at play even when they are not behaviourally expressed or detected (Bertoli et al., 2005). This is an important factor to take into

account with respect to clinical situations where the possibility exists that patients are overestimated due to a lack of power in behavioural tests.

5. Conclusion

In summary we can conclude that during auditory phoneme discrimination all three phonemic contrasts are differently affected by aging influences. PoA is the most resistant against aging and voicing the most vulnerable. This can be due to fading of neuronal sensory-memory traces in the brain and interacts with attention and variability in complexity of the phonemic contrasts. During word recognition, lexical processes are relatively unharmed and advancing age mainly has an impact on semantic processing. Additionally, it appears that very early sensory-perceptual processes (N100/P50) are free from aging influences both during phoneme discrimination and word recognition. Neurophysiological normative data for latencies (ms) and amplitudes (µV) have been developed for six age groups. It must be mentioned that the 70+ age group has a rather small sample size (n=6). However, a separate category was created for this group, because the averages of the 60-69 years-old group diverged to a great extent from the ones of the 70+ group. Eventually, the 70+ group, but also the other groups, should be extended with more healthy controls to obtain equally distributed normative groups. Until then, the current preliminary normative data can be applied in the evaluation of acquired language disorders and the knowledge of aging influences can provide a guideline for stimulus choice when developing clinical paradigms.

6. References

Alain, C., Mcdonald, K. L., Ostroff, J. M. & Schneider, B. (2004). Aging: A switch from automatic to controlled processing of sounds? *Psychology and Aging, 19* (1), 125–133.

Alexandrov, A. A., Boricheva, D. O., Pulvermüller, F. & Shtyrov, Y. (2011). Strength of Word-Specific Neural Memory Traces Assessed Electrophysiologically. *PLoS ONE, 6* (8).

Angrilli, A., Elbert, T., Cusumano, S., Stegagno, L. & Rockstroh, B. (2000). Temporal dynamics of linguistic processes are reorganized in aphasics' cortex: An EEG mapping study. *NeuroImage, 20*, 657–666.

Bastiaanse, R., Bosje, M. & Visch-Brink, E. G. (1995). *Psycholinguïstische Testbatterij voor Onderzoek naar de Taalverwerking van Afasiepatiënten (PALPA).* Hove, East Sussex: Psychology Press.

Benichov, J., Cox, L. C., Tun, P. A. & Wingfield, A. (2012). Word recognition within a linguistic context: Effects of age, hearing acuity, verbal ability, and cognitive function. *Ear & Hearing, 33* (2), 250–256.

Bertoli, S., Smurzynski, J. & Probst, R. (2002). Temporal resolution in young and elderly subjects as measured by mismatch negativity and a psychoacoustic gap detection task. *Clinical Neurophysiology, 113*, 396–406.

Bertoli, S., Smurzynski, J. & Probst, R. (2005). Effects of age, age-related hearing loss, and contralateral cafeteria noise on the discrimination of small frequency changes: Psychoacoustic and electrophysiological measures. *Journal of the Association for Research in Otolaryngology, 6*, 207–222.

Boersma, P. & Weenink, D. (2010). Praat: doing phonetics by computer [Computer program]. Version 5.1.45, retrieved 26 October 2010 from http://www.praat.org/

Brown, C. & Hagoort, P. (1993). The processing nature of the N400: Evidence from masked priming. *Journal of Cognitive Neuroscience, 5* (1), 34-44.

Cooper, R. J., Todd, J., McGill, K. & Michie, P. (2006). Auditory sensory memory and the aging brain: A mismatch negativity study. *Neurobiology of Aging, 27*, 752–762.

Crowley, K. E. & Colrain, I. M. (2004). A review of the evidence for P2 being an independent component process: Age, sleep and modality. *Clinical Neurophysiology, 115*, 732–744.

Crowley, K. E., Trinder, J. & Colrain, I. M. (2002). An examination of evoked K-complex amplitude and frequency of occurrence in the elderly. *Journal of Sleep Research, 11*, 129–140.

Csèpe, V., Osman-Sági, J., Molnár, M. & Gósy, M. (2001). Impaired speech perception in aphasic patients: event-related potential and neuropsychological assessment. *Neuropsychologia, 39*, 1194-1208.

Czigler, I., Csibra, G. & Csontos, A. (1992). Age and inter-stimulus interval effects on event-related potentials to frequent and infrequent auditory stimuli. *Biological Psychology, 33*, 195-206.

Deacon, D., Dynowska, A., Ritter, W. & Grose-Fifer, J. (2004). Repetition and semantic priming of nonwords: Implications for theories of N400 and word recognition. *Psychophysiology, 41*, 60–74.

Dehaene-Lambertz, G. (1997). Electrophysiological correlates of categorical phoneme perception in adults. *NeuroReport, 8*, 919–924.

Federmeier, K. D., Van Petten, C., Schwartz, T. J. & Kutas, M. (2003). Sounds, words, sentences: Age-related changes across levels of language processing. *Psychology and Aging, 18* (4), 858–872.

Folstein, M., Folstein, S. E. & McHugh, P. R. (1975). "Mini-Mental State" a practical method for grading the cognitive state of patients for Clinician. *Journal of Psychiatric Research, 12* (3), 189–98.

Gaeta, H., Friedman, D., Ritter, W. & Hunt, G. (2002). Age-related changes in neural trace generation of rule-based auditory features. *Neurobiology of Aging, 23*, 443–455.

Ghyselinck, M., Custers, R., & Brysbaert, M. (2003). Age-of-acquisition ratings for 2332 Dutch words from 49 different semantic categories. *Psychologica Belgica, 43* (3), 181-214.

Giaquinto, S., Ranghi, F. & Butler, S. (2007). Stability of word comprehension with age: An electrophysiological study. *Mechanisms of Aging and Development, 128*, 628–636.

Holmes, A.E., Kricos, P. B., Kessler, R. A. (1988). *British Journal of Audiology, 22* (1), 29-33.

International Phonetic Association (1999). *Handbook of the International Phonetic Association: a guide to the use of the international phonetic alphabet.* Cambridge University Press.

Juckel, G., Karch, S., Kawohl, W., Kirsch, V., Jäger, L., Leicht, G. et al. (2012). Age effects on the P300 potential and the corresponding fMRI BOLD-signal. *NeuroImage, 60*, 2027-2034.

Karayanidis, F., Andrews, S., Ward, P. B. & McConaghy, N. (1993). Event-related potentials and repetition priming in young, middle-aged and elderly normal subjects. *Cognitive Brain Research, l*, 123-134.

Kay, J., Lesser, R. & Coltheart, M. (1992). *PALPA: Psycholinguistic Assessments of Language Processing in Aphasia.* Hove, East Sussex: Psychology Press.

Keuleers, E., Brysbaert, M. & New, B. (2010). SUBTLEX-NL: A new frequency measure for Dutch words based on film subtitles. *Behavior Research Methods, 42* (3), 643-650.

Kiang, M., Braff, D. L., Sprock, J. & Light, G. A. (2009). The relationship between pre-attentive sensory processing deficits and age in schizophrenia patients. *Clinical Neurophysiology, 120*, 1949–1957.

Kisley, M. A., Davalos, D. B., Engleman, L. L., Guinthera, P. M. & Davis, H. P. (2005). Age-related change in neural processing of time-dependent stimulus features. *Cognitive Brain Research, 25*, 913 – 925.

Kok, A. (2000). Age-related changes in involuntary and voluntary attention as reflected in components of the event-related potential (ERP). *Biological Psychology, 54*, 107–143.

Kotz, S. A. & Friederici, A. D. (2003). Electrophysiology of normal and pathological language processing. *Journal of Neurolinguistics, 16*, 43-58.

Kutas, M. & Federmeier, K. D. (2000). Electrophysiology reveals semantic memory use in language comprehension. *Trends in Cognitive Sciences, 4* (12), 463-470.

Kutas, M. & Federmeier, K. D. (2011). Thirty Years and Counting: Finding Meaning in the N400 Component of the Event-Related Brain Potential (ERP). *Annual Review of Psychology, 62*, 621-647.

Kutas, M. & Hillyard, S. A. (1980). Reading senseless sentences: Brain potentials reflect semantic incongruity. *Science, 207*, 203–205.

Laszlo, S., Stites, M. & Federmeier, K. D. (2012). Won't get fooled again: An event-related potential study of task and repetition effects on the semantic processing of items without semantics. *Language and Cognitive Processes, 27* (2), 257-274.

Linden, D. E. J. (2005). The P300: Where in the brain is it produced and what does it tell us? *The Neuroscientist, 11* (6), 563-576.

McClelland, J. L. & Elman, J. L. (1986). The TRACE model of speech perception. *Cognitive Psychology, 18*, l-86.

Moran, M. (2003). Arguments for rejecting the sequential Bonferroni in ecological studies. *Oikos, 100* (2), 403-405.

Näätänen, R. (2001). The perception of speech sounds by the human brain as reflected by the mismatch negativity (MMN) and its magnetic equivalent (MMNm). *Psychophysiology, 38*, 1–21.

Näätänen, R., Gaillard, A. W., & Mäntysalo, S. (1978). Early selective-attention effect on evoked potential reinterpreted. *Acta Psychologica (Amsterdam), 42*, 313–329.

Näätänen, R., Kujala, T. & Winkler, I. (2011). Auditory processing that leads to conscious perception: A unique window to central auditory processing opened by the mismatch negativity and related responses. *Psychophysiology, 48*, 4–22.

Näätänen, R., Paavilainen, P., Rinne, T. & Alho, K. (2007). The mismatch negativity (MMN) is basic research of central auditory processing: A review. *Clinical Neurophysiology, 118*, 2544–2590.

Näätänen, R., Lehtokoski, A., Lennes, M., Cheour, M., Huotilainen, M., Iivonen, A. et al. (1997). Language-specific phoneme representations revealed by electric and magnetic brain responses. *Nature, 385*, 432–434.

Näätänen, R., Kujala, T., Escera, C., Baldeweg, T., Kreegipuu, K., Carlson, S., et al. (2012). The mismatch negativity (MMN): A unique window to disturbed central auditory processing in aging and different clinical conditions. *Clinical Neurophysiology, 123*, 424–458.

Nakagawa, S. (2004). A farewell to Bonferroni: the problems of low statistical power and publication bias. *Behavioral Ecology, 15* (6), 1044-1045.

Obleser, J., Scott, S. K. & Eulitz C. (2006). Now you hear it, now you don't: Transient traces of consonants and their nonspeech analogues in the human brain. *Cerebral Cortex, 16*, 1069-1076.

Pekkonen, E., Rinne, T., Reinikainen, K., Kujala, T., Alho, K. & Näätänen, R. (1996). Aging effects on auditory processing: an event-related potential study. *Experimental Aging Research, 22* (2), 171-184.

Perneger, T. (1998). What's wrong with Bonferroni adjustments. *British Medical Journal, 316*, 1236-1238.

Poeppel, D., Idsardi, W. J. & van Wassenhove, V. (2008). Speech perception at the interface of neurobiology and linguistics. *Philosophical Transactions of the Royal Society B-Biological Sciences, 363*, 1071–1086.

Polich, J. (2004). Clinical application of the P300 event-related brain potential. *Physical Medicine and Rehabilitation Clinics of North America, 15*, 133-161.

Pulvermüller, F. (1999). Words in the brain's language. *Behavioral and Brain Sciences, 22*, 253–336.

Pulvermüller, F., Shtyrov, Y., Kujala, T., & Näätänen, R. (2004b). Word-specific cortical activity as revealed by the mismatch negativity. *Psychophysiology, 41*, 106–112.

Pulvermüller, F., Kujala, T., Shtyrov, Y., Simola, J., Tiitinen, H., Alku, P. et al. (2001). Memory traces for words as revealed by the mismatch negativity. *NeuroImage, 14* (3), 607–616.

Schiff, S., Valenti, P., Pellegrini, A., Lot, M., Bisiacchi, P., Gatta, A. et al. (2008). The effect of aging on auditory components of event-related brain potentials. *Clinical Neurophysiology, 119*, 1795–1802.

Schneider, B. A., Daneman, M. & Pichora-Fuller, M. K. (2002). Listening in aging adults: From discourse comprehension to psychoacoustics. *Canadian Journal of Experimental Psychology, 56* (3), 139-152.

Shtyrov, Y. & Pulvermüller, F. (2002). Neurophysiological evidence of memory traces for words in the human brain. *NeuroReport, 13*, 521–525.

Sommers, M. S., Hale, S., Myerson, J., Rose, N., Tye-Murray, N. & Spehar, B. (2011). Listening comprehension across the adult lifespan. *Ear & Hearing, 32* (6), 775–781.

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L. & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience, 6* (3), 309-315.

Stern, C., Prather, P., Swinney, D. & Zurif, E. (1991). The time course of automatic lexical access and aging. *Brain and Language, 40*, 359-372.

Sutton, S., Braren, M., Zubin, J. & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. *Science, 150* (3700), 1187-1188.

Tavabi, K., Obleser, J., Dobel, C. & Pantev, C. (2007). Auditory evoked fields differentially encode speech features: An MEG investigation of the P50m and N100m time courses during syllable processing. *European Journal of Neuroscience, 25*, 3155–3162.

Van Strien, J.W. (1992). Classificatie van links- en rechtshandige proefpersonen. *Nederlands Tijdschrift voor de Psychologie en Haar Grensgebieden, 47*, 88-92.

7. Appendices

Tables 5A.1 – 5A.8 provide normative data for the latencies and amplitudes per paradigm and per ERP subdivided in age categories.

Table 5A.1: Amplitudes (µV) for Auditory Phoneme Discrimination – Mean, Standard Deviation and Range

Age (y)	PC	Attended (P300)			Unattended (MMN)		
		M	SD ±	Range	M (-)	SD ±	Range (-)
20-29 *(n=9)*	PoA	13.03	5.65	6.08 – 21.92	4.48	2.12	1.68 – 7.10
	Voicing	14.25	4.18	8.44 – 20.76	4.04	1.83	1.51 – 7.19
	MoA	13.24	5.39	5.63 – 21.78	3.41	2.07	0.59 – 5.80
30-39 *(n=9)*	PoA	14.08	5.58	4.10 – 22.50	2.87	1.35	1.47 – 5.42
	Voicing	14.74	5.77	8.54 – 28.57	3.81	1.05	2.08 – 5.76
	MoA	11.34	4.58	6.69 – 18.78	2.89	1.69	1.01 – 6.28
40-49 *(n=12)*	PoA	13.09	4.00	5.53 – 19.37	3.22	2.43	0.37 – 7.59
	Voicing	12.67	3.72	5.03 – 18.84	2.73	1.48	1.20 – 6.04
	MoA	11.63	4.07	3.52 – 17.00	2.51	1.53	0.24 – 5.36
50-59 *(n=17)*	PoA	12.19	4.78	5.48 – 23.19	3.98	1.46	2.03 – 6.94
	Voicing	11.89	5.99	4.07 – 22.96	3.64	1.41	1.24 – 5.72
	MoA	12.49	4.47	5.00 – 24.38	2.94	1.94	0.18 – 7.16
60-69 *(n=18)*	PoA	11.58	3.46	5.90 – 17.29	3.53	1.60	1.40 – 7.89
	Voicing	9.77	3.29	3.70 – 17.01	2.61	1.86	0.78 – 6.72
	MoA	10.07	3.80	1.87 – 15.69	2.42	1.71	0.04 – 5.66
70 + *(n=6)*	PoA	11.45	3.10	7.73 – 15.61	3.64	1.17	1.52 – 5.09
	Voicing	11.93	3.87	5.54 – 15.88	2.67	1.61	0.38 – 4.40
	MoA	12.04	5.31	5.57 – 18.44	1.91	1.83	0.05 – 5.16

Legend: y = years; PC = phonemic contrast; PoA = place of articulation; MoA = manner of articulation; M = mean; SD = standard deviation; (-) = negative amplitudes

Table 5A.2: Amplitudes (µV) for Auditory Phoneme Discrimination – Percentiles

Age (y)	PC	Attended (P300)			Unattended (MMN)		
		25	50	75	25 (-)	50 (-)	75 (-)
20-29 *(n=9)*	PoA	7.36	12.53	18.34	2.38	4.19	6.81
	Voicing	11.09	13.76	17.91	2.67	3.55	5.61
	MoA	7.76	14.06	17.08	1.29	4.33	5.29
30-39 *(n=9)*	PoA	10.20	14.51	18.16	1.70	2.47	3.90
	Voicing	11.02	14.10	15.85	3.09	3.76	4.36
	MoA	7.61	9.96	15.98	1.52	2.48	3.99
40-49 *(n=12)*	PoA	10.94	12.76	15.60	1.04	3.19	4.91
	Voicing	10.11	13.00	14.99	1.44	2.39	3.47
	MoA	9.15	10.82	16.08	1.44	2.45	3.71
50-59 *(n=17)*	PoA	7.82	11.74	14.90	2.74	3.71	5.34
	Voicing	6.21	11.79	17.24	2.49	4.02	4.73
	MoA	9.92	10.71	14.96	1.83	2.43	4.61
60-69 *(n=18)*	PoA	8.60	12.51	14.09	2.31	3.31	4.31
	Voicing	8.34	9.31	12.16	1.42	1.97	2.94
	MoA	7.64	11.14	13.27	0.87	1.98	3.87
70 + *(n=6)*	PoA	7.93	11.89	14.08	2.99	3.84	4.33
	Voicing	8.59	12.68	15.38	1.13	2.84	4.23
	MoA	6.67	12.30	17.06	0.37	1.75	3.00

Legend: y = years; PC = phonemic contrast; PoA = place of articulation; MoA = manner of articulation; (-) = negative amplitudes

Table 5A.3: Latencies (ms) Auditory Phoneme Discrimination – Mean, Standard Deviation and Range

Age (y)	PC	Attended (P300)			Unattended (MMN)		
		M	SD ±	Range	M	SD ±	Range
20-29 *(n=9)*	PoA	409	37.71	332 – 442	171	28.17	136 – 221
	Voicing	395	40.05	336 – 464	159	39.45	108 – 217
	MoA	385	58.01	312 – 466	159	13.04	136 – 178
30-39 *(n=9)*	PoA	398	46.75	338 – 488	153	24.39	129 – 193
	Voicing	385	41.34	338 – 454	166	50.59	89 – 237
	MoA	376	32.49	338 – 430	180	25.59	155 – 238
40-49 *(n=12)*	PoA	403	60.04	352 – 578	171	27.28	141 – 219
	Voicing	396	47.99	306 – 512	164	37.95	110 – 240
	MoA	376	33.51	328 – 434	174	28.47	133 – 234
50-59 *(n=17)*	PoA	418	50.11	310 – 518	184	38.57	133 – 242
	Voicing	416	53.18	350 – 546	173	40.00	89 – 232
	MoA	387	65.35	320 – 562	176	20.51	140 – 211
60-69 *(n=18)*	PoA	417	40.36	350 – 534	171	24.09	131 – 227
	Voicing	440	63.23	344 – 594	177	36.60	99 – 243
	MoA	400	50.69	304 – 508	190	26.10	135 – 241
70 + *(n=6)*	PoA	479	77.52	358 – 580	172	33.97	134 – 214
	Voicing	516	51.93	428 – 566	184	42.27	141 – 248
	MoA	451	53.79	396 – 550	182	16.43	158 – 202

Legend: y = years; PC = phonemic contrast; PoA = place of articulation; MoA = manner of articulation; M = mean; SD = standard deviation

Table 5A.4: Latencies (ms) Auditory Phoneme Discrimination – Percentiles

Age (y)	PC	Attended (P300)			Unattended (MMN)		
		25	**50**	**75**	**25**	**50**	**75**
20-29 *(n=9)*	PoA	385	426	441	148	172	193
	Voicing	363	394	426	118	172	193
	MoA	334	378	450	151	160	169
30-39 *(n=9)*	PoA	367	382	434	134	144	180
	Voicing	357	370	425	123	160	218
	MoA	347	370	408	159	175	191
40-49 *(n=12)*	PoA	364	391	419	143	171	191
	Voicing	367	397	141	128	163	185
	MoA	352	368	411	153	164	197
50-59 *(n=17)*	PoA	402	412	450	144	179	231
	Voicing	383	399	428	156	180	198
	MoA	342	369	422	164	168	195
60-69 *(n=18)*	PoA	391	412	430	157	168	184
	Voicing	405	433	459	146	180	206
	MoA	364	391	440	175	194	203
70 + *(n=6)*	PoA	422	477	547	143	164	211
	Voicing	476	529	557	143	177	222
	MoA	414	437	488	165	184	195

Legend: y = years; PC = phonemic contrast; PoA = place of articulation; MoA = manner of articulation

Table 5A.5: Amplitudes (µV) Auditory Word Recognition – Mean, Standard Deviation and Range

Age (y)	Wordness	Unattended (N100)			Unattended (P200)			Unattended (N400)		
		M (-)	SD ±	Range (-)	M	SD ±	Range	M (-)	SD ±	Range (-)
20-29 *(n=9)*	Words	2.03	1.12	0.86 – 4.09	1.67	1.34	0.09 – 3.99	3.26	1.26	1.35 – 5.28
	Pseudowords	3.16	2.35	0.45 – 6.60	3.52	3.26	0.87 – 10.89	4.37	2.83	0.35 – 7.70
30-39 *(n=9)*	Words	1.69	1.07	0.68 – 4.02	1.91	1.18	0.07 – 3.69	3.38	1.30	1.86 – 5.62
	Pseudowords	1.79	1.18	0.03 – 3.57	2.53	2.01	0.06 – 5.86	4.15	2.33	0.61 – 7.36
40-49 *(n=12)*	Words	1.50	1.27	0.07 – 4.62	1.72	1.04	0.20 – 3.62	2.60	1.17	0.74 – 5.68
	Pseudowords	3.08	3.10	0.01 – 8.18	3.07	1.89	0.64 – 7.29	3.60	1.93	0.11 – 7.54
50-59 *(n=17)*	Words	1.83	1.35	0.17 – 4.90	2.19	1.33	0.79 – 5.76	3.05	1.36	0.71 – 4.97
	Pseudowords	3.44	1.89	0.62 – 6.77	3.26	1.31	1.03 – 5.08	5.22	2.36	2.23 – 9.37
60-69 *(n=18)*	Words	1.55	1.00	0.25 – 3.97	2.84	1.36	0.16 – 4.97	2.21	1.16	0.28 – 4.55
	Pseudowords	2.77	2.12	0.18 – 8.55	3.94	2.11	0.75 – 7.88	2.91	2.31	0.19 – 6.96
70 + *(n=6)*	Words	1.50	1.03	0.51 – 2.66	3.29	2.24	0.79 – 7.45	2.05	1.35	0.04 – 3.67
	Pseudowords	2.84	2.12	0.25 – 5.48	3.90	2.85	1.15 – 9.08	3.77	2.64	0.09 – 7.33

Legend: y = years; M = mean; SD = standard deviation; (-) = negative amplitudes

Table 5A.6: Amplitudes (µV) Auditory Word Recognition – Percentiles

Age (y)	Wordness	Unattended (N100)			Unattended (P200)			Unattended (N400)		
		25 (-)	50 (-)	75 (-)	25	50	75	25 (-)	50 (-)	75 (-)
20-29	Words	1.13	1.77	2.86	0.31	1.57	2.76	2.39	3.11	4.40
(n=9)	Pseudowords	0.78	2.61	5.43	1.18	1.95	5.20	1.65	4.95	7.19
30-39	Words	0.83	1.71	2.16	0.82	2.13	2.83	2.21	3.10	4.58
(n=9)	Pseudowords	0.74	1.88	2.83	0.81	1.90	4.14	2.01	4.09	5.98
40-49	Words	0.82	1.13	1.81	0.80	1.64	2.56	1.95	2.57	2.89
(n=12)	Pseudowords	0.57	1.60	6.67	1.27	3.31	4.18	2.62	3.68	4.44
50-59	Words	0.66	1.52	2.98	1.08	2.01	2.79	2.42	3.10	4.06
(n=17)	Pseudowords	1.91	3.24	4.58	2.11	3.41	4.46	3.03	5.09	7.03
60-69	Words	0.75	1.28	2.38	1.75	2.76	4.07	1.40	2.07	2.89
(n=18)	Pseudowords	0.81	2.78	4.27	1.91	3.97	5.72	1.15	2.04	5.36
70 +	Words	0.56	1.37	2.54	1.91	2.84	4.51	1.07	1.97	3.35
(n=6)	Pseudowords	0.57	3.18	4.59	1.45	3.56	5.65	1.88	3.35	6.36

Legend: y = years; (-) = negative amplitudes

Table 5A.7: Latencies (ms) Auditory Word Recognition – Mean, Standard Deviation and Range

Age (y)	Wordness	Unattended (N100)			Unattended (P200)			Unattended (N400)		
		M	SD ±	Range	M	SD ±	Range	M	SD ±	Range
20-29 *(n=9)*	Words	92	8.41	78 – 102	182	18.74	164 – 215	494	60.02	406 – 586
	Pseudowords	94	16.39	72 – 124	170	19.40	139 – 199	507	54.51	430 – 584
30-39 *(n=9)*	Words	94	14.54	76 – 118	173	6.84	161 – 184	487	59.66	422 – 582
	Pseudowords	87	13.86	70 – 110	182	28.59	143 – 225	498	58.65	416 – 564
40-49 *(n=12)*	Words	89	16.70	60 – 112	193	23.67	155 – 235	504	61.86	410 – 582
	Pseudowords	83	16.59	60 – 110	169	20.78	143 – 215	496	53.61	410 – 594
50-59 *(n=17)*	Words	96	20.77	64 – 128	192	16.69	167 – 217	489	61.41	406 – 586
	Pseudowords	95	24.42	60 – 124	177	27.36	134 – 228	508	61.46	414 – 590
60-69 *(n=18)*	Words	92	17.01	66 – 118	191	24.01	157 – 242	512	64.30	416 – 588
	Pseudowords	90	17.54	60 – 122	189	25.10	155 – 230	512	59.39	412 – 584
70 + *(n=6)*	Words	107	23.42	76 – 138	179	7.87	169 – 191	511	48.06	456 – 566
	Pseudowords	94	19.74	74 – 118	173	17.88	153 – 203	492	42.45	436 – 542

Legend: y = years; M = mean; SD = standard deviation

Table 5A.8: Latencies (ms) Auditory Word Recognition – Percentiles

Age (y)	Wordness	Unattended (N100)			Unattended (P200)			Unattended (N400)		
		25	**50**	**75**	**25**	**50**	**75**	**25**	**50**	**75**
20-29 *(n=9)*	Words	84	94	97	165	174	199	449	476	554
	Pseudowords	80	92	105	156	170	188	447	526	548
30-39 *(n=9)*	Words	81	92	106	169	174	178	442	456	548
	Pseudowords	75	86	98	157	176	208	430	510	553
40-49 *(n=12)*	Words	72	93	103	177	195	208	440	517	558
	Pseudowords	67	83	99	151	164	183	445	509	521
50-59 *(n=17)*	Words	83	96	116	178	194	208	430	471	552
	Pseudowords	67	95	117	158	171	198	441	502	569
60-69 *(n=18)*	Words	79	85	109	174	180	204	440	539	568
	Pseudowords	75	87	106	167	186	216	476	524	563
70 + *(n=6)*	Words	80	113	123	170	180	184	469	505	563
	Pseudowords	75	93	110	158	169	188	458	486	539

Legend: y = years

CHAPTER 6

Sex differences in neurophysiological activation patterns during phonological processing: An influencing factor for normative data

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Santens, P. & De Letter, M. (revised). **Sex differences in neurophysiological activation patterns during phonological processing: An influencing factor for normative data**. Archives of Sexual Behavior.

Abstract

In the context of neurophysiological normative data, it has been established before that aging has a significant impact on neurophysiological correlates of auditory phonological input processes, such as phoneme discrimination (PD) and word recognition (WR). Besides age, sex is another demographic factor that influences several language processes. We aimed to disentangle whether sex has a similar effect on PD and WR. Event-related potentials (ERPs) were recorded in 20 men and 24 women. During PD, three phonemic contrasts (place and manner of articulation and voicing) were compared using the attentive P300 and pre-attentive Mismatch Negativity. To investigate WR, real words were contrasted with pseudowords in a pre-attentive oddball task. Women demonstrated a larger sensitivity to spectrotemporal differences, as evidenced by larger P300 responses to the place of articulation (PoA) contrast and larger P300 and MMN responses than men in PoA-based PD. Men did not display such sensitivity. Attention played an important role, considering that women needed more attentional resources to differentiate between PoA and the other phonemic contrasts. During WR, pseudowords evoked larger amplitudes already 100 msec post-stimulus independent of sex. However, women had decreased P200 latencies, but longer N400 latencies in response to pseudowords, whereby men showed increased N400 latencies compared to women in response to real words. The current results demonstrate significant sex-related influences on phonological input processes. Therefore, existing neurophysiological normative data for age should be complemented for the factor sex.

Keywords

sex; Mismatch Negativity (MMN); P300; phonology; N400 pseudoword effect; gender

1. Introduction

When perceiving an auditory speech stimulus (e.g., a spoken word), several phases have to be accounted for until a definite match can be made with conceptual information in the semantic system (Basso, 2003; Bormann & Weiller, 2012; Coltheart, 2004; Ellis & Young, 1996). One of the first phases is auditory phonological analysis during which the extraction of and discrimination between different speech sounds (phonemes) occurs and in which phonemic contrasts, such as place of articulation (PoA) and voicing, play an important role. Subsequently, a reconstructed phonological representation can be matched with stored lexical representations in the phonological input lexicon, which ultimately leads to word recognition (WR) and word comprehension in the semantic system.

Behavioural research has already indicated important differences between men and women in these language processes (Liederman et al., 2013; Majeres, 1999; Weiss, Kemmler, Deisenhammer, Fleischhacker, & Delazer, 2003), showing better verbal language skills in women than men. At a higher, semantic level, women revealed more effective use of delayed semantic information in disambiguating a disrupted word presented earlier in a sentence (Liederman et al., 2013). This confirmed an earlier study which evidenced that women are more subject to interference of misinformative semantic context when processing disrupted speech (Liederman et al., 2010). At a lower, lexico-phonological level, women showed an advantage over men when speeded letter matching and reading aloud of irregular (pseudo)words depends more on phonology-based speech codes (Majeres, 1999). This may indicate that women have a more "qualitative" representation of abstract phonological units. However, at a more basic acoustic level, men seemed to be more proficient in using smaller differences in formant distances when performing size judgments on vocal stimuli (Charlton, Taylor, & Reby, 2013).

Structural, neuroanatomical brain differences can potentially underlie certain behavioural sex differences, considering that women already demonstrated to have thicker lateral cortical regions, higher percentage of grey matter and proportionally larger language areas, such as superior temporal cortex and Broca's area (Gur et al., 1999; Harasty, Double, Halliday, Kril, & McRitchie, 1997; Sowell et al., 2007). Sex differences also exist in the context of functional lateralization, in which roughly three cortical activation patterns have been put forward: (1) more left-lateralized hemispheric activation in men with a more bilateral engagement in women (Baxter et al., 2003; Kansaku, Yamaura, & Kitazawa, 2000; Shaywitz et al., 1995), (2) more left-lateralized hemispheric activation in women and a bilateral pattern in men (Obleser, Eulitz, Lahiri, & Elbert, 2001) or (3) left-lateralized activation in both men and women (Allendorfer et al., 2012; Frost et al., 1999; Sommer, Aleman, Bouma, & Kahn, 2004).

More detailed information about specific brain activation patterns related to the above mentioned language processes can also be obtained, with a very high temporal resolution, through the use of event-related brain potentials (ERPs). Phoneme discrimination (PD) can be investigated with the Mismatch Negativity (MMN; Näätänen, Gaillard, & Mäntysalo, 1978), which represents pre-attentive and preconscious deviance detection and categorical perception (Näätänen, Paavilainen, Rinne, & Alho, 2007) and the attentive P300 potential (Sutton, Braren, Zubin, & John, 1965), representing working memory, context updating, attentional resources and stimulus classification and categorization (Linden, 2005; Polich, 2004). The N400 potential is sensitive to semantic (word comprehension) and lexical (WR) processes (Kutas & Hillyard, 1980), such as lexical access and semantic or contextual priming and integration (Giaquinto, Ranghi, & Butler, 2007; Kutas & Federmeier, 2000). ERPs like the N100 and P200 potential emerging in response to language stimuli, such as phonemes or spoken words, are associated with sensory-perceptual processes and intermediate stages of auditory feature analysis, detection and identification (Cooper, Todd, McGill, & Michie, 2006; Näätänen, Kujala, & Winkler, 2011).

Various ERPs components have verified influences of sex on (phonological) discrimination processes. Findings such as larger N100-P200 amplitudes in men without differences in latency (Gölgeli et al., 1999), shorter N100-P200 latencies in women without differences in amplitude (Swink & Stuart, 2012), larger P200 amplitudes in women without differences in P200 latency (Nagy, Potts, & Loveland, 2003) and a more left-lateralized N100 in women in response to vowels (Obleser et al., 2001) evidence some form of dissociation between men and women during primary acoustic-phonological analysis. Regarding MMN, absence of sex differences in amplitude or latency has been reported (Kasai et al., 2002; Nagy et al., 2003), whereas other studies revealed either a more bilateral distribution in women due to larger amplitudes in the right hemisphere or more lateralized activation patterns in men with larger magnitude of the MMN for the left hemisphere (Ikezawa et al., 2008; Matsubayashi et al., 2008). Sex-related differences in deviance detection even appear to be modality-specific, suggested by higher P300 amplitudes in women primarily in the visual domain (Jaušovec & Jaušovec, 2009). Apart from sex differences, ERPs also demonstrated a clear differentiation within phonemic contrasts during processes like phoneme perception and discrimination. For place of articulation (PoA), front stop-consonants or vowels, e.g. /d/ or /i/, elicit a shorter N100 latency and attenuated electrocortical responses compared to posteriorly articulated stop-consonants or vowels, like /g/ or /u/ (Obleser, Lahiri, & Eulitz, 2003, 2004). An opposite pattern can occur in the P50 time window showing stronger activation but longer latencies for anterior PoA features (Tavabi, Obleser, Dobel, & Pantev, 2007). Within the voicing continuum, voiced consonants with a shorter voice onset time, e.g. /d/, are generally processed faster and display a single peaked

N100 whereas voiceless consonants with a prolonged voice onset time, e.g. /t/, are processed slower and can display an N100 comprising two subcomponents (Sharma & Dorman, 1999). Moreover, N100 and P200 amplitudes in response to voiceless consonants are larger than to voiced consonants, which can be related to differences in spectrotemporal patterns or attentional state (Digeser, Wohlberedt, & Hoppe, 2009; Horev, Most, & Pratt, 2007). With respect to manner of articulation (MoA), N100 latency and amplitude appear to be marked by the length of the fricative when plosives (e.g. /p/) and fricatives (e.g. /f/) are compared (Kaukoranta, Hari, & Lounasmaa, 1987; Ostroff, Martin, & Boothroyd, 1998). However, more profound research on this contrast is missing, such as the effect of nasality (degree of resonance in the nasal cavity). Studies measuring MMN and P300 potentials related to a certain phonemic contrast mostly compared speech with non-speech stimuli, consonant with vowel contrasts, two stimuli of the same phonemic feature continuum (e.g. 9 items going from [bɑ] to [dɑ] in a PoA continuum) or examined language-specific processing of phonemic contrasts (Dalebout & Stack, 1999; Diesch & Luce, 1997; Hessler, Jonkers, Stowe, & Bastiaanse, 2013; Maiste, Wiens, Hunt, Scherg, & Picton, 1995; Sharma & Dorman, 2000; Tampas, Harkrider, & Hedrick, 2005). When PD based on two different phonemic contrasts was eventually compared (e.g. P300 voicing and P300 PoA) no significant differences emerged (Korczak & Stapells, 2010). At present, a detailed comparison of discrimination processes involving the three phonemic contrasts with a differentiation between men and women and pre-attentive and attentive processing is lacking.

At the lexical, WR level, real words are discerned from non-existing pseudowords in the phonological input lexicon. This is characterized neurophysiologically by a larger and longer lasting ERP in response to pseudowords around 400 msec post-stimulus (N400) and has been named the “N400 pseudoword effect” (Attias & Pratt, 1992; Soares, Collet, & Duclaux, 1991). The N400 amplitude is generally linked to expectation, becoming smaller when information is more expected and thus easier to process (Kutas & Federmeier, 2011). With respect to the pseudoword effect, it is potentially related to an enhanced search for lexical representations and the amount of attentional load (Aerts, van Mierlo, Hartsuiker, Hallez, Santens, & De Letter, 2013; Friedrich, Eulitz, & Lahiri, 2006; Garagnani, Wennekers, & Pulvermüller, 2008; Giaquinto et al., 2007). The N400 has been investigated with respect to sex effects in both lexical and semantic contexts and has yielded rather diverging results. During lexical decision tasks, men have displayed a more left-hemispheric N400 amplitude distribution (Tressoldi & Cusumano, 1992; Wegesin, 1998), while other studies have found a larger or earlier and more persistent N400 (congruency) effect to semantic priming in women (Daltrozzo, Wioland, & Kotchoubey, 2007; Wang, Bastiaansen, Yang, & Hagoort, 2011; Wirth et al., 2007). However, Soares et al. (1991) did not establish a difference between men and women for the N400 pseudoword effect.

Clearly, differences between men and women should not be disregarded, and considering the aforementioned inconsistencies, further exploration in the context of neurophysiological activation patterns of phonological input processes is necessary. The present study aimed to provide more clarity about the effect of sex on the neurophysiological activation patterns of auditory PD and WR, based on the MMN, P300 and N400. We questioned whether men and/or women demonstrate a specific difference between three phonemic contrasts (PoA, voicing and MoA) and attentional load during PD and responses to real words and pseudowords during WR. Based on these results it could be determined whether sex should be considered as an influential factor for normative ERP data, as was the case for age (Aerts et al., 2013). If so, previously developed normative data (Aerts et al., 2013) might have to be refined to account for differences between men and women.

2. Materials and methods

2.1 Subjects

Forty-four healthy subjects (20 men, 24 women) were randomly selected from the original sample of 71 subjects of our previous study (Aerts et al., 2013), to obtain a more equal distribution of men and women and, considering the previously established aging influences, an equivalent age distribution in men (mean: 45.60 +/- 13.67) and women (mean: 44.46 +/- 13.76) (independent t-test; $t(42) = 0.275$, $p = 0.785$). All participants investigated were right-handed, as verified with the Dutch Handedness Inventory (Van Strien, 1992), and had Dutch as native language. All the participants reported to have normal hearing and none of them had neurological, psychiatric or speech- and language developmental disorders. At time of testing, none of the participants was on medication. The study was approved by the Ethics Committee of the Ghent University Hospital and an informed consent was obtained from all the subjects.

2.2 Paradigms and stimuli

2.2.1 Auditory phoneme discrimination

The first experiment (a PD task) consisted of three different auditory oddball paradigms both in a passive (MMN) and active (P300) experiment. During the passive oddball task, the subjects were instructed to ignore the stimuli and to focus their attention on a silent movie. During the active oddball task, the subjects pushed a button every time they heard the infrequent stimulus. Within the passive and active paradigm, each block consisted of 250 stimuli and 150 stimuli, respectively. The standard phoneme was /b/ and the deviant phonemes were /g/ (covering PoA), /p/ (covering voicing) and /m/ (covering MoA). The stimuli were created in such a way that the standard and deviant stimulus only differed in one phonemic contrast. Stimuli were generated using the website NeXTeNS (http://nextens.uvt.nl/demo.html) where text could be converted to speech (for more

information on the nature of this text-to-speech system see Marsi et al., 2002). In all stimulus blocks, the standard and deviant phoneme appeared with a probability of 0.80 and 0.20, respectively. The stimuli were given in a random order in which two deviants could not follow each other without having one standard in between. All the spoken phonemes had a duration of 150 msec. The interstimulus interval (ISI) was set at 500 msec in the passive paradigm and 2000 msec in the active paradigm. The stimuli were presented binaurally at 70 dB sound pressure level (SPL) using Apple Inc. earphones placed directly in the external ear.

2.2.2 Auditory word recognition

The second experiment consisted of a WR passive oddball task where pseudowords were implemented as deviant stimuli and real words as standard stimuli. The subjects were instructed to ignore the stimuli and to focus their attention on a silent movie. The standard stimuli and deviant stimuli appeared with a probability of 0.80 and 0.20, respectively. A total of 125 stimuli were presented, including 100 real words (all nouns) and 25 pseudowords. Pseudowords were derived from the real words by replacing one vowel and one consonant in 25 real words randomly selected from the list of 100 existing words. Stimuli were spoken by a 24 year old female Dutch native speaker with a flat intonation and digitally recorded with a sampling frequency of 44.1 kHz. The stimuli were given in a random order in which two pseudowords could not follow each other without having one real word in between. The real words were controlled for lexical frequency (mean 3.15 log10freq) (Keuleers, Brysbaert, & New, 2010), age of acquisition (mean 6.0 years) (Ghyselinck, Custers, & Brysbaert, 2003) and length (5 phonemes; 1 or 2 syllables). The stimuli were presented with an ISI of 1000 msec and presented binaurally at 70 dB sound pressure level (SPL) using Apple Inc. earphones placed directly in the external ear.

2.3 Electroencephalogram (EEG) – recording and analysis

The EEG (0.5 – 100 Hz band-pass, notch filter disabled) was recorded through 23 Ag/AgCl-electrodes using a linked earlobes reference and an electrode placed on the forehead as ground. Electrodes were placed on the scalp according to the international 10-20 system. The impedance of the electrodes was kept below 5 kΩ. Data was collected using a SynAmp (Neuroscan) amplifier and was continuously digitized at a 500 Hz sampling rate.

EEG analysis was performed using BrainVision Analyzer 2 (Brain Products, Munich, Germany). The EEG signal was filtered with a 0.5 – 30 Hz band-pass filter. Using independent component analysis (ICA), artefacts caused by eye movements were removed by excluding two components (eye blinks and left-right movements) based on inspection of the components' spatial distribution. For the three active oddball paradigms the EEG was segmented into 1100 msec long epochs from 100 msec pre-stimulus to 1000 msec post-stimulus. For the three passive oddball paradigms the EEG was

segmented into 500 msec long epochs from 100 msec pre-stimulus to 400 msec post-stimulus. Finally, for the WR passive oddball paradigm the EEG was segmented into 1000 msec long epochs from 100 msec pre-stimulus to 900 msec post-stimulus. The epochs were baseline corrected using a pre-stimulus window of 100 msec. All epochs containing data exceeding $\pm$ 100 µV were rejected for further analysis. The standard and deviant trials were averaged separately. Finally, to compute the MMN in the PD task the average ERP of the standard trials was subtracted from the average ERP of the deviant trials. Peak detection was carried out semi-automatically. Peak latencies and peak amplitudes were measured in time windows determined by the grand averages (GA) and were different for every ERP. For PD, the MMN was measured between 120 – 250 msec for PoA and MoA, between 80 – 275 msec for voicing and all P300s were analysed between 300 – 600 msec. For WR, the N100 was measured between 60 – 140 msec, the P200 between 140 – 250 msec and the N400 between 400 and 600 msec.

Based on GA waveforms, six clusters with the average activity/latency of two electrodes were created: Anterior Left (AL: F3, F7), Anterior Right (AR: F4, F8), Central Left (CL: T3, C3), Central Right (CR: T4, C4), Posterior Left, (PL: T5, P3), Posterior Right (PR: T6, P4). To elaborate on possible laterality effects, additional laterality indices (LI) were calculated as the difference between the mean amplitude of the right and left anterior, central and posterior clusters (R−L) (Spironelli, Angrilli, & Pertile, 2008). This means that for the negative potentials a positive value indicated left lateralization and a negative value indicated right lateralization. For the positive potentials a positive value indicated right lateralization and a negative value indicated left lateralization.

A repeated measures ANOVA was carried out for amplitudes, latencies, and LI of every ERP. Sex (men vs. women) served as between-subject factor. For the PD task the following within-subject factors co-entered the model: contrasts (PoA vs. voicing vs. MoA) x region (anterior vs. central vs. posterior) x laterality (left vs. right; only for amplitudes and latencies as outcome measures). For the WR passive oddball task the same factors were used, though the factor wordness (real words vs. pseudowords) replaced the factor contrasts. The within-subject factors (contrasts, wordness, region and laterality) were only of interest if they interacted with the between-subject factor sex, so interactions not containing the factor sex were excluded from the model. Greenhouse-Geisser correction (GG) was applied when the assumption of sphericity was violated. Significance level was set at ≤ 0.05. Post-hoc pairwise comparisons were computed using Bonferroni correction. All the statistical analyses were performed using IBM SPSS Statistics 21.

3. Results

Mean amplitudes and latencies (and standard deviations) for auditory PD (i.e., P300 and MMN) and for auditory WR (i.e., N100, P200 and N400) are presented in Table 6.1 and Table 6.2, respectively, as a function of sex (i.e., men and women).

Table 6.1: Mean amplitudes and latencies (and standard deviations) of all auditory PD ERP measures as a function of sex (i.e. men and women) and phonemic contrasts (i.e. PoA vs. voicing vs. MoA) for PZ and CZ electrodes.

			P300		MMN	
			PZ		CZ	
Outcome measure	**Sex**	**PC**	**M**	**SD +/-**	**M (-)**	**SD +/-**
AMPLITUDE (μV)	Men	PoA	11.60	4.29	2.89	1.47
		Voicing	12.02	4.12	3.28	1.44
		MoA	10.81	4.81	2.52	1.52
	Women	PoA	15.45	3.99	4.25	2.02
		Voicing	13.76	5.13	3.02	1.37
		MoA	13.77	3.87	3.07	1.99
LATENCY (msec)	Men	PoA	423	49.37	180	31.43
		Voicing	407	38.98	150	40.27
		MoA	380	26.52	179	27.53
	Women	PoA	394	37.49	175	36.80
		Voicing	394	38.79	177	51.56
		MoA	380	46.78	169	27.28

Legend: PC = phonemic contrast; PoA = place of articulation; MoA = manner of articulation; M = mean; SD = standard deviation; (-) = negative amplitudes

Table 6.2: Mean amplitudes and latencies (and standard deviations) of all auditory WR ERP measures as a function of sex (i.e. men and women) and word type (i.e. RW vs. PW) for CZ electrode.

			N100		P200		N400	
Outcome measure	**Sex**	**Word type**	**M (-)**	**SD +/-**	**M**	**SD +/-**	**M (-)**	**SD +/-**
AMPLITUDE (μV)	Men	RW	1.67	1.10	1.76	1.30	2.65	0.85
		PW	2.41	1.53	2.20	1.80	3.74	2.28
	Women	RW	1.88	1.19	1.93	1.10	3.09	1.62
		PW	3.20	2.52	3.42	2.13	4.38	2.56
LATENCY (msec)	Men	RW	88	15.03	188	24.10	526	62.45
		PW	92	16.65	187	24.35	512	50.58
	Women	RW	95	14.54	191	23.16	475	52.37
		PW	90	19.37	166	23.30	508	50.82

Legend: RW = real words; PW = pseudowords; M = mean; SD = standard deviation; (-) = negative amplitudes

3.1 Auditory phoneme discrimination

Pre-attentive PD

Amplitudes. A significant main effect arose for sex [F(1, 42) = 4.12, p = 0.049], revealing larger amplitudes for women. However, a significant contrasts by sex interaction [F(2, 84) = 3.51, p = 0.034] indicated that the MMN amplitude was significantly larger in women than in men, but only for the phonemic contrast PoA (p < 0.01; Figure 6.1).

Latencies. A significant four-way region by laterality by contrasts by sex interaction was found [F(4, 168) = 3.12, p = 0.034, GG ε = 0.67]. During MoA PD, women exhibited shorter latencies right-anterior compared to men (p < 0.05). Furthermore, within men, shorter latencies were found left-central and right-anterior during voicing PD compared to PoA and MoA PD (p < 0.05).

LI (R-L amplitude). No significant main or interaction effects were detected, although a trend towards a main effect of sex was observed [F(1, 42) = 3.50, p = 0.068]. Men showed more positive values than women, indicating a trend towards more left lateralized activation in men.

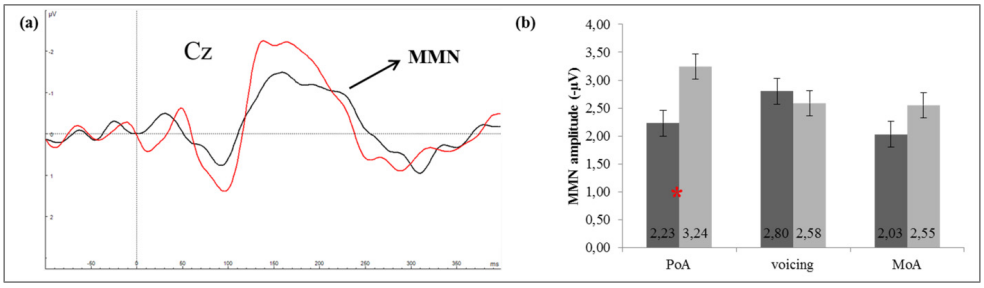

Figure 6.1: (a) Difference between men and women displayed in Cz electrode when PoA was the discriminating phonemic contrast during pre-attentive phoneme discrimination; men = black, women = red. (b) The interaction between Contrasts and Sex presented graphically; men = dark grey, women = light grey, * = significant difference.

Attentive PD

Behavioural results. Men showed a mean response time of 558.88 msec (+/- 78.31) for PoA, 540.41 msec (+/- 89.27) for voicing and 506.96 msec (+/- 86.34) for MoA. Women showed a mean response time of 570.90 msec (+/- 86.01) for PoA, 578.72 msec (+/- 98.13) for voicing and 557.35 msec (+/- 84.63) for MoA. A main effect emerged, showing a significant difference between phonemic contrasts [F(2, 82) = 5.38, p = 0.006] for both men and women. This revealed faster response times for the phonemic contrast MoA (532.15 msec), yet only significantly faster compared to PoA (564.89 msec, p < 0.001, Bonferroni corrected) and not voicing (559.56 msec, p = 0.081, Bonferroni corrected).

Amplitudes. A significant main effect emerged for the factor sex [$F(1, 41) = 5.36$, $p = 0.026$], showing larger amplitudes for women. However, a significant contrasts by sex interaction [$F(2, 82) = 3.39$, $p = 0.038$] indicated larger amplitudes in women only during PoA PD compared to men ($p < 0.01$; Figure 6.2). Within women separately, the PoA contrast elicited larger amplitudes than the voicing and MoA contrasts ($p < 0.05$; Figure 6.3).

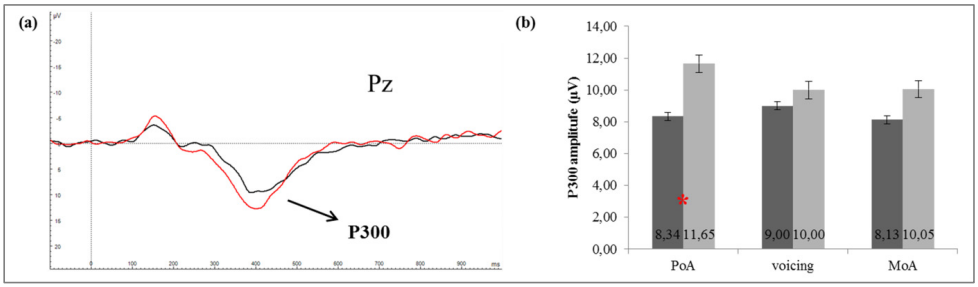

Figure 6.2: (a) Difference between men and women displayed in Pz electrode when PoA was the discriminating phonemic contrast during attentive phoneme discrimination; men = black, women = red. (b) The interaction between Contrasts and Sex presented graphically; men = dark grey, women = light grey, * = significant difference.

Latencies. A significant main effect was found for contrasts [$F(2, 82) = 14.58$, $p < 0.001$], showing significantly shorter latencies in the MoA condition compared to latencies in the PoA and voicing condition ($p < 0.05$). No interactions with sex were observed.

LI (R-L amplitude). A significant region by contrasts by sex interaction [$F(4, 168) = 2.91$, $p = 0.032$, GG $\varepsilon = 0.82$]. This interaction revealed for the PoA and MoA condition more left lateralization in posterior regions in women (resp. $p < 0.001$ and $p < 0.05$) and for the voicing condition more left lateralization in posterior regions in men ($p < 0.01$) and women ($p < 0.05$).

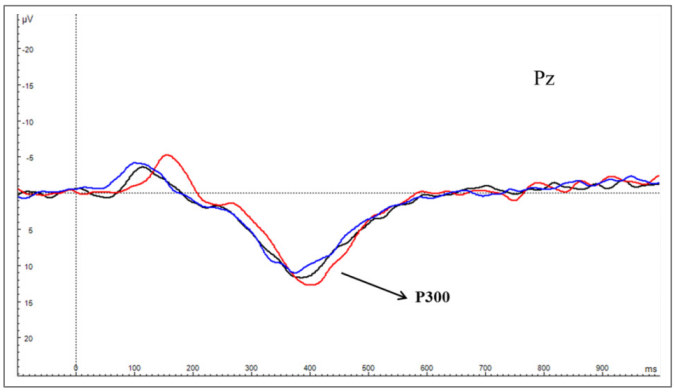

Figure 6.3: Difference between phonemic contrasts in women during attentive phoneme discrimination displayed in Pz electrode; PoA = red, MoA = blue, voicing = black.

3.2 Auditory word recognition

N100 time window

Amplitudes. A significant main effect was found with respect to wordness [F(1, 41) = 13.74, *p* = 0.001]. This means that the N100 in response to pseudowords was significantly greater than the N100 in response to real words, for both men and women (Figure 6.4). No significant interactions with sex were established.

Latencies. No significant main or interaction effects were detected.

LI (R-L amplitude). No significant main or interaction effects were detected.

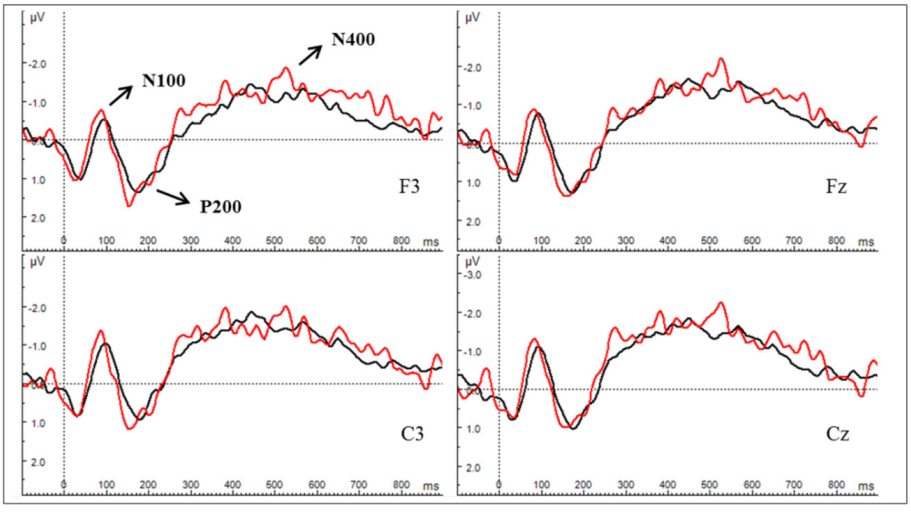

Figure 6.4: N400 pseudoword-effect visible in N100, P200 and N400; pseudowords = red, real words = black.

P200 time window

Amplitudes. A significant main effect was found for wordness [$F(1, 41) = 19.39$, $p < 0.002$], meaning that responses to pseudowords were significantly larger than responses to real words, for both men and women (Figure 6.4). No interactions with sex were identified.

Latencies. A significant wordness by sex interaction [$F(1, 41) = 5.66$, $p = 0.022$] emerged. This indicated that in women, but not in men, shorter latencies were found for pseudowords than for real words ($p < 0.01$, Figure 6.5).

LI (R-L amplitude). No significant main or interaction effects were detected.

N400 time window

Amplitudes. A significant main effect was found for wordness [$F(1, 41) = 24.03$, $p < 0.001$]. This implies that N400 amplitude in response to pseudowords was significantly greater than N400 amplitude in response to real words, for both men and women (Figure 6.4). No interactions with sex were detected.

Latencies. There was a significant wordness by sex interaction [$F(1, 41) = 5.18$, $p = 0.028$], showing that in this time window higher latencies were found for pseudowords than for real words in women, but not in men, ($p < 0.01$; Figure 6.5) and during processing of real words women showed significantly shorter latencies than men ($p < 0.01$). There was also a significant region by sex interaction [$F(2, 82) = 4.34$, $p = 0.016$, GG $\varepsilon = 0.94$], demonstrating shorter latencies in posterior regions compared to anterior or central regions in men, but not women ($p < 0.01$).

LI (R-L amplitude). No significant main or interaction effects were detected.

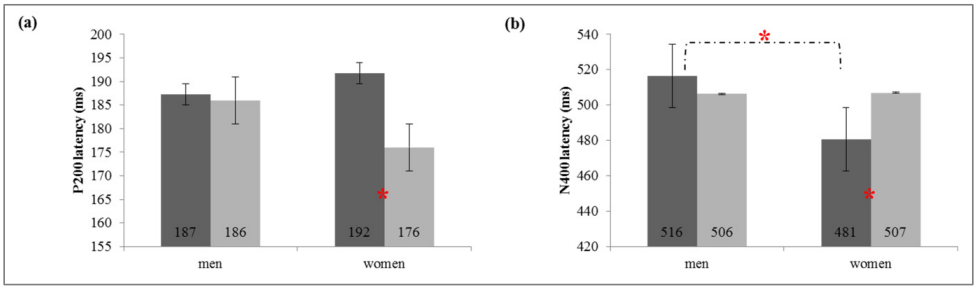

Figure 6.5: Difference in processing speed of real words and pseudowords between men and women in the P200 (a) and N400 (b) time window; real words = dark grey, pseudowords = light grey, * = significant difference.

4. Discussion

The present study clearly demonstrated significant neurophysiological sex differences during auditory PD and WR, influenced by phonemic contrasts and word type:

1) Women displayed a larger sensitivity to the phonemic contrasts during auditory PD, whereas men did not show that sensitivity.
2) Degree of attention played an important role in this sex-related sensitivity to the phonemic contrasts.
3) During WR the pseudoword effect was already established 100 msec after stimulus presentation, in both men and women.
4) However, differences between men and women became apparent in the time course of real word-pseudoword dissociation, showing more differentiation in women.

4.1 Auditory phoneme discrimination

During active, attentive PD, significant differences between the phonemic contrasts were observed in women, displaying larger P300 amplitudes with the PoA contrast compared to the voicing and MoA contrast. This sex difference was corroborated by higher P300 and MMN amplitudes in women compared to men during active and passive PD based on PoA. This means that men and women complete auditory phonological analysis processes (Ellis & Young, 1996) in a distinct and individual manner, dependent on the phonemic contrasts. The larger amplitudes in women in the PoA condition can be associated with the recruitment of a higher number of active neurons (Duncan et al., 2009), or an increased synchronicity of neuronal oscillations, during PD. Previous literature findings suggesting structural brain differences between men and women might support this finding of the engagement of a larger neuronal network in women. Women would have a proportionally larger superior temporal cortex and Broca's area (Harasty et al., 1997) and show a higher percentage of grey matter volume and increased cortical thickness in posterior temporal regions (Gur et al., 1999; Sowell et al., 2007). Frontal and temporal regions are in turn important neuronal generators of the language-related MMN and P300 (Näätänen et al., 2007; Volpe et al., 2007). This can be of great relevance as these regions are linked to phonological, sublexical processes (Hickok & Poeppel, 2004). However, this study was not constructed to determine precise cortical generators of this specific PD task, so we must remain cautious at this point. The fact that a larger MMN and P300 amplitude in women only occurs during PoA PD, and not when voicing or MoA are the phonemic contrasts, can potentially be explained by the amount of deviance between the standard and deviant phoneme in which differences in spectral and phonetic properties most likely play an important role. It has indeed been established before that a broader frequency spectrum within vowel contrasts can elicit greater ERP responses than the more narrow frequency range in consonant contrasts (Diesch & Luce

1997; Korczak & Stapells, 2010). A broader frequency spectrum may lead to a more salient contrast (Tampas et al., 2005), engage more active cortical neurons during the discrimination process and lead to a greater ERP response. This can be additionally confirmed by the larger P300 amplitudes in women when PoA is compared with voicing and MoA, as the frequency separation between /b/ and /g/ is larger than the spectrum between the phonemic contrasts /b/-/p/ or /b/-/m/. The large spectrotemporal difference within the /b/-/g/ contrast can be related to the position of the articulators, as the frontal PoA of /b/ and the back PoA of /g/ gives rise to a low or a high second formant, respectively (Rietveld & van Heuven, 2009). The fact that this PoA-advantage compared to the other phonemic contrasts only occurred during active PD and not during passive PD suggests that women need more attentional resources to detect spectrotemporal differences between phonemic contrasts (Johnson, 1986). Since men did not demonstrate such sensitivity to the different phonemic contrasts and presented smaller amplitudes than women during discrimination based on PoA phonemic contrast, it is likely that men do not engage their neuronal networks in the same (sensitive) way as women do. Another possibility is that men have less extensive and/or less specific neuronal networks accessible during auditory phonological analysis, which are not activated in function of subtle spectrotemporal acoustic differences such as female networks (Brumback, Arbel, Donchin, & Goldman, 2012), even when more attentional resources are accessible.

Regarding laterality patterns, at first sight no clear sex-related differences were observed and both men and women showed a more or less equal distribution of electrocortical activity at left and right scalp regions during PD. However, the laterality indices did reveal laterality differences at the scalp between men and women, most firmly established in the active oddball task. Specifically, with voicing as phonemic contrast, laterality effects occurred at left posterior scalp regions in both men and women, whereas with PoA and MoA, only women showed laterality effects at left posterior scalp regions. Previous findings from structural brain research can corroborate region-specific laterality patterns, showing either left lateralization in more anterior language areas (inferior frontal gyrus) in men during higher-order phonological tasks (Shaywitz et al., 1995) or left lateralization in posterior regions during higher-level semantic comprehension tasks (Kansaku et al., 2000). The current PD task confirms left-lateralization during phonological input processing, in both men and women, but with a clear dependence on spectrotemporal differences between the phonemic contrasts. Again, this demonstrates that men and women cope with PD in a neurologically distinct way, based on different phonemic contrasts. Left-lateralization at posterior scalp regions can be explained from the most commonly described scalp distribution of the P300 potential and the engagement of more attentional resources, which generally addresses a posterior neuronal network (Linden, 2005; Peers et al., 2005). A trend towards sex differences in lateralization at the scalp was also shown in the

passive oddball task, demonstrating higher left-lateralized amplitudes in men and a more bilateral voltage distribution in women due to higher amplitudes at right scalp-electrodes. Nonetheless, this has to be interpreted with extreme caution as the main effect did not reach the 5 % significance level.

To our knowledge, this is the first time that electrocortical correlates of auditory PD were investigated with respect to sex differences. Consequently, the present study has revealed influences of sex on proper neurophysiological correlates of PD with a clear discrepancy between different phonemic contrasts and a dissociation between attentive and pre-attentive processing.

4.2 Auditory word recognition

Both men and women elicited larger neurophysiological responses to pseudowords in the N400 time window, demonstrating a pseudoword effect in accordance with earlier literature findings (Friedrich et al., 2006; Sinai & Pratt, 2002; Soares et al., 1991) and our previous aging study (Aerts et al., 2013). However, the pseudoword effect was already established earlier within the N100 time window, continued within the P200 potential and eventually ended within the longer-lasting N400 time window. This means that both men and women displayed an enhanced search through the mental lexicon already 100 msec after stimulus presentation, already detecting the difference between real words and pseudowords at this early stage. A similar early pseudoword effect has been established before around 110 msec when reading real words and pseudowords (Hauk, Davis, Ford, Pulvermüller, & Marslen-Wilson, 2006; Taroyan & Nicolson, 2009) and is consistent with the time window represented by the current N100. Probably, around this time period greater phonological processing is needed in response to pseudowords, which continues in the P200 time period, and may be related to an enhanced alertness for these pseudowords, comparable with a higher P200 sensitivity to low-frequency words (Chétail, Colin, & Content, 2012; Hauk & Pulvermüller, 2004; Laszlo, Stites, & Federmeier, 2012; Martin-Loeches, Hinojosa, Gómez-Jarabo, & Rubia, 1999). Ultimately, around 400 msec an increased search for lexical entries ensues with a greater sensitivity to and competition with other possible word forms in case of pseudowords and might be related to some form of reanalysis/integration of different kinds of information (Desroches, Newman, & Joanisse, 2008; Hauk et al., 2006; Laszlo et al., 2012; Pylkkänen, Stringfellow, & Marantz, 2002).

Because of established sex effects on the N400 in more semantic-related settings (Daltrozzo et al., 2007; Wang et al., 2011; Wirth et al., 2007) and taken together with the above presented sex differences during PD, one would expect some form of differentiation between men and women during WR as well. However, this was not the case and both men and women displayed the early-starting enhanced processing of pseudowords. The “amplitude advantage” women once had in earlier phonological processing stages apparently does not continue in the following prelexical

stages, but re-appears in subsequent semantic stages (Daltrozzo et al., 2007; Wang et al., 2011; Wirth et al., 2007). It seems that women only demonstrate enhanced, differential processing in the most basic (phonemic) and advanced (semantic) levels in language processing, while both sexes show an equal sensitivity to unfamiliar pseudowords during WR. However, a sex differentiation did become apparent when looking at the processing of real words and pseudowords in time. Approximately 200 msec after stimulus presentation women processed pseudowords (178 msec) faster than real words (193 msec), which is not entirely unprecedented (Sinai & Pratt, 2002), whereas about 400 msec after stimulus presentation women processed pseudowords (506 msec) slower than real words (479 msec). Men processed real words slower than women in the N400 time window, but they made no difference in processing pseudowords or real words in either time window (see Figure 6.5). Women seem to benefit more from the early detection of an unfamiliar pseudoword (N100 amplitude increase), hence the ensuing enhanced phonological processing of pseudowords (P200 amplitude increase) can proceed with a faster processing speed (though with increased alertness) (Proverbio & Adorni, 2008). However, during the actual lexical search in the mental lexicon later in time (N400 amplitude increase) pseudowords may impede fluent reanalysis and integration of different kinds of information and slows down (eventually unsuccessful) word recognition, whereas real words can be unequivocally matched with the correct word form. The slower real word processing in men than women suggests that men are more susceptible to other possible lexical candidates, which probably slows down reanalysis and integration throughout the N400 time window, even for familiar words.

5. Conclusion

The present study further contributed to the knowledge of sex-related differences in brain activation patterns during phonological input processing. Women displayed a larger sensitivity to spectrotemporal differences related to the phonemic contrasts during auditory PD processes. This was evidenced by larger responses to the PoA contrast compared to the other contrasts in the active oddball task and larger responses than men in the active and passive PoA oddball task. Men did not demonstrate such sensitivity. During WR the difference between men and women became apparent in the time course of processing activity during word-pseudoword dissociation, showing more efficiency in women. To conclude, sex should definitely be looked upon as an influencing factor when developing normative data, for both auditory PD and WR. Hence, it is recommended to refine the existing neurophysiological normative data for age (Aerts et al., 2013) by implementing the above described sex differences and create a justified distinction between men and women in the norm group.

6. References

Aerts, A., van Mierlo, P., Hartsuiker, R. J., Hallez, H., Santens, P., & De Letter, M. (2013). Neurophysiological investigation of phonological input: Aging effects and development of normative data. *Brain and Language, 125* (3), 253-263.

Allendorfer, J. B., Lindsell, C. J., Siegel, M., Banks, C. L., Vannest, J., Holland, S. K., & Szaflarski, J. P. (2012). Females and males are highly similar in language performance and cortical activation patterns during verb generation. *Cortex, 48* (9), 1218-1233.

Attias, J. & Pratt, H. (1992). Auditory event related potentials during lexical categorization in the oddball paradigm. *Brain and Language, 43* (2), 230-239.

Basso, A. (2003). *Aphasia and its therapy*, 1st ed. New York: Oxford University Press.

Baxter, L. C., Saykin, A. J., Flashman, L. A., Johnson, S. C., Guerin, S. J., Babcock, D. R., & Wishart, H. A. (2003). Sex differences in semantic language processing: A functional MRI study. *Brain and Language, 84*, 264-272.

Bormann, T. & Weiller, C. (2012). "Are there lexicons?" A study of lexical and semantic processing in word-meaning deafness suggests "yes". *Cortex, 48*, 294-307.

Brumback, T., Arbel, Y., Donchin, E., & Goldman, M. S. (2012). Efficiency of responding to unexpected information varies with sex, age, and pubertal development in early adolescence. *Psychophysiology, 49*, 1330-1339.

Charlton, B. D., Taylor, A. M., & Reby, D. (2013). Are men better than women at acoustic size judgements? *Biology Letters, 9*, 20130270.

Chétail, F., Colin, C., & Content, A. (2012). Electrophysiological markers of syllable frequency during written word recognition in French. *Neuropsychologia, 50*, 3429-3439.

Coltheart, M. (2004). Are there lexicons? *Quarterly Journal of Experimental Psychology, 57*, 1153-1171.

Cooper, R. J., Todd, J., McGill, K., & Michie, P. (2006). Auditory sensory memory and the aging brain: A mismatch negativity study. *Neurobiology of Aging, 27*, 752–762.

Dalebout, S. D. & Stack, J. W. (1999). Mismatch negativity to acoustic differences not differentiated behaviorally. *Journal of the American Academy of Audiology, 10* (7), 388-399.

Daltrozzo, J., Wioland, N., & Kotchoubey, B. (2007). Sex differences in two event-related potentials components related to semantic priming. *Archives of Sexual Behavior, 36*, 555-568.

Desroches, A. S., Newman, R. L., & Joanisse, M. F. (2008). Investigating the time course of spoken word recognition: Electrophysiological evidence for the influences of phonological similarity. *Journal of Cognitive Neuroscience, 21* (10), 1893-1906.

Diesch, E. & Luce, T. (1997). Magnetic mismatch fields elicited by vowels and consonants. *Experimental Brain Research, 116*, 139-152.

Digeser, F. M., Wohlberedt, T., & Hoppe, U. (2009). Contribution of spectrotemporal features on auditory event-related potentials elicited by consonant-vowel syllables. *Ear and Hearing, 30*, 704-712.

Duncan, C. C., Barry, R. J., Connolly, J. F., Fischer, C., Michie, P. T., Näätänen, R., … Van Petten, C. (2009). Event-related potentials in clinical research: Guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clinical Neurophysiology, 120*, 1883-1908.

Ellis, A. W. & Young, A. W. (1996). *Human Cognitive Neuropsychology: A textbook with readings*, 2nd ed. Hove: Psychology Press.

Friedrich, C. K., Eulitz, C., & Lahiri, A. (2006). Not every pseudoword disrupts word recognition: An ERP study. *Behavioral and Brain Functions, 2* (36).

Frost, J. A., Binder, J. R., Springer, J. A., Hammeke, T. A., Bellgowan, P. S. F., Rao, S. M., & Cox, R. W. (1999). Language processing is strongly left lateralized in both sexes. Evidence from functional MRI. *Brain, 122*, 199-208.

Garagnani, M., Wennekers, T., & Pulvermüller, F. (2008). A neuroanatomically grounded Hebbian-learning model of attention–language interactions in the human brain. *European Journal of Neuroscience, 27*, 492-513.

Ghyselinck, M., Custers, R., & Brysbaert, M. (2003). Age-of-acquisition ratings for 2332 Dutch words from 49 different semantic categories. *Psychologica Belgica, 43* (3), 181-214.

Giaquinto, S., Ranghi, F., & Butler, S. (2007). Stability of word comprehension with age: An electrophysiological study. *Mechanisms of Aging and Development, 128*, 628-636.

Gölgeli, A., Süer, C., Özesmi, Ç., Dolu, N., Ascioğlu, M., & Sahin, Ö. (1999). The effect of sex differences on event-related potentials in young adults. *International Journal of Neuroscience, 99*, 69-77.

Gur, R. C., Turetsky, B. I., Matsui, M., Yan, M., Bilker, W., Hughett, P., & Gur, R. E. (1999). Sex differences in brain gray and white matter in healthy young adults: Correlations with cognitive performance. *The Journal of Neuroscience, 19* (10), 4065-4072.

Harasty, J., Double, K. L., Halliday, G. M., Kril, J. J., & McRitchie, D. A. (1997). Language-associated cortical regions are proportionally larger in the female brain. *Archives of Neurology, 54* (2), 171-176.

Hauk, O. & Pulvermüller, F. (2004). Effects of word length and frequency on the human event-related potential. *Clinical Neurophysiology, 115*, 1090-1103.

Hauk, O., Davis, M. H., Ford, M., Pulvermüller, F., & Marslen-Wilson, W. D. (2006). The time course of visual word recognition as revealed by linear regression analysis of ERP data. *NeuroImage, 30*, 1383-1400.

Hessler, D., Jonkers, R., Stowe, L., & Bastiaanse, R. (2013). The whole is more than the sum of its parts: Audiovisual processing of phonemes investigated with ERPs. *Brain and Language, 124*, 213-224.

Hickok, G. & Poeppel, D. (2004). Dorsal and ventral streams: A framework for understanding aspects of the functional anatomy of language. *Cognition, 92*, 67-99.

Horev, N., Most, T., & Pratt, H. (2007). Categorical perception of speech (VOT) and analogous non-speech (FOT) signals: Behavioral and electrophysiological correlates. *Ear and Hearing, 28*, 111-128.

Ikezawa, S., Nakagome, K., Mimura, M., Shinoda, J., Itoh, K., Homma, I., & Kamijima, K. (2008). Gender differences in lateralization of mismatch negativity in dichotic listening tasks. *International Journal of Psychophysiology, 68*, 41-50.

Jaušovec, N. & Jaušovec, K. (2009). Gender related differences in visual and auditory processing of verbal and figural tasks. *Brain Research, 1300*, 135-145.

Johnson, R. (1986). A triarchic model of P300 amplitude. *Psychophysiology, 23*, 367-384.

Kansaku, K., Yamaura, A., & Kitazawa, S. (2000). Sex differences in lateralization revealed in the posterior language areas. *Cerebral Cortex, 10* (9), 866-872.

Kasai, K., Nakagome, K., Iwanami, A., Fukuda, M., Itoh, K., Koshida, I., & Kato, N. (2002). No effect of gender on tonal and phonetic mismatch negativity in normal adults assessed by a high-resolution EEG recording. *Cognitive Brain Research, 13*, 305-312.

Kaukoranta, E., Hari, R., & Lounasmaa, O. V. (1987). Responses of the human auditory cortex to vowel onset after fricative consonants. *Experimental Brain Research, 69*, 19-23.

Keuleers, E., Brysbaert, M., & New, B. (2010). SUBTLEX-NL: A new frequency measure for Dutch words based on film subtitles. *Behavior Research Methods, 42* (3), 643-650.

Korczak, P. A. & Stapells, D. R. (2010). Effects of various articulatory features of speech on cortical event-related potentials and behavioral measures of speech-sound processing. *Ear and Hearing, 31*, 491-504.

Kutas, M. & Federmeier, K. D. (2000). Electrophysiology reveals semantic memory use in language comprehension. *Trends in Cognitive Sciences, 4* (12), 463-470.

Kutas, M. & Federmeier, K. D. (2011). Thirty years and counting: Finding meaning in the N400 component of the event-related brain potential (ERP). *Annual Review of Psychology, 62*, 621-47.

Kutas, M. & Hillyard, S. A. (1980). Reading senseless sentences: Brain potentials reflect semantic incongruity. *Science, 207*, 203-205.

Laszlo, S., Stites, M., & Federmeier, K. D. (2012). Won't get fooled again: An event-related potential study of task and repetition effects on the semantic processing of items without semantics. *Language and Cognitive Processes, 27* (2), 257-274.

Liederman, J., Gilbert, K., McGraw-Fisher, J., Mathews, G., Frye, R. E., & Joshi, P. (2010). Are women more influenced than men by top-down semantic information when listening to disrupted speech? *Language and Speech, 54*, 33-48.

Liederman, J., McGraw-Fisher, J., Coty, A., Matthews, G., Frye, R. E., Lincoln, A., & Alexander, R. (2013). Sex differences in the use of delayed semantic context when listening to disrupted speech. *Archives of Sexual Behavior*, 42, 197-201.

Linden, D. E. J. (2005). The P300: Where in the brain is it produced and what does it tell us? *The Neuroscientist, 11* (6), 563-576.

Maiste, A. C., Wiens, A. S., Hunt, M. J., Scherg, M., & Picton, T. W. (1995). Event-related potentials and the categorical perception of speech sounds. *Ear and Hearing, 16*, 68-90.

Majeres, R.L. (1999). Sex differences in phonological processes: Speeded matching and word reading. *Memory and Cognition, 27* (2), 246-253.

Marsi, E., Busser, B., Daelemans, W., Hoste, V., Reynaert, M., & van den Bosch, A. (2002). Combining information sources for memory-based pitch accent placement. *International Conference on Spoken Language Processing, Denver Co*, 1273-1276.

Martin-Loeches, M., Hinojosa, J. A., Gomez-Jarabo, G., & Rubia, F. J. (1999). The recognition potential: An ERP index of lexical access. *Brain and Language, 70*, 364-384.

Matsubayashi, J., Kawakubo, Y., Suga, M., Takei, Y., Kumano, S., Fukuda, M., … Kasai, K. (2008). The influence of gender and personality traits on individual difference in auditory mismatch: A magnetoencephalographic (MMNm) study. *Brain Research, 1236*, 159-165.

Näätänen, R., Gaillard, A. W., & Mäntysalo, S. (1978). Early selective-attention effect on evoked potential reinterpreted. *Acta Psychologica (Amsterdam), 42*, 313–329.

Näätänen, R., Paavilainen, P., Rinne, T., & Alho, K. (2007). The mismatch negativity (MMN) in basic research of central auditory processing: A review. *Clinical Neurophysiology, 118*, 2544-2590.

Näätänen, R., Kujala, T., & Winkler, I. (2011). Auditory processing that leads to conscious perception: A unique window to central auditory processing opened by the mismatch negativity and related responses. *Psychophysiology, 48*, 4–22.

Nagy, E., Potts, G. F., & Loveland, K. A. (2003). Sex-related ERP differences in deviance detection. *International Journal of Psychophysiology, 48*, 285-292.

Obleser, J., Eulitz, C., Lahiri, A., & Elbert, T. (2001). Gender differences in functional hemispheric asymmetry during processing of vowels as reflected by the human brain magnetic response. *Neuroscience Letters, 314*, 131-134.

Obleser, J., Lahiri, A., & Eulitz, C. (2003). Auditory-evoked magnetic field codes place of articulation in timing and topography around 100 milliseconds post syllable onset. *NeuroImage, 20*, 1839-1847.

Obleser, J., Lahiri, A., & Eulitz, C. (2004). Magnetic brain response mirrors extraction of phonological features from spoken vowels. *Journal of Cognitive Neuroscience, 16* (1), 31-39.

Ostroff, J. M., Martin, B. A., & Boothroyd, A. (1998). Cortical evoked response to acoustic change within a syllable. *Ear and Hearing, 19* (4), 290-297.

Peers, P. V., Ludwig, C. J., Rorden, C., Cusack, R., Bonfiglioli, C., Bundesen, C., … Duncan, J., (2005). Attentional functions of parietal and frontal cortex. *Cerebral Cortex, 15*, 1469-1484.

Polich, J. (2004). Clinical application of the P300 event-related brain potential. *Physical Medicine and Rehabilitation Clinics of North America, 15*, 133-161.

Proverbio, A. M. & Adorni, R. (2008). Orthographic familiarity, phonological legality and number of orthographic neighbours affect the onset of ERP lexical effects. *Behavioral and Brain Functions, 4* (27).

Pylkkänen, L., Stringfellow, A., & Marantz, A. (2002). Neuromagnetic evidence for the timing of lexical activation: An MEG component sensitive to phonotactic probability but not to neighborhood density. *Brain and Language, 81* (1-3), 666-678.

Rietveld, A. C. M. & van Heuven, V. J. (2009). *Algemene fonetiek* (3rd edition). Bussum, The Netherlands: Coutinho.

Sharma, A. & Dorman, M. F. (1999). Cortical auditory evoked potential correlates of categorical perception of voice-onset time. *Journal of the Acoustical Society of America, 106* (2), 1078-1083.

Sharma, A. & Dorman, M. F. (2000). Neurophysiologic correlates of cross-language phonetic perception. *Journal of the Acoustical Society of America, 107* (5), 2697-2703.

Shaywitz, B. A., Shaywitz, S. E., Pugh, K. R., Constable, R. T., Skudlarski, P., Fulbright, R. K., … Gore, J. C. (1995). Sex differences in the functional organization of the brain for language. *Nature, 373* (6515), 607-609.

Sinai, A. & Pratt, H. (2002). Electrophysiological evidence for priming in response to words and pseudowords in first and second language. *Brain and Language, 80*, 240-252.

Soares, I., Collet, L., & Duclaux, R. (1991). Electrophysiological correlates of auditory lexical decision: an attempt to test the "Cohort Model". *International Journal of Neuroscience, 57* (1-2), 111-122.

Sommer, I. E. C., Aleman, A., Bouma, A., & Kahn, R. S. (2004). Do women really have more bilateral language representation than men? A meta-analysis of functional imaging studies. *Brain, 127*, 1845-1852.

Sowell, E. R., Peterson, B. S., Kan, E., Woods, R. P., Yoshii, J., Bansal, R., … Toga, A. W. (2007). Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. *Cerebral Cortex, 17*, 1550-1560.

Spironelli, C., Angrilli, A., & Pertile, M. (2008). Language plasticity in aphasics after recovery: Evidence from slow evoked potentials. *NeuroImage, 40*, 912-922.

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. *Science, 150* (3700), 1187-1188.

Swink, S. & Stuart, A. (2012). The effect of gender on the N1–P2 auditory complex while listening and speaking with altered auditory feedback. *Brain and Language, 122*, 25-33.

Tampas, J. W., Harkrider, A. W., & Hedrick, M. S. (2005). Neurophysiological indices of speech and nonspeech stimulus processing. *Journal of Speech, Language and Hearing Research, 48*, 1147-1164.

Taroyan, N. A. & Nicolson, R. I. (2009). Reading words and pseudowords in dyslexia: ERP and behavioural tests in English-speaking adolescents. *International Journal of Psychophysiology, 74*, 199-208.

Tavabi, K., Obleser, J., Dobel, C., & Pantev, C. (2007). Auditory evoked fields differentially encode speech features: An MEG investigation of the P50m and N100m time courses during syllable processing. *European Journal of Neuroscience, 25*, 3155-3162.

Tressoldi, P. E. & Cusumano, S. (1992). Visual evoked potentials related to behavioral asymmetries during foveal attention in the two extrapersonal hemispaces. *Brain and Cognition, 18*, 125-137.

Van Strien, J. W. (1992). Classificatie van links- en rechtshandige proefpersonen. *Nederlands Tijdschrift voor de Psychologie en Haar Grensgebieden, 47*, 88-92.

Volpe, U., Mucci, A., Bucci, P., Merlotti, E., Galderisi, S., & Maj, M. (2007). The cortical generators of P3a and P3b: A LORETA study. *Brain Research Bulletin, 73*, 220-230.

Wang, L., Bastiaansen, M., Yanga, Y., & Hagoort, P. (2011). The influence of information structure on the depth of semantic processing: How focus and pitch accent determine the size of the N400 effect. *Neuropsychologia, 49*, 813-820.

Wegesin, D. J. (1998). Event-related potentials in homosexual and heterosexual men and women: Sex-dimorphic patterns in verbal asymmetries and mental rotation. *Brain and Cognition, 36*, 73-92.

Weiss, E. M., Kemmler, G., Deisenhammer, E. A., Fleischhacker, W. W., & Delazer, M. (2003). Sex differences in cognitive functions. *Personality and Individual Differences, 35*, 863-875.

Wirth, M., Horn, H., Koenig, T., Stein, M., Federspiel, A., Meier, B., … Strik, W. (2007). Sex differences in semantic processing: Event-related brain potentials distinguish between lower and higher order semantic analysis during word reading. *Cerebral Cortex, 17*, 1987-1997.

CHAPTER 7

Neurophysiological sensitivity for impaired phonological processing in the acute stage of aphasia

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Santens, P. & De Letter, M. (under review). **Neurophysiological sensitivity for impaired phonological processing in the acute stage of aphasia**. Brain and Language.

Abstract

The present study aims to investigate neurophysiological substrates of phoneme and word discrimination in 10 patients with acute aphasia. More specifically, phoneme discrimination is studied in a pre-attentive (MMN) and attentive (P300) task with respect to different phonemic contrasts, while the word discrimination task consists of differentiating real words from pseudowords. Concerning phoneme discrimination, patients with aphasia in the acute stage have smaller MMN and P300 amplitudes than the norm group for voicing, whereas for place and manner they only demonstrate smaller P300 amplitudes. Patients with aphasia show a distinct pattern of impaired phonemic contrast sensitivity, with place being the most resistant and voicing the most vulnerable. Concerning word discrimination, pseudowords elicit larger responses than real words in patients with aphasia with a delay compared to the norm group. For clinical practice, pre-attentive MMN tasks seem to be more suitable than attentive P300 tasks in the acute stage of aphasia.

Keywords

MMN; P300; N400; phonology; aphasia; neurophysiology; phoneme and word discrimination

1. Introduction

Deficits in phonological and lexical input processes can cause a destabilization in the consecutive language process, as they form part of the first processing steps in language comprehension (Pulvermüller, Shtyrov & Hauk, 2009). The ability to detect and discern different phonemes from each other and subsequently use the outcome of this process in successive stages like word recognition and comprehension is often disturbed in patients with aphasia (Blumstein, Baker & Goodglass, 1977; Mirman, Yee, Blumstein & Magnuson, 2011; Robson, Keidel, Lambon Ralph & Sage, 2012).

Event-related potentials (ERPs), especially the oddball-paradigm based studies, have a great potential in characterizing, evaluating and monitoring these specific phonological problems in patients with aphasia. The pre-attentive Mismatch Negativity (MMN) (Näätänen, Gaillard & Mäntysalo, 1978) and the attentive P300 potential (Sutton, Braren, Zubin & John, 1965) are very suitable to gauge auditory phoneme discrimination and these ERPs already demonstrated to be a good measure for monitoring recovery patterns in early stages of aphasia and long-term follow-up periods (Ilvonen et al., 2003; Nolfe, Cobianchi, Mossuto-Agatiello & Giaquinto, 2006). In general, the MMN is more reduced in patients with aphasia when discriminating speech sound stimuli (vowels, phonemes) than tone stimuli differing in frequency or duration, potentially because tone stimuli address different cortical generators than the speech stimuli (Aaltonen, Tuomainen, Laine & Niemi, 1993; Csépe, Osman-Sági, Molnár & Gósy, 2001; Ilvonen et al., 2004; Wertz et al., 1998). Within speech sound discrimination, consonant contrasts are more vulnerable than vowel contrasts (Csépe et al., 2001), perhaps due to the clear acoustic relation between the first three formant frequencies for different vowels. Especially discrimination of the phonemic contrast voicing is neurophysiologically reflected by a total absence of the MMN, whereas a difference in place of articulation elicits a MMN, yet heavily distorted and with an abnormal scalp distribution (Csépe et al., 2001). However, when the difference between two speech stimuli is large (by differentiating in more than one phonemic contrast, e.g. voicing and place of articulation), it is possible that the P300 potential does not show a reduced amplitude in patients with aphasia during active speech sound discrimination (Becker & Reinvang, 2007b).

The MMN and P300 have also been applied to evaluate auditory word processing in patients with aphasia. When the neurophysiological response to real words and pseudowords is compared in healthy controls, on the one hand a MMN is elicited with a larger negativity to real words during a passive discrimination task and on the other hand a P300-like ERP emerges with a larger positivity to real words during an active discrimination task, both referred to as a "real word advantage" (Pulvermüller et al., 2001; Shtyrov & Pulvermüller, 2002). The MMN is often attenuated in response

to both real words and pseudowords in patients with aphasia, but despite these attenuated responses a similar significant "real word advantage" as previously evidenced in healthy controls is still present (Pettigrew et al., 2005). This is not necessarily the case for the P300 potential, which can be reduced in response to real words in patients with aphasia during a visual word discrimination task, thereby presenting a smaller positivity to real words than to pseudowords (Pulvermüller, Mohr & Lutzenberger, 2004). The early word-evoked MMN can also be used to monitor neuronal recovery patterns in patients with aphasia, whether or not in the context of treatment effects, in the form of enhanced neurophysiological responses to real words throughout recovery and has even been referred to as an "aphasia recovery potential" (Pulvermüller, Hauk, Zohsel, Neininger & Mohr, 2005). This is of great relevance, also with respect to laterality patterns as it has been established that different laterality patterns can arise throughout the recovery from stroke (Saur et al., 2006). The MMN and P300 can be used to explore hemispherical distribution of brain activity, which allows determining potential contralesional contributions to auditory discrimination processes (Becker & Reinvang, 2007a, 2007b; Ilvonen et al., 2003).

Another promising and interesting ERP measure to assess word processing is the N400 potential. The N400 is mostly linked to language comprehension at sentence level, typically showing an enhanced amplitude in response to an incongruent ending of a sentence (e.g. I eat soup with a *candle*) (Kutas & Federmeier, 2011; Kutas & Hillyard, 1980). In this context, poor comprehending patients with aphasia have worse semantic integration abilities, reflecting a delay or absence of an N400 effect in response to incongruent stimuli in sentences, while good comprehending patients with aphasia show an N400, though prolonged in timing (Kawohl et al., 2010; Swaab, Brown & Hagoort, 1997). Such lexical-semantic integration deficits have been demonstrated at the word level as well, revealing a reduced N400 effect to associatively or semantically unrelated words in low comprehending patients (Hagoort, Brown & Swaab, 1996). The N400 is also a measure for single-word recognition, more at the level of lexical access processes (Friedrich, Eulitz & Lahiri, 2006; Giaquinto, Ranghi & Butler, 2007; Karayanidis, Andrews, Ward & McConaghy, 1993; Kutas & Federmeier, 2011; Laszlo & Federmeier, 2009; Van Petten & Rheinfelder, 1995), though in this context it has only been employed in healthy controls. In patients with aphasia the N400 has mostly been used to measure pure semantic processing. In a semantic categorization task, patients with aphasia demonstrate a more pronounced left lateralized negativity compared to healthy controls who show a more bilateral distribution (Dobel et al., 2001). The N400 can also be implemented to monitor effects of treatment in patients with aphasia, in analogy with the MMN and P300 for phoneme and word discrimination, and reveal a shift from a more right-lateralized N400 amplitude to a more left-lateralized scalp distribution after

intensive speech language therapy (Wilson et al., 2012). Both studies demonstrate the value of the N400 potential in monitoring language-related reorganization patterns.

Despite the great advanced knowledge these group studies have provided on the neurophysiological substrate of phonological disorders in patients with aphasia, they do not seem to control for the large heterogeneity existent in such a patient population. Nonetheless, this is a factor to be taken into account, as the structural brain alterations due to the stroke in patients with aphasia can differ significantly from patient to patient. The fact that a group study by Becker and Reinvang (2007a) failed to find significant MMN amplitude reductions to phonemes and tones in patients with aphasia, while this was found in other studies (Ilvonen et al., 2004; Pettigrew et al., 2005; Wertz et al., 1998), might be interpreted as a potential lack of controlling for the large variability among patients with aphasia. Taken together with a general individual variability in healthy functional brain activation patterns (Burton, Noll & Small, 2001) and recent findings of significant age-related influences on ERPs in healthy subjects (Aerts et al., 2013), this denotes the risk of neglecting the heterogeneity and variability within a group of patients with aphasia. In view of practically implementing event-related potentials in the linguistic evaluation of patients with aphasia and subsequently making justified decisions when interpreting these ERPs, controlling for heterogeneity and variability is an important issue that should not be disregarded. A second remarkable observation from the literature is that only a few studies have investigated patients with aphasia in the acute stage of stroke (e.g. within 2 weeks after stroke) (Ilvonen et al., 2003; Nolfe et al., 2006). Nonetheless, it is highly likely that extensive behavioural evaluation is problematic or even impossible at this stage of stroke due to severe comprehension problems (Ilvonen et al., 2003). When this is the case, especially the ERPs that can be elicited with a simple passive oddball task in which no explicit cooperation of the patient is required, such as the MMN, can provide a means for counteracting this practical problem.

The present study aims to elaborate on specific language-related neurophysiological activation patterns in patients with aphasia in the acute stage of stroke (within 2 weeks after stroke), while explicitly controlling for group heterogeneity and variability. First, auditory phoneme discrimination based on three different phonemic contrasts (place of articulation (PoA), manner of articulation (MoA) and voicing) is investigated with a pre-attentive (MMN) and attentive (P300) oddball task, to additionally explore the effects of attention and the possibility of using active oddball tasks in patients with aphasia at the acute stage of stroke. Second, auditory word recognition is investigated by including a Real Word/Pseudoword pre-attentive discrimination oddball task. Third, it is examined whether a correlation exists between neurophysiological and behavioural results in patients with aphasia at the acute stage of stroke.

2. Material and Methods

2.1 Subjects

Ten patients with aphasia (5 men, 5 women) were recruited from the Hospitalization department of Neurology at Ghent University Hospital (Belgium) and were compared to 44 healthy control participants (20 men, 24 women) (Aerts et al., submitted). All patients 1) suffering from a first-ever stroke in the left hemisphere, 2) having Dutch as native language and 3) displaying acute phonological disorders as established with the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) (Bastiaanse, Bosje & Visch-Brink, 1995) were included in the study. Patients with aphasia admitted with 1) a recurrent stroke, 2) left handedness, as confirmed with the Dutch Handedness Inventory (DHI) (Van Strien, 1992), 3) indications for comorbid cognitive disorders, which was screened with MMSE (Folstein, Folstein & McHugh, 1975) in patients above 70 years and 4) severe hearing deficits as reported by patients themselves or judged by the examiner were excluded from the study. The complete test battery (ERP and behavioural tests) was administered in the acute stage (within two weeks after stroke). The mean age of the patients was 69.4 years (± 3.46 SD), ranging between 46 and 85 years. Patient characteristics with regard to gender, age, education, type of aphasia, scores behavioural tests, site of lesion, etiology and time post injury are represented in Table 7.1. MRIs of the patients' lesions are displayed in Figure 7.1. The norm group showed an equivalent age distribution between men (mean: 45.60 years ± 13.67) and women (mean: 44.46 years ± 13.76). All participants investigated were right-handed, as verified with the Dutch Handedness Inventory (DHI; Van Strien, 1992), and had Dutch as native language. They reported to have normal hearing and none of them had neurological, psychiatric or speech- and language developmental disorders. At time of testing, none of the participants was on medication. The study was approved by the Ethics Committee of the University Hospital Ghent and an informed consent was obtained from all the participants (patients and norm group).

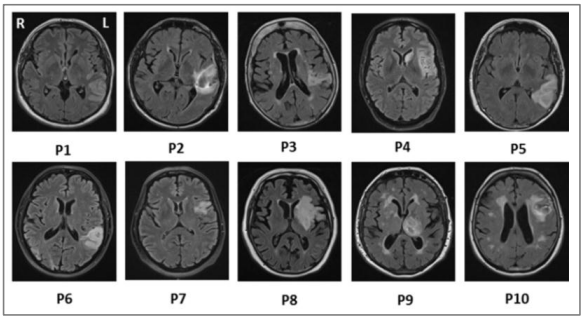

Figure 7.1: Individual lesion locations as represented on MRI-images (T2-weighted, flair axial). MRI scans were taken within two weeks after stroke. Left and right are inverted. P = patient; L = left; R = right.

Table 7.1: Demographical and clinical data of the patients with aphasia

Patient	Gender	Age	Years of education	Type of aphasia	AAT Token Test	AAT - Com	AAT - AC	PALPA 1 total score	PALPA 2 total score	PALPA 5 total score	Lesion site	Etiology	Time after stroke
P1	M	62	16	W	43	91/120	42/60	26/36	28/36	126/160	L TP	I	< 2 weeks
P2	M	74	6	W	19	83/120	41/60	34/36	35/36	113/160	L T	H	< 2 weeks
P3*	F	85	12	W	27	66/120	31/60	24/36	27/36	109/160	L CER/THAL	I	< 2 weeks
P4	M	46	16	B	45	74/120	35/60	36/36	36/36	145/160	L P + NC	I	< 2 weeks
P5	F	70	12	C	8	98/120	51/60	26/36	34/36	131/160	L pT + F/O	I	< 2 weeks
P6	M	63	15	W	46	84/120	47/60	33/36	35/36	152/160	L TP	I	< 2 weeks
P7	F	68	6	B	24	104/120	58/60	34/36	36/36	153/160	L insula	I	< 2 weeks
P8*	M	69	6	B	39	71/120	31/60	24/36	27/36	111/160	L DLPFC	I	< 2 weeks
P9	F	78	12	TSA	50	84/120	41/60	19/36	29/36	105/160	L THAL	H	< 2 weeks
P10	F	79	12	W	29	56/120	36/60	35/36	35/36	155/160	L F	H	< 2 weeks

Legend: * = only performed auditory word recognition task; M = male; F = female; years of education = starts from elementary school; B = Broca's aphasia; C = conduction aphasia; W = Wernicke's aphasia; TSA = transcortical sensory aphasia; AAT = Aachen Aphasia Test; Token Test represents number of mistakes (the less, the better); Com = total score comprehension; AC = auditory comprehension; PALPA = Psycholinguistic Assessment of Language Processing in Aphasia; L = left; p = posterior; T = temporal; P = parietal; TP = temporoparietal; CER = cerebellum; THAL = thalamus; F = frontal; O = occipital; DLPFC = dorsolateral prefrontal cortex; NC = caudate nucleus; I = ischemia; H = haemorrhage

2.2 Paradigms and stimuli

2.2.1 Auditory phoneme discrimination (APD)

The first experiment (a phoneme discrimination task) consisted of three different auditory oddball paradigms both in a pre-attentive (MMN) and attentive (P300) condition and was administered in 8 (4 men, 4 women) out of 10 patients with aphasia. During the pre-attentive condition, the subjects were instructed to ignore the stimuli and to focus their attention on a silent movie. During the attentive condition, the subjects were asked to push a button every time they heard the infrequent stimulus. Within the MMN and P300 paradigm, each block consisted of 250 and 150 stimuli, respectively. The standard phoneme was /b/ and the deviant phonemes were /g/ (covering PoA), /p/ (covering voicing) and /m/ (covering MoA). The stimuli were created in such a way that the standard and deviant stimulus only differed in one phonemic contrast. Stimuli were generated using the website NeXTeNS (http://nextens.uvt.nl/demo.html) where text could be converted to speech (Marsi, Busser, Daelemans, Hoste & Reynaert, 2002). In all stimulus blocks, the standard and deviant phoneme appeared with a probability of 0.80 and 0.20, respectively. The stimuli were given in a random order in which two deviants could not follow each other without having one standard in between. All the spoken phonemes had a duration of 150 ms. The interstimulus interval (ISI) was set at 500 ms in the MMN paradigm and 2000 ms in the P300 paradigm. The stimuli were presented binaurally at 70 dB sound pressure level (SPL) using Apple Inc. earphones placed directly in the external ear.

2.2.2 Auditory word recognition (AWR)

The second experiment consisted of a pre-attentive word recognition task where pseudowords were implemented as deviant stimuli and real words as standard stimuli and was conducted in all 10 patients with aphasia. The subjects were instructed to ignore the stimuli and to focus their attention on a silent movie. The standard stimuli and deviant stimuli appeared with a probability of 0.80 and 0.20, respectively. A total of 125 stimuli were presented, including 100 real words (all nouns) and 25 pseudowords. Pseudowords were derived from the real words by replacing one vowel and one consonant in 25 real words randomly selected from the list of 100 real words. Stimuli were spoken by a 24 year old female Dutch native speaker with a flat intonation and digitally recorded with a sampling frequency of 44.1 kHz. The stimuli were given in a random order in which two pseudowords could not follow each other without having one real word in between. The real words were controlled for lexical frequency (mean 3.15 log10freq) (Keuleers, Brysbaert & New, 2010), age of acquisition (mean 6.0 years) (Ghyselinck, Custers & Brysbaert, 2003) and length (5 phonemes; 1 or 2 syllables). The stimuli were presented with an ISI of 1000 ms and presented binaurally at 70 dB sound pressure level (SPL) using Apple Inc. earphones placed directly in the external ear.

2.3 Electroencephalogram (EEG) – recording and analysis

The EEG (0.5 – 100 Hz band-pass, notch filter disabled) was recorded through 23 Ag/AgCl-electrodes using a linked ears reference and an electrode placed on the forehead as ground. Electrodes were placed on the scalp according to the international 10-20 system. The impedance of the electrodes was kept below 5 kΩ. Data was collected using a SynAmp (Neuroscan) amplifier and was continuously digitized at a 500 Hz sampling rate.

EEG analysis was performed using BrainVision Analyzer 2 (Brain Products, Munich, Germany). The EEG signal was filtered with a 0.5 – 30 Hz band-pass filter and notch filter enabled at 50 Hz. Using independent component analysis (ICA) artefacts caused by eye movements were removed by excluding two components (eye blinks; left-right movements) based on inspection of the components' spatial distribution. For the three P300 paradigms the EEG was segmented into 1100 ms long epochs from 100 ms pre-stimulus to 1000 ms post-stimulus. For the three phoneme discrimination MMN paradigms the EEG was segmented into 500 ms long epochs from 100 ms pre-stimulus to 400 ms post-stimulus. Finally, for the word recognition MMN paradigm the EEG was segmented into 1000 ms long epochs from 100 ms pre-stimulus to 900 ms post-stimulus. The epochs were baseline corrected using a pre-stimulus window of 100 ms. All epochs containing data exceeding 100 µV were rejected for further analysis. The standard and deviant trials were averaged separately. Finally, to compute the MMN in the phoneme discrimination task the average ERP of the standard trials was subtracted from the average ERP of the deviant trials. Peak amplitudes and latencies were measured in time windows determined by the grand averages (GA) and were different for every ERP. For phoneme discrimination, the MMN was measured between 140 – 230 ms for PoA, between 160 – 220 ms for MoA and between 80 – 260 ms for voicing. The P300 was measured between 370 – 650 ms for PoA, between 350 – 510 ms for MoA and between 400 – 570 ms for voicing. For word recognition, the N100 was measured between 60 – 140 ms, the P200 between 140 – 280 ms and the N400 between 400 – 650 ms. Based on these GA, six clusters with the average activity/latency of two electrodes were created, keeping midline electrodes separate: Anterior Left (AL: F3, F7), Anterior Midline (AM: Fz), Anterior Right (AR: F4, F8), Central Left (CL: T3, C3), Central Midline (CM: Cz), Central Right (CR: T4, C4), Posterior Left, (PL: T5, P3) Posterior Midline (PM: Pz), Posterior Right (PR: T6, P4). To elaborate on possible laterality effects, additional laterality indices (LI) were calculated as the difference between the mean amplitude of the right and left anterior, central and posterior clusters (R−L) (Spironelli, Angrilli & Pertile, 2008). This means that for the negative potentials a positive value indicated left lateralization and a negative value indicated right lateralization. For the positive potentials a positive value indicated right lateralization and a negative value indicated left lateralization.

2.4 Behavioural language assessment

Firstly, all subtests of the Dutch version of the Aachen Aphasia Test (AAT) (Graetz, De Bleser & Willmes, 1992) were administered as part of routine linguistic examination and mainly to determine the type of aphasia. Thereafter, three different subtests of the PALPA (Bastiaanse et al., 1995) were administered. The phoneme discrimination tests consisted of a same-different judgment task in which the participants had to judge whether pairs of pseudowords (PALPA 1) or pairs of real words (PALPA 2) were the same or not. The patients were instructed to say "yes" as a response to a similar word pair and to say "no" to a dissimilar word pair. The aurally presented stimuli were monosyllabic (pseudo)words of consonant/vowel/consonant (CVC)-structure. They all differed in phonemic contrasts voicing, PoA or MoA which were either initial, final or based on metathesis (i.e. an altered sequence of phonemes). The lexical decision task in the subtest PALPA 5 contained 80 real words and 80 pseudowords. The pseudowords were derived from the real words by changing one or multiple phonemes, making them legal pseudowords. The participants were asked to decide after each spoken word whether the stimulus was a real word or not, by saying "yes" to a real word or "no" to a pseudoword. In both tests, the answers of the participants were written down on a score sheet, giving 1 for correct answers and 0 for wrong answers. The patients in Table 7.1 were included when performance on the above mentioned PALPA subtests was 2 SD below the mean of the normative data (Aerts, Santens & De Letter, 2012, unpublished data; Bastiaanse et al., 1995). However, for patient 10 PALPA 1, PALPA 2 and the total score of PALPA 5 revealed only very mild phonological disorders and patient 10 presented with an additional impairment of the semantic system. Considering that the separate score for detecting pseudowords as such was just 2 SD below the mean (75/80), despite the total score on PALPA 5 not being 2 SD below the mean, patient 10 was still included in the group of patients with aphasia.

2.5 Statistical analysis

First, the covariance parameters inherent to the group of patients with aphasia and the norm group were determined, as a measure for homogeneity within the groups (the larger, the more heterogeneous; the smaller, the more homogeneous). Next, an explicit test for detecting differences between covariance parameters of the group of patients with aphasia and the norm group, based on the restricted likelihood, was performed. When significant differences in covariance parameters were detected, significant differences in heterogeneity between groups were established, evidencing more heterogeneity in one of both groups.

Second, a group analysis was performed to compare amplitudes, latencies and laterality indices between the group of patients with aphasia and norm group (Aerts et al., submitted), in which potential larger variances among the patients with aphasia (or norm group) were taken into account.

A linear mixed model was carried out, with subjects included as random intercept and residuals. Group (aphasia vs. norm group) served as between-subject factor. For the phoneme discrimination task the following factors entered the model: contrasts (PoA vs. voicing vs. MoA) x region (anterior vs. central vs. posterior) x laterality (left vs. midline vs. right; only for amplitudes and latencies as outcome measures). For the word recognition task the same factors were used, though the factor wordness (real words vs. pseudowords) replaced the factor contrasts. The within-subject factors (contrasts, wordness, region and laterality) were only of interest if they interacted with the between-subject factor group, so significant effects not containing the factor group were excluded from the model. Significance level was set at ≤ 0.05. Post-hoc pairwise comparisons were computed using simple effect comparisons with Tukey adjustment.

Finally, correlations between amplitudes and latencies of FZ (MMN; N100, P200, N400), CZ (N100, P200, N400) and PZ (P300) electrode and two subtests of the AAT (Token Test; Auditory Language Comprehension), the phoneme discrimination tests PALPA 1 (total score) and PALPA 2 (total score) and the lexical decision task PALPA 5 (total score, pseudowords and real words) were calculated with the non-parametric Spearman's rank correlation coefficient. Considering the large amount of correlations, the significance level was reduced to ≤ 0.01. All the statistical analyses were performed using SAS 9.4.

3. Results

3.1 Comparison patients with aphasia – norm group accounting for heterogeneity

3.1.1 Auditory phoneme discrimination

Figure 7.2 and 7.3 show the grand average ERP waves of the patients with aphasia compared to the norm group and the response to every phonemic contrast for the patients with aphasia separately during pre-attentive (MMN; Figure 7.2) and attentive (P300; Figure 7.3) auditory phoneme discrimination. Mean amplitudes and latencies (and standard deviations) of MMN and P300 for both groups can be found in Table 7.2.

Table 7.2: Mean amplitudes and latencies (and standard deviations) of all ERP measures for the norm group and patients with aphasia as a function of task (i.e., APD and AWR), phonemic contrasts (i.e., PoA vs. voicing vs. MoA) and word type (i.e., RW vs. PW). For APD only CZ and PZ values are shown and for AWR only CZ values.

Outcome measure	Task	Group	PC	MMN		P300		Task	Group	Word type	N100		P200		N400	
				Cz		Pz					Cz					
				M	SD ±	M	SD ±				M	SD ±	M	SD ±	M	SD ±
AMPLITUDE (µV)	APD	Norm	PoA	-3.64	1.90	13.70	4.52	AWR	Norm	RW	-1.79	1.14	1.85	1.18	-2.89	1.34
			Voicing	-3.14	1.39	12.97	4.73			PW	-2.85	2.15	2.88	2.06	-4.09	2.43
			MoA	-2.82	1.79	12.46	4.51									
		Aphasia	PoA	-2.88	1.63	6.15	3.27		Aphasia	RW	-1.05	1.45	1.99	1.96	-1.71	1.22
			Voicing	-2.31	3.65	5.27	3.07			PW	-2.13	2.38	5.04	2.75	-2.76	2.30
			MoA	-2.10	1.86	6.51	5.42									
LATENCY (ms)	APD	Norm	PoA	177.95	34.15	408.00	45.18	AWR	Norm	RW	92.70	15.01	189.95	23.35	497.95	61.77
			Voicing	165.14	48.15	400.64	38.97			PW	91.16	18.06	175.81	25.65	510.09	50.14
			MoA	174.18	27.58	380.33	38.73									
		Aphasia	PoA	171.50	37.08	483.75	96.16		Aphasia	RW	125.20	40.20	225.60	59.55	566.00	43.82
			Voicing	242.75	49.82	523.50	65.53			PW	124.20	68.15	235.60	87.17	583.60	56.69
			MoA	203.75	28.95	436.25	71.02									

Legend: APD = auditory phoneme discrimination; PC = phonemic contrast; PoA = place of articulation; MoA = manner of articulation; AWR = auditory word recognition; RW = real words; PW = pseudowords; M = mean; SD = standard deviation; (-) = negative amplitudes

MMN

Amplitudes. Significantly higher variances and heterogeneity were established in the patients with aphasia ($p<0.0001$). A significant group*contrasts interaction ($F=3.04$, $p<0.05$) was found. Only with voicing as phonemic contrast patients with aphasia showed smaller amplitudes than the norm group ($p<0.01$). Moreover, patients with aphasia showed higher amplitudes for PoA compared to voicing and MoA ($p<0.05$), without a difference between voicing and MoA.

Latencies. There were no significant differences in heterogeneity between the patients with aphasia and the norm group ($p=0.321$). A significant group*contrasts interaction emerged ($F=78.72$, $p<0.0001$). Patients with aphasia displayed longer latencies compared to the norm group with voicing ($p<0.0001$) and MoA ($p<0.001$) as phonemic contrast, but not with PoA, and within the patients with aphasia there were significantly longer latencies for voicing, followed by MoA and then PoA ($p<0.0001$), which showed the shortest latencies.

Laterality indices (R-L amplitude). Significantly higher variances and heterogeneity were established in the patients with aphasia ($p<0.001$). A group*contrasts interaction ($F=5.53$, $p < 0.01$) showed more negative values in patients with aphasia than in the norm group, indicating more right lateralized activation, though only for voicing ($p<0.05$). Within patients with aphasia, voicing showed more negative values than PoA, again indicating more right lateralization for voicing.

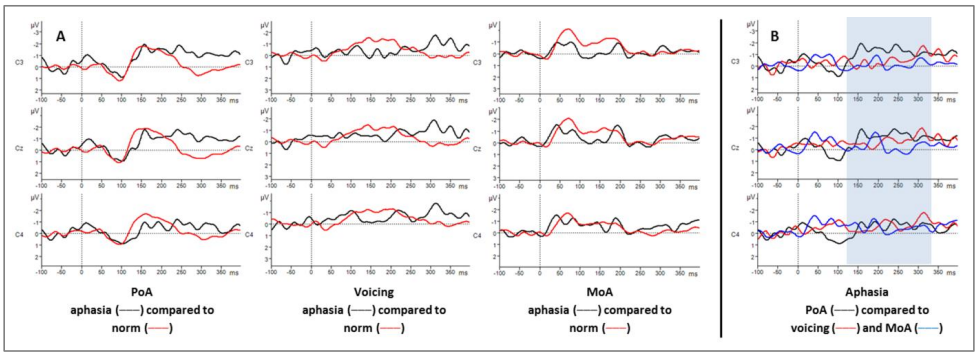

Figure 7.2: Grand average ERPs of the patients with aphasia compared to the norm group for every phonemic contrast (panel A) and the patients with aphasia separately (panel B) during pre-attentive (MMN) auditory phoneme discrimination in electrodes C3, Cz and C4. Latency (x-axis) is represented in milliseconds (ms) and amplitude (y-axis) in microvolts (μV). Negative is plotted upwards. The box in panel B indicates the MMN.

P300

Behavioural results. Response rate of patients with aphasia for button-press ranged from 41.37% correct trials (± 39.77) for PoA, 42.89% correct trials (± 31.71) for voicing to 57.37% correct trials (±

42.06) for MoA. This indicates that attentive phoneme discrimination was difficult for all three phonemic contrasts for the current group of patients with aphasia, with a large variability among the patients.

Amplitudes. There were no significant differences in heterogeneity between the patients with aphasia and the norm group (p=0.355). A group*laterality interaction was found (F=18.69, p<0.0001), showing smaller amplitudes in patients with aphasia than the norm group on the midline, left and right hemisphere (p<0.0001). A group*contrasts interaction (F=3.67, p=0.029) showed smaller amplitudes in patients with aphasia compared to the norm group with all three phonemic contrasts (p<0.0001). Among the patients with aphasia larger amplitudes were established for PoA compared to voicing (p<0.01), without a difference between voicing and MoA or PoA and MoA.

Latencies. Significantly higher variances were established in the patients with aphasia (p<0.0001). A two-way group*contrasts interaction was found (F=12.79, p<0.0001), which showed longer latencies in patients with aphasia than in the norm group with all three phonemic contrasts. Within the patients with aphasia there were significantly longer latencies for voicing, followed by PoA and then MoA (p<0.0001), which showed the shortest latencies.

Laterality indices (R-L amplitude). There were no significant differences in heterogeneity between the patients with aphasia and the norm group (p=0.249). No significant main or interaction effects were detected.

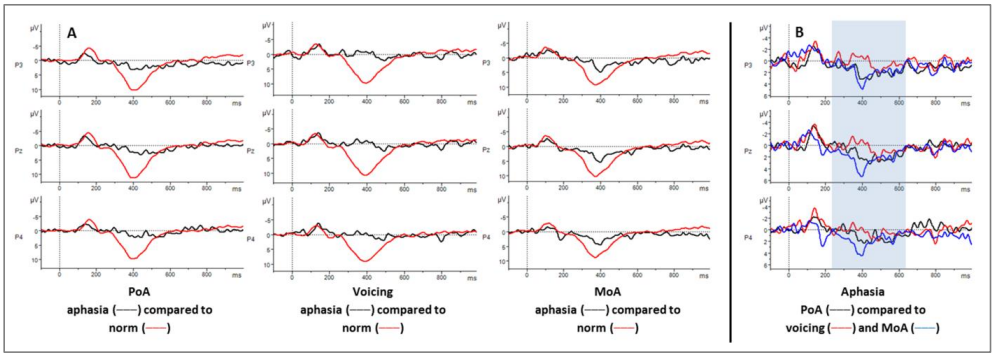

Figure 7.3: Grand average ERPs of the patients with aphasia compared to the norm group for every phonemic contrast (panel A) and the patients with aphasia separately (panel B) during attentive (P300) auditory phoneme discrimination in electrodes P3, Pz and P4. Latency (x-axis) is represented in milliseconds (ms) and amplitude (y-axis) in microvolts (µV). Positive is plotted downwards. The box in panel B indicates the P300.

3.1.2 Auditory word recognition

Mean amplitudes and latencies (and standard deviations) of N100, P200 and N400 for both groups can be found in Table 7.2.

N100

Amplitudes. The test of covariance parameters showed significantly higher variances in the patients with aphasia ($p<0.0001$). A main effect arose for wordness ($F=51.94$, $p<0.0001$), showing larger amplitudes for pseudowords in both groups (Figure 7.4). A significant interaction between group and region ($F=4.47$, $p<0.05$) showed larger amplitudes posterior compared to anterior regions in both groups, and larger amplitudes central compared to anterior regions only in the norm group.

Latencies. The test of covariance parameters showed significantly higher variances in the patients with aphasia ($p<0.0001$). A two-way group*wordness interaction was found ($F=4.71$, $p<0.05$), revealing longer latencies in patients with aphasia compared to the norm group for pseudowords ($p<0.01$) with a trend for real words ($p=0.056$), without a difference between both word types among the patients with aphasia.

Laterality indices (R-L amplitude). Significantly higher variances and heterogeneity were established in the patients with aphasia ($p<0.0001$). No significant main or interaction effects were detected.

P200

Amplitudes. The test of covariance parameters showed significantly higher variances in the patients with aphasia ($p<0.0001$). A significant group*wordness interaction ($F=52.28$, $p<0.0001$) showed larger amplitudes in patients with aphasia compared to the norm group for pseudowords but not for real words ($p<0.0001$; Figure 7.4). Within the patients with aphasia larger amplitudes were found for pseudowords compared to real words ($p<0.0001$; Figure 7.4). A group*region interaction was marginally significant ($F=3.01$, $p=0.054$). Post-hoc comparisons revealed significant smaller amplitudes posterior than anterior and central in both groups ($p<0.01$) and patients with aphasia had larger amplitudes than the norm group at anterior and central regions ($p<0.05$).

Latencies. The test of covariance parameters showed significantly higher variances in the patients with aphasia ($p<0.0001$). A significant interaction emerged between group and wordness ($F=8.60$, $p<0.05$) showing for both pseudowords and real words longer latencies in patients with aphasia compared to the norm group ($p<0.05$), without a difference between both word types in the patients with aphasia.

Laterality indices (R-L amplitude). Significantly higher variances and heterogeneity were established in the patients with aphasia ($p<0.0001$). A trend towards a group*wordness interaction ($F=3.48$, $p=0.068$) was observed, tending to more positive values for real words within patients with aphasia ($p=0.056$), implying more right lateralization.

N400

Amplitudes. The test of covariance parameters showed significantly higher variances in the patients with aphasia ($p<0.0001$). A main effect arose for wordness ($F=65.82$, $p<0.0001$), showing larger amplitudes for pseudowords in both groups (Figure 7.4). A significant group*laterality interaction ($F=3.42$, $p<0.05$) revealed only on midline electrodes smaller amplitudes in patients with aphasia compared to the norm group ($p<0.05$) and patients with aphasia did not show higher midline amplitudes compared to left and right electrode site.

Latencies. The test of covariance parameters showed significantly higher variances in the norm group ($p<0.01$). A main effect arose for group ($F=89.71$, $p<0.0001$) and wordness ($F=8.67$, $p<0.01$), showing longer latencies in the aphasia group and longer latencies for pseudowords.

Laterality indices (R-L amplitude). Significantly higher variances and heterogeneity were established in the patients with aphasia ($p<0.0001$). No significant main or interaction effects were detected.

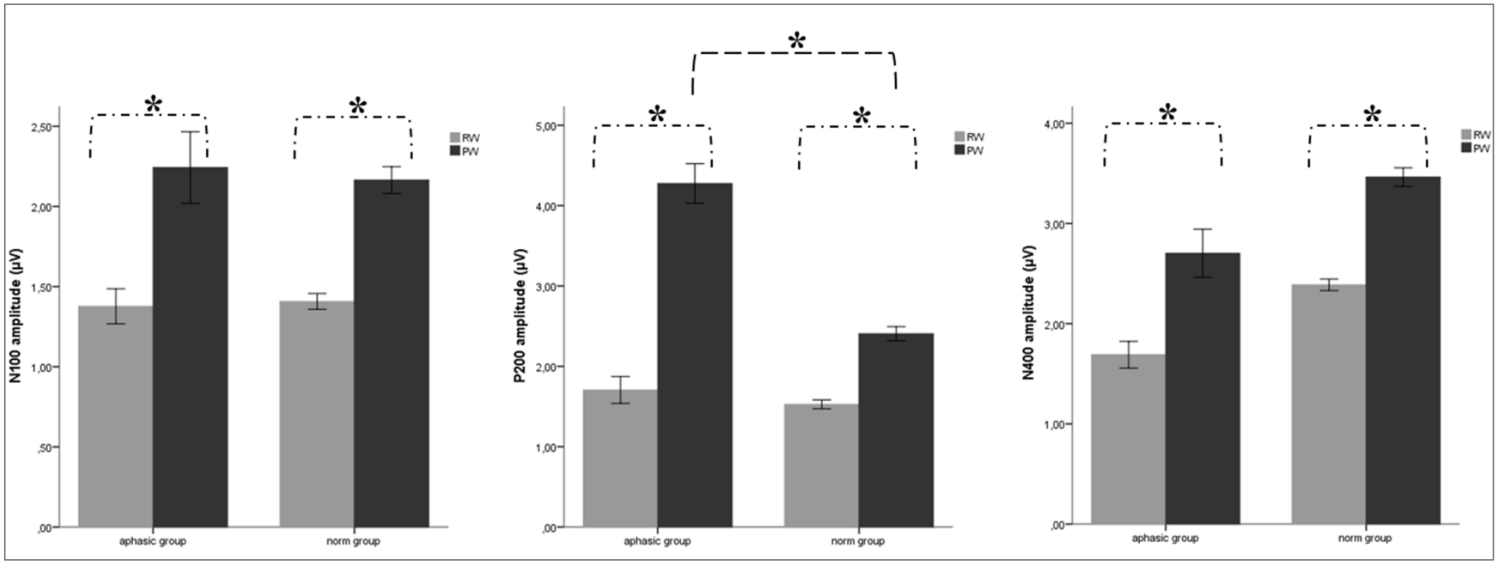

Figure 7.4: Pseudoword effect present in both patients with aphasia and norm group. Absolute values are represented for the negative potentials in view of visibility. RW = real words; PW = pseudowords; * = significant difference.

3.2 Correlation neurophysiological results APD and behavioural results in patients with aphasia

Significant Spearman's correlation R-values together with their p-values can be found in Table 7.3. One significant correlation was found between P300 PZ amplitude with PoA as phonemic contrast and the subtest real words of the PALPA 5.

3.3 Correlation neurophysiological results AWR and behavioural results in patients with aphasia

Significant Spearman's correlation R-values together with their p-values can be found in Table 7.3. A significant correlation was found between N100 and P200 FZ amplitude in response to pseudowords and the subtest auditory comprehension of the AAT. Secondly, P200 FZ latency and N400 FZ amplitude in response to real words correlated with total score of PALPA 5. Thirdly, N100 FZ amplitude and P200 FZ latency in response to pseudowords was associated with the subtest real words of the PALPA 5. Finally, N400 FZ amplitude in response to real words and N400 FZ latency in response to pseudowords was correlated with the subtest pseudowords of the PALPA 5.

Table 7.3: Significant Spearman's correlation R-values together with their p-values for APD (MMN and P300) and AWR (N100, P200 and N400)

					AAT – TT	AAT – AC	PALPA 1 tot	PALPA 2 tot	PALPA 5 tot	PALPA 5 RW	PALPA 5 PW
AMPLITUDE (μV)	**APD**	**P300 (Pz)**	**PoA**	***r***	-0.476	0.707	-0.289	-0.221	0.048	***- 0.886***	0.309
				p	0.2329	0.0501	0.4873	0.599	0.9108	***0.0034***	0.4556
	AWR	**N100 (Fz)**	**PW**	***r***	0.191	***- 0.898***	0.602	0.246	0.071	***0.826***	-0.214
				p	0.6514	***0.0024***	0.114	0.5578	0.8665	***0.0114***	0.6103
		P200 (Fz)	**PW**	***r***	0.333	***- 0.850***	0.157	-0.196	-0.214	0.707	-0.428
				p	0.4198	***0.0075***	0.7111	0.6411	0.6103	0.0501	0.2894
		N400 (Fz)	**RW**	***r***	0.119	-0.395	-0.253	-0.282	***- 0.857***	0.204	***- 0.905***
				p	0.7789	0.3325	0.545	0.4981	***0.0065***	0.6287	***0.002***
LATENCY (ms)	**AWR**	**P200 (Fz)**	**RW**	***r***	0.024	0.096	-0.699	-0.724	***- 0.857***	-0.455	-0.667
				p	0.9554	0.8215	0.0538	0.0422	***0.0065***	0.2572	0.071
			PW	***r***	0.619	-0.778	0.277	0.221	-0.143	***0.826***	-0.333
				p	0.1017	0.0229	0.5064	0.599	0.7358	***0.0114***	0.4198
		N400 (Fz)	**PW**	***r***	-0.047	-0.347	-0.072	0.025	-0.619	0.479	***- 0.881***
				p	0.9108	0.3993	0.8649	0.9540	0.1017	0.2297	***0.0039***

Legend: APD = auditory phoneme discrimination; AWR = auditory word recognition; PoA = place of articulation; PW = pseudowords; RW = real words; AAT = Aachen Aphasia Test; TT = Token Test; AC = auditory comprehension; PALPA = Psycholinguistic Assessment of Language Processing in Aphasia; tot = total score; bold and italic = significant at the 0.01 level.

4. Discussion

With the present study we aimed to disentangle the neurophysiological correlates of phoneme and word processing in the acute stage of aphasia (< 2 weeks after stroke) and compare them with a norm group, while taking the large variability and heterogeneity among patients with aphasia into account. Eleven out of 15 neurophysiological outcome measures (73%) showed significantly larger variability among patients with aphasia, emphasizing the need to control for heterogeneity and the potential risk of overestimating results when not doing so. In a first experiment we investigated possible effects of three different phonemic contrasts during auditory phoneme discrimination and whether the request for an active response played an additional role in this discrimination process. In a second experiment we wanted to explore the process of discriminating between real words and pseudowords and see to what extent patients with aphasia differ from a norm group.

4.1 Auditory phoneme discrimination

In the pre-attentive condition, patients with aphasia only showed amplitude reductions with voicing as phonemic contrast, whereas in the attentive condition all three phonemic contrasts revealed smaller P300 amplitudes compared to the norm group. Moreover, within the patients with aphasia a larger response to PoA was detected compared to MoA and voicing in the pre-attentive condition. However, the difference between PoA and MoA vanished when higher cognitive resources were required during attentive phoneme discrimination, preserving only the larger PoA response compared to voicing.

Patients with aphasia clearly demonstrate a distinctive impairment of phoneme discrimination influenced by three different phonemic contrasts and a substantial effect of attention, i.e. higher cognitive load, on this discrimination process. PoA seems to be the most salient phonemic contrast within patients with aphasia, indicated by the higher response in both the pre-attentive and attentive condition and the need for higher attentional load to elicit PoA amplitude reductions compared to the norm group. The idea of the phonemic contrast PoA being neurophysiologically more resistant, in comparison with voicing which was characterized by a total lack or distorted MMN in patients with aphasia, has been suggested before (Csépe et al., 2001). However, for the first time to our knowledge MoA was introduced as an extra phonemic contrast, differentiating between an oral (/b/) and a nasal (/m/) phoneme. In this way, a complete and detailed investigation of all phonemic contrasts present in the Dutch language could be performed in patients with aphasia. The fact that the larger amplitude for PoA compared to MoA during pre-attentive phoneme discrimination disappeared in the attentive condition, illustrates an interaction between both phonemic contrasts and therefore supports the inclusion of MoA in the comparison of phonemic contrasts.

The diverse responses to the phonemic contrasts within patients with aphasia can be explained in light of the spectrotemporal differences each phonemic contrast represents and the potential effect stroke has on these phonemic representations. The frequency separation representing PoA (/b/ – /g/) is larger than the spectrum representing voicing (/b/ – /p/) or MoA (/b/ – /m/), in which differences in voicing are conveyed via temporal cues (voice-onset time) rather than spectral cues. Spectral cues of PoA are related to the position of the articulators, as a frontal PoA such as /b/ and a back PoA such as /g/ gives rise to a low or a high second formant, respectively (Rietveld & van Heuven, 2009). In general, a broader frequency spectrum might lead to a more salient contrast (Tampas, Harkrider & Hedrick, 2005), engage more active cortical neurons during the discrimination process and lead to a greater ERP response (Diesch & Luce, 1997; Korczak & Stapells, 2010). Thus, phonemes differing in PoA likely invoke a larger neuronal network related to the larger spectral differences between respective phonemes (Aaltonen, Eerola, Lang, Uusipaikka & Tuomainen, 1994). Moreover, the auditory-motor integration network substantiated for PoA most likely provides additional support when phonemic categorization is impaired (Möttönen & Watkins, 2009). On the other hand, the overall impairment in the distinction between phonemes differing in voicing indicates that patients with aphasia might have trouble with processing rapid temporal cues inherent to perceiving the difference between voiced (/b/) and voiceless phonemes (/p/) (Hessler, Jonkers & Batiaanse, 2010). Stroke in the acute stage implies a range of physiological and neurological instabilities, such as brain oedema and haemorrhagic transformation in ischemia (Balami, Chen, Grunwald & Buchan, 2011) or early brain injury (increased intracranial pressure, decreased cerebral blood flow and secondary cerebral ischemia) and delayed cerebral vasospasm in case of a brain haemorrhage (Ayer & Zhang, 2010). This can ultimately lead to a damaged and altered neuronal network caused by neuronal cell death. When the stroke and its neurological consequences occur in vital language areas responsible for phoneme discrimination, as is the case in certain patients with aphasia, the detection of different phonemic contrasts will be altered. With respect to the present study, this is expressed as amplitude reductions in patients with aphasia compared with a norm group in the pre-attentive and attentive condition. However, despite these neuronal alterations and general amplitude reduction, patients with aphasia still differentiate between the phonemic contrasts. This is evidenced by amplitude differences between PoA and the other two phonemic contrasts in favour of PoA, arguing for a qualitative pattern of phonemic contrast sensitivity in aphasia.

However, the study by Hessler et al. (2010) comparing phoneme discrimination embedded in a non-word context could not establish a difference between PoA and MoA on top of the difference between PoA and voicing. Besides the additional support from the auditory-motor integration

network, an explanation for the current difference between these phonemic contrasts might be found in the used outcome measures. Hessler et al. (2010) employed a behavioural task, the subtest PALPA 2, which might have a poorer sensitivity than the currently used neurophysiological measures, as has been suggested before in an aging study (Aerts et al., 2013). The fact that the difference between PoA and MoA only surfaces in the pre-attentive condition (MMN amplitude) and disappears in the attentive condition (P300 amplitude) supports this proposition, considering that the PALPA task used in Hessler et al. (2010) requires active participation as well. It is possible that the requirement for higher cognitive processes in terms of attention allocation exerts a substantial effect on phoneme discrimination and phonemic contrast sensitivity in aphasia. On the one hand, the response to voicing was affected with a sparing of PoA and MoA during the pre-attentive condition whereas in the attentive condition all three phonemic contrasts were affected. On the other hand, when attention was required the patients with aphasia no longer displayed a larger amplitude for PoA compared to MoA as was established in the pre-attentive condition. Possibly, the recruitment of additional neuronal resources for voluntary attention allocation to the deviant stimulus in the attentive condition suppresses neuronal activation necessary for detecting differences in phonemic contrasts (e.g. between PoA and MoA). On the contrary, during the pre-attentive condition involuntary attention-switch to deviant stimuli requires less cognitive load, leaving more room for genuine detection of differences between phonemes. This might explain why patients with aphasia reached a distinction between PoA and MoA in the pre-attentive condition and not during the attentive condition. The fact that the difference between PoA and voicing sustains with higher cognitive load advocates for some form of hierarchy in detection of phonemic contrasts in patients with aphasia. Decreases in processing speed, i.e. latencies, during phoneme discrimination corroborate the idea of a hierarchical pattern of impaired detection of the different phonemic contrasts. Among patients with aphasia the phonemic contrast voicing was the most affected, with the highest processing speed during both pre-attentive and attentive phoneme discrimination. Above that, patients with aphasia discriminate phonemes slower than the norm group for voicing and MoA in the pre-attentive condition and also for PoA when attention-allocation is required. A suggestion might be that PoA represents the largest separation in spectrotemporal properties and additionally relies on a well-established auditory-motor interface (Guenther, Ghosh & Tourville, 2006; Pulvermüller et al., 2006), which is therefore the most spared after stroke. Voicing embodies the smallest separation and mostly relies on rapid temporal cues, which is therefore the most vulnerable after stroke, and MoA is located in between. Interestingly, this corresponds with a pattern established with respect to aging influences on phonemic contrasts (Aerts et al., 2013), which

demonstrated that voicing was the most affected by aging processes and PoA remained relatively robust against aging.

In the pre-attentive condition, patients with aphasia showed a more right lateralized scalp distribution than the norm group, but only when voicing was the phonemic contrast. This was confirmed by more right lateralized MMN amplitudes for voicing compared to PoA within the patients with aphasia, while the norm group demonstrated a bilateral amplitude distribution for all phonemic contrasts. Apparently, less than two weeks after stroke patients with aphasia rely more on right hemisphere activation during phoneme discrimination based on voicing, whereas this is not the case for PoA and MoA. This supports two main findings from previous studies. On the one hand this fits into the early acute stage of a three-phasic recovery model suggested by Saur et al. (2006), which unveiled an elevation of right hemisphere activation about two weeks after stroke that could be related to an improvement in language performance. The present study could not associate the right hemisphere preponderance during voicing-based phoneme discrimination to specific behavioural outcome measures, so no definitive conclusions can be made with respect to a potential (dis)advantage of the current higher right hemisphere involvement. A lack of correlations between increased MMN amplitudes at right hemispheric sites and behavioural outcome has also been demonstrated before (Becker & Reinvang, 2007a). However, in the present study diminished amplitudes for voicing compared to the norm group were established in the pre-attentive condition, which was not the case in the study by Becker and Reinvang (2007a). So, this indicates some degree of difficulty with discriminating phonemes differing in voicing and advocates against a beneficial compensatory right hemispheric contribution during this discrimination process in the present study. On the other hand, the laterality-based differentiation between voicing and PoA and MoA provides another argument for the presence of a qualitative pattern of phonemic contrast sensitivity. The difference in laterality patterns suggest different neurophysiological substrates for the different phonemic contrasts, at least for voicing compared to the other two contrasts, and can be supported by previous studies suggesting different ERP generator loci for different deviant types (Aaltonen et al., 1993; Ilvonen et al., 2003; Ilvonen et al., 2004). Interestingly, a clear effect of attention once again emerged with respect to the topographical scalp distribution. In the attentive condition, patients with aphasia showed a bilateral scalp distribution with equal amplitudes at left and right hemisphere, though reduced compared to the norm group, and was confirmed by a lack of differences in laterality indices.

With the above outlined argumentation in mind, the active oddball task and the ensuing P300 potential do not seem an optimal clinical, neurophysiological measure for phoneme discrimination in the acute stage of aphasia. Large confounding effects of attention and requirements for higher

cognitive load interfere with, and presumably predominate, neuronal activation related to actual phoneme discrimination processes. Although it would provide valuable additional information, considering the established discrepancy between MMN and P300 with respect to age effects in healthy subjects (Aerts et al., 2013), it does not seem to fulfil the demands for application in the acute stage of aphasia in light of seeking a valid and reliable clinical neurophysiological diagnostic tool for phoneme discrimination. The poor behavioural results in the attentive condition, which barely showed a 50% correct response rate and a very high standard deviation among the patients for all three phonemic contrasts, confirm this conclusion and indicate that phoneme discrimination based on all three phonemic contrasts was difficult for the patients with aphasia. This is in contradiction with a study that indicated that attentive syllable detection was rather easy for the subjects with aphasia, who performed almost without errors (Becker & Reinvang, 2007b). The choice of stimuli definitely has an important influence on this matter. In the present study, phonemes were used (/b/) which differed only in one phonemic contrast, whereas the study by Becker and Reinvang (2007b) used syllables ([bɑ] - [tɑ]) which differed in more than one phonemic contrast. This enhances the difference and separation between standard and deviant stimulus in the oddball task en consequently facilitates attentive deviance detection. On the other hand, differences in patient characteristics such as severity of aphasia and time post-stroke between the present study and the study by Becker and Reinvang (2007b) can also play an influencing role.

4.2 Auditory word recognition

From 100 ms onwards, a pseudoword effect was present in both patients with aphasia and the norm group, i.e. higher responses to pseudowords, even though patients with aphasia processed the pseudowords slower than the norm group. Despite the initial slower processing speed, the pseudoword effect continued in a later time window, around 200 ms, in both groups. However, the patients with aphasia processed pseudowords as well as real words slower than the norm group, in spite of their much larger response to pseudowords compared to the norm group. In the final N400 time window, pseudowords continued to elicit higher responses in both groups, though at a slower processing speed in general and in which the patients with aphasia were slower than the norm group. In summary, patients with aphasia manage to detect a difference between real words and pseudowords across all time windows, by showing statistically significant higher amplitudes to pseudowords, yet with a significant delay compared to the norm group. Interestingly, patients with aphasia did not show reduced amplitudes compared to the norm group, neither for pseudowords nor for real words, except in the P200 time window where they presented much higher responses than the norm group for pseudowords.

An N400 pseudoword effect can be explained in terms of an enhanced search through the mental lexicon for a word's phonological form in case of pseudowords, which indicates that a pseudoword is detected as such and reflects the need for a greater effort when a pseudoword is encountered (Friedrich et al., 2006; Lau, Phillips & Poeppel, 2008). Our previous study demonstrated that the pseudoword effect already occurred ± 100 ms after stimulus presentation, continued through the P200 time window and eventually ended in the N400 potential (Aerts et al., submitted), which is confirmed by the current results. The finding that patients with aphasia display a higher sensitivity for pseudowords already 100 ms post-stimulus and in later time windows, suggests that they also (pre-attentively) perceive an irregularity in the phoneme sequence during an initial phonological decoding phase (N100). This leads to an enhanced alertness during form based processes (P200) (Van Den Brink, Brown & Hagoort, 2001), in which aphasia patients need to deliver more cognitive effort for the processing of several lexical properties (e.g. phonological legality, phonotactic probability) as reflected in the higher P200 amplitudes anterior and central in response to pseudowords compared to the norm group. Notwithstanding this required increased cognitive effort, the patients still perform an increased search for lexical entries with a greater sensitivity to other possible word forms in case of pseudowords, as reflected by larger N400 amplitudes (Aerts et al., submitted).

Despite the relatively intact sensitivity for pseudowords in the patients with aphasia, implicating intact lexical access processing, there was a significant delay throughout all time windows compared to the norm group, especially for processing of the pseudowords. This is more or less comparable with studies which employed the N400 to measure lexical-semantic integration deficits in patients with aphasia, at the sentence or word level (D'Arcy et al., 2003; Hagoort et al., 1996; Kawohl et al., 2010; Swaab et al., 1997). A converging finding was the presence of an N400 congruency effect, though significantly reduced or delayed compared to healthy controls, indicating a lack of semantic integration capacities in the patients with aphasia. With respect to the present study, the intact sensitivity to pseudowords in a context of real words throughout all time windows proves that the delay in lexical access processing not necessarily leads to a disturbed processing at the word level. Moreover, this also demonstrates that a potential dissociation exists between pure lexical processing and lexical-semantic integration in patients with aphasia. A difference in the amount of required and available "computational resources" in patients with aphasia has been appointed as a possible cause for the delay and the apparent dissociation in lexical access and lexical-semantic integration (Swaab et al., 1997). From a more neurophysiological point of view, the stroke lesions most likely influenced the general conductive properties of the brain tissue, leading to a less efficient information transfer and therefore a delayed cognitive processing.

In the P200 time window patients with aphasia tended towards a more right lateralization in response to real words, in contrast to the norm group who showed a more bilateral scalp distribution which is in line with expectations (Van Petten & Luka, 2006). Apparently, the patients with aphasia in the acute stage of stroke depend more on right hemispheric involvement during real word processing, which is in itself relatively intact. Right hemisphere cooperation in the acute stage of stroke is not unusual or detrimental per se, as it has been demonstrated before that it can contribute to an improvement in language performance within two weeks after stroke (Saur et al., 2006). Considering that patients with aphasia display a more right lateralized distribution in the P200 time window implicates that it is only during the form based analysis the right hemisphere additionally contributes to the detection of a real word. The occurrence of abnormal ERP patterns (Angrilli, Elbert, Cusumano, Stegagno & Rockstroh, 2003) and their recovery in the post-acute stage (Laganaro, Morand, Schwitter, Zimmermann & Schnider, 2008) in specific time windows, corresponding to different stages in language processing, supports this conclusion. With respect to the present study, it appears that patients with aphasia rely more on right lateralized activation mainly during processing of lexical properties, such as evaluating whether a certain phoneme sequence is valid. However, considering the slower processing speed in the P200 time window, right hemispheric cooperation does not seem to be a fully proper compensatory mechanism during form based analysis of real words.

4.3 Points of consideration

Two important aspects must be adduced when giving interpretation to possible (re)organization ERP patterns in patients with aphasia. Although the current statistical analysis accounts for the large heterogeneity among patients with aphasia, it is not an absolute measure, yet merely a way of controlling, at least in part, for the variability among the patients. The large heterogeneity among the patients with aphasia is associated with large differences in site of lesion (ranging from frontal to temporoparietal lesions) and type of lesion (haemorrhage, ischemia). Despite the stringent control for heterogeneity among patients with aphasia at the statistical level, it is still very likely that different lesions at different sites with different causes lead to a variety of neurophysiological alterations. Consequently, it is possible that a compensatory activation pattern of one patient suppresses or interferes with a compensatory mechanism of another patient, creating overlapping effects. From a more methodological point of view, when using ERP measures one has to be aware of phenomenon inherent to electrocortical properties such as volume conduction. This means that right hemisphere electrodes can pick up electrocortical activity from left hemisphere generators due to a rightward orientation of fissures and gyri and conductance properties (Luck, 2005; Van Petten & Luka, 2006). Keeping this in mind, interpretations with respect to reorganizational patterns in aphasia

must be treated with caution and ideally and definitely for clinical purposes, every patient should be treated as an individual. A patient with aphasia can be compared with a norm group or with itself over different time periods to monitor potential therapeutic effects in order to get a better insight into possible stroke-related reorganization patterns. This approach is currently pursued in an ongoing study.

5. Conclusion

The currently used paradigms, for which preliminary normative data have already been developed (Aerts et al., 2013), have proven to be sensitive enough to be used in the clinical evaluation of phoneme and word processing in patients with aphasia in the acute stage of stroke. The auditory phoneme discrimination task showed a differentiation between phonemic contrasts, in which PoA was the most robust and voicing together with MoA the most vulnerable, arguing for a qualitative pattern of phonemic contrast discrimination in patients with aphasia. In the context of implementing ERPs in clinical practice, the passive oddball task eliciting the MMN is preferred over the attentively evoked P300 potential because of other confounding, cognitive factors. During word recognition, patients with aphasia mainly suffered from a delayed processing, which did not impair the response to pseudowords. In future research, efforts must be delivered to obtain normative data for the patients with aphasia as well, with respect to the different types of aphasia but also site, size and cause of lesion. In this way, when using the current neurophysiological language tasks in the clinical evaluation of patients with aphasia, they can be compared to a norm group of healthy subjects of comparable age and gender on the one hand and with patients having similar semiology on the other hand.

6. References

Aaltonen, O., Eerola, O., Lang, A. H., Uusipaikka, E., & Tuomainen, J. (1994). Automatic discrimination of phonetically relevant and irrelevant vowel parameters as reflected by mismatch negativity. *Journal of the Acoustical Society of America,* 96(3), 1489-1493.

Aaltonen, O., Tuomainen, J., Laine, M., & Niemi, P. (1993). Cortical differences in tonal versus vowel processing as revealed by an ERP component called mismatch negativity (MMN). *Brain and language,* 44(2), 139-152.

Aerts, A., van Mierlo, P., Hartsuiker, R. J., Hallez, H., Santens, P., & De Letter, M. (2013). Neurophysiological investigation of phonological input: Aging effects and development of normative data. *Brain and language,* 125(3), 253-263.

Aerts, A., van Mierlo, P., Hartsuiker, R. J., Santens, P., & De Letter, M. (submitted). Sex differences in neurophysiological activation patterns during phonological processing: An influential factor for normative data. *Archives of Sexual Behavior.*

Aerts, A., Santens, P., & De Letter, M. (2012). [Flemish normative data of the first column PALPA 1 and PALPA 2]. Unpublished raw data.

Angrilli, A., Elbert, T., Cusumano, S., Stegagno, L., & Rockstroh, B. (2003). Temporal dynamics of linguistic processes are reorganized in aphasics' cortex: an EEG mapping study. *Neuroimage,* 20(2), 657-666.

Ayer, R., & Zhang, J. (2010). Connecting the Early Brain Injury of Aneurysmal Subarachnoid Hemorrhage to Clinical Practice. *Turkish Neurosurgery,* 20(2), 159-166.

Balami, J. S., Chen, R. L., Grunwald, I. Q., & Buchan, A. M. (2011). Neurological complications of acute ischaemic stroke. *Lancet Neurology,* 10(4), 357-371.

Bastiaanse, R., Bosje, M., & Visch-Brink, E. (1995). Psycholinguistic Assessment of Language Processing in Aphasia: The Dutch version): Hove, UK: Lawrence Erlbaum Associates Ltd.

Becker, F., & Reinvang, I. (2007a). Mismatch negativity elicited by tones and speech sounds: Changed topographical distribution in aphasia. *Brain and language,* 100(1), 69-78.

Becker, F., & Reinvang, I. (2007b). Successful syllable detection in aphasia despite processing impairments as revealed by event-related potentials. *Behavioral and Brain Functions,* 3(1), 6.

Blumstein, S. E., Baker, E., & Goodglass, H. (1977). Phonological factors in auditory comprehension in aphasia. *Neuropsychologia,* 15(1), 19-30.

Burton, M. W., Noll, D. C., & Small, S. L. (2001). The anatomy of auditory word processing: individual variability. *Brain and Language,* 77(1), 119-131.

Csépe, V., Osman-Sági, J., Molnár, M., & Gósy, M. (2001). Impaired speech perception in aphasic patients: event-related potential and neuropsychological assessment. *Neuropsychologia,* 39(11), 1194-1208.

D'Arcy, R. C., Marchand, Y., Eskes, G. A., Harrison, E. R., Phillips, S. J., Major, A., et al. (2003). Electrophysiological assessment of language function following stroke. *Clinical neurophysiology,* 114(4), 662-672.

Diesch, E., & Luce, T. (1997). Magnetic fields elicited by tones and vowel formants reveal tonotopy and nonlinear summation of cortical activation. *Psychophysiology,* 34(5), 501-510.

Dobel, C., Pulvermüller, F., Härle, M., Cohen, R., Köbbel, P., Schönle, P., et al. (2001). Syntactic and semantic processing in the healthy and aphasic human brain. *Experimental Brain Research,* 140(1), 77-85.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research,* 12(3), 189-198.

Friedrich, C. K., Eulitz, C., & Lahiri, A. (2006). Not every pseudoword disrupts word recognition: an ERP study. *Behavioral and Brain Functions,* 2(36), doi: 10.1186/1744-9081-1182-1136.

Ghyselinck, M., Custers, R., & Brysbaert, M. (2003). Age-of-acquisition ratings for 2332 Dutch words from 49 different semantic categories. *Psychologica Belgica*.

Giaquinto, S., Ranghi, F., & Butler, S. (2007). Stability of word comprehension with age: An electrophysiological study. *Mechanisms of ageing and development,* 128(11), 628-636.

Graetz, P., De Bleser, R., & Willmes, K. (1992). Akense afasietest (AAT). *Amsterdam: Hogrefe*.

Guenther, F. H., Ghosh, S. S., & Tourville, J. A. (2006). Neural modeling and imaging of the cortical interactions underlying syllable production. *Brain and language,* 96(3), 280-301.

Hagoort, P., Brown, C. M., & Swaab, T. Y. (1996). Lexical—semantic event–related potential effects in patients with left hemisphere lesions and aphasia, and patients with right hemisphere lesions without aphasia. *Brain,* 119(2), 627-649.

Hessler, D., Jonkers, R., & Bastiaanse, R. (2010). The influence of phonetic dimensions on aphasic speech perception. *Clinical Linguistics & Phonetics, 24* (12), 980-996.

Ilvonen, T.-M., Kujala, T., Kiesiläinen, A., Salonen, O., Kozou, H., Pekkonen, E., et al. (2003). Auditory Discrimination After Left-Hemisphere Stroke A Mismatch Negativity Follow-Up Study. *Stroke,* 34(7), 1746-1751.

Ilvonen, T., Kujala, T., Kozou, H., Kiesiläinen, A., Salonen, O., Alku, P., et al. (2004). The processing of speech and non-speech sounds in aphasic patients as reflected by the mismatch negativity (MMN). *Neuroscience letters,* 366(3), 235-240.

Karayanidis, F., Andrews, S., Ward, P. B., & McConaghy, N. (1993). Event-related potentials and repetition priming in young, middle-aged and elderly normal subjects. *Cognitive Brain Research,* 1(2), 123-134.

Kawohl, W., Bunse, S., Willmes, K., Hoffrogge, A., Buchner, H., & Huber, W. (2010). Semantic event-related potential components reflect severity of comprehension deficits in aphasia. *Neurorehabilitation and neural repair,* 24(3), 282-289.

Keuleers, E., Brysbaert, M., & New, B. (2010). SUBTLEX-NL: A new measure for Dutch word frequency based on film subtitles. *Behavior Research Methods,* 42(3), 643-650.

Korczak, P. A., & Stapells, D. R. (2010). Effects of Various Articulatory Features of Speech on Cortical Event-Related Potentials and Behavioral Measures of Speech-Sound Processing. *Ear and Hearing,* 31(4), 491-504.

Kutas, M., & Federmeier, K. D. (2011). Thirty years and counting: finding meaning in the N400 component of the event-related brain potential (ERP). *Annual review of psychology,* 62, 621-647.

Kutas, M., & Hillyard, S. A. (1980). Reading senseless sentences: Brain potentials reflect semantic incongruity. *Science,* 207(4427), 203-205.

Laganaro, M., Morand, S., Schwitter, V., Zimmermann, C., & Schnider, A. (2008). Normalisation and increase of abnormal ERP patterns accompany recovery from aphasia in the post-acute stage. *Neuropsychologia,* 46(8), 2265-2273.

Laszlo, S., & Federmeier, K. D. (2009). A beautiful day in the neighborhood: An event-related potential study of lexical relationships and prediction in context. *Journal of Memory and Language,* 61(3), 326-338.

Lau, E. F., Phillips, C., & Poeppel, D. (2008). A cortical network for semantics:(de) constructing the N400. *Nature Reviews Neuroscience,* 9(12), 920-933.

Luck, S. J. (2005). An introduction to the event-related potential technique (cognitive neuroscience).

Marsi, E., Busser, B., Daelemans, W., Hoste, V., & Reynaert, M. (2002). Combining information sources for memory-based pitch accent placement. International Conference on Spoken Language Processing, Denver Co, 1273-1276.

Mirman, D., Yee, E., Blumstein, S. E., & Magnuson, J. S. (2011). Theories of spoken word recognition deficits in aphasia: evidence from eye-tracking and computational modeling. *Brain and language,* 117(2), 53-68.

Möttönen, R., & Watkins, K. E. (2009). Motor representations of articulators contribute to categorical perception of speech sounds. *The Journal of Neuroscience,* 29(31), 9819-9825.

Näätänen, R., Gaillard, A. W. K., & Mäntysalo, S. (1978). Early selective-attention effect on evoked potential reinterpreted. *Acta psychologica,* 42(4), 313-329.

Nolfe, G., Cobianchi, A., Mossuto-Agatiello, L., & Giaquinto, S. (2006). The role of P300 in the recovery of post-stroke global aphasia. *European journal of neurology,* 13(4), 377-384.

Pettigrew, C., Murdoch, B., Kei, J., Ponton, C., Alku, P., & Chenery, H. (2005). The mismatch negativity (MMN) response to complex tones and spoken words in individuals with aphasia. *Aphasiology,* 19(2), 131-163.

Pulvermüller, F., Hauk, O., Zohsel, K., Neininger, B., & Mohr, B. (2005). Therapy-related reorganization of language in both hemispheres of patients with chronic aphasia. *Neuroimage,* 28(2), 481-489.

Pulvermüller, F., Huss, M., Kherif, F., del Prado Martin, F. M., Hauk, O., & Shtyrov, Y. (2006). Motor cortex maps articulatory features of speech sounds. *Proceedings of the National Academy of Sciences,* 103(20), 7865-7870.

Pulvermüller, F., Kujala, T., Shtyrov, Y., Simola, J., Tiitinen, H., Alku, P., et al. (2001). Memory traces for words as revealed by the mismatch negativity. *Neuroimage,* 14(3), 607-616.

Pulvermüller, F., Mohr, B., & Lutzenberger, W. (2004). Neurophysiological correlates of word and pseudo-word processing in well-recovered aphasics and patients with right-hemispheric stroke. *Psychophysiology,* 41(4), 584-591.

Pulvermüller, F., Shtyrov, Y., & Hauk, O. (2009). Understanding in an instant: neurophysiological evidence for mechanistic language circuits in the brain. *Brain and Language,* 110(2), 81-94.

Rietveld, A., & van Heuven, V. (2009). Algemene fonetiek.

Robson, H., Keidel, J. L., Lambon Ralph, M. A., & Sage, K. (2012). Revealing and quantifying the impaired phonological analysis underpinning impaired comprehension in Wernicke's aphasia. *Neuropsychologia,* 50(2), 276-288.

Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., et al. (2006). Dynamics of language reorganization after stroke. *Brain,* 129(6), 1371-1384.

Shtyrov, Y., & Pulvermüller, F. (2002). Neurophysiological evidence of memory traces for words in the human brain. *Neuroreport,* 13(4), 521-525.

Spironelli, C., Angrilli, A., & Pertile, M. (2008). Language plasticity in aphasics after recovery: evidence from slow evoked potentials. *Neuroimage,* 40(2), 912-922.

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. *Science,* 150(3700), 1187-1188.

Swaab, T., Brown, C., & Hagoort, P. (1997). Spoken sentence comprehension in aphasia: Event-related potential evidence for a lexical integration deficit. *Journal of Cognitive Neuroscience,* 9(1), 39-66.

Tampas, J. W., Harkrider, A. W., & Hedrick, M. S. (2005). Neurophysiological indices of speech and nonspeech stimulus processing. *Journal of Speech, Language and Hearing Research,* 48(5), 1147.

Van Den Brink, D., Brown, C. M., & Hagoort, P. (2001). Electrophysiological evidence for early contextual influences during spoken-word recognition: N200 versus N400 effects. *Journal of Cognitive Neuroscience,* 13(7), 967-985.

Van Petten, C., & Luka, B. J. (2006). Neural localization of semantic context effects in electromagnetic and hemodynamic studies. *Brain and Language,* 97(3), 279-293.

Van Petten, C., & Rheinfelder, H. (1995). Conceptual relationships between spoken words and environmental sounds: Event-related brain potential measures. *Neuropsychologia,* 33(4), 485-508.

Van Strien JW. Classificatie van links- en rechtshandige proefpersonen. Nederlands Tijdschrift voor de Psychologie en Haar Grensgebieden, 47: 88-92, 1992.

Wertz, R. T., Auther, L. L., Burch-Sims, G. P., Abou-Khalil, R., Kirshner, H. S., & Duncan, G. W. (1998). A comparison of the mismatch negativity (MMN) event-related potential to tone and speech stimuli in normal and aphasic adults. *Aphasiology,* 12(7-8), 499-507.

Wilson, K. R., O'Rourke, H., Wozniak, L. A., Kostopoulos, E., Marchand, Y., & Newman, A. J. (2012). Changes in N400 topography following intensive speech language therapy for individuals with aphasia. *Brain and Language,* 123(2), 94-103.

CHAPTER 8

Therapy-related language improvement in an aphasic patient evidenced by behavioural and neurophysiological measures: A 1-year follow-up after stroke

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Abstract

Background: There is still considerable debate concerning the effectiveness of speech and language therapy in acute, subacute and chronic stages of aphasia. Earlier reports suggest that several variables can influence therapy outcome, such as content, type and amount of therapy. Neurophysiological measures, event-related brain potentials such as the N400 and P300, have shown to be sensitive markers of therapeutic effects. As a supplement to the usual behavioural evaluation methods neurophysiological measures might help to further disentangle the effect of content, type and/or amount of therapy.

Aims: The present single case study aims to investigate the effect of language therapy by combining behavioural and neurophysiological outcome measures in a patient with aphasia during the first year after stroke. By further subdividing the therapy period into different therapy blocks, possible influence of content, type, and/or amount of therapy is investigated.

Methods & Procedures: RL is a 47-year old man with stroke-related aphasia, who received 3 periods of therapy in the first 4 months after his stroke. First, he received an intensive language treatment of 30 hours in 3 weeks, which was followed by a conventional treatment of 30 hours in 7 weeks. Then, RL received a second, intensive language therapy of 30 hours in 3 weeks. This was followed by a period of 6 months without any form of language treatment. Behavioural and neurophysiological measures were collected after every therapy and therapy-free period. The effect of therapy was examined by comparing the therapy period with the therapy-free period, without differentiating between the intensive and conventional treatment. In a second analysis a comparison was made between the intensive therapy periods and the conventional therapy program.

Outcomes & Results: RL showed a general improvement on both behavioural and neurophysiological measures after the therapy period, which was preserved throughout the therapy-free period. Intensive treatment yielded better linguistic outcome as indicated by a behavioural and neurophysiological improvement in contrast with the behavioural stagnation or deterioration and decline of the N400 neurophysiological marker, after the conventional therapy.

Conclusions: The present study illustrates the effectiveness of early language treatment after stroke in which intensity can play an important role, even in the first months after stroke. In addition, the use of neurophysiological outcome measures provides added value to the behavioural evaluations in the context of therapeutic follow-up.

Key words

Intensity; aphasia therapy; neurophysiology; acute stroke; case study

1. Introduction

Aphasia is one of the most common symptoms following stroke. It affects one or more language modalities (expressive and/or receptive) and occurs in approximately 30-45 % of all stroke patients (Dickey et al., 2010; Kauhanen et al., 2000). Evidence for the effectiveness of language therapy in post-stroke aphasia still remains ambiguous. Language therapy might have some effect with respect to functional communication (therapy vs. no therapy), yet no consensus has been reached about the treatment variables that contribute the most to language improvement (Brady, Kelly, Godwin, & Enderby, 2012). Content of therapy (semantic-, syntactic-, phonological based), type of therapy (impairment-based, social stimulation, communicative), the adopted outcome measures (functional communication measures, impairment-specific measures), timing of therapy (acute, subacute, chronic phase) and intensity (frequency and duration) of therapy can have a significant influence on treatment outcome.

Effects of content and type of therapy naturally cohere, as an impairment-oriented therapy will always target certain aspects of language that are affected in patients with aphasia. Consequently, training of sublexical phonological decoding and encoding embedded in an impairment-based treatment can induce an improvement of disturbed phonological processing capacities (Corsten, Mende, Cholewa, & Huber, 2007). Word-finding treatment improves word-finding abilities of patients with aphasia, regardless whether the therapy is semantically or phonologically oriented, or as a combination of both (Wisenburn & Mahoney, 2009). With respect to the interpretation of therapy effect, it is important to distinguish between outcome measures. For instance, for phonological versus semantic treatment a differentiation exists on impairment-specific measures, whereas no differences are found on more general, functional outcome measures (Doesborgh et al., 2004; van Hees, McMahon, Angwin, de Zubicaray & Copland, 2014). This is an important issue to be taken into account when interpreting results from therapy studies. For instance, de Jong-Hagelstein et al. (2011) demonstrated that a functional verbal communication measure does not differentiate between an impairment-based (semantic or phonological) treatment and communicative treatment in the acute stage after stroke. On the contrary, impairment-specific, semantic or phonological, outcome measures did differentiate between communicative treatment and impairment-based, semantic or phonological treatment, in favour of the latter.

In terms of timing of therapy after stroke, language treatment seems to improve communication outcome in people with moderate to severe aphasia in both very early and chronic stages of stroke (Corsten et al., 2007; Godecke, Hird, Lalor, Rai, & Phillips, 2012; Godecke et al., 2013; Wisenburn & Mahoney, 2009). However, others have suggested that aphasia therapy might not provide added value in the acute stage, as functional communication sometimes improves equally after speech- and

language therapy, with regular social contacts or even without therapy (Bowen et al., 2012; Laska, Kahan, Hellblom, Murray, & von Arbin, 2011). But again, in these studies the primary outcome was focussed on functional communication measures, so these negative results must be interpreted accordingly.

The role of intensity (frequency and duration) of therapy has recently been recognized as a predictive factor for aphasia recovery (Godecke et al., 2013). As treatment intensity increases, therapy outcome improves (Cherney, Patterson, Raymer, Frymark, & Schooling, 2008), whereby more hours over a short period (8.8 hours per week for 11.2 weeks) shows more benefit than less hours over a longer period (2 hours per week for 22.9 weeks) (Bhogal, Teasell, & Speechley, 2003). When applying the principle of massed practice (a large amount of language exercises in a short period of time), patients with aphasia show a general improvement of their language abilities (Barthel, Meinzer, Djundja, & Rockstroh, 2008; Code, Torney, Gildea-Howardine, & Willmes, 2010; Kirmess & Maher, 2010; Maher et al., 2006; Meinzer, Djundja, Barthel, Elbert, & Rockstroh, 2005; Meinzer, Rodriguez, & Rothi, 2012; Meinzer, Streiftau, & Rockstroh, 2007; Pulvermuller et al., 2001; Szaflarski et al., 2008). Moreover, intensive therapy appears to provide long-term stability of improved language performance (Meinzer et al., 2005), even in the acute stage after stroke (Kirmess & Maher, 2010). Despite these overall positive effects of intensive language treatment, Bakheit et al. (2007) did not report a difference between an intensive and standard language therapy within 12 weeks directly after stroke. Similarly, Hinckley and Carr (2005) did not find an advantage of intensive (20 hours individual and 5 hours group weekly) training of functional communication ("catalogue-ordering task") relative to a non-intensive (4 hours weekly) program. When taking a closer look at the methodology of both studies however, the intensive therapy in the former study merely contained 1 hour sessions resulting in only 5 hours of therapy per week. Most likely, this amount was too limited, considering the recommended 8 to 9 hours of treatment to obtain an intensive therapy (Boghal et al., 2003). Moreover, both studies applied (at least in part) a functional communication strategy, and it is possible that higher intensity does not provide added value with more communicative-based treatment, but still does so with other approaches. It is worth noting though that the latter study reports more generalization to other language modalities in the intensively treated group. In light of investigating effects of intensity, it remains difficult to isolate this factor from other methodological factors, considering that it is recommended to adjust the type of therapy and the content of an impairment-based therapy to the nature of a patient's language impairment (Kendall et al., 2006). Nevertheless, the combination of high intensity and impairment-based therapy seems to result in a language improvement in both acute and chronic stages of stroke compared to less intensive therapy based on functional communication.

Therapeutic outcome can also be affected by secondary neuronal plasticity phenomena that initiate immediately after a left hemisphere stroke (Saur et al., 2006). This can occur in the form of restitution of damaged, premorbid language regions, recruitment of perilesional areas directly surrounding the damaged area or even activation of homotopic language areas in the right hemisphere (Breier et al., 2004; Tyler, Wright, Randall, Marslen-Wilson, & Stamatakis, 2010). Activation of right-hemisphere homotopic areas is mostly a consequence of larger lesions due to reduced transcallosal inhibition, yet efficient language recovery can only be achieved when a re-shift to left-hemisphere regions occurs, at least in case of an acute stroke (Heiss & Thiel, 2006). Saur et al. (2006) postulated a model of language recovery in terms of time post-stroke proceeding in 3 phases: days after stroke, mild left hemisphere activation co-occurs with a minimum of language recovery. Weeks after stroke, a significant increase in right hemisphere activation co-occurs with substantial improvement of language functions. Finally, months and years after stroke, a "re-shift" to the left hemisphere with a concomitant decrease of right hemisphere activation is related to further progression of language improvement. An important characteristic of neurons is the ability to form new connections and the more frequent neurons are active simultaneously, the stronger their connections become (Hebbian learning) (Kleim & Jones, 2008; Pulvermüller & Berthier, 2008). By combining an intensive with an impairment-based treatment, enhancement of neuronal connections can be achieved in the preferred left hemispheric lesional and perilesional areas in both the acute and chronic stage of stroke, and this is related to a favourable outcome (Belin et al., 1996; Davis, Harrington, & Baynes, 2006; Fridriksson, Richardson, Fillmore, & Cai, 2012; Leger et al., 2002; Mattioli et al., 2014; Meinzer et al., 2004; Rochon et al., 2010).

Therapy-related differences in brain recovery and plasticity patterns can also be explored and monitored by means of neurophysiological measures. Event-related potentials (ERPs) have shown great potential in characterizing, evaluating, and monitoring language abilities in patients with aphasia. The pre-attentive Mismatch Negativity (MMN) (Näätänen, Gaillard, & Mäntysalo, 1978), the attentive P300 potential (Sutton, Braren, Zubin, & John, 1965) and the N400 potential (Kutas & Hillyard, 1980) are very suitable to evaluate phonological and lexical-semantic input processes during the course of aphasia recovery (Becker & Reinvang, 2007; Csépe, Osman-Sági, Molnár, & Gósy, 2001; Kawohl et al., 2010), as an amplitude re-enhancement can be associated with improvement of language functions over time (Ilvonen et al., 2003; Nolfe, Cobianchi, Mossuto-Agatiello, & Giaquinto, 2006; Pulvermüller, Mohr, & Lutzenberger, 2004). Surprisingly, ERP studies measuring therapeutic effects on language abilities and its underlying reorganization of neuronal circuits are scarce and are always performed in patients with aphasia at least 1 year post-stroke. Nonetheless, the outcome is promising, demonstrating positive effects of intensive, impairment-based treatment in the form of

increased amplitudes of P300 in response to meaningful words (Pulvermüller, Hauk, Zohsel, Neininger, & Mohr, 2005) or a shift from a more right-lateralized scalp distribution of the N400 before therapy to a more left-lateralized distribution after therapy (Wilson et al., 2012). In these studies the neurophysiological changes were associated with an improvement in behavioural language performance. On the other hand, ERPs can also shed light on potential neuronal processing deficits despite intact behavioural performance (Becker & Reinvang, 2007). ERPs provide a complementary instrument in the diagnostic and therapeutic evaluation of patients with aphasia and make it possible to connect neurological findings with clinical observations. This will not only support clinical practice, but will enhance understanding of the neurophysiological mechanisms involved in language processing and its evolution after stroke (Kim & Tomaino, 2008). A long-term follow-up study of therapy effects, integrating clinical behavioural measures and neurophysiological recovery patterns has not been presented in the literature until now. The development of neurophysiological normative data for phonological input processing (Aerts et al., 2013) offers the opportunity to field-test the clinical relevance of ERPs. The present single case study aims at investigating the effect of language therapy on behavioural and neurophysiological outcome measures during the course of 1 year after stroke. On the one hand, a period of 4 months therapy in the (sub) acute stage is compared with a six-month period without a targeted therapeutic language intervention in the post-acute stage. Additionally, it is tested if the implementation of neurophysiological correlates provides added value in the diagnostic and therapeutic language evaluation. On the other hand, within the therapy period, a differentiation is made between three different therapy blocks, in which 3 weeks of intensive therapy (2 hours per day, 5 days a week) in the acute and subacute stage are compared with 7 weeks of conventional therapy (1 hour per day, 4 days a week) in the subacute stage of stroke.

2. Method

2.1 Patient description

The patient under study (RL) is a Dutch speaking, right-handed (tested with the methodology of Van Strien, 1992) physical trainer who was struck by an ischemic stroke at the age of 47. He had normal hearing and sight prior to his stroke, as confirmed by the annual medical controls within the scope of his professional activity. There was no history of neurological or psychiatric disorders or of speech or language (developmental) disorders prior to the stroke.

He was acutely admitted to the stroke unit after sustaining a complex partial seizure, characterized by unresponsiveness and confusion. Subsequently he was unable to speak or execute orders. Neuroimaging confirmed the presence of an ischemic lesion in the left hemisphere, encompassing the caudate nucleus, the insula and the parietal cortex (see Figure 8.1). A clear picture of a non-fluent aphasia persisted, with only a single word expressed (“ja” [“yes”]), and with severely

compromised auditory and lexical comprehension. In addition, there were signs of orofacial apraxia (e.g. dissociation voluntary oral movements versus automatic oral movements and groping). There was no hemiparesis or hemisensory disorder.

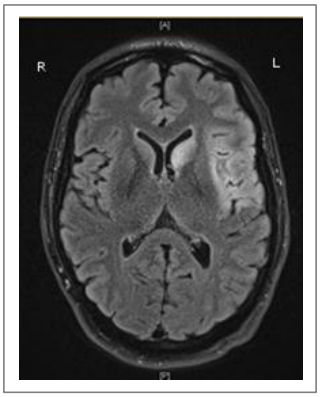

Figure 8.1: MRI-scan ten days post-stroke confirming the presence of an ischaemic lesion in the left hemisphere, encompassing the caudate nucleus, the insula and the parietal cortex. Left and right are inverted. R = right; L = left.

2.2 Study design

Behavioural and neurophysiological evaluations were performed in the course of the first year after stroke (see Figure 8.2). After the first diagnostic testing (T1), RL was given a first block of three weeks of (intensive) therapy. The training program consisted of 30 hours of therapy in a 3 week period. Each therapy session lasted 2 hours and was provided 5 days a week. After this therapy block, a second evaluation took place (T2). Then, a second block of therapy (between T2 and T3) entailed a conventional program, and provided the maximum amount of therapy hours per week as prescribed by the National Institute for Health and Disability Insurance in Belgium, that is 1 hour a day, 5 days a week. Given that the total amount of therapy hours in the conventional therapy needed to be the same as the intensive therapy block, 30 hours of therapy were provided over a 7 week period. A third evaluation occurred after the conventional therapy program (T3). After T3, a third block of intensive therapy of again three weeks was implemented (2 hours per session, 5 days a week) and was followed by another evaluation (T4). Finally, a 6 month period of no intervention was introduced, which was followed by a fifth testing (T5). Thus, in total 5 evaluation moments were implemented.

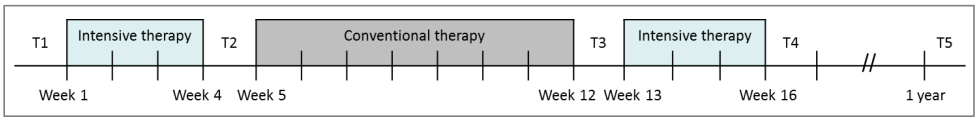

Figure 8.2: Timeline of all test moments and therapy blocks. T1 = first evaluation moment; T2 = evaluation after first intensive therapy; T3 = evaluation after conventional therapy; T4 = evaluation after second intensive therapy; T5 = evaluation after therapy-free period.

2.3 Language assessment

Diagnostic language testing was conducted within the first week after stroke. The same tests were also administered within one week before and after each block of therapy.

2.3.1 Behavioural language evaluation

In order to obtain an overall objective impression of RL's post-stroke language abilities, all subtests of the complete Dutch version of the Aachen Aphasia Test (AAT) (Graetz, De Bleser, & Willmes, 2005) were administered.

Subsequently, 3 different subtests of the Dutch version of the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) (Bastiaanse, Bosje, & Visch-Brink, 1995) were conducted. The phoneme discrimination tests consisted of a same-different judgment task in which RL had to judge whether pairs of pseudowords (PALPA 1) or minimal pairs of real words (PALPA 2) were the same or not. RL was instructed to say "yes" as a response to a similar word pair and to say "no" to a dissimilar word pair. Only the first column of PALPA 1 and PALPA 2 were administered, as allowed by the guidelines (Bastiaanse et al., 1995). The results of PALPA 1 and PALPA 2 were compared with normative data (N=71) (Aerts, Santens & De Letter, 2012, unpublished data). The aurally presented stimuli were monosyllabic (pseudo)words of consonant/vowel/consonant (CVC)-structure. They all differed in phonemic contrasts voicing, place of articulation (PoA) or manner of articulation (MoA), which were either initial, final or based on metathesis (i.e., an altered sequence of phonemes). The lexical decision task in the subtest PALPA 5 contained 80 real words and 80 pseudowords. The pseudowords were derived from the real words by changing one or multiple phonemes, making them genuine pseudowords. RL was asked to decide after each spoken word whether the stimulus was a real word or not, by saying "yes" to a real word or "no" to a pseudoword. In both tests, the answers of RL were written down on a score sheet, giving 1 for correct answers and 0 for wrong answers.

Some additional subtests of the PALPA (Bastiaanse et al., 1995) were administered in order to get more insight in the phonological disorders of this patient. The ability to repeat pseudowords was tested by using the subtest PALPA 8. The length of the pseudowords varied from 1 to 3 syllables, but the number of phonemes stayed constant, namely 5. RL was asked to repeat the pseudoword after

the investigator propounded it orally. Finally, the subtest PALPA 12 was included, examining the verbal attention for digits. Here, RL was asked to repeat a series of numbers in an incremental way, ranging from 10 sequences of 2 digits to 10 sequences of 7 digits. In total 60 sequences had to be remembered and subsequently repeated.

Finally, two additional impairment-based linguistic tests were conducted, only during the diagnostic phase (T1), without further implementation after the therapy blocks. The first test was the "Werkwoord en Zinnen Test" (WEZT), the Dutch version of "Verb and Sentence Test" (VAST) (Bastiaanse, Edwards, & Rispens, 2002), which is designed to analyse verb and sentences processing. Only the 4 production tasks were administered, comprising naming of verbs, production of non-finite verbs in sentences, production of finite verbs in sentences and construction of sentence anagrams. Secondly, the subtests "naming" and "verbal association" of the "Semantische Associatie Test", the Dutch version of "Semantic Association Test" (SAT), were conducted (Visch-Brink, Denes, & Stachowiak, 1993).

2.3.2 Neurophysiological language evaluation

2.3.2.1 Paradigms and stimuli

Auditory phoneme discrimination (APD)

The first experiment (a phoneme discrimination task) consisted of three different auditory oddball paradigms both in a pre-attentive (MMN) and attentive (P300) condition. During the pre-attentive condition, RL was instructed to ignore the stimuli and to focus his attention on a silent movie. During the attentive condition, RL pushed a button every time he heard the infrequent stimulus. Within the MMN and P300 paradigm, each block consisted of 750 stimuli and 150 stimuli, respectively. The standard phoneme was /b/ and the deviant phonemes were /g/ (covering PoA), /p/ (covering voicing) and /m/ (covering MoA). The stimuli were created in such a way that the standard and deviant stimulus only differed in one phonemic contrast. Stimuli were generated using the website NeXTeNS (http://nextens.uvt.nl/demo.html; Marsi, Busser, Daelemans, Hoste, & Reynaert, 2002) where text could be converted to speech. In all stimulus blocks, the standard and deviant phoneme appeared with a probability of 0.80 and 0.20, respectively. The stimuli were given in a random order in which two deviants could not follow each other without having one standard in between. All the spoken phonemes had a duration of 150 ms. The interstimulus interval (ISI) was set to 500 ms in the MMN paradigm and 2000 ms in the P300 paradigm. The stimuli were presented binaurally between 60 and 70 dB sound pressure level (SPL) using Apple Inc. earphones placed directly in the external ear.

Auditory word recognition (AWR)

The second experiment consisted of a word recognition task where pseudowords were implemented as deviant stimuli and real words as standard stimuli. RL was instructed to ignore the stimuli and to focus his attention on a silent movie. The standard stimuli and deviant stimuli appeared with a probability of 0.80 and 0.20, respectively. A total of 125 stimuli were presented, including 100 real words (all nouns) and 25 pseudowords. Pseudowords were derived from the real words by replacing one vowel and one consonant in 25 real words randomly selected from the list of 100 existing words. Stimuli were spoken by a 24 year old female Dutch native speaker with a flat intonation and digitally recorded with a sampling frequency of 44.1 kHz. The stimuli were given in a random order, with the constraint that two pseudowords could not follow each other without having one real word in between. The real words had a mean lexical frequency of 3.15 log10freq (SD=0.39) (Keuleers, Brysbaert, & New, 2010), a mean age of acquisition of 6.0 years (SD=1.21) (Ghyselinck, Custers, & Brysbaert, 2003) and the length was 5 phonemes in 1 or 2 syllables. The stimuli were presented with an ISI of 1000 ms and presented binaurally between 60 and 70 dB sound pressure level (SPL) using Apple Inc. earphones placed directly in the external ear.

2.3.2.2 Electroencephalogram (EEG) – recording and analysis

The EEG (0.5 – 100 Hz band-pass, notch filter disabled) was recorded through 23 Ag/AgCl-electrodes using a linked ears reference and an electrode placed on the forehead as ground. Electrodes were placed on the scalp according to the international 10-20 system. The impedance of the electrodes was kept below 5kΩ. Data were collected using a SynAmp (Neuroscan) amplifier and were continuously digitized at a 500 Hz sampling rate.

EEG analysis was performed using BrainVision Analyzer 2 (Brain Products, Munich, Germany). The EEG signal was filtered with a 0.5 – 30 Hz band-pass filter and notch filter enabled at 50 Hz. Using independent component analysis (ICA) artefacts caused by eye movements were removed by excluding two components (eye blinks and saccades) based on inspection of the components' topography. For the three P300 paradigms the EEG was segmented into 1100 ms long epochs from 100 ms pre-stimulus to 1000 ms post-stimulus. For the three phoneme discrimination MMN paradigms, the EEG was segmented into 500 ms long epochs from 100 ms pre-stimulus to 400 ms post-stimulus. Finally, for the word recognition MMN paradigm the EEG was segmented into 1000 ms long epochs from 100 ms pre-stimulus to 900 ms post-stimulus. The epochs were baseline corrected using a pre-stimulus window of 100 ms. All epochs containing data exceeding 100 µV were rejected for further analysis. The standard and deviant trials were averaged separately. Finally, to compute the MMN in the phoneme discrimination task the average ERP of the standard trials was subtracted from the average ERP of the deviant trials. Peak detection was carried out semi-automatically at

electrodes corresponding to normative data previously developed (Aerts et al., 2013). Peak latencies and peak amplitudes were measured in time windows determined by the averaged standard/deviant (P300; N400) and difference (MMN) waveform which were different for every ERP. For phoneme discrimination, all MMNs were measured between 100 – 300 ms at Cz and Fz. All P300s were analysed between 200 – 700 ms at Pz. For word recognition, the N400 was measured between 300 and 800 ms at Cz.

2.4 Therapeutic methodology

Before entering this study, RL received no other form of language therapy. Therapy was conducted at the patient's house or at the speech therapist's office. The therapy period consisted of 3 well defined blocks of impairment-based therapy. The first block of therapy (between T1 and T2) consisted of an intensive, tailored therapy program, which was composed based on the diagnostic results of both the neurolinguistic and neurophysiological tests. The linguistic exercises focused on the enhancement of the connection between phonological auditory representations of words and their semantic content. The second block of therapy (between T2 and T3) entailed a conventional program, based on the neurolinguistic test results and the error pattern observed by the speech therapist. Auditory and visual phonological exercises at word and sentence level were combined with syntactically orientated assignments. The third and final block of therapy (between T3 and T4) was again an intensive therapy program with the same intensity and duration as the therapy block between T1 and T2. Once again the content of the therapy was based on the neurolinguistic and neurophysiological results. The exercises focused on improving the sublexical processes. Finally, a therapy-free period of 6 months (between T4 and T5) was incorporated, after which an additional assessment was administered to measure any effects of a period without extra language stimulation. All therapy sessions were given by two qualified speech and language pathologists (SLP) (authors KB and EH). KB gave all intensive therapy sessions (between T1 and T2 and between T3 and T4) and EH conventional therapy sessions (between T2 and T3). To prevent methodological bias, both SLP's did not report about the therapy progress to each other. All the diagnostic and post-therapy neurophysiological evaluations were conducted by a third SLP (author AA). No other linguistic or cognitive therapies were allowed during the therapy periods.

2.5 Statistical analysis

2.5.1 Behavioural measures

All AAT results were analysed using the computer program for analysis of AAT score profiles, by means of a chi-square test (Graetz, De Bleser, & Willmes, 2005). Effect sizes were calculated to estimate the magnitude of differences between the different test moments of all PALPA tasks. The

effect size was classified as reported in the Robey, Schultz, Crawford, and Sinner (1999) review of single-subject research in aphasia where 2.6, 3.9, and 5.8, corresponds to small-, medium-, and large-sized effects, respectively.

2.5.2 Neurophysiological measures

Firstly, neurophysiological outcome measures of RL were compared to neurophysiological normative data recently developed by our research group (Aerts et al., 2013). Peak latency and amplitude values were compared to norm values of RL's age group (40-49 years old) at every evaluation moment (T1, T2, T3, T4 and T5) for every paradigm. Considering that the normative data are only developed for a limited number of electrodes (MMN: Fz and Cz; P300: Pz; N400: Cz), RL was only compared to the norms for these electrode sites. Effect sizes were calculated to estimate the magnitude of difference between the norm values and RL's values. Standardized mean difference (*d*) and the corresponding scale (0.2 equals a small effect, 0.5 a medium effect and 0.8 a large effect) was used (Cohen, 1988) in concurrence with other neurophysiological research papers using effect sizes (Ferreira-Santos et al., 2012; Kwon et al., 2010).

Secondly, a comparison between evaluation moments was performed (T1-T2, T2-T3, T3-T4, T1-T4, and T4-T5) at every electrode site, to map potential brain reorganization patterns. However, an important issue with a single case repeated measure comparison is the lack of a between-subject estimate of variability in peak latency and amplitude (Oruç et al., 2011). Recently, a new approach that assesses within-subject (individual) variability has been proposed and has proven to be a valuable and viable statistical method (Lin, Wu, Wu, Liu, & Gao, 2013; Oruç et al., 2011; Parker, 2006; Picton et al., 2000; Rousselet et al., 2009). This approach is based on the nonparametric bootstrapping technique, in which the individual ERP data of one subject is treated as a population from which smaller samples are taken (resampled) with replacement (which means that once a trial is randomly selected it is put back into the original sample and continues to have an equal chance of being selected the next time) for a large number of times (e.g. 50,000 resamples) (Field, 2009; Oruç et al., 2011). Based on these smaller samples (deducted from the resampling), statistics of interest can be calculated (e.g. mean amplitudes), the sampling distribution can be estimated, confidence intervals determined and significance tests computed. The bootstrapping technique has already shown to be sensitive enough for demonstrating the presence of the face-selective N170, feedback error-related negativity and P300 in healthy controls (Oruç et al., 2011), so it definitely provides a feasible and valuable tool in the clinical, therapeutic evaluation of individual patients with aphasia. Consequently, this approach was chosen to compare results at different evaluation moments.

For passive, pre-attentive phoneme discrimination (MMN), analysis was performed on the difference waveforms (deviant – standard), containing +/- 750 trials, in a fixed temporal window of 200 ms (100

– 300 ms) containing the MMN peak. For active, attentive phoneme discrimination (P300) analysis was performed on the deviant waveforms, containing +/- 30 trials, in a fixed temporal window of 500 ms (200 – 700 ms) containing the P300 peak. Finally, for passive, pre-attentive word recognition analysis was performed for pseudowords (25 trials) and real words (100 trials) separately with a focus on the N400 potential, evaluated in a fixed temporal window of 600 ms (300 – 900 ms). The difference between maximum amplitudes in the fixed temporal windows was taken to represent the contrast between evaluation moments (T1-T2, T2-T3, T3-T4, T1-T4, and T4-T5). To test whether this contrast was significantly larger than zero (for a negative potential) or smaller than zero (for a positive potential), the bootstrap analysis was performed as explained above. Eventually, a histogram of contrast values obtained from 50,000 resampled datasets was constructed. The lower 5^{th} percentile point of this histogram served as the critical value for (one-tailed, e.g. T1 < T2) significance at the 0.05 alpha-value.

3. Results

3.1 Overall therapy effect (T1-T4; T4-T5)

3.1.1 Behavioural results

At T1, the ALLOC classification of the AAT (Graetz et al., 2005) suggested Broca's aphasia with a certainty of 100 % without outliers in the subtests. On the PALPA assessments, RL reached maximum scores (36/36) on the behavioural phoneme discrimination tests (PALPA 1 and 2). There were deficits in the auditory lexical decision (PALPA 5; 145/160), which were caused by difficulties in recognizing pseudowords (real words 79/80; pseudowords 66/80). The repetition of pseudowords (24/30) revealed only phonological paraphasias. Auditory verbal attention (PALPA 12) was severally impaired (25/60). The SAT revealed semantic disturbances indicated by a disruption of the subtests naming (15/30) and verbal association (21/30). The VAST indicated morphosyntactic problems, by showing an impairment in naming of action verbs (15/30), production of non-finite verbs in sentences (2/30), production of finite verbs in sentences (3/10) and construction of sentence anagrams (16/20).

After the whole therapy period (T1-T4), AAT analyses indicated an overall significant improvement up to the level that the ALLOC could not classify the remaining language problems to an aphasic syndrome (33.8 % certainty for aphasia), and classification into an aphasia type was also not possible. RL reached the maximum score for phoneme discrimination (PALPA test 1 and 2), auditory lexical decision for real words (PALPA 5 RW) and repetition of pseudowords (PALPA 8) after T4. The auditory lexical decision for pseudowords (PALPA 5 PW) improved significantly over the whole therapy period. Verbal attention (PALPA 12) was the only test which showed no significant improvement or deteriorations. There were no significant improvements on any of the behavioural tests after the therapy free period (T4-T5). The results of the AAT and PALPA are summarized in Table 8.1.

Table 8.1: Overview of all behavioural test results of AAT and PALPA.

AAT	MAX		T1	T2	T3	T4	T5
Token Test	0		45	13	8	8	5
Repetition	150		107	146	148	147	148
Written production	90		44	87	88	88	87
Naming	120		47	111	117	115	115
Language comprehension	120		74	103	112	118	120
PALPA	**MAX**	**SD**	**T1**	**T2**	**T3**	**T4**	**T5**
1 Phoneme discrimination - pseudowords	36	0.83	36	35	32	36	35
2 Phoneme discrimination - minimal pairs	36	0.75	36	36	36	36	36
5 lexical decision - total	160	2.27	145	156	152	154	158
5 Lexical decision - real words	80	0.88	79	80	78	80	80
5 Lexical decision - pseudowords	80	1.81	66	76	73	74	78
8 Repetition pseudowords	30	1.30	24	30	30	30	29
12 Verbal attention: digit span	60	5.93	25	42	36	35	39

Legend: MAX = maximum score; SD = standard deviation; T1= test moment 1; T2= test moment 2; T3 = test moment 3; T4 = test moment 4; T5 = test moment 5.

3.1.2 Neurophysiological results

RL's ERP amplitudes and latencies of the MMN, P300 and N400 compared with neurophysiological normative data, as calculated with the Cohen's *d* effect size, are summarized in Table 8.2 with respect to every evaluation moment. At T1, amplitude and latency of every MMN, P300 and N400 (except N400 RW latency) deviated from the norm group with a large effect size. After the whole therapy period (T4), MMN PoA and N400 PW amplitude and MMN voicing and MoA and all P300 latencies no longer deviated from the norm group with a large effect size. After the therapy-free period (T5), all MMN and P300 amplitudes and MMN PoA, all P300 and N400 RW latencies again deviated from the norm group with a large effect size.

The topographical distribution of the amplitude and latency alterations after the therapy period (T1 – T4) and therapy-free period (T4 – T5) can be found in Table 8.3. A clear description of an interpretation of the electrode denomination is provided in the legend. The ERP waveform of the N400 PW before and after therapy (T1 – T4) and after the therapy free period (T4 – T5) is represented in Figure 8.3.

3.1.2.1 Auditory phoneme discrimination

After the therapy period (T1-T4) MMN MoA amplitude increased. The amplitude of P300 PoA, voicing and MoA increased, yet P300 PoA and voicing latency increased as well after the therapy period.

The therapy-free period (T4-T5) caused a MMN PoA amplitude decrease, a MMN voicing latency decrease and a generalized MMN MoA amplitude decrease. P300 PoA, voicing and MoA amplitudes decreased.

3.1.2.2 Auditory word recognition

After the therapy period (T1-T4) N400 RW and N400 PW amplitude increased.

After the therapy-free period (T4-T5) N400 PW amplitude decreased.

Table 8.2: Normative data (first column; Aerts et al., 2013) and RL's results for peak amplitudes and latencies at the five evaluation moments.

		Norm 40 – 49 years	T1	T2	T3	T4	T5
AMPLITUDE							
MMN **(Fz+Cz)**	**PoA**	M: -3.22 SD: 2.43	*-1,23* d=0.82	*-2,70* d=0.21	*-2,58* d=0.26	*-1,78* d=0.59	*-0,99* d=0.92
	Voicing	M: -2.73 SD: 1.48	*-0,06* d=1.80	*-1,55* d=0.80	*-1,97* d=0.51	*-1,27* d=0.99	*-1,16* d=1.06
	MoA	M: -2.51 SD: 1.53	*-0,12* d=1.56	*-1,35* d=0.76	*-1,69* d=0.54	*-0,55* d=1.28	*0,04* d=1.61
P300 **(Pz)**	**PoA**	M: 13.09 SD: 4.00	*5,19* d=1.97	*4,44* d=2.16	*7,67* d=1.35	*9,15* d=0.98	*6,47* d=1.65
	Voicing	M: 12.67 SD: 3.72	*3,75* d=2.40	*2,86* d=2.64	*9,62* d=0.82	*7,60* d=1.36	*4,75* d=2.13
	MoA	M: 11.63 SD: 4.07	*3,90* d=1.90	*7,98* d=0.90	*10,54* d=0.27	*4,75* d=1.69	*5,54* d=1.50
N400 **(Cz)**	**RW**	M: -2.60 SD: 1.17	*-0,72* d=1.61	*-2,58* d=0.02	*-2,80* d=-0.17	*-1,16* d=1.23	*-1,94* d=0.56
	PW	M: -3.60 SD: 1.93	*-1,47* d=1.10	*-4,22* d=-0.32	*1,15* d=-2.46	*-4,92* d=-0.68	*-3,06* d=0.28
LATENCY							
MMN **(Fz+Cz)**	**PoA**	M: 171 SD: 27.28	*120* d=1.87	*134* d=1.36	*232* d=-2.24	*146* d=0.92	*144* d=0.99
	Voicing	M: 164 SD: 37.95	*206* d=-1.11	*287* d=-3.24	*211* d=-1.24	*191* d=-0.71	*156* d=0.21
	MoA	M: 174 SD: 28.47	*145* d=1.02	*143* d=1.09	*156* d=0.63	*184* d=-0.35	*158* d=0.56
P300 **(Pz)**	**PoA**	M: 403 SD: 60.04	*346* d=0.95	*492* d=-1.48	*440* d=-0.62	*420* d=-0.28	*322* d=1.35
	Voicing	M: 396 SD: 47.99	*466* d=-1.46	*402* d=-0.12	*506* d=-2.29	*394* d=0.04	*464* d=-1.42
	MoA	M: 376 SD: 33.51	*446* d=-2.09	*410* d=-1.01	*432* d=-1.67	*394* d=-0.54	*424* d=-1.43
N400 **(Cz)**	**RW**	M: 504 SD: 61.86	*490* d=0.23	*480* d=0.39	*602* d=-1.58	*554* d=-0.81	*404* d=1.62
	PW	M: 496 SD: 53.61	*624* d=-2.39	*560* d=-1.19	*594* d=-1.83	*606* d=-2.05	*472* d=0.45

Legend: Electrode of interest is denoted in the table; PoA = place of articulation; MoA = manner of articulation; RW = real words; PW = pseudowords; T1 = first evaluation moment; T2 = evaluation after first intensive therapy; T3 = evaluation after conventional therapy; T4 = evaluation after second intensive therapy; T5 = evaluation after therapy-free period; M = mean; SD = standard deviation; amplitudes = µV; latencies = ms; d = effect size Cohen's *d*; 0.2 = small effect, 0.5 = medium effect, 0.8 = large effect

Table 8.3: Results bootstrap analysis for ERP amplitudes and latencies – overall therapy effect

	MMN PoA		MMN voicing		MMN MoA		P300 PoA		P300 voicing		P300 MoA		N400 RW		N400 PW	
	T1 – T4	T4 – T5	T1 – T4	T4 – T5	T1 – T4	T4 – T5	T1 – T4	T4 – T5	T1 – T4	T4 – T5	T1 – T4	T4 – T5	T1 – T4	T4 – T5	T1 – T4	T4 – T5
FP1						↓*							↑*		↑*	
F7		↓*													↑**	↓**
F3						↓*									↑*	
C3						↓*	↑*		↑*							
T3						↓*										
T5						↓**										
P3						↓*	↑*									
FPz							↑***		↑*	↓*	↑***	↓***			↑*	↓*
Fz							↑*								↑**	↓*
Cz				˅*		↓*	↑*	↓*	↑***	↓*		↓*			↑*	
Pz						↓*	↑*		↑**	↓*					↑*	
FP2						↓*	↑**	↓*				↓*			↑**	↓*
F8		↓*			↑*	↓**	↑*									↓*
F4		↓*			↑*	↓*	↑*	↓*	^*			↓*			↑*	
C4				˅*		↓*			↑***	↓**					↑*	
T4						↓*			↑*	↓**						
T6					↑*	↓*			↑*	↓*						↓*
P4							*↑^*		↑**	↓**					↑*	

Legend: T1 – T4 = after therapy period; T4 – T5 = after therapy-free period; ↑ = amplitude increase; ˅ = latency decrease; ↓ = amplitude decrease; ^ = latency increase; * p = <0.05; ** p = <0.01; *** p = <0.001; FP1 = left prefrontal electrode; F7 and F3 = left anterior frontal electrodes; C3 = left posterior frontal electrode; T3 = left anterior temporal electrode; T5 = left posterior temporal electrode; P3 = left parietal electrode; FPz = central prefrontal electrode; Fz = central anterior frontal electrode; Cz = central posterior frontal electrode; Pz = central parietal electrode; FP2 = right prefrontal electrode; F8 and F4 = right anterior frontal electrodes; C4 = right posterior frontal electrode; T4 = right anterior temporal electrode; T6 = right posterior temporal electrode; P4 = right parietal electrode.

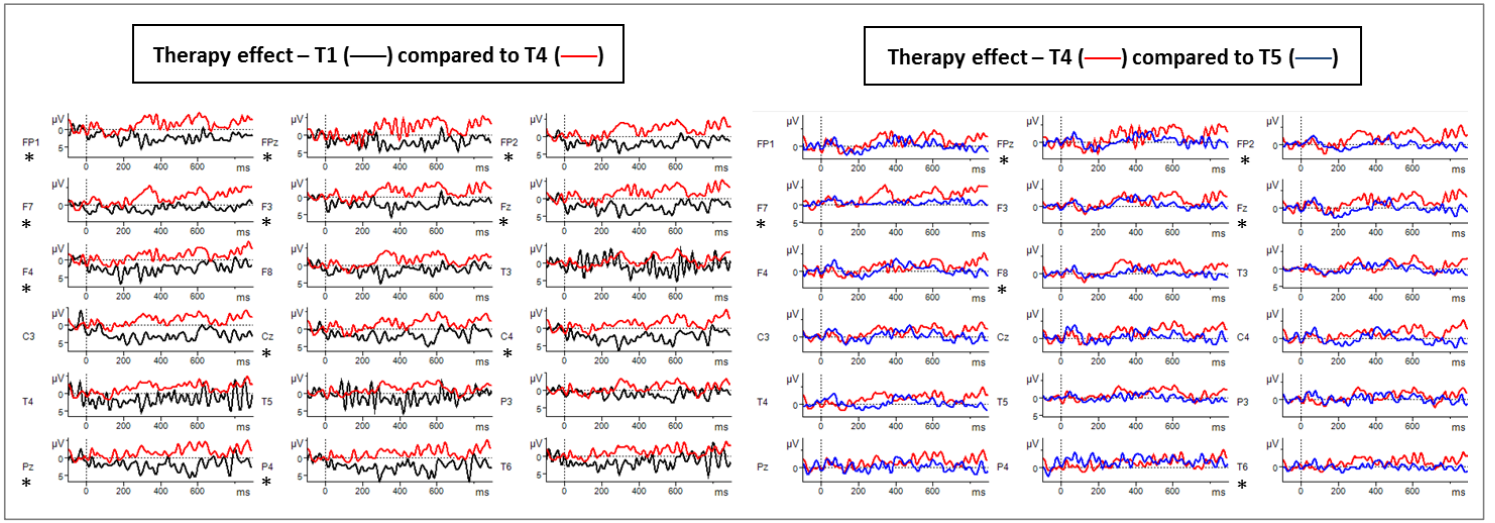

Figure 8.3: N400 in response to pseudowords before and after therapy (T1 – T4) and after the therapy free period (T4 – T5); T1 = first evaluation moment (black); T4 = evaluation after whole therapy period (red); T5 = evaluation after therapy-free period (blue); * = significant difference in the Bootstrap analysis.

3.2 Effect of therapy per period (T1-T2, T2-T3; T3-T4)

3.2.1 Behavioural results

Already after the first, intensive therapy period (T1-T2), AAT analyses indicated an overall significant improvement up to the level that the ALLOC classification does not allow to attribute the language problems to an aphasic syndrome (33.8 % certainty for aphasia), and classification into an aphasia type was not possible. No significant changes could be reported after the other therapy periods (T2-T3 and T3-T4). The score on PALPA 1 remained stable after the first, intensive therapy block (T1-T2), reduced significantly after the conventional therapy period (T2-T3) and restored again after the second, intensive therapy period (T3-T4). RL achieved the maximum score on PALPA 2 at every evaluation moment (T1-T2, T2-T3 and T3-T4). Lexical decision of pseudowords (PALPA 5), repetition of pseudowords (PALPA 8) and verbal attention (PALPA 12) showed a significant improvement after the first, intensive therapy period (T1-T2). None of the results changed significantly at the evaluation moments thereafter (T2-T3 and T3-T4). The effect sizes of all PALPA test are represented in Figure 8.4.

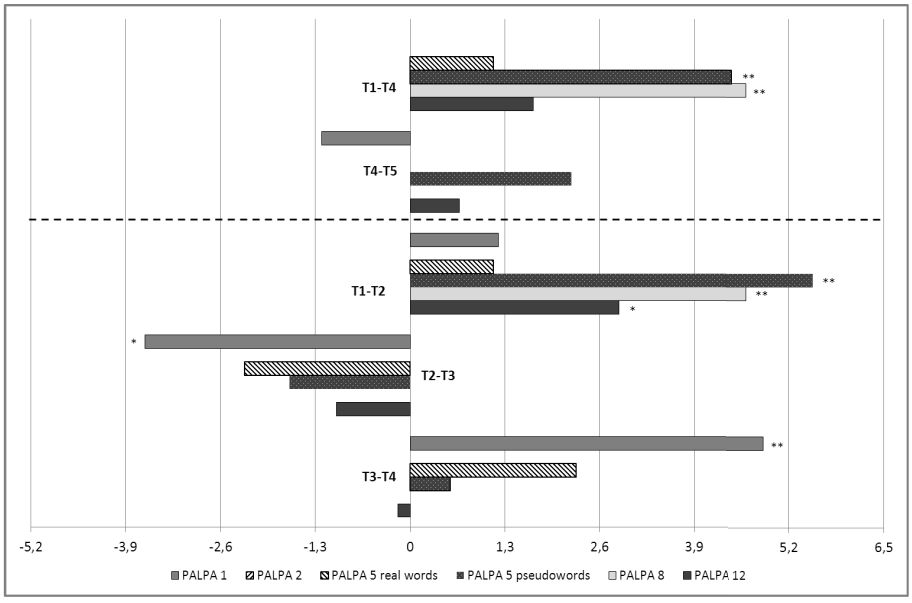

Figure 8.4: Overview of the effect sizes of all PALPA tests with respect to the overall therapy effect (above the striped line) and effect of therapy per period (underneath the striped line); T1 = first evaluation moment; T2 = evaluation after first intensive therapy; T3 = evaluation after conventional therapy; T4 = evaluation after second intensive therapy; T5 = evaluation after therapy-free period; * effect size > 2.6; ** effect size > 3.9.

3.2.2 Neurophysiological results

The topographical distribution of the amplitude and latency alterations after the first and second intensive (T1 – T2; T3 – T4) therapy and after the conventional (T2 – T3) therapy can be found in Table 8.4. A clear description of an interpretation of the electrode denomination is provided in the legend. The ERP waveform of the N400 PW before and after the intensive (T1 – T2; T3 – T4) and conventional (T2 – T3) therapy is represented in Figure 8.5.

3.2.2.1 Auditory phoneme discrimination

After the first intensive therapy (T1-T2) MMN PoA amplitude increased. P300 PoA amplitude decreased, while P300 PoA latency significantly increased. P300 MoA amplitude significantly increased.

After the conventional therapy (T2-T3) MMN PoA latency significantly increased. MMN MoA amplitude increased. P300 PoA, voicing and MoA amplitude increased.

After the second intensive therapy (T3-T4) MMN MoA amplitude decreased, whereas its latency decreased as well. P300 PoA amplitude was augmented, but P300 voicing and MoA amplitude decreased.

3.2.2.2 Auditory word recognition

After the first intensive therapy (T1-T2) N400 RW and N400 PW amplitude significantly increased.

After the conventional therapy (T2-T3) N400 PW amplitude decreased.

After the second intensive therapy (T3-T4) N400 PW amplitude increased.

Table 8.4: Results bootstrap analysis for ERP amplitudes and latencies – effect of therapy per period

	MMN PoA			MMN voicing			MMN MoA			P300 PoA			P300 voicing			P300 MoA			N400 RW			N400 PW		
	T1 – T2	T2 – T3	T3 – T4	T1 – T2	T2 – T3	T3 – T4	T1 – T2	T2 – T3	T3 – T4	T1 – T2	T2 – T3	T3 – T4	T1 – T2	T2 – T3	T3 – T4	T1 – T2	T2 – T3	T3 – T4	T1 – T2	T2 – T3	T3 – T4	T1 – T2	T2 – T3	T3 – T4
FP1		^*																				↑*		
F7		^*						↑**	↓*	↓*				↑*			↑**	↓**				↑**	↓*	↑**
F3	↑*	^*												↑*			↑*					↑**	↓**	↑**
C3		^*								↓*	↑**				↓*							↑*	↓*	
T3		^*						↑*						↑*	↓*								↓*	
T5										↓***				↑*			↑*	↓**						
P3																			↑*			↑**	↓*	
FPz		^*										↑***		↑*									↓*	↑**
Fz		^*										↑*										↑*	↓*	↑**
Cz		^*																				↑*	↓**	↑**
Pz		^*								^*	↑*			↑*		↑*						↑*	↓*	↑*
FP2		^*										↑*					↑**							↑*
F8		^*						↑*			↑*						↑*							
F4		^*										↑*		↑*								↑*		↑*
C4		^*									↑*			↑*								↑*	↓*	↑*
T4																↑*								
T6									˅*							↑*						↑*	↓**	↑*
P4		^*								*↓^*	↑*					↑*						↑**	↓**	↑*

Legend: T1 – T2 = after first intensive therapy; T2 – T3 = after conventional therapy; T3 – T4 = after second intensive therapy; ↑ = amplitude increase; ˅ = latency decrease; ↓ = amplitude decrease; ^ = latency increase; * p = <0.05; ** p = <0.01; *** p = <0.001; FP1 = left prefrontal electrode; F7 and F3 = left anterior frontal electrodes; C3 = left posterior frontal electrode; T3 = left anterior temporal electrode; T5 = left posterior temporal electrode; P3 = left parietal electrode; FPz = central prefrontal electrode; Fz = central anterior frontal electrode; Cz = central posterior frontal electrode; Pz = central parietal electrode; FP2 = right prefrontal electrode; F8 and F4 = right anterior frontal electrodes; C4 = right posterior frontal electrode; T4 = right anterior temporal electrode; T6 = right posterior temporal electrode; P4 = right parietal electrode.

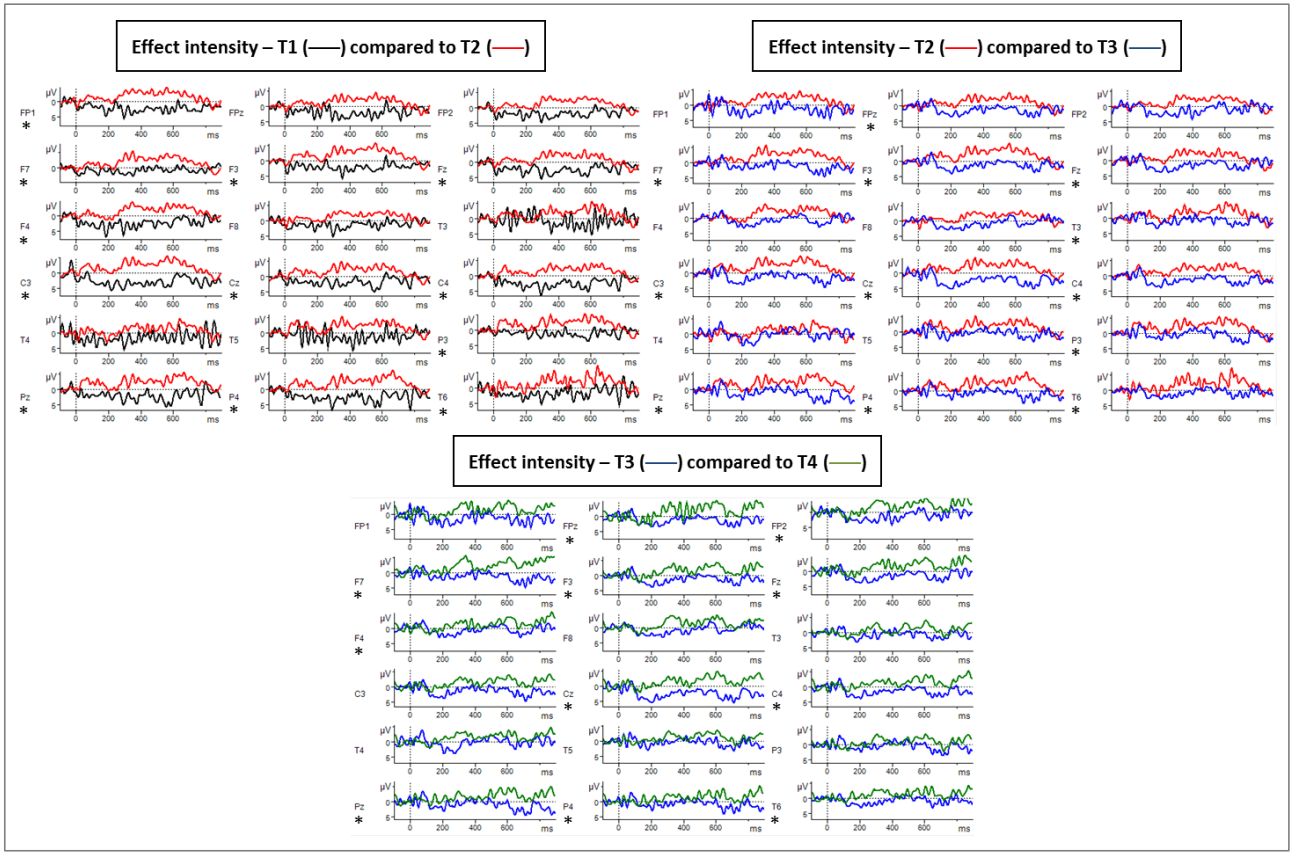

Figure 8.5: N400 in response to pseudowords before and after the intensive (T1 – T2; T3 – T4) and conventional (T2 – T3) therapy; T1 = first evaluation moment (black); T2 = evaluation after first intensive therapy (red); T3 = evaluation after conventional therapy (blue); T4 = evaluation after second intensive therapy (green); * = significant difference in the Bootstrap analysis.

4. Discussion

The aim of the present study was to objectify the effect of language therapy during the course of the first year after stroke and to compare the linguistic results achieved during the complete therapy period with the language abilities after a period without any form of language therapy. By further subdividing the whole therapy period into different therapy blocks, the present study sought to gain additional insight into possible therapy-related influencing variables.

After the complete language therapy period, RL showed a substantial improvement on all behavioural measures, except for verbal attention (PALPA 12). The neurophysiological measures confirmed the behavioural findings, as the P300, MMN (only for MoA) and N400 ERP components were aberrant before therapy when compared to normative data, and improved after therapy. Throughout the therapy-free period, the behavioural improvement was maintained and no additional progression was found. RL himself spontaneously reported no signs of decline or advance in his communicative abilities, although it was not confirmed with a self-reporting scale. In contrast to the behavioural results, neurophysiological correlates showed a decline after the therapy-free period. Based on these findings, RL seems to benefit from therapeutic intervention in the early phase after stroke, although the long-term effect is still a bit mixed due to the discrepancy between the behavioural and neurophysiological results. Continued follow-up would be necessary to identify further neurophysiological evolution and to get a better understanding of its relation to linguistic outcome. RL's therapeutic gain corresponds with the growing body of evidence for the efficacy of aphasia therapy early after stroke (Brady et al., 2012; Godecke et al., 2012; Mattioli et al., 2014). Despite these positive reports, two studies have recently postulated that language intervention early after stroke, in the acute and post-acute stage of aphasia is not beneficial (Bowen et al., 2012) or even not recommended (Laska et al., 2011). A possible explanation for the lack of therapy success in these studies might be the low intensity (maximum of 3 hours and 45 minutes per week) and the use of functional outcome measures rather than impairment-specific measures. Moreover, Bowen et al. (2012) did not differentiate between patients with dysarthria and patients with aphasia when interpreting the effect of language therapy, which might be considered as a methodological weakness. Another factor to take into account is that most studies investigating the effect of aphasia therapy, including the studies of Bowen et al. (2012) and Laska et al. (2011), are randomized controlled trials (RCTs). As illustrated above, such studies can lead to very contradictory conclusions regarding the usefulness of aphasia therapy, considering the complex heterogeneity of a group of patients with aphasia. This makes RCTs a criticized study design in aphasia research and therefore there has been a plea to encourage sufficiently detailed single-case patient studies and carry-out meta-analyses instead of using RCTs (Code, 2000; Robey et al., 1999). By focusing on a single patient

with aphasia, the present study contributed to a valuable collection of single-case studies investigating the effects of aphasia therapy early after stroke.

The implementation of neurophysiological measures in the present study made it possible to refine the diagnostic and therapeutic monitoring with respect to neuronal modulation. Linguistic changes were detected with neurophysiological tasks when no behavioural alterations were measurable. For example, neurophysiological correlates showed a decline after the therapy-free period, in contrast to the behavioural stagnation. The neurophysiological examination also obviated the problem of ceiling effects. Some behavioural measures (PALPA 1, 2, 5 RW) already reached the maximum scores at the first evaluation, whereas at that point the P300, MMN and N400 ERP components were aberrant when compared to normative data. These more refined results on the neurophysiological measures are in line with a previous study where patients with aphasia performed seemingly normal on behavioural language tasks, despite the fact that ERPs still revealed subtle deficiencies in central auditory processing (Becker & Reinvang, 2007). The neurophysiological measures also provided information about the effects of therapy on the neuronal localization of phonological input processes. After the therapy period the increased MMN MoA responses occurred in right-lateralized frontotemporal areas and the N400 PW increased significantly in bilateral anterior frontal areas and in right posterior frontoparietal areas. According to the recovery model posed by Saur et al. (2006), in the first weeks and months after stroke, an upregulation of homologue right hemisphere language areas can coincide with a significant improvement of language performance. So, it seems that a contribution of right hemispheric areas at this point after stroke was not counterproductive for RL. Moreover, the increased P300 responses in bilateral frontoparietal areas demonstrate an upregulation of lesional and perilesional areas in the left hemisphere. A re-shift to the left hemisphere might be related to a favourable neuronal reorganization and further beneficial recovery (Fridriksson et al., 2012). Thus, at 4 months post stroke, RL demonstrates a combination of recovery patterns. After the therapy-free period (1 year post-stroke) one would expect a higher participation of the left hemisphere, considering the time after RL's stroke (Saur & Hartwigsen, 2012; Saur et al., 2006), which could not be established for any of the ERPs. Moreover, there was even a significant decrease of left frontal areas for the MMN (PoA and MoA) and N400 PW. On the one hand, an unfavourable neurophysiological evolution might indicate that the length of therapy period was insufficient to progress towards a more normal activation pattern (Kleim & Jones, 2008; Van Hees et al., 2014). Perhaps when a re-shift towards the left hemisphere was already visible directly after the therapy period, the neuronal networks would have been strong enough to prevent a decrease. On the other hand, these neurophysiological alterations might reflect a change towards a more effective, yet modified pattern of neural activation supporting successful phonological input

processing after language therapy (Laganaro et al., 2008; Wilson et al., 2012). The implementation of neurophysiological measures clearly identifies therapeutic effects in terms of neuronal localization and modulation, which would not be possible when only the behavioural measures are considered. The combination of findings of the present case study and those of previous studies using ERPs in the monitoring of aphasia therapy definitely encourages the implementation of ERPs in therapeutic follow-up of patients with aphasia (Breier, Maher, Schmadeke, Hasan & Papanicolaou, 2007; Pulvermüller et al., 2005; Wilson et al., 2012).

Disentangling the intensive and conventional therapy within the present study reveals some form of dichotomy within the whole therapy period, as demonstrated by differences in the neurophysiological and behavioural outcome measures. After each intensive therapy period, all behavioural measures, except the ones showing a ceiling effect (PALPA 2 and PALPA 5 RW), revealed substantial improvement. This contrasts with the lack of an improvement on the behavioural measures, and even a small deterioration of auditory discrimination, after the conventional therapy period. The most striking neurophysiological difference between the intensive therapy and conventional therapy were the N400 alterations, especially the N400 in response to pseudowords (PW). After each intensive therapy block N400 PW increased, whereas after the conventional therapy the N400 PW amplitude decreased. The neurophysiological results reflect the results on the behavioural tests comprising pseudowords (PALPA 1, 5 PW and 8), which improve after intensive therapy and show a decline or a stagnation after the conventional therapy. Taken together with the ceiling effect being obviated by the N400 PW, it becomes clear that this neurophysiological correlate is sensitive enough to measure therapy effects. Moreover, the N400 PW can be seen as a pure linguistic measure, targeting sublexical representations which are essential for learning and processing new, unfamiliar or ambiguous words (Vitevitch, 2003). So, the intensive therapy periods seem to improve RL's capacity to address his sublexical capacities, which is important for fluent auditory language processing. With respect to the N400 RW, the same pattern as for the N400 PW is noticeable, but only after the first, intensive therapy period. The N400 amplitude increase in response to real words and pseudowords contrasts with another study applying the N400 potential to measure aphasia therapy effects, which demonstrated no differences in amplitudes pre- and post-therapy (Wilson et al., 2012). The clinical linguistic improvement of the patients with aphasia was associated with a shift from a more right-lateralized distribution to a more left-lateralized N400. On the other hand, intensive therapy has previously led to an amplitude increase between 250 and 300 ms in response to meaningful words (Pulvermüller et al., 2005). Together with the present study, these ERP changes confirm that intensive therapy can induce significant neurophysiological modifications.

However, when investigating therapeutic effects within the first months after stroke spontaneous neuronal recovery is an important confounding factor (Lazar, Speizer, Festa, Krakauer, & Marshall, 2008). The major part of recovery is expected to occur within the first three months after stroke (El Hachioui, van de Sandt-Koenderman, Dippel, Koudstaal, & Visch-Brink, 2011; Lendrem & Lincoln, 1985), but it is impossible to determine with certainty whether neurophysiological or behavioural changes observed in acute patients are due to pure neuronal reorganization or a by-product of a spontaneous restitution processes (Pulvermüller & Berthier, 2008). However, it seems that aphasia therapy within the acute stage has shown benefits over, or triggers spontaneous recovery (Godecke et al., 2012; Lazar et al., 2010), whereby intensity seems to play a critical role (Godecke et al., 2014). Furthermore, the linguistic decline after the conventional therapy period, which was still within the first three months after stroke, provides additional indication that the overall progression made by RL likely exceeds spontaneous recovery. The behavioural deterioration together with the lack of further improvement of the amplitude of the N400 PW after the conventional therapy favours at least a partial contribution of intensive treatment during the first therapy block.

Based on the above results, it can be suggested that RL benefited from intensive language treatment, as it yielded an important improvement in his linguistic performance compared to the stagnation or deterioration after the conventional therapy. Although all therapy periods consisted of impairment-based assignments, the specific content of all three therapy periods varied. The first intensive therapy period focussed on the mapping of phonological information onto semantic representations, while during the second intensive therapy sublexical processes were more emphasised. It was a conscious decision to adapt therapy content to RL's needs, based on the most recent diagnostic information available and according to clinical best practice. Notwithstanding, the variation in content might have affected the behavioural test results (Doesborgh et al., 2004) or neuronal mechanisms (van Hees et al., 2014), it cannot provide a sufficient answer why both intensive periods yield the same positive change of N400 PW in similar brain regions, which targets sublexical processes. Considering that duration and frequency of both intensive periods were equal, it is most likely that the intensity substantially influenced RL's therapeutic outcome. This can be supported by the majority of studies providing evidence for the efficacy of intensive treatment (e.g. Breitenstein et al., 2009; Meinzer et al., 2012; Pulvermuller et al., 2005; Pulvermuller et al., 2001, Godecke et al., 2013). Some studies claim that intensity does not provide an added value to therapy results (Bakheit et al., 2007; Hinckley & Carr, 2005). However, when taking a closer look at the methodology, there seems to be a difference compared to the present study concerning the actual definition of intensity and type of therapy. On the one hand, the present study introduced 10 hours per week as the intensive treatment, based on the results of Bhogal et al. (2003) which suggest that an average of 8.8

hours per week is necessary to achieve positive effects. Bakheit et al. (2007) introduced an intensive treatment of only 5 hours per week, so it is possible that this was not intensive enough to elicit potential therapy effects. On the other hand, in contrast with the present study which focused on an impairment-based approach, Hinckley and Carr (2005) provided a communicative-based therapy program. Taken together with the findings of Godecke et al. (2014), RL's behavioural and neurophysiological linguistic improvement seems to be based on the combination of three essential therapeutic elements, namely intensive, impairment-based treatment in the (sub) acute stage.

It must be mentioned that not all neurophysiological results were as straightforward as the N400 potential. The neurophysiological correlates of auditory discrimination (MMN and P300) fluctuated throughout both intensive therapy blocks. Dependent on the phonemic contrasts, amplitude increases as well as decreases occurred together with latency alterations. Considering that phonemic contrasts strongly rely on both acoustic-phonetic and sensorimotor properties (Digeser, Wohlberedt, & Hoppe, 2009; Obleser, Lahiri, & Eulitz, 2004; Pulvermüller et al., 2006), it is conceivable that they are very susceptible to neuronal modifications, which might explain the strong fluctuations throughout the course of therapy. Despite this apparent instability, a positive trend emerges when considering a longer timeframe. Thus, MMN and P300 are definitely worth including in a neurophysiological therapy-oriented evaluation (Ilvonen et al., 2003; Nolfe et al., 2006). It would be particularly interesting to investigate if these fluctuating results are inherent to recovery of aphasia in the first months after stroke or are due to methodological shortcomings of the present study.

5. Conclusion

RL benefited from early therapeutic intervention after stroke, as was shown by a general language improvement, marked by behavioural and neurophysiological indicators 4 months after stroke. It can be suggested that therapy intensity is one of the important variables throughout the therapy periods, which was supported by the stagnation and deterioration of language abilities after the conventional, non-intensive treatment. Implementing ERPs definitely provided added value during this therapy follow-up. Ceiling effects at the behavioural level could be obviated and underlying, advantageous or disadvantageous, neuronal activation patterns of certain behavioural improvements could be identified. The alterations of the N400 in particular proved to be very sensitive for mapping the effects of intensity on therapy progression. Moreover, the behavioural and neurophysiological evolution throughout the different therapy periods provides additional support that RL's early language improvement within the first 4 months after stroke most likely exceeds, at least in part, spontaneous recovery mechanisms.

6. References

Aerts, A., van Mierlo, P., Hartsuiker, R. J., Hallez, H., Santens, P., & De Letter, M. (2013). Neurophysiological investigation of phonological input: Aging effects and development of normative data. *Brain and Language, 125*(3), 253-263.

Aerts, A., Santens, P., & De Letter, M. (2012). [Flemish normative data of the first column PALPA 1 and PALPA 2]. Unpublished raw data.

Bakheit, A. M. O., Shaw, S., Barrett, L., Wood, J., Carrington, S., Griffiths, S., & Koutsi, F. (2007). A prospective, randomized, parallel group, controlled study of the effect of intensity of speech and language therapy on early recovery from poststroke aphasia. *Clinical Rehabilitation, 21*(10), 885-894.

Barthel, G., Meinzer, M., Djundja, D., & Rockstroh, B. (2008). Intensive language therapy in chronic aphasia: Which aspects contribute most? *Aphasiology, 22*(4), 408-421.

Bastiaanse, R., Bosje, M., & Visch-Brink, E. (1995). Psycholinguistic Assessment of Language Processing in Aphasia: The Dutch version: Hove, UK: Lawrence Erlbaum Associates Ltd.

Bastiaanse, R., Edwards, S., & Rispens, J. (2002). The verb and sentence test (VAST). *Thurston, Suffolk: Thames Valley Test Company*

Becker, F., & Reinvang, I. (2007). Successful syllable detection in aphasia despite processing impairments as revealed by event-related potentials. *Behavioral and Brain Functions, 3*(1), 6.

Belin, P., VanEeckhout, P., Zilbovicius, M., Remy, P., Francois, C., Guillaume, S., & Samson, Y. (1996). Recovery from nonfluent aphasia after melodic intonation therapy: A PET study. *Neurology, 47*(6), 1504-1511.

Bhogal, S. K., Teasell, R., & Speechley, M. (2003). Intensity of aphasia therapy, impact on recovery. *Stroke, 34*(4), 987-992.

Bowen, A., Hesketh, A., Patchick, E., Young, A., Davies, L., Vail, A., & Tyrrell, P. (2012). Effectiveness of enhanced communication therapy in the first four months after stroke for aphasia and dysarthria: a randomised controlled trial. *British Medical Journal, 345*, 15.

Brady, M. C., Kelly, H., Godwin, J., & Enderby, P. (2012). Speech and language therapy for aphasia following stroke. *Cochrane Database of Systematic Reviews*(5), 234.

Breier, J. I., Castillo, E. M., Boake, C., Billingsley, R., Maher, L., Francisco, G., & Papanicolaou, A. C. (2004). Spatiotemporal patterns of language-specific brain activity in patients with chronic aphasia after stroke using magnetoencephalography. *Neuroimage, 23*(4), 1308-1316.

Breier, J. I., Maher, L. M., Schmadeke, S., Hasan, K. M., & Papanicolaou, A. C. (2007). Changes in language-specific brain activation after therapy for aphasia using magnetoencephalography: A case study. *Neurocase, 13*(3), 169-177.

Breitenstein, P. D. C., Kramer, K., Meinzer, M., Baumgärtner, A., Flöel, A., & Knecht, S. (2009). Intensives Sprachtraining bei Aphasie. *Der Nervenarzt, 80*(2), 149-154.

Cherney, L. R., Patterson, J. P., Raymer, A., Frymark, T., & Schooling, T. (2008). Evidence-Based Systematic Review: Effects of Intensity of Treatment and Constraint-Induced Language Therapy for Individuals With Stroke-Induced Aphasia. *Journal of Speech Language and Hearing Research, 51*(5), 1282-1299.

Code, C. (2000). The problem with RCTs. *RCSLT Bulletin, 574*, 14-15.

Code, C., Torney, A., Gildea-Howardine, E., & Willmes, K. (2010). Outcome of a one-month therapy intensive for chronic aphasia: variable individual responses. *Semin Speech Lang, 31*(1), 21-33.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciencies*: Routledge.

Corsten, S., Mende, M., Cholewa, J., & Huber, W. (2007). Treatment of input and output phonology in aphasia: A single case study. *Aphasiology, 21*(6-8), 587-603.

Csépe, V., Osman-Sági, J., Molnár, M., & Gósy, M. (2001). Impaired speech perception in aphasic patients: event-related potential and neuropsychological assessment. *Neuropsychologia, 39*(11), 1194-1208.

Davis, C. H., Harrington, G., & Baynes, K. (2006). Intensive semantic intervention in fluent aphasia: A pilot study with fMRI. *Aphasiology, 20*(1), 59-83.

de Jong-Hagelstein, M., van de Sandt-Koenderman, W. M. E., Prins, N. D., Dippel, D. W. J., Koudstaal, P. J., & Visch-Brink, E. G. (2011). Efficacy of early cognitive-linguistic treatment and communicative treatment in aphasia after stroke: a randomised controlled trial (RATS-2). *Journal of Neurology Neurosurgery and Psychiatry, 82*(4), 399-404.

Dickey, L., Kagan, A., Lindsay, M. P., Fang, J. M., Rowland, A., & Black, S. (2010). Incidence and Profile of Inpatient Stroke-Induced Aphasia in Ontario, Canada. *Archives of Physical Medicine and Rehabilitation, 91*(2), 196-202.

Digeser, F. M., Wohlberedt, T., & Hoppe, U. (2009). Contribution of Spectrotemporal Features on Auditory Event-Related Potentials Elicited by Consonant-Vowel Syllables. *Ear and Hearing, 30*(6), 704-712.

Doesborgh, S. J. C., van de Sandt-Koenderman, M. W. E., Dippel, D. W. J., van Harskamp, F., Koudstaal, P. J., & Visch-Brink, E. G. (2004). Effects of semantic treatment on verbal communication and linguistic processing in aphasia after stroke - A randomized controlled trial. *Stroke, 35*(1), 141-146.

El Hachioui, H., van de Sandt-Koenderman, M. W. M. E., Dippel, D. W. J., Koudstaal, P. J., & Visch-Brink, E. G. (2011). A 3-year evolution of linguistic disorders in aphasia after stroke. *International Journal of Rehabilitation Research, 34*(3), 215-221.

Ferreira-Santos, F., Silveira, C., Almeida, P. R., Palha, A., Barbosa, F., & Marques-Teixeira, J. (2012). The auditory P200 is both increased and reduced in schizophrenia? A meta-analytic dissociation of the effect for standard and target stimuli in the oddball task. *Clinical Neurophysiology, 123*(7), 1300-1308.

Field, A. (2009). *Discovering statistics using SPSS*: Sage publications.

Fridriksson, J., Richardson, J. D., Fillmore, P., & Cai, B. (2012). Left hemisphere plasticity and aphasia recovery. *Neuroimage, 60*(2), 854-863.

Ghyselinck, M., Custers, R., & Brysbaert, M. (2003). Age-of-acquisition ratings for 2332 Dutch words from 49 different semantic categories. *Psychologica Belgica, 43* (3), 181-214.

Godecke, E., Hird, K., Lalor, E. E., Rai, T., & Phillips, M. R. (2012). Very early poststroke aphasia therapy: a pilot randomized controlled efficacy trial. *International Journal of Stroke, 7*(8), 635-644.

Godecke, E., Rai, T., Ciccone, N., Armstrong, E., Granger, A., & Hankey, G. J. (2013). Amount of Therapy Matters in Very Early Aphasia Rehabilitation after Stroke: A Clinical Prognostic Model. *Seminars in Speech and Language, 34*(3), 129-141.

Godecke, E., Ciccone, N. A., Granger, A. S., Rai, T., West, D., Cream, A., & Hankey, G. J. (2014). A comparison of aphasia therapy outcomes before and after a Very Early Rehabilitation programme following stroke. *International Journal of Language & Communication Disorders, 49*(2), 149-161.

Graetz, P., De Bleser, R., & Willmes, K. (2005). *Akense afasie test*: Harcourt Test Publishers.

Heiss, W. D., & Thiel, A. (2006). A proposed regional hierarchy in recovery of post-stroke aphasia. *Brain and Language, 98*(1), 118-123.

Hinckley, J. J., & Carr, T. H. (2005). Comparing the outcomes of intensive and non-intensive context-based aphasia treatment. *Aphasiology, 19*(10-11), 965-974.

Ilvonen, T.-M., Kujala, T., Kiesiläinen, A., Salonen, O., Kozou, H., Pekkonen, E., & Näätänen, R. (2003). Auditory Discrimination After Left-Hemisphere Stroke A Mismatch Negativity Follow-Up Study. *Stroke, 34*(7), 1746-1751.

Kauhanen, M. L., Korpelainen, J. T., Hiltunen, P., Maatta, R., Mononen, H., Brusin, E., & Myllyla, V. V. (2000). Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. *Cerebrovascular Diseases, 10*(6), 455-461.

Kawohl, W., Bunse, S., Willmes, K., Hoffrogge, A., Buchner, H., & Huber, W. (2010). Semantic event-related potential components reflect severity of comprehension deficits in aphasia. *Neurorehabilitation and neural repair, 24*(3), 282-289.

Kendall, D. L., Nadeau, S. E., Conway, T., Fuller, R. H., Riestra, A., & Rothi, L. J. G. (2006). Treatability of different components of aphasia - Insights from a case study. *Journal of Rehabilitation Research and Development, 43*(3), 323-335.

Keuleers, E., Brysbaert, M., & New, B. (2010). SUBTLEX-NL: A new measure for Dutch word frequency based on film subtitles. *Behavior Research Methods, 42*(3), 643-650.

Kim, M., & Tomaino, C. A. (2008). Protocol Evaluation for Effective Music Therapy for Persons with Nonfluent Aphasia. *Topics in Stroke Rehabilitation, 15*(6), 555-569.

Kirmess, M., & Maher, L. M. (2010). Constraint induced language therapy in early aphasia rehabilitation. *Aphasiology, 24*(6-8), 725-736.

Kleim, J. A., & Jones, T. A. (2008). Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *Journal of Speech, Language, and Hearing Research*, *51*(1), S225-S239.

Kurland, J., Pulvermueller, F., Silva, N., Burke, K., & Andrianopoulos, M. (2012). Constrained Versus Unconstrained Intensive Language Therapy in Two Individuals With Chronic, Moderate-to-Severe Aphasia and Apraxia of Speech: Behavioral and fMRI Outcomes. *American Journal of Speech-Language Pathology, 21*(2), S65-S87.

Kutas, M., & Hillyard, S. A. (1980). Reading senseless sentences: Brain potentials reflect semantic incongruity. *Science, 207*(4427), 203-205.

Kwon, M. S., Huotilainen, M., Shestakova, A., Kujala, T., Naatanen, R., & Hamalainen, H. (2010). No Effects of Mobile Phone Use on Cortical Auditory Change-Detection in Children: An ERP Study. *Bioelectromagnetics, 31*(3), 191-199.

Laganaro, M., Morand, S., Schwitter, V., Zimmermann, C., & Schnider, A. (2008). Normalisation and increase of abnormal ERP patterns accompany recovery from aphasia in the post-acute stage. *Neuropsychologia, 46*(8), 2265-2273.

Laska, A. C., Kahan, T., Hellblom, A., Murray, V., & von Arbin, M. (2011). A randomized controlled trial on very early speech and language therapy in acute stroke patients with aphasia. *Cerebrovasc Dis Extra, 1*(1), 66-74.

Lazar, R. M., Speizer, A. E., Festa, J. R., Krakauer, J. W., & Marshall, R. S. (2008). Variability in language recovery after first-time stroke. *Journal of Neurology Neurosurgery and Psychiatry, 79*(5), 530-534.

Leger, A., Demonet, J. F., Ruff, S., Aithamon, B., Touyeras, B., Puel, M., & Cardebat, D. (2002). Neural substrates of spoken language rehabilitation in an aphasic patient: An fMRI study. *Neuroimage, 17*(1), 174-183.

Lendrem, W., & Lincoln, N. B. (1985). Spontaneous-recovery of language in patients with aphasia between 4 and 34 weeks after stroke. *Journal of Neurology Neurosurgery and Psychiatry, 48*(8), 743-748.

Lin, Y., Wu, W., Wu, C., Liu, B., & Gao, X. (2013). Extraction of mismatch negativity using a resampling-based spatial filtering method. *Journal of Neural Engineering, 10*(2).

Maher, L. M., Kendall, D., Swearengin, J. A., Rodriguez, A., Leon, S. A., Pingel, K., & Rothi, L. J. G. (2006). A pilot study of use-dependent learning in the context of Constraint Induced Language Therapy. *Journal of the International Neuropsychological Society, 12*(6), 843-852.

Marsi, E., Busser, B., Daelemans, W., Hoste, V., & Reynaert, M. (2002). Combining information sources for memory-based pitch accent placement. *International Conference on Spoken Language Processing, Denver Co*, 1273-1276.

Mattioli, F., Ambrosi, C., Mascaro, L., Scarpazza, C., Pasquali, P., Frugoni, M., & Gasparotti, R. (2014). Early Aphasia Rehabilitation Is Associated With Functional Reactivation of the Left Inferior Frontal Gyrus A Pilot Study. *Stroke, 45*(2), 545-552.

Meinzer, M., Djundja, D., Barthel, G., Elbert, T., & Rockstroh, B. (2005). Long-term stability of improved language functions in chronic aphasia after constraint-induced aphasia therapy. *Stroke, 36*(7), 1462-1466.

Meinzer, M., Elbert, T., Wienbruch, C., Djundja, D., Barthel, G., & Rockstroh, B. (2004). Intensive language training enhances brain plasticity in chronic aphasia. *BMC Biol, 2*, 20.

Meinzer, M., Flaisch, T., Breitenstein, C., Wienbruch, C., Elbert, T., & Rockstroh, B. (2008). Functional re-recruitment of dysfunctional brain areas predicts language recovery in chronic aphasia. *Neuroimage, 39*(4), 2038-2046.

Meinzer, M., Rodriguez, A. D., & Rothi, L. J. G. (2012). First Decade of Research on Constrained-Induced Treatment Approaches for Aphasia Rehabilitation. *Archives of Physical Medicine and Rehabilitation, 93*(1), S35-S45.

Meinzer, M., Streiftau, S., & Rockstroh, B. (2007). Intensive language training in the rehabilitation of chronic aphasia: Efficient training by laypersons. *Journal of the International Neuropsychological Society, 13*(5), 846-853.

Näätänen, R., Gaillard, A. W. K., & Mäntysalo, S. (1978). Early selective-attention effect on evoked potential reinterpreted. *Acta psychologica, 42*(4), 313-329.

Nolfe, G., Cobianchi, A., Mossuto-Agatiello, L., & Giaquinto, S. (2006). The role of P300 in the recovery of post-stroke global aphasia. *European journal of neurology, 13*(4), 377-384.

Obleser, J., Lahiri, A., & Eulitz, C. (2004). Magnetic brain response mirrors extraction of phonological features from spoken vowels. *Journal of Cognitive Neuroscience, 16*(1), 31-39.

Oruc, I., Krigolson, O., Dalrymple, K., Nagamatsu, L. S., Handy, T. C., & Barton, J. J. S. (2011). Bootstrap analysis of the single subject with event related potentials. *Cognitive Neuropsychology, 28*(5), 322-337.

Parker, R. I. (2006). Increased reliability for single-case research results: Is the bootstrap the answer? *Behavior Therapy, 37*(4), 326-338.

Picton, T. W., Bentin, S., Berg, P., Donchin, E., Hillyard, S. A., Johnson, R., & Taylor, M. J. (2000). Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. *Psychophysiology, 37*(2), 127-152.

Pulvermuller, F., & Berthier, M. L. (2008). Aphasia therapy on a neuroscience basis. *Aphasiology, 22*(6), 563-599.

Pulvermuller, F., Hauk, O., Zohsel, K., Neininger, B., & Mohr, B. (2005). Therapy-related reorganization of language in both hemispheres of patients with chronic aphasia. *Neuroimage, 28*(2), 481-489.

Pulvermüller, F., Huss, M., Kherif, F., del Prado Martin, F. M., Hauk, O., & Shtyrov, Y. (2006). Motor cortex maps articulatory features of speech sounds. *Proceedings of the National Academy of Sciences, 103*(20), 7865-7870.

Pulvermüller, F., Mohr, B., & Lutzenberger, W. (2004). Neurophysiological correlates of word and pseudo-word processing in well-recovered aphasics and patients with right-hemispheric stroke. *Psychophysiology, 41*(4), 584-591.

Pulvermuller, F., Neininger, B., Elbert, T., Mohr, B., Rockstroh, B., Koebbel, P., & Taub, E. (2001). Constraint-induced therapy of chronic aphasia after stroke. *Stroke, 32*(7), 1621-1626.

Robey, R. R., Schultz, M. C., Crawford, A. B., & Sinner, C. A. (1999). Single-subject clinical-outcome research: designs, data, effect sizes, and analyses. *Aphasiology, 13*(6), 445-473.

Rochon, E., Leonard, C., Burianova, H., Laird, L., Soros, P., Graham, S., & Grady, C. (2010). Neural changes after phonological treatment for anomia: An fMRI study. *Brain and language, 114*(3), 164-179.

Rousselet, G. A., Husk, J. S., Pernet, C. R., Gaspar, C. M., Bennett, P. J., & Sekuler, A. B. (2009). Age-related delay in information accrual for faces: Evidence from a parametric, single-trial EEG approach. *Bmc Neuroscience, 10*.

Saur, D., & Hartwigsen, G. (2012). Neurobiology of Language Recovery After Stroke: Lessons From Neuroimaging Studies. *Archives of Physical Medicine and Rehabilitation, 93*(1), S15-S25.

Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., & Weiller, C. (2006). Dynamics of language reorganization after stroke. *Brain, 129*, 1371-1384.

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. *Science, 150*(3700), 1187-1188.

Szaflarski, J. P., Ball, A., Grether, S., Al-Fwaress, F., Griffith, N. M., Neils-Strunjas, J., & Reichhardt, R. (2008). Constraint-induced aphasia therapy stimulates language recovery in patients with chronic aphasia after ischemic stroke. *Medical Science Monitoring, 14*(5), CR243-250.

Tyler, L. K., Wright, P., Randall, B., Marslen-Wilson, W. D., & Stamatakis, E. A. (2010). Reorganization of syntactic processing following left-hemisphere brain damage: does right-hemisphere activity preserve function? *Brain, 133*, 3396-3408.

van Hees, S., McMahon, K., Angwin, A., de Zubicaray, G., & Copland, D. A. (2014). Neural activity associated with semantic versus phonological anomia treatments in aphasia. *Brain and language*, *129*, 47-57.

Van Strien, J. W. (1992). Classificatie van links- en rechtshandige proefpersonen. *Nederlands tijdschrift voor de psychologie, 47*, 88-92.

Visch-Brink, E., Denes, G., & Stachowiak, F. (1993). A European base-line test for word-picture processing. *Developments in the Assessment and Rehabilitation of Brain-Damaged Patients. Tubingen, Germany: Gunter Narr Verlag*, 211-216.

Vitevitch, M. S. (2003). The influence of sublexical and lexical representations on the processing of spoken words in English. *Clinical Linguistics & Phonetics, 17*(6), 487-499.

Wilson, K. R., O'Rourke, H., Wozniak, L. A., Kostopoulos, E., Marchand, Y., & Newman, A. J. (2012). Changes in N400 topography following intensive speech language therapy for individuals with aphasia. *Brain and Language, 123*(2), 94-103.

Wisenburn, B., & Mahoney, K. (2009). A meta-analysis of word-finding treatments for aphasia. *Aphasiology, 23*(11), 1338-1352.

CHAPTER 9

Spatio-temporal differentiation of neural activity in auditory and motor regions during pre-attentive and attentive phoneme discrimination

Aerts, A., Strobbe, G., van Mierlo, P., Hartsuiker, R.J., Corthals, P., Santens, P. & De Letter, M. (submitted). **Spatio-temporal differentiation of neural activity in auditory and motor regions during pre-attentive and attentive phoneme discrimination**. Behavioural Brain Research.

Abstract

Auditory phoneme discrimination (APD) is supported by both auditory and motor regions through a sensorimotor interface embedded in a fronto-temporo-parietal cortical network. However, the specific spatiotemporal organization of this network during APD with respect to different phonemic contrasts is still unclear. Here, we use source reconstruction, applied to event-related potentials in a group of 47 participants, in order to uncover a potential spatiotemporal differentiation in these brain regions during a passive and active APD task with respect to place of articulation (PoA), voicing and manner of articulation (MoA).

Results demonstrate that in an early stage (50-110 ms), auditory, motor and sensorimotor regions elicit more activation during the passive and active APD task with MoA and active APD task with voicing compared to PoA. In a later stage (130-175 ms), the same auditory and motor regions elicit more activation during the APD task with PoA compared to MoA and voicing, yet only in the active condition. Important timing differences during the active APD task are revealed as well. Degree of attention influences a fronto-parietal network during the APD task with PoA, whereas auditory regions are more affected during the APD task with MoA and voicing. No hemispheric differences are present during the passive or active APD tasks. Based on these findings, it can be carefully suggested that APD is supported by the integration of early activation of auditory-acoustic properties in superior temporal regions, more perpetuated for MoA and voicing, and later auditory-to-motor integration in sensorimotor areas, more perpetuated for PoA.

Keywords

Mismatch Negativity (MMN); P300; neurophysiology; electrical source reconstruction; phonology

1. Introduction

Auditory phoneme perception, identification and discrimination in the context of speech perception requires explicit access to certain sublexical speech segments, in contrast to phoneme perception in the context of more holistic speech recognition, and is supported by a dorsal processing stream running from posterior superior temporal gyrus (STG) via inferior parietal regions towards frontal regions (Friederici, 2011; Hickok and Poeppel, 2007; Saur et al., 2008). Initial, primary acoustic-phonetic analysis is subserved by the middle and posterior part of the STG and superior temporal sulcus (STS) bilaterally (Binder et al., 2000; DeWitt and Rauschecker, 2012; Friederici, 2011; Friederici, 2012; Hickok and Poeppel, 2004; 2007; Jäncke et al., 2002), although hemispheric asymmetries do occur (Boemio et al., 2005; Trébuchon-Da Fonseca et al., 2005; Zatorre and Belin, 2001). From then on, activation spreads from the posterior STG via the inferior parietal cortex to the motor cortex and inferior frontal gyrus (BA 44/45) along the superior longitudinal and arcuate fascicle (Burton, 2009; Friederici, 2009; Hickok and Poeppel, 2004; Hickok and Poeppel, 2007; Saur et al., 2008). Within the dorsal pathway, the inferior parietal cortex serves as an auditory-motor interface between auditory features and articulatory-based representations in achieving successful detection of phonological changes (Celsis et al., 1999; Hickok et al., 2003; Turkeltaub and Branch Coslett, 2010). Several studies have shown that the premotor and primary motor regions, usually active during speech production, are differentially activated in a somatotopic manner, based on articulatory characteristics of the phonemic contrasts, during phoneme perception and discrimination processes (e.g. activation of lip area during perception of bilabial place of articulation) (D'Ausilio et al., 2009; Meister et al., 2007; Pulvermüller et al., 2006; Pulvermüller and Fadiga, 2010; Wilson et al., 2004). Moreover, inferior frontal regions have been implicated in speech recognition as well (Binder et al., 1997; Kotz and Schwartze, 2010), when a new, non-familiar word or a pseudoword is encountered. Such word stimuli require more intensive segmentation processes and articulatory-based representations of the different segments (i.e. phonemes), hence sublexical processing, which involves more participation of frontal and motor areas within the dorsal circuitry (Burton, 2001; Burton, 2009; Londei et al., 2010; Zaehle et al., 2008).

Importantly, by measuring event-related potentials (ERPs) and estimating the source of this event-related electrical activity through non-invasive source reconstruction, some interesting findings have been revealed regarding the time course of neural activity during phoneme perception. Already 100 ms after phoneme presentation, based on the N100m (magnetic counterpart of the N100) and Mismatch Field, auditory association cortices (STG) are supposed to be spatially mapped along an anterior-posterior dimension determined by mutually exclusive place of articulation (PoA) features (Diesch and Luce, 1997; Obleser et al., 2003; Obleser et al., 2004; Obleser et al., 2006). Moreover,

even earlier, around 50 ms after phoneme presentation, neuronal generators of the P50m are topographically aligned in more primary auditory regions, such as Heschl's gyrus, along a medial-lateral dimension according to PoA features (Tavabi et al., 2007). Generally, ERPs like the P50 and N100 potential represent earlier, sensory-perceptual processes of phoneme detection and identification (Cooper et al., 2006; Tavabi et al., 2007), while ERPS like the (pre-attentive) Mismatch Negativity (MMN) and (attentive) P300 potential represent more phoneme discrimination processes (Linden, 2005; Näätänen et al., 1997). Furthermore, by comparing the neuronal generators of the MMN in a pre-attentive (passive) and attentive (active) condition, attentional variation was linked to greater participation of motor areas and inferior frontal regions during discrimination processes (Shtyrov et al., 2010).

Clearly, phonemic contrasts play a significant role in terms of neural activity in auditory and motor regions during phoneme perception and discrimination. Especially for PoA an important interaction has been demonstrated between the spatial mapping and temporal organization of neural activity associated with PoA features (Obleser et al., 2003; Tavabi et al., 2007). However, it is remarkable that phonemes have only been compared at opposite sides of one phonemic contrast continuum (e.g. /d/ and /g/ for PoA) with respect to their somatotopic organization in auditory and motor cortices, whereby the focus mainly was on the PoA features (D'Ausilio et al., 2009; Tavabi et al., 2007). This can be related to the more unambiguous, invariable articulatory gestures inherent to PoA features for which potentially more clear-cut spatial representations exist in the brain (Möttönen and Watkins, 2009). Such motor properties are less well distinguishable for phonemic contrasts like voicing (e.g. /d/ and /t/) and manner of articulation (MoA) (e.g. /d/ and /z/), for which perception and discrimination processes rely more on well-defined acoustic cues (Sinnott and Gilmore, 2004). On the contrary, acoustic cues of the PoA contrast are highly variable depending on the phonetic context, whereby invariant acoustic features are missing. Because of the different motor and acoustic nature of the phonemic contrasts PoA, voicing and MoA and the important temporal aspect of somatotopic spatial mapping, a spatiotemporal differentiation in auditory and motor cortical activity can be expected during phoneme discrimination based on these three contrasts.

The present study aims to investigate on the one hand whether phoneme discrimination based on PoA elicits more motor cortical activity, considering its lack of invariant acoustic cues and clear-cut motor representations, and on the other hand whether phoneme discrimination based on voicing or MoA evokes more auditory cortical activity, considering their well-defined acoustic features and unclear motor representations. Because of the important temporal aspect of neural activity during speech processing (MacGregor et al., 2012; Pulvermüller et al., 2003; Tavabi et al., 2007), the current study implements neurophysiological measures (MMN, P300) in response to an auditory oddball

paradigm on which source reconstruction is performed. As such, it is examined whether a spatial cortical pattern associated with a particular phonemic contrast occurs with a certain temporal differentiation compared to the other phonemic contrasts. A second part of the study was to compare pre-attentive, passive (MMN) and attentive, active (P300) phoneme discrimination for every phonemic contrast, to investigate whether effects of attention can be related to higher activation of frontal areas, which would be in line with a previous study demonstrating greater participation of motor and inferior frontal regions during attentive discrimination (Shtyrov et al., 2010).

2. Methods

2.1 Subjects

Forty-seven subjects (mean age: 47.64 years +/- 13.81) were included (23 male, 24 female). All persons investigated were right-handed, as verified with the Dutch Handedness Inventory (DHI; (Van Strien, 2003). All the participants had Dutch as native language and reported to have normal hearing. None of them had neurological, psychiatric or speech- and language developmental disorders. At time of testing, none of the participants was on medication. The study was approved by the Ethics Committee of the University Hospital Ghent (Belgium) and an informed consent was obtained from all the subjects.

2.2 Paradigm and stimuli

The experiment, an auditory phoneme discrimination (APD) task, consisted of three different auditory oddball paradigms both in a pre-attentive, passive and attentive, active condition. During the passive APD tasks, the subjects were instructed to ignore the stimuli and to focus their attention on a silent movie. During the active APD tasks, the subjects had to push a button every time they heard the infrequent stimulus. Within the passive and active APD tasks, each block consisted of 250 stimuli and 150 stimuli, respectively. The standard phoneme was /b/ and the deviant phonemes were /g/ (covering a PoA difference), /p/ (covering a voicing difference) and /m/ (covering a MoA difference) (Figure 9.1). A summary of the acoustic-phonetic composition of every phoneme as analysed with PRAAT (Boersma and Weenink, 2010) is provided in Table 9.1. The APD tasks were created in such a way that the standard and deviant stimulus only differed in one phonemic contrast. Stimuli were generated using the Dutch website NeXTeNS (http://nextens.uvt.nl/demo.html) where text was converted to speech (Marsi et al., 2002). In all stimulus blocks, the standard and deviant phoneme appeared with a probability of 0.80 and 0.20, respectively. The stimuli were presented in a random order in which two deviants could not follow each other without having a standard in between. All the spoken phonemes had a duration of 150 ms. The interstimulus interval (ISI) was set

at 500 ms in the passive APD tasks and 2000 ms in the active APD tasks. The stimuli were presented binaurally at 70 dB sound pressure level (SPL) using Apple Inc. earphones placed directly in the external ear.

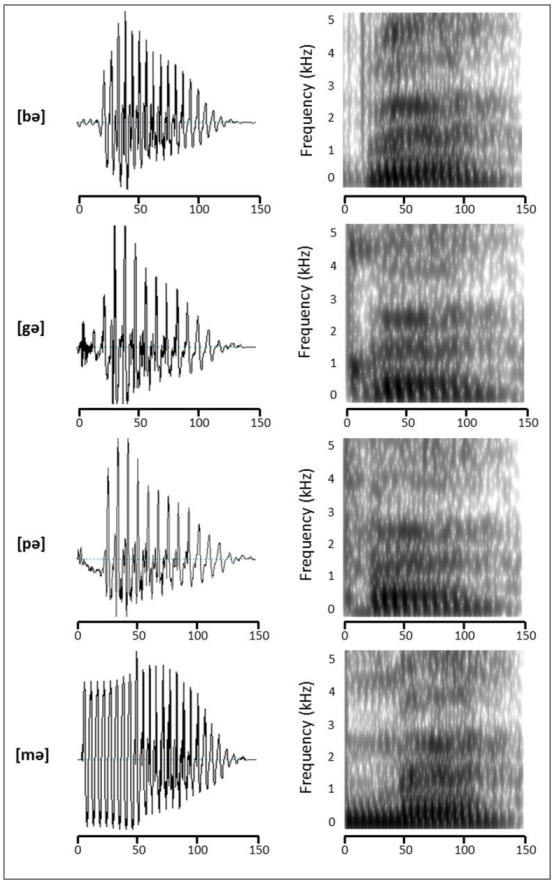

Figure 9.1: Phoneme stimuli and their spectrograms. The left-side column represents the speech waveforms of every phoneme in the time domain (150 ms duration). The right-side column represents their spectrograms in the frequency domain, with time on the x-axis and frequency (kHz) on the y-axis.

Table 9.1: Detailed acoustic-phonetic composition of the phoneme stimuli

	Standard /b/	PoA deviant /g/	Voicing deviant /p/	MoA deviant /m/
Voice-onset time (ms)	8	14	30	6
Formant frequencies (Hz)				
F0	151	135	136	152
F1	420	472	464	439
F2	1507	1435	1415	1476
F3	2331	2330	2318	2325
Formant transitions (Hz)				
F1				
minimum	256	368	430	194
maximum	417	450	469	421
% increase	38.2	17.4	8.5	51.8
F2				
minimum	1169	1135	1150	710
maximum	1442	1375	1395	1406
% increase	18.3	16.8	17.1	47.1
F3				
minimum	2294	2152	2277	2318
maximum	2336	2314	2352	2369
% increase	1.8	6.9	3.2	2.2
Intensity (dB)				
global	72.3	70.2	70.8	72.8
F1	48	46	45	46
dB re $_{\text{mean phoneme level}}$	-24.3	-24.2	-25.8	-26.8
F2	25	23	26	23
dB re $_{\text{mean phoneme level}}$	-47.3	-47.2	-44.8	-49.8
F3	24	22	22	19
dB re $_{\text{mean phoneme level}}$	-48.3	-48.2	-48.8	-53.8
Phonetic properties				
PoA	bilabial	velar	bilabial	bilabial
voicing	voiced	voiced	voiceless	voiced
MoA	oral	oral	oral	nasal

Legend: Formant transitions were measured as the frequency change between minimum and maximum formant frequency (of F1, F2 and F3) and were calculated with respect to the median formant frequency of the "midvowel" (=percentage increase). The global intensity of all phonemes was as good as equal, with only a maximum difference of 2.6 dB. The intensity of F1, F2 and F3 was measured with reference to this global intensity value (dB re $_{\text{mean phoneme level}}$). The negative sign indicates that formant intensity in a limited frequency band (± 50 Hz around median frequency) will always be smaller than the global intensity of the whole spectrum. Analyses were performed using PRAAT with the Burg-algorithm (Boersma and Weenink, 2010); ms = milliseconds; Hz = Hertz; F1 = first formant; F2 = second formant; F3 = third formant; dB = decibel; re = reference; PoA = place of articulation; MoA = manner of articulation.

2.3 Electroencephalogram (EEG) recording and analysis

The EEG (0.5 – 100 Hz band-pass, notch filter disabled) was recorded through 23 Ag/AgCl-electrodes using a linked earlobes reference and an electrode placed on the forehead as ground. Electrodes were placed on the scalp according to the international 10-20 system. The impedance of the electrodes was kept below 5 kΩ. Data was collected using a SynAmp (Neuroscan) amplifier and was continuously digitized at a 500 Hz sampling rate.

EEG analysis was performed using BrainVision Analyzer 2 (Brain Products, Munich, Germany). The EEG signal was filtered with a 0.5 – 30 Hz band-pass filter. Using independent component analysis (ICA) artefacts caused by eye movements were removed by excluding two components based on inspection of the components' spatial distribution. These components comprised blinking and horizontal and vertical eye movements (saccades). For the three active APD tasks the EEG was segmented into 1100 ms long epochs from 100 ms pre-stimulus to 1000 ms post-stimulus. For the three passive APD tasks the EEG was segmented into 500 ms long epochs from 100 ms pre-stimulus to 400 ms post-stimulus. The epochs were baseline corrected using a pre-stimulus window of 100 ms. All epochs containing artefacts exceeding 100 µV were rejected from further analysis, as were false responses in the active APD tasks (not responding to deviant, responding to standard). The data was converted to an average reference for further source reconstruction analysis. Standard and deviant trials were averaged separately. Difference waves were calculated only for the passive APD tasks to elicit the MMN by subtracting the average ERP of standard trials from the average ERP of deviant trials. Peak detection was carried out semi-automatically to measure peak latencies of the MMN in the passive APD tasks and peak latencies of the N100 and P300 in the active APD tasks. For the active APD tasks, button press responses to the deviant trials were analysed and reaction times and percentage of correct responses were calculated as well.

2.4 Source reconstruction

All analyses were performed in the Statistical Parametric Mapping 8 software package (SPM 8: Welcome Department of Cognitive Neurology, University College, London, United Kingdom) implemented in MATLAB (the MathWorks, Inc., Massachusetts, USA).

First, a sensor-space analysis was executed to search for time points with significant differences in activation between phonemic contrasts PoA, voicing and MoA and the passive and active APD tasks. In the sensor-space analysis, the ERP data for each trial and each condition were converted into 3D images. These were generated by constructing 2D, 64 x 64 voxels resolution, scalp maps for each time point (using interpolation to estimate the activation between the electrodes) and by stacking the scalp maps over peristimulus time, resulting in [64 x 64 x number of time points]-images (Litvak et al., 2011). Using these images, statistical analyses were performed for each condition. Paired t-

tests were used to calculate two-tailed, two-sided (both activations AND deactivations) F-contrasts for the main effect of phonemic contrast (PoA vs voicing; voicing vs MoA; PoA vs MoA) and main effect of attention (P300 vs MMN for every phonemic contrast). The resulting statistical parametric map (SPM) was family-wise error (FWE) corrected for multiple comparisons using Random Field Theory (Kiebel and Friston, 2004; Litvak et al., 2011; Worsley et al., 1996), which takes into account the spatial correlation across voxels (i.e., that the tests are not independent). The sensor analysis was performed to search for maximal differences between conditions, so time windows were not chosen based on the peaks of the evoked waveforms for statistical analysis at the source level (Gross et al., 2013).

In a next step, source reconstruction was executed at the significant time points from the sensor analysis. The default 3-layered scalp-skull-brain template head model (the MNI brain) was used based on the Colin27 template (Collins et al., 1998), implemented in the SPM software. The default electrode positions were transformed to match the template head model, in which 8196 dipoles are assumed on a template cortical surface mesh. During the reconstruction, the coordinate system in which the electrode positions were originally represented was coregistered with the coordinate system of the template head model (i.e., MNI coordinates), again using the default electrode positions. In a next step, the forward model was calculated for each dipole on the cortical mesh, based on assumptions about the physical properties of the head, using the “bemcp” method (BEM) implemented in FieldTrip (Oostenveld et al., 2011). Finally, the actual inverse reconstruction was performed at group level for every condition over the whole ERP time window and was based on an empirical approach using the multiple sparse priors (MSP) algorithm (Friston et al., 2008). Based on these reconstructions, 3D images were generated containing the evoked energy of the reconstructed activity in time windows corresponding with the significant time points from the sensor analysis. Using these images, additional second level analyses were performed to identify the most significant areas over subjects. Now, paired t-tests were used to calculate one-tailed, one sided (activations OR deactivations) T-contrasts for the main effect of phonemic contrast (PoA vs voicing; voicing vs MoA; PoA vs MoA) and main effect of attention (P300 vs MMN for every phonemic contrast). Having corrected for multiple comparisons at the sensor-level, an uncorrected p-value was set at 0.05 at the source level (Gross et al., 2013). The resulting MNI coordinates holding significant activation differences between conditions, were explored by means of the SPM Anatomy toolbox developed by Eickhoff et al. (2007). The resulting MNI coordinates were grouped to calculate the average activity of the following regions of interest: inferior frontal cortex (IFC), sensorimotor cortex (SMC), inferior parietal cortex (IPC) and superior temporal cortex (STC). Despite the seemingly limited spatial resolution inherent to less dense EEG recordings (as with the present study), it has been established

in previous research that low-density recordings provide an accurate estimate of the underlying ERP generators and are sufficient to fully describe the variance of a typical ERP data set collected during an auditory oddball paradigm, when compared to high-density recordings (Kayser and Tenke, 2006).

2.5 Additional statistical analyses

Additional statistical analyses were performed using IBM SPSS Statistics 22 on peak latencies in the passive and active APD tasks (MMN and N100/P300, respectively). For this, six clusters with the average latency of two electrodes were created, keeping midline electrodes separate: Anterior Left (F3, F7), Anterior Midline (Fz), Anterior Right (F4, F8), Central Left (T3, C3), Central Midline (Cz), Central Right (T4, C4), Posterior Left, (T5, P3) Posterior Midline (Pz), Posterior Right (T6, P4). Repeated measures ANOVA was carried out with factor contrasts (PoA vs. voicing vs. MoA), region (anterior vs. central vs. posterior) and laterality (left vs. midline vs. right). Reaction time of the button press in the active APD tasks was statistically analysed as well, using repeated measures ANOVA with the factor contrasts (PoA vs. voicing vs. MoA). Greenhouse-Geisser correction (GG) was applied when the assumption of sphericity was violated. Significance level was set at ≤ 0.05. Post-hoc pairwise comparisons were computed using Bonferroni correction.

3. Results

3.1 Behavioural results for the active APD tasks

Response rates show that the active APD tasks were rather easy. With PoA as phonemic contrast, 97.65 % of the deviant stimuli were identified, with voicing 96.8 % and with MoA 98.34 %. Subjects showed a mean response reaction time of 565.72 ms (+/- 80.32) with PoA, 561.35 ms (+/- 94.52) with voicing and 535.44 ms (+/- 85.63) with MoA. There was a significant main effect for the phonemic contrasts [F(2,90)=5.78, p=0.004]. Faster response times occurred for the phonemic contrast MoA compared to PoA (p=0.001) and voicing (p=0.047).

3.2 ERP waveforms

A MMN was elicited in the passive APD task for all three phonemic contrasts, but with differences in morphology (Figure 9.2). In the active APD task an N100 and P300 was elicited with all three phonemic contrasts, but without clear differences in morphology (Figure 9.3).

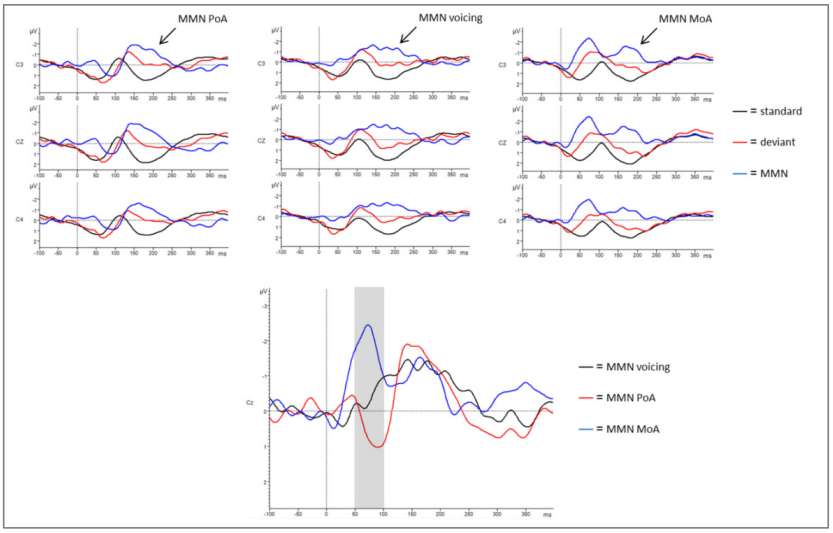

Figure 9.2: Grand average ERPs for the passive, pre-attentive phoneme discrimination paradigm (MMN). In the upper panel, grand averaged ERPs are depicted for C3, Cz and C4 showing the response to the standard and deviant stimulus and the difference waveform (black = standard; red = deviant; blue = difference waveform). In the lower panel, a detailed transcription is displayed at the Cz electrode with an overlay of the MMN in response to the three phonemic contrasts (black = voicing; red = PoA; blue = MoA). The time window (50 – 100 ms) which contains significant differences at source level during source reconstruction is indicated. Negative is plotted upwards.

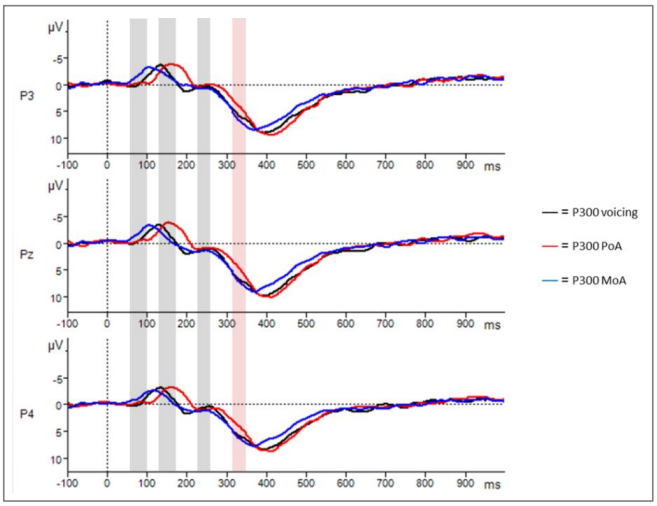

Figure 9.3: Grand average ERPs for the active, attentive phoneme discrimination paradigm (P300). Grand averaged ERPs are depicted for P3, Pz and P4 with an overlay of the three phonemic contrasts (black = voicing; red = PoA; blue = MoA) showing the response to the deviant stimulus. Three time windows (65 – 110 ms; 130 – 175 ms; 225 – 250 ms) containing significant differences at source level during source reconstruction are indicated in translucent blue. The last time window (310 – 340 ms) did not contain significantly different clusters at source level and is indicated in translucent red. Negative is plotted upwards.

3.3 Sensor analysis

3.3.1 Effect of phonemic contrast

Within the passive APD task, voxels with significant differences between PoA and voicing [$F(1,46)=28.43$, $p<0.001$, FWE-corrected], PoA and MoA [$F(1,46)=85.76$, $p<0.001$, FWE-corrected] and MoA and voicing [$F(1,46)=54.43$, $p<0.001$, FWE-corrected] were found within roughly the same time window, namely 50 – 100 ms after stimulus presentation. Within the ERP waveforms (Figure 9.2) this corresponds with an epoch before the onset of the actual MMN in which clear differences between negative and positive potentials are displayed. Within the active APD task, multiple time windows emerged with voxels holding significant differences between all three phonemic contrasts (Figure 9.3). In a first, early time window, between 65 and 110 ms, significant differences emerged between PoA and voicing [$F(1,46)=85.39$, $p<0.001$, FWE-corrected], PoA and MoA [$F(1,46)=112.10$, $p<0.001$, FWE-corrected] and MoA and voicing [$F(1,46)=41.02$, $p<0.001$, FWE-corrected]. Further on, in a second time window, between 130 and 175 ms, significant differences arose only between PoA and voicing [$F(1,46)=90.26$, $p<0.001$, FWE-corrected] and PoA and MoA [$F(1,46)=91.11$, $p<0.001$, FWE-corrected]. Lastly, a third (225 – 250 ms) time window only contained differences between PoA and MoA [$F(1,46)=36.18$, $p<0.001$, FWE-corrected], as did a fourth time window (310 – 340 ms) [$F(1,46)=35.23$, $p<0.001$, FWE-corrected].

3.3.2 Effect of attention

For all three phonemic contrasts, multiple time windows showed to have voxels with significant differences in activation between the active and passive APD task. Firstly, with PoA as phonemic contrast, significantly different voxels were found in four consecutive time windows, namely 100 – 130 ms [F(1,46)=26.96, p<0.001, FWE-corrected], 130 – 160 ms [F(1,46)=120.19, p<0.001, FWE-corrected], 190 – 240 ms [F(1,46)=64.01, p<0.001, FWE-corrected] and 370 – 400 ms [F(1,46)=115.23, p<0.001, FWE-corrected]. Secondly, with voicing as phonemic contrast, voxels with significant differences were found in three successive time windows being 100 – 130 ms [F(1,46)=107.32, p<0.001, FWE-corrected], 190 – 220 ms [F(1,46)=72.53, p<0.001, FWE-corrected] and 370 – 400 ms [F(1,46)=116.78, p<0.001, FWE-corrected]. Lastly, with MoA as phonemic contrast, significantly different voxels were found again in three successive time windows, namely 80 – 120 ms [F(1,46)=92.45, p<0.001, FWE-corrected], 150 – 210 ms [F(1,46)=107.73, p<0.001, FWE-corrected] and 370 – 400 ms [F(1,46)=67.00, p<0.001, FWE-corrected]. So roughly three time periods were distinguished: an early time period (80 – 160 ms) with an extra subdivision for PoA, an intermediate time period (190 – 240 ms) with an earlier start and end for MoA and a late time period (370 – 400 ms).

3.4 Source reconstruction

3.4.1 Effect of phonemic contrast

Passive APD task

50 – 100 ms. The passive APD task based on MoA elicited higher activation in bilateral sensorimotor regions compared to voicing [T(46)=4.28, p<0.001] and PoA [T(46)=4.05, p<0.001], inferior parietal regions compared to voicing [T(46)=2.79, p=0.004] and PoA [T(46)=3.05, p=0.002] and superior temporal regions compared to voicing [T(46)=3.64, p<0.001] and PoA [T(46)=3.66, p<0.001] (Figure 9.4). No differences in activation were detected in any of the regions of interest when voicing and PoA were compared. Additionally, based on the ERP waveforms (Figure 9.2), the time window with these activation differences (50 – 100 ms) corresponded to an epoch before the actual MMN onset and to a clear peak between 50 and 100 ms with MoA as phonemic contrast. No significant timing differences between the phonemic contrasts were found at the level of MMN peak latency.

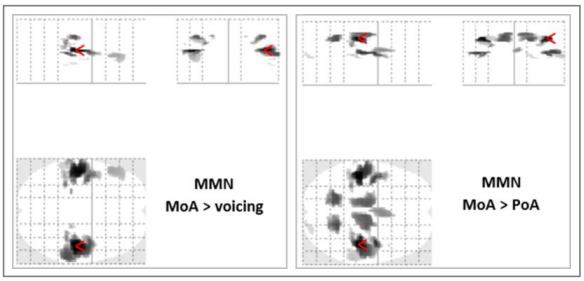

Figure 9.4: Maximum intensity projections (MIP) of differences between phonemic contrasts during the pre-attentive phoneme discrimination task. The maximum intensity is projected on a glass brain in three orthogonal planes; axial (bottom plot), sagittal (top left plot) and coronal (top right plot). In the top plots of each box the time course of the region(s) with statistical differences in maximal activity is represented, with time going from the bottom of the plot to the top. The bottom plot shows the MIP at the time of the maximal activation. The MIP can be seen as an image in which all relevant activity above the α=0.05 (uncorrected) threshold is superimposed in a certain direction (axial, sagittal, and coronal). The red arrow indicates the global maximum activity.

Active APD task

65 – 110 ms. The active APD task based on MoA elicited higher activation compared to PoA in left-lateralized inferior frontal [T(46)=2.25, p=0.015], bilateral sensorimotor [T(46)=4.85, p<0.001], inferior parietal [T(46)=3.94, p<0.001] and superior temporal regions [T(46)=4.27, p<0.001] and higher activation compared to voicing in bilateral sensorimotor areas [T(46)=2.84, p=0.003]. In turn, the active APD task based on voicing elicited higher activation in left-lateralized inferior frontal [T(46)=3.46, p=0.001], bilateral sensorimotor [T(46)=4.67, p<0.001], inferior parietal [T(46)=3.57, p<0.001] and superior temporal regions [T(46)=3.67, p<0.001] compared to PoA (Figure 9.5).

130 – 175 ms. In this time window, the difference between the active APD task based on MoA and voicing disappeared. Moreover, a reversed pattern emerged showing higher activation for PoA in left-lateralized inferior frontal regions compared to both voicing [T(46)=3.19, p=0.001] and MoA [T(46)=4.23, p<0.001], bilateral sensorimotor regions compared to both voicing [T(46)=3.79, p<0.001] and MoA [T(46)=3.90, p<0.001] and inferior parietal regions compared to both voicing [T(46)=3.12, p=0.002] and MoA [T(46)=2.94, p=0.003] with an additional higher activation in right-lateralized superior temporal regions for PoA compared to MoA [T(46)=2.52, p=0.008] (Figure 9.5). Based on the ERP waveforms (Figure 9.3), the established differences in this and the previous time window occurred around the N100 potential and were most likely related to latency differences between phonemic contrasts. This was confirmed by the region*contrasts interaction in the statistical analysis on the N100 peak latency [F(4,180)=15.27, p<0.001, GG ε=0.68]. Results revealed a longer latency for PoA compared to voicing (p=0.001) and MoA (p<0.001) and voicing compared to MoA (p<0.001) in

anterior regions, a longer latency for PoA ($p<0.001$ and voicing ($p<0.001$) compared to MoA in central regions and a longer latency for voicing compared to MoA ($p=0.003$) in posterior regions. Because of these latency differences, possible differences in activation in the regions of interest between phonemic contrasts are searched for in different segments of the N100 potential (i.e. onset and peak).

225 – 250 ms. In this subsequent time window, only the difference between PoA and MoA remained. Higher activation of bilateral sensorimotor [$T(46)=3.34$, $p=0.001$] and left-lateralized superior temporal regions [$T(46)=2.84$, $p=0.003$] was elicited during the active APD task with PoA compared to MoA (Figure 9.5). The difference that existed between phoneme discrimination based on PoA and voicing disappeared at this point in time.

310 – 340 ms. Although this time window emerged as holding significantly different voxels between PoA and MoA, statistical analysis on source level could not confirm this. Seeing that this time window corresponded to the onset of the P300 wave (Figure 9.3), it seems that no differences in activation in the regions of interest exist between phonemic contrasts during the actual phoneme discrimination process at source level. However, from the statistical analysis on the P300 peak latency a significant main effect for contrasts emerged, showing a longer latency for PoA compared to MoA [$F(2,90)=12.15$, $p<0.001$], which indicates that timing differences exist in the active APD task with PoA and MoA as phonemic contrast.

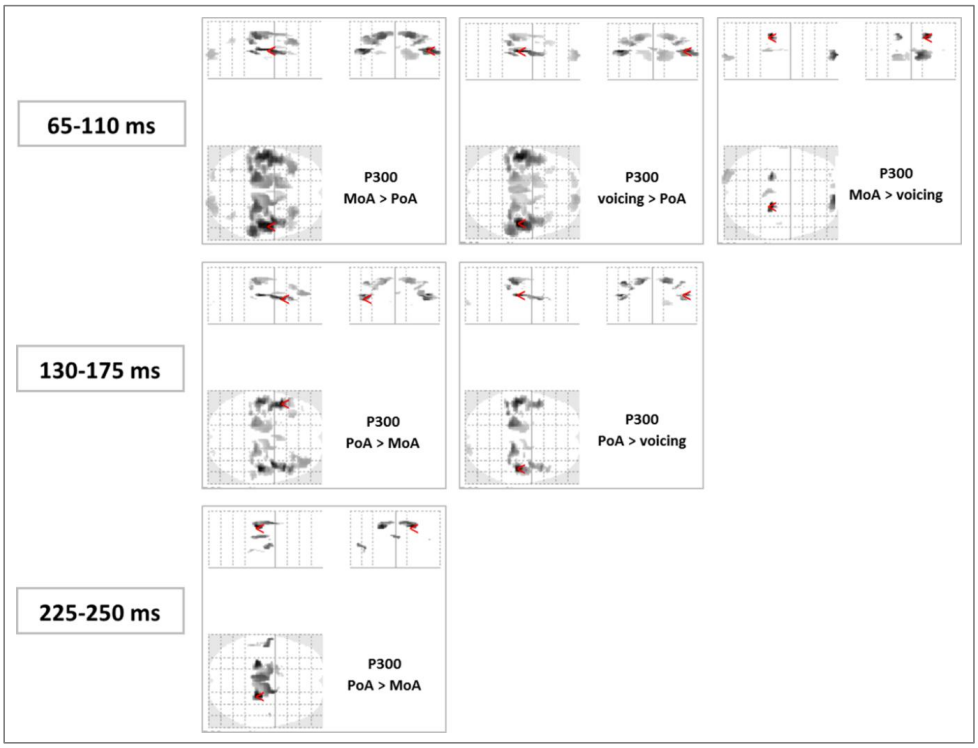

Figure 9.5: Maximum intensity projections (MIP) of differences between phonemic contrasts during the attentive phoneme discrimination task. The maximum intensity is projected on a glass brain in three orthogonal planes; axial (bottom plot), sagittal (top left plot) and coronal (top right plot). In the top plots of each box the time course of the region(s) with statistical differences in maximal activity is represented, with time going from the bottom of the plot to the top. The bottom plot shows the MIP at the time of the maximal activation. The MIP can be seen as an image in which all relevant activity above the α=0.05 (uncorrected) threshold is superimposed in a certain direction (axial, sagittal, and coronal). The red arrow indicates the global maximum activity.

Interim summary

The passive APD task based on MoA elicited more activation of sensorimotor, inferior parietal and superior temporal regions between 50 – 100 ms (Figure 9.6). The active APD task based on MoA and voicing elicited more activation of motor areas like inferior frontal, sensorimotor and inferior parietal regions and auditory superior temporal regions between 65 and 110 ms. A reversed pattern emerged between 130 – 175 ms, showing more activation in the same motor and auditory areas during the active APD task based on PoA instead of MoA and voicing (Figure 9.7). Finally, between 225 and 250 ms only the active APD task based on PoA evoked more sensorimotor and superior temporal activation. Between 310 – 340 ms, no differences in activation in the regions of interest were found between the phonemic contrasts during both the passive and active APD task, yet differences in P300

peak latency were present. Table 9.2 and Table 9.3 report the significant regions of interest with respect to the extent of voxels.

Table 9.2: Results of the source reconstruction for the comparison between the phonemic contrasts PoA, voicing and MoA during passive, pre-attentive phoneme discrimination (MMN).

Time window	*p*	*Cluster*	*Extent of voxels*	*Direction of difference*
50 – 100 ms	<0.001	L sensorimotor cortex	1116	MoA > PoA
	<0.001	R sensorimotor cortex	1131	
	0.004	L inferior parietal cortex	80	
	0.006	R inferior parietal cortex	51	
	0.001	L superior temporal cortex	425	
	0.020	R superior temporal cortex	79	
	<0.001	L sensorimotor cortex	695	MoA > voicing
	<0.001	R sensorimotor cortex	725	
	0.002	L inferior parietal cortex	124	
	0.003	R inferior parietal cortex	612	
	0.004	L superior temporal cortex	36	
	0.001	R superior temporal cortex	288	

Legend: Reported are clusters of interest holding MNI coordinates with significant differences between phonemic contrasts, of which the extent of voxels is stated. Only the most significant p-value within a significant cluster is displayed. The last column represents which phonemic contrast evoked the most energy; ms = millisecond; p = level of significance; L = left; R = right; PoA = place of articulation; MoA = manner of articulation.

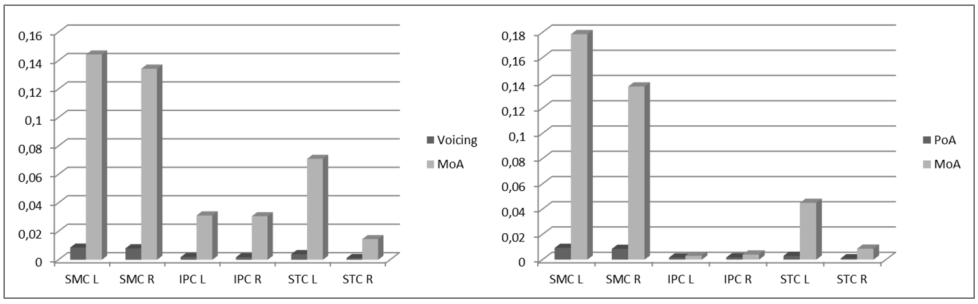

Figure 9.6: Differences in activity levels between phonemic contrasts during pre-attentive phoneme discrimination (MMN). The y-axis represents the amount of reconstructed activity per cluster (x-axis), which is a number without unit. On the x-axis the sensorimotor, inferior parietal and superior temporal cortex are displayed for the left and right hemisphere.

Table 9.3: Results of the source reconstruction for the comparison between the phonemic contrasts PoA, voicing and MoA during active, attentive phoneme discrimination (P300).

Time window	*p*	*Cluster*	*Extent of voxels*	*Direction of difference*
65 – 110 ms	0.029	L inferior frontal cortex	24	MoA > PoA
	<0.001	L sensorimotor cortex	1697	
	<0.001	R sensorimotor cortex	1736	
	<0.001	L inferior parietal cortex	157	
	0.001	R inferior parietal cortex	173	
	0.001	L superior temporal cortex	78	
	<0.001	R superior temporal cortex	197	
	0.001	L inferior frontal cortex	529	Voicing > PoA
	<0.001	L sensorimotor cortex	1366	
	<0.001	R sensorimotor cortex	1242	
	0.001	L inferior parietal cortex	149	
	0.001	R inferior parietal cortex	119	
	0.003	L superior temporal cortex	61	
	0.001	R superior temporal cortex	205	
	0.011	L sensorimotor cortex	93	MoA > voicing
	0.007	R sensorimotor cortex	129	
130 – 175 ms	<0.001	L inferior frontal cortex	398	PoA > MoA
	<0.001	L sensorimotor cortex	773	
	<0.001	R sensorimotor cortex	876	
	0.005	L inferior parietal cortex	30	
	0.008	R inferior parietal cortex	31	
	0.015	R superior temporal cortex	32	
	0.003	L inferior frontal cortex	243	PoA > voicing
	0.001	L sensorimotor cortex	703	
	<0.001	R sensorimotor cortex	573	
	0.003	L inferior parietal cortex	49	
	0.006	R inferior parietal cortex	35	
225 – 250 ms	0.002	L sensorimotor cortex	362	PoA > MoA
	0.002	R sensorimotor cortex	546	
	0.007	L superior temporal cortex	65	

Legend: Reported are clusters of interest holding MNI coordinates with significant differences between phonemic contrasts, of which the extent of voxels is stated. Only the most significant p-value within a significant cluster is displayed. The last column represents which phonemic contrast evoked the most energy; ms = millisecond; p = level of significance; L = left; R = right; PoA = place of articulation; MoA = manner of articulation.

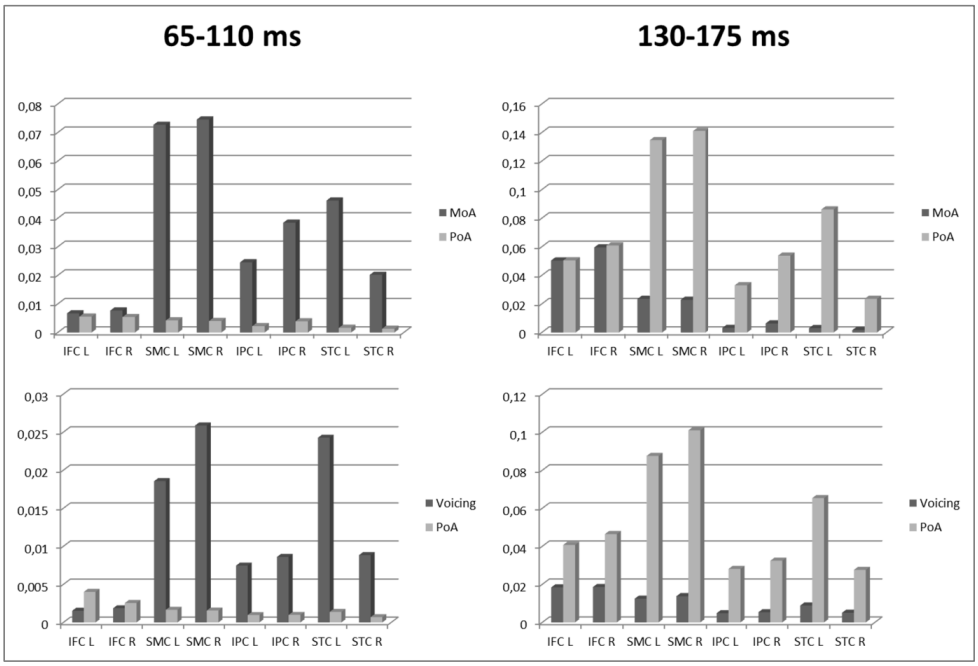

Figure 9.7: Differences in activity levels between phonemic contrasts during attentive phoneme discrimination (P300) represented in the first two time windows. The y-axis represents the amount of reconstructed activity per cluster (x-axis), which is a number without unit. On the x-axis the inferior frontal, sensorimotor, inferior parietal and superior temporal cortex are shown for the left and right hemisphere.

3.4.2 Effect of attention

Phonemic contrast PoA

Early time window (80 – 160 ms). For the APD task based on PoA there was an extra subdivision within this time window. Between 100 and 130 ms higher activation was elicited in bilateral inferior frontal [T(46)=3.97, p<0.001], sensorimotor [T(46)=2.68, p=0.005] and left-lateralized inferior parietal regions [T(46)=2.43, p=0.009] during the passive APD task. However, in the second time window (130 – 160 ms) a reversed pattern emerged and higher activation of bilateral sensorimotor [T(46)=3.47, p=0.001] and inferior parietal areas [T(46)=2.84, p=0.003] was elicited during the active APD task without bilateral inferior frontal activation (Figure 9.8).

Intermediate time window (190 – 240 ms). In this time window the passive APD task evoked more activation in left-lateralized inferior parietal regions compared to the active APD task with PoA as phonemic contrast [T(46)=2.15, p=0.018] (Figure 9.8). Differences in activation in the other regions were not present anymore.

Late time window (370 – 400 ms). Finally, at this point in time again higher activation in bilateral inferior frontal [T(46)=4.37, p<0.001], sensorimotor [T(46)=3.11, p=0.002] and inferior parietal regions [T(46)=3.09, p=0.002] was elicited during the active APD task compared to the passive APD task (Figure 9.8).

Phonemic contrast voicing

Early time window (80 – 160 ms). During the APD task based on voicing the passive APD task elicited more activation only in bilateral sensorimotor regions [T(46)=2.72, p=0.005] (Figure 9.8).

Intermediate time window (190 – 240 ms). In a later time window the passive APD task evoked higher activation in bilateral inferior frontal [T(46)=3.69, p<0.001], sensorimotor [T(46)=2.72, p=0.005], inferior parietal [T(46)=2.83, p=0.002] and superior temporal regions [T(46)=2.23, p=0.015] (Figure 9.8).

Late time window (370 – 400 ms). Finally, the active APD task induced more left-lateralized inferior frontal activation [T(46)=5.05, p<0.001] and bilateral sensorimotor activity [T(46)=2.45, p=0.009] with voicing as phonemic contrast (Figure 9.8).

Phonemic contrast MoA

Early time window (80 – 160 ms). For the APD task based on MoA, the passive APD task elicited more activation only in right-lateralized superior frontal [T(46)=2.77, p=0.004] and middle frontal areas [T(46)=3.57, p<0.001] (Figure 9.8).

Intermediate time window (190 – 240 ms). The APD task with MoA as phonemic contrast corresponded to an earlier intermediate time window (150 – 210 ms) in which higher activation was detected in bilateral sensorimotor [T(46)=2.46, p=0.009], inferior parietal [T(46)=2.67, p=0.005] and right-lateralized superior temporal regions [T(46)=2.07, p=0.022] again in the passive APD task (Figure 9.8).

Late time window (370 – 400 ms). Finally, with MoA as phonemic contrast inferior frontal [T(46)=3.66, p<0.001] and sensorimotor regions [T(46)=2.86, p=0.003] were bilaterally more active in the active APD task without activation of inferior parietal regions (Figure 9.8).

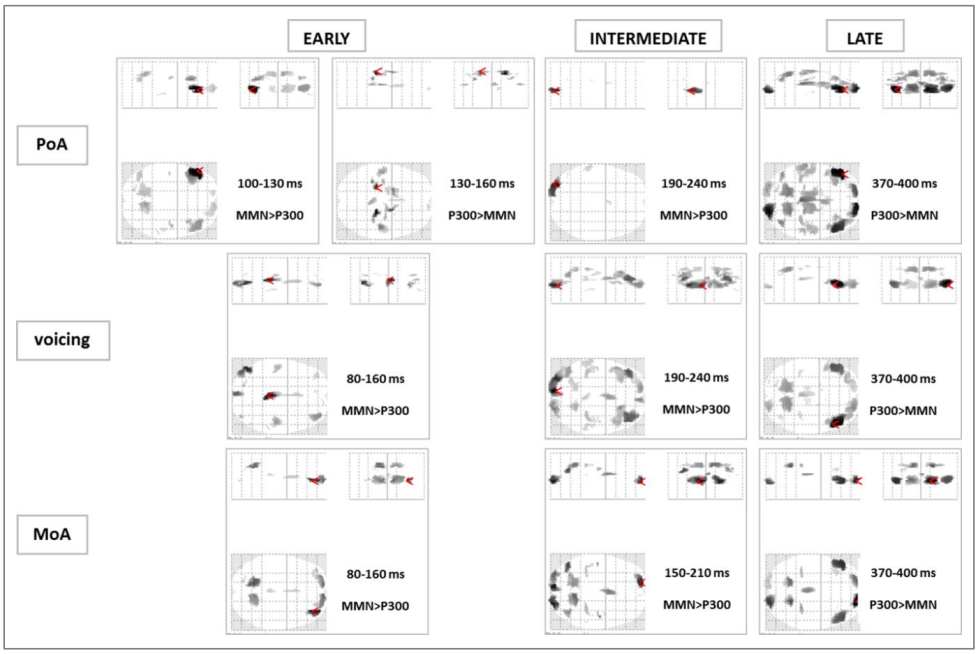

Figure 9.8: Maximum intensity projections (MIP) of differences in attentional level during phoneme discrimination with PoA, voicing and MoA. The maximum intensity is projected on a glass brain in three orthogonal planes; axial (bottom plot), sagittal (top left plot) and coronal (top right plot). In the top plots of each box the time course of the region(s) with statistical differences in maximal activity is represented, with time going from the bottom of the plot to the top. The bottom plot shows the MIP at the time of the maximal activation. The MIP can be seen as an image in which all relevant activity above the α=0.05 (uncorrected) threshold is superimposed in a certain direction (axial, sagittal, and coronal). The red arrow indicates the global maximum activity.

Interim summary

The phonemic contrast PoA showed attention-related variations in activation of both frontal and parietal areas in four consecutive time windows, whereas this was not the case for the phonemic contrasts MoA and voicing. Around the intermediate time frame (190 – 240 ms) attention-related effects were also present in activation of auditory superior temporal regions for the phonemic contrasts MoA and voicing, but not PoA.

4. Discussion

We aimed to determine whether phoneme discrimination based on PoA elicits more motor cortical activity, considering its lack of invariant acoustic cues and clear-cut motor representations, and whether phoneme discrimination based on voicing or MoA evokes more auditory cortical activity, considering their well-defined acoustic features and rather vague motor representations. Moreover,

we investigated whether a spatial cortical pattern associated with a particular phonemic contrast occurred with a certain temporal differentiation compared to the other phonemic contrasts. Finally, we questioned whether effects of attention would primarily be related to frontal activity and if so, whether this is the case for every phonemic contrast. The current data show several time windows with significant differences in activation of auditory and motor regions associated with phoneme discrimination based on the three different phonemic contrasts. The pre-attentive and attentive condition showed differences in an early time window (50 – 110 ms) while only the attentive condition revealed other, later time windows (130 – 175 ms; 225 – 250 ms) presenting distinct neural activity patterns determined by the phonemic contrasts. Moreover, when the pre-attentive and attentive condition were compared to search for an effect of attention, an early, intermediate and late time window revealed distinct activation patterns for every phonemic contrast.

4.1 Effect of phonemic contrast

Already between 50 and 100 ms, pre-attentive phoneme discrimination with MoA as phonemic contrast elicits more activation in sensorimotor, inferior parietal and auditory superior temporal regions. Further on in time no dissimilarities arose between the different phonemic contrasts. Within the MoA-related ERP waveform this time window corresponds to a pronounced peak before the definite MMN onset (Figure 9.2). It seems that this pronounced pre-MMN peak represents the need for higher activation of auditory, temporal regions in conjunction with sensorimotor regions during phoneme discrimination based on MoA, which seems to correspond to a dorsal processing stream typically involved in sublexical speech processing (Chevillet et al., 2013; Dehaene-Lambertz et al., 2006). Moreover, considering that this effect occurs before the actual MMN, it is possible that a preparatory phase before the actual phoneme discrimination process is needed, specifically when discrimination is dependent on MoA. So probably, during this preparatory phase a higher reliance on integration of both auditory features and motor based representations of the articulatory movements related to the phonemic contrast MoA is needed (Hickok and Poeppel, 2004). MoA is a phonemic contrast that has been rarely investigated, whereas PoA has been investigated extensively with respect to its representation in both auditory and motor regions (D'Ausilio et al., 2011; Meister et al., 2007; Möttönen et al., 2013; Obleser et al., 2003; Obleser et al., 2004). Most of the studies implemented PoA as phonemic contrast most likely because of its clear-cut somatotopic correlates of the articulatory movements in the motor cortex (i.e. the lip/tongue area) (Bouchard et al., 2013; D'Ausilio et al., 2011; Pulvermüller et al., 2006). This is less straightforward for MoA, as it determines phonemes from two perspectives: 1) *nasality (height of the velum)*, which differentiates between oral (/b/) and nasal (/m/) phonemes; 2) *duration or degree of constriction*, which differentiates between plosives (/b/) and fricatives (/v/). This possibly makes it more difficult to define proper

subregions to investigate in the motor cortex. Nevertheless, the present study demonstrates that MoA compared to PoA and voicing reflects more auditory processing, probably related to the large formant transition of F1 and F2 due to deep resonances inherent to nasal sounds, and auditory-to-motor mapping in the run-up to phoneme discrimination, which partially corresponds to our first hypothesis.

During attentive phoneme discrimination, a spatial differentiation starts already between 65 and 110 ms, just as during the pre-attentive condition, where motor areas, inferior parietal regions and auditory superior temporal regions are more activated during phoneme discrimination based on MoA and voicing. Later on between 130 – 175 ms a reversed pattern emerged showing more activation of exactly the same motor and auditory regions during phoneme discrimination based on PoA, instead of MoA and voicing. Finally, between 225 and 250 ms only the difference between PoA and MoA remained, showing more sensorimotor and superior temporal activation during phoneme discrimination based on PoA. Based on the underlying ERP waveforms, it appears that in the early time window (65 – 110 ms) an initiation of an N100 is not yet present with PoA as phonemic contrast while this is the case for MoA and voicing. Moreover, the following time frame (130 – 175 ms) corresponds to the N100 onset of PoA while the N100 in response to MoA and voicing is already in its offset phase. These timing differences around the N100 potential are supported by statistically significant differences between phonemic contrasts in N100 peak latency. The N100 potential is generally related to primary analyses, preparatory processes like detection and identification of phonemes based on their different constituent features (Cooper et al., 2006; Näätänen et al., 2011; Obleser et al., 2003). So, the preparation for phoneme discrimination based on PoA occurs later than the preparation for phoneme discrimination based on MoA and voicing, which clearly illustrates the importance of taking temporal processing into account. Nonetheless, the same structures are engaged, showing auditory-motor integration during these preparatory processes, seemingly rejecting the hypothesis of more auditory cortical activity for MoA and/or voicing. However, in the comparison between PoA and voicing the latter relies on both auditory temporal and motor regions between 65 and 110 ms, whereas the former does not and depends only on motor areas in the later time window between 130 and 175 ms. Hence, PoA does appear to be more motor imprinted, most likely due to its distinctive articulatory gestures, while voicing is more acoustically imprinted in the brain, probably related to its distinct rapid temporal cues (voice-onset time), at least during active, attentive phoneme discrimination.

A last finding is the absence of differences between any of the phonemic contrasts during pre-attentive or attentive phoneme discrimination in the time window associated with the MMN peak or onset of the P300 peak (between 310 and 340 ms). Proper pre-attentive as well as attentive deviance

detection does not seem to have an influence on the degree of activation of motor or auditory brain regions in relation to the three different phonemic contrasts. However, in the attentive condition there were significant longer latencies for PoA compared to MoA, showing a similar pattern as the timing differences around the N100 potential as mentioned above. So, attentive phoneme discrimination with PoA remains to be prolonged compared to MoA. Apparently, in contrast with the phonological preparatory processes, the actual phoneme discrimination process does not evoke an increased activation of auditory-motor regions depending on the phonemic contrast, despite the timing differences. In addition, studies which found differences between articulatory representations in the motor cortex mainly used passive listening to phonemes, merely probing phoneme perception and recognition of one single phonemic contrast (D'Ausilio et al., 2009; Meister et al., 2007; Pulvermüller et al., 2006; Wilson, 2004). Perhaps purely discriminating between phonemes does not lead to altered activity in auditory and motor regions with respect to different phonemic contrasts whereas the preparatory phases, such as phoneme detection and identification, do so. In any way, it is demonstrated for the first time that starting from 50 ms after phoneme presentation, activity of inferior frontal, sensorimotor, inferior parietal and auditory regions (corresponding to a dorsal processing stream) temporally differentiates between the three phonemic contrasts during phoneme discrimination.

4.2 Effect of attention

A first general effect of attention was already observed when the different phonemic contrasts were compared in the pre-attentive and attentive condition itself. Activity differences between phonemic contrasts were found in the inferior frontal region during attentive phoneme discrimination, whereas no such dissimilarities were found during pre-attentive phoneme discrimination. Frontal regions have repeatedly been associated with selective and directed attention processes (Duncan and Owen, 2000; Fuster, 2000; Peers et al., 2005). Moreover, a study where the MMN was compared in an attentive and pre-attentive condition attributed greater inferior frontal involvement during the attentive condition to some form of “attention-switching towards auditory linguistic input” (Shtyrov et al., 2010). With respect to the present results in the attentive condition, this might indicate that a voluntary switch of attention to the heard phonemes occurs in an early time window for MoA and voicing and later in time, between 130 and 175 ms, for PoA. This might also explain why the PoA-related preparatory analyses start later in time than the MoA-related and voicing-related preparatory processes. In the direct comparison between pre-attentive and attentive phoneme discrimination, the phonemic contrast PoA distinguished itself by showing attention-related variations in activation of both frontal and parietal areas in four consecutive time frames, whereas the phonemic contrasts MoA and voicing showed no such clear attention-related variations in time. This confirms the idea of

a widely distributed attention-modulating network in the fronto-parietal regions (Peers et al., 2005) and shows its greater role and influence during phoneme discrimination based on PoA. Furthermore, frontal and parietal areas were also active during passive phoneme discrimination with all three phonemic contrasts, which corresponds to previous reports of involuntary deviance detection during passive tasks (Näätänen et al., 2011) assigned to frontal networks (Restuccia et al., 2005). Based on the present findings, passive, involuntary attention switching appears to engage roughly the same network as active, voluntary switching, including the co-activation of parietal areas in a larger fronto-parietal neuronal network, yet in earlier time frames. Moreover, involuntary attention-allocation during phoneme discrimination based on MoA and voicing relies more on activation of auditory regions around the intermediate time frame (150 – 240 ms), while this is not the case for phoneme discrimination based on PoA.

Combined with the difference between voicing and PoA in auditory regions in the attentive condition, it can be suggested that the phonemic contrasts MoA and voicing are more acoustic-auditory imprinted in the brain and that the phonemic contrast PoA receives more additional support from motor areas, and therefore seems to support the first hypothesis of this study. The fact that PoA lacks genuine invariant acoustic cues for perception of phonemes like /b/-/d/-/g/ or /p/-/t/-/k/ across vowel contexts (variable second formant transitions due to coarticulation of the following vowel), relative to other contrasts such as voicing or MoA (Sinnott and Gilmore, 2004), might explain the higher reliance on motor-phonetic properties of PoA. It is possible that this divergence originates already during speech development and acquisition in infants, or even earlier during foetal development (Partanen et al., 2013), where the phonemic contrasts MoA and voicing rely more on acoustic-auditory properties as they simply cannot depend on clear (visual) motor features during development. The phonemic contrast PoA allows much more audiovisual processing of its acoustic-motor properties (lip and tongue movements) (Hickok and Poeppel, 2007; Yeung and Werker, 2013). So, the integration of the three phonemic contrasts into one phoneme (e.g. /b/), during acquisition as well as more advanced use later in life, probably arises from a combination of early activation of auditory-acoustic properties in superior temporal auditory regions, more perpetuated for MoA and voicing, with auditory-to-motor and motor-to-auditory interaction in sensorimotor (frontal and parietal) areas, more perpetuated for PoA, in a speech perception-production feedback-feedforward neuronal network (Guenther et al., 2006; Hickok et al., 2011).

4.3 Right hemisphere involvement

Both left- and right hemispheric activation differences were found in the auditory-motor regions during auditory phoneme discrimination. In general, auditory language material evokes more bilateral activation in contrast to visual linguistic material, which elicits more left-lateralized

activation (Hickok and Poeppel, 2004; Marinković, 2004). Especially initial acoustic-phonological analysis processes have been very consistently related with bilateral superior temporal activation (Binder et al., 2000; Hickok and Poeppel, 2004; Hickok and Poeppel, 2007; MacGregor et al., 2012; Specht et al., 2008). Therefore, the present result of early (50 – 150 ms) bilateral superior temporal activation is in line with expectations. However, later on the activation remains bilateral in the auditory-motor regions.

Many studies investigating the motor area contribution to phoneme perception actually target a single left-lateralized cortical area rather than differentiating between both hemispheres (D'Ausilio et al., 2009; D'Ausilio et al., 2011; Meister et al., 2007; Möttönen et al., 2013; Pulvermüller et al., 2006). Nonetheless, participation of right hemispheric frontal structures is not completely unobserved. A notable study by Wilson et al. (2004) showed bilateral premotor activation during phoneme perception. The specific role of the right hemisphere in phonemic processing is, however, still largely unknown, definitely regarding motor cortex contribution during speech perception, and has mainly been attributed a supportive more than a critical or causal involvement (Wolmetz et al., 2011). The present study illustrates right hemisphere contribution within the motor areas during phoneme processing, but cannot draw too strong conclusions with respect to causality or specific function. Clearly, several studies attribute some role to the right hemisphere in phonological language processes (Baumgaertner et al., 2013; Boatman et al., 1998; Donnelly et al., 2011; Patterson et al., 2007; Wolmetz et al., 2011). Taken together with the present findings, further investigation into the role of right hemispheric activation during phoneme processing definitely seems worthwhile.

5. Conclusion

Pre-attentive as well as attentive auditory phoneme discrimination demonstrated a clear differentiation between all three phonemic contrasts. Firstly, during the early, preparatory phases (50 – 100 ms) more intense auditory processing and auditory-to-motor mapping was required for pre-attentive phoneme discrimination based on MoA. Secondly, there was a delayed initiation of the preparatory phases with the phonemic contrast PoA, though the same auditory and motor areas were engaged as the other two phonemic contrasts (65 – 110 ms; 130 – 175 ms), during attentive phoneme discrimination. Moreover, similar brain regions were recruited to the same extent for all three phonemic contrasts during proper discrimination of phonemes, as evidenced by the absence of altered activation patterns in auditory or motor regions during pre-attentive or attentive deviance detection. Nonetheless, important timing differences during attentive phoneme discrimination were detected. Attention-switching to the deviant phoneme was supported by inferior frontal regions, early-on in time for MoA and voicing (50 – 110 ms) and later-on in time for PoA (130 – 175 ms), during attentive phoneme discrimination. A larger fronto-parietal attention-related network was

active during attentive (voluntary) as well as pre-attentive (involuntary) phoneme discrimination, but showed greater variation in time and degree of influence for the phonemic contrast PoA. Above that, with the phonemic contrasts MoA and voicing there was a higher emphasis on auditory regions during involuntary attention-allocation, whereas for PoA attention-allocation relied solely on motor areas. There was a bilateral involvement during phoneme discrimination, though at this moment the right hemisphere's role still remains speculative and largely unclear.

6. References

Baumgaertner, A., Hartwigsen, G., Siebner, H.R., 2013. Right-hemispheric processing of non-linguistic word features: Implications for mapping language recovery after stroke. Human brain mapping. 34**,** 1293-1305.

Binder, J., Frost, J., Hammeke, T., Bellgowan, P., Springer, J., Kaufman, J., Possing, E., 2000. Human temporal lobe activation by speech and nonspeech sounds. Cerebral Cortex. 10**,** 512-528.

Binder, J.R., Frost, J.A., Hammeke, T.A., Cox, R.W., Rao, S.M., Prieto, T., 1997. Human brain language areas identified by functional magnetic resonance imaging. The Journal of Neuroscience. 17**,** 353-362.

Boatman, D., Hart, J., Lesser, R., Honeycutt, N., Anderson, N., Miglioretti, D., Gordon, B., 1998. Right hemisphere speech perception revealed by amobarbital injection and electrical interference. Neurology. 51**,** 458-464.

Boemio, A., Fromm, S., Braun, A., Poeppel, D., 2005. Hierarchical and asymmetric temporal sensitivity in human auditory cortices. Nature neuroscience. 8**,** 389-395.

Boersma, P. and Weenink, D. (2010). Praat: Doing phonetics by computer [Computer program]. Version 5.1.45. (http://www.praat.org/) Retrieved 26.10.10.

Bouchard, K.E., Mesgarani, N., Johnson, K., Chang, E.F., 2013. Functional organization of human sensorimotor cortex for speech articulation. Nature. 495**,** 327-332.

Burton, M.W., 2001. The role of inferior frontal cortex in phonological processing. Cognitive Science. 25**,** 695-709.

Burton, M.W., 2009. Understanding the role of the prefrontal cortex in phonological processing. Clinical linguistics & phonetics. 23**,** 180-195.

Celsis, P., Boulanouar, K., Doyon, B., Ranjeva, J., Berry, I., Nespoulous, J., Chollet, F., 1999. Differential fMRI responses in the left posterior superior temporal gyrus and left supramarginal gyrus to habituation and change detection in syllables and tones. Neuroimage. 9**,** 135-144.

Chevillet, M.A., Jiang, X., Rauschecker, J.P., Riesenhuber, M., 2013. Automatic phoneme category selectivity in the dorsal auditory stream. J Neurosci. 33**,** 5208-15.

Collins, D.L., Zijdenbos, A.P., Kollokian, V., Sled, J.G., Kabani, N.J., Holmes, C.J., Evans, A.C., 1998. Design and construction of a realistic digital brain phantom. IEEE Trans Med Imaging. 17**,** 463-8.

Cooper, R.J., Todd, J., McGill, K., Michie, P.T., 2006. Auditory sensory memory and the aging brain: a mismatch negativity study. Neurobiology of aging. 27**,** 752-762.

D'Ausilio, A., Pulvermüller, F., Salmas, P., Bufalari, I., Begliomini, C., Fadiga, L., 2009. The motor somatotopy of speech perception. Current Biology. 19**,** 381-385.

D'Ausilio, A., Bufalari, I., Salmas, P., Busan, P., Fadiga, L., 2011. Vocal pitch discrimination in the motor system. Brain and language. 118**,** 9-14.

Dehaene-Lambertz, G., Hertz-Pannier, L., Dubois, J., 2006. Nature and nurture in language acquisition: anatomical and functional brain-imaging studies in infants. Trends Neurosci. 29**,** 367-73.

DeWitt, I., Rauschecker, J.P., 2012. Phoneme and word recognition in the auditory ventral stream. Proceedings of the National Academy of Sciences. 109**,** E505-E514.

Diesch, E., Luce, T., 1997. Magnetic fields elicited by tones and vowel formants reveal tonotopy and nonlinear summation of cortical activation. Psychophysiology. 34**,** 501-510.

Donnelly, K.M., Allendorfer, J.B., Szaflarski, J.P., 2011. Right hemispheric participation in semantic decision improves performance. Brain research. 1419**,** 105-116.

Duncan, J., Owen, A.M., 2000. Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends in neurosciences. 23**,** 475-483.

Eickhoff, S.B., Paus, T., Caspers, S., Grosbras, M.-H., Evans, A.C., Zilles, K., Amunts, K., 2007. Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. Neuroimage. 36**,** 511-521.

Friederici, A.D., 2009. Pathways to language: fiber tracts in the human brain. Trends in cognitive sciences. 13**,** 175-181.

Friederici, A.D., 2011. The brain basis of language processing: from structure to function. Physiological reviews. 91**,** 1357-1392.

Friederici, A.D., 2012. The cortical language circuit: from auditory perception to sentence comprehension. Trends in cognitive sciences. 16**,** 262-268.

Friston, K., Harrison, L., Daunizeau, J., Kiebel, S., Phillips, C., Trujillo-Barreto, N., Henson, R., Flandin, G., Mattout, J., 2008. Multiple sparse priors for the M/EEG inverse problem. Neuroimage. 39**,** 1104-1120.

Fuster, J.M., 2000. Executive frontal functions. Experimental Brain Research. 133**,** 66-70.

Gross, J., Baillet, S., Barnes, G.R., Henson, R.N., Hillebrand, A., Jensen, O., Jerbi, K., Litvak, V., Maess, B., Oostenveld, R., Parkkonen, L., Taylor, J.R., van Wassenhove, V., Wibral, M., Schoffelen, J.M., 2013. Good practice for conducting and reporting MEG research. Neuroimage. 65**,** 349-63.

Guenther, F.H., Ghosh, S.S., Tourville, J.A., 2006. Neural modeling and imaging of the cortical interactions underlying syllable production. Brain and language. 96**,** 280-301.

Hickok, G., Buchsbaum, B., Humphries, C., Muftuler, T., 2003. Auditory–motor interaction revealed by fMRI: speech, music, and working memory in area Spt. Journal of Cognitive Neuroscience. 15**,** 673-682.

Hickok, G., Poeppel, D., 2004. Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. Cognition. 92**,** 67-99.

Hickok, G., Poeppel, D., 2007. The cortical organization of speech processing. Nature Reviews Neuroscience. 8**,** 393-402.

Hickok, G., Houde, J., Rong, F., 2011. Sensorimotor integration in speech processing: computational basis and neural organization. Neuron. 69**,** 407-422.

Jäncke, L., Wüstenberg, T., Scheich, H., Heinze, H.-J., 2002. Phonetic perception and the temporal cortex. Neuroimage. 15**,** 733-746.

Kayser, J., Tenke, C.E., 2006. Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: II. Adequacy of low-density estimates. Clin Neurophysiol. 117**,** 369-80.

Kiebel, S.J., Friston, K.J., 2004. Statistical parametric mapping for event-related potentials (II): a hierarchical temporal model. Neuroimage. 22**,** 503-520.

Kotz, S.A., Schwartze, M., 2010. Cortical speech processing unplugged: a timely subcortico-cortical framework. Trends in cognitive sciences. 14**,** 392-399.

Linden, D.E.J., 2005. The P300: Where in the brain is it produced and what does it tell us? Neuroscientist. 11**,** 563-576.

Litvak, V., Mattout, J., Kiebel, S., Phillips, C., Henson, R., Kilner, J., Barnes, G., Oostenveld, R., Daunizeau, J., Flandin, G., 2011. EEG and MEG data analysis in SPM8. Computational intelligence and neuroscience. 2011.

Londei, A., D'Ausilio, A., Basso, D., Sestieri, C., Gratta, C.D., Romani, G.L., Belardinelli, M.O., 2010. Sensory-motor brain network connectivity for speech comprehension. Human brain mapping. 31**,** 567-580.

MacGregor, L.J., Pulvermüller, F., van Casteren, M., Shtyrov, Y., 2012. Ultra-rapid access to words in the brain. Nature communications. 3**,** 711.

Marinković, K., 2004. Spatiotemporal dynamics of word processing in the human cortex. The Neuroscientist. 10**,** 142-152.

Marsi, E., Busser, B., Daelemans, W., Hoste, V., Reynaert, M., 2002. Combining information sources for memory-based pitch accent placement.

Meister, I.G., Wilson, S.M., Deblieck, C., Wu, A.D., Iacoboni, M., 2007. The essential role of premotor cortex in speech perception. Current Biology. 17**,** 1692-1696.

Möttönen, R., Dutton, R., Watkins, K.E., 2013. Auditory-Motor Processing of Speech Sounds. Cerebral Cortex. 23**,** 1190-1197.

Möttönen, R., Watkins, K.E., 2009. Motor representations of articulators contribute to categorical perception of speech sounds. The Journal of Neuroscience. 29**,** 9819-9825.

Näätänen, R., Lehtokoski, A., Lennes, M., Cheour, M., Huotilainen, M., Iivonen, A., Vainio, M., Alku, P., Ilmoniemi, R.J., Luuk, A., Allik, J., Sinkkonen, J., Alho, K., 1997. Language-specific phoneme representations revealed by electric and magnetic brain responses. Nature. 385**,** 432-434.

Näätänen, R., Kujala, T., Winkler, I., 2011. Auditory processing that leads to conscious perception: a unique window to central auditory processing opened by the mismatch negativity and related responses. Psychophysiology. 48**,** 4-22.

Obleser, J., Lahiri, A., Eulitz, C., 2003. Auditory-evoked magnetic field codes place of articulation in timing and topography around 100 milliseconds post syllable onset. Neuroimage. 20**,** 1839-1847.

Obleser, J., Lahiri, A., Eulitz, C., 2004. Magnetic brain response mirrors extraction of phonological features from spoken vowels. Journal of Cognitive Neuroscience. 16**,** 31-39.

Obleser, J., Boecker, H., Drzezga, A., Haslinger, B., Hennenlotter, A., Roettinger, M., Eulitz, C., Rauschecker, J.P., 2006. Vowel sound extraction in anterior superior temporal cortex. Human brain mapping. 27**,** 562-571.

Oostenveld, R., Fries, P., Maris, E., Schoffelen, J.M., 2011. FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci. 2011**,** 156869.

Partanen, E., Kujala, T., Näätänen, R., Liitola, A., Sambeth, A., Huotilainen, M., 2013. Learning-induced neural plasticity of speech processing before birth. Proc Natl Acad Sci U S A. 110**,** 15145-50.

Patterson, K., Nestor, P.J., Rogers, T.T., 2007. Where do you know what you know? The representation of semantic knowledge in the human brain. Nature Reviews Neuroscience. 8**,** 976-987.

Peers, P.V., Ludwig, C.J., Rorden, C., Cusack, R., Bonfiglioli, C., Bundesen, C., Driver, J., Antoun, N., Duncan, J., 2005. Attentional functions of parietal and frontal cortex. Cerebral Cortex. 15**,** 1469-1484.

Pulvermüller, F., Shtyrov, Y., Ilmoniemi, R., 2003. Spatiotemporal dynamics of neural language processing: an MEG study using minimum-norm current estimates. Neuroimage. 20**,** 1020-1025.

Pulvermüller, F., Huss, M., Kherif, F., del Prado Martin, F.M., Hauk, O., Shtyrov, Y., 2006. Motor cortex maps articulatory features of speech sounds. Proceedings of the National Academy of Sciences. 103**,** 7865-7870.

Pulvermüller, F., Fadiga, L., 2010. Active perception: sensorimotor circuits as a cortical basis for language. Nature Reviews Neuroscience. 11**,** 351-360.

Restuccia, D., Della Marca, G., Marra, C., Rubino, M., Valeriani, M., 2005. Attentional load of the primary task influences the frontal but not the temporal generators of mismatch negativity. Cognitive Brain Research. 25**,** 891-899.

Saur, D., Kreher, B.W., Schnell, S., Kümmerer, D., Kellmeyer, P., Vry, M.-S., Umarova, R., Musso, M., Glauche, V., Abel, S., 2008. Ventral and dorsal pathways for language. Proceedings of the National Academy of Sciences. 105**,** 18035-18040.

Shtyrov, Y., Kujala, T., Pulvermüller, F., 2010. Interactions between language and attention systems: early automatic lexical processing? Journal of Cognitive Neuroscience. 22**,** 1465-1478.

Sinnott, J.M., Gilmore, C.S., 2004. Perception of place-of-articulation information in natural speech by monkeys versus humans. Percept Psychophys. 66**,** 1341-50.

Specht, K., Huber, W., Willmes, K., Shah, N.J., Jäncke, L., 2008. Tracing the ventral stream for auditory speech processing in the temporal lobe by using a combined time series and independent component analysis. Neuroscience letters. 442**,** 180-185.

Tavabi, K., Obleser, J., Dobel, C., Pantev, C., 2007. Auditory evoked fields differentially encode speech features: an MEG investigation of the P50m and N100m time courses during syllable processing. European journal of neuroscience. 25**,** 3155-3162.

Trébuchon-Da Fonseca, A., Giraud, K., Badier, J.-M., Chauvel, P., Liégeois-Chauvel, C., 2005. Hemispheric lateralization of voice onset time (VOT) comparison between depth and scalp EEG recordings. Neuroimage. 27**,** 1-14.

Turkeltaub, P.E., Branch Coslett, H., 2010. Localization of sublexical speech perception components. Brain and language. 114**,** 1-15.

Van Strien, J. V. (2003). Vragenlijst voor handvoorkeur.

Wilson, S.M., Saygin, A.P., Sereno, M.I. & Iacoboni, M., 2004. Listening to speech activates motor areas involved in speech production. Nature neuroscience. 7**,** 701-702.

Wolmetz, M., Poeppel, D., Rapp, B., 2011. What does the right hemisphere know about phoneme categories? Journal of Cognitive Neuroscience. 23**,** 552-569.

Worsley, K.J., Marrett, S., Neelin, P., Vandal, A.C., Friston, K.J., Evans, A.C., 1996. A unified statistical approach for determining significant signals in images of cerebral activation. Human brain mapping. 4**,** 58-73.

Yeung, H.H., Werker, J.F., 2013. Lip Movements Affect Infants' Audiovisual Speech Perception. Psychological science. 24**,** 603-612.

Zaehle, T., Geiser, E., Alter, K., Jancke, L., Meyer, M., 2008. Segmental processing in the human auditory dorsal stream. Brain research. 1220**,** 179-190.

Zatorre, R.J., Belin, P., 2001. Spectral and temporal processing in human auditory cortex. Cerebral Cortex. 11**,** 946-953.

GENERAL DISCUSSION

CHAPTER 10

Discussion of the results and future perspectives

10.1 General discussion and conclusion

Cerebrovascular accidents are frequently associated with aphasia and almost 30-45 % of all stroke patients suffer from some form of acquired speech- and language disorder (Dickey et al., 2010; Kauhanen et al., 2000). However, in the acute stage of stroke, it is not always possible to administer behavioural tests, such as the PALPA (Kay et al., 1992), because some patients cannot be instructed due to severely impaired comprehension, reduced consciousness or confusion. When this is the case, ERPs can circumvent such problems as they have already demonstrated their sensitivity and usefulness in measuring certain language processes in both a healthy and clinical population. The main objective of this doctoral thesis was to develop normative data for specific ERPs related to phonological input processes and to gauge them as a diagnostic and therapeutic evaluation method in a population of aphasic patients in the acute stage of stroke.

Two important biological demographic factors known to influence certain language processes and its neuro(physio)logical organization, are age and sex. Already from the age of 40, a decrease of grey matter starts concomitant with a degradation of white matter pathways, signalling the initiation of a general, but non-pathological, degeneration of the brain (Sowell et al., 2003). Similarly, differences related to sex emerge as well, already in late childhood and throughout life, mainly in terms of structural differences, such as cortical thickness, and lateralization of language functions (Sommer et al., 2004; Shaywitz et al., 1995; Sowell et al., 2007). Consequently, stroke in language-sensitive brain regions can induce a variety of aphasic symptoms co-determined by age and sex of the patient. Hence, in the framework of developing actual normative ERP data, the first aim of this doctoral thesis was to investigate the effects of age and sex on auditory phoneme discrimination and word recognition (chapter five and six). A clear hierarchical age-related degeneration of the MMN and to a higher degree of the P300 arose during phoneme discrimination, dependent on the different phonemic contrasts (PoA ↓, MoA ↓↓, voicing ↓↓↓). Moreover, phoneme discrimination based on PoA, and not voicing or MoA, revealed that women potentially address a larger neuronal network as reflected in a larger MMN and P300 compared to men. Word recognition also revealed sex-related differences at the level of the P200 and N400, but in terms of information processing speed during word-pseudoword dissociation. There were no differences between men and women with respect to the magnitude of the pseudoword effect. Additionally, advancing age did not affect the P200 and N400 elicited by pseudowords, yet did so with the P200 and N400 elicited by real words. Earlier ERPs such as the P50 and N100 were not affected by increasing age, neither during auditory phoneme discrimination nor during word recognition. Clearly, both age and sex should be taken into account in

the context of neurophysiological normative data, especially for the later occurring, cognitive ERPs (MMN and P300; P200 and N400).

To see whether the ERP paradigms were suitable to be applied in an acute aphasic population and investigate to what degree the pattern of auditory phoneme discrimination and word recognition diverges from the normative pattern established in Aerts et al. (2013) and Aerts, van Mierlo, Hartsuiker, Santens and De Letter (under review), 10 acute aphasic patients with phonological input disorders were examined neurophysiologically (chapter seven). We chose to use the selection of the normative group from chapter six, because of the 1:1 male/female ratio among the aphasic patients and the importance to control for age and minimize its effect. Phoneme discrimination was differentially impaired among the aphasic patients according to the phonemic contrasts, showing the same degradation pattern as the healthy subjects in the aging study (PoA ↓, MoA ↓↓, voicing ↓↓↓) (Aerts et al., 2013). The fact that a PoA difference was the least affected by stroke, can also be related to larger PoA responses found in healthy subjects (Aerts et al., under review). As expected, the increased processing load inherent to an enhanced attentional level during the active task had an adverse effect on the performance of the aphasic patients and the P300 response. The aphasic patients showed some sparing of word recognition, with an intact pseudoword effect but delayed compared to the norm group. The fact that lexical processing is spared to some degree after stroke is reminiscent of the effects of aging, which did not affect lexical processing in a significant way. These results demonstrate the potential of using ERPs in the diagnostic evaluation of phonological input processes in the acute stage of aphasia and definitely deserve further research including more patients.

Because of the encouraging ERP results in the diagnostic study, it was questioned to what extent neurophysiological data can complement behavioural measures when investigating therapeutic effects. To date and to our knowledge, only three studies have used ERPs to measure therapy effects (Breier, Maher, Schmadeke, Hasan & Papanicolaou, 2007; Pulvermüller, Hauk, Zohsel, Neininger & Mohr, 2005; Wilson et al., 2012), so this study would provide valuable information. The goal was to implement both behavioural and neurophysiological data and to investigate to what extent a patient with aphasia in the acute stage of stroke would benefit from an intensive and conventional form of therapy (chapter eight). Early language intervention after stroke was beneficial, as evidenced by a general language improvement at the behavioural and neurophysiological level 4 months after stroke. Intensity of therapy, combined with an impairment-based approach, appeared to play an important role throughout the therapy periods, which is in line with several studies proclaiming that intensity might be a decisive therapeutic factor (Kelly, Brady & Enderby, 2010; Meinzer, Rodriguez &

Gonzalez Rothi, 2012). Furthermore, because of the implementation of the ERPs it was possible to monitor the underlying neuro(physio)logical reorganization and compensation mechanisms and demonstrate a combination of recovery patterns early after stroke. For further validation of ERPs as an evaluation tool for therapeutic follow-up, more similar studies should be executed. Moreover, in view of the heterogeneity among aphasic patients, certainly in the acute stage, we concur with Code (2000) that more single-case studies should be performed on which meta-analyses and case-series can be carried out, instead of (non)randomized group studies.

Finally, in an exploratory study it was evaluated whether a relatively novel source reconstruction technique (Friston et al., 2008) was sensitive enough to disentangle the spatiotemporal organization of auditory-motor regions in a frontotemporoparietal network during auditory phoneme discrimination (chapter nine). The analysis unravelled an early, anticipatory activation of auditory-acoustic properties in superior temporal auditory regions, more perpetuated for MoA/voicing, and auditory-to-motor and motor-to-auditory interaction in sensorimotor areas, more perpetuated for PoA (Guenther, Ghosh & Tourville, 2006; Hickok, Houde & Rong, 2011). Inferior frontal regions and a larger fronto-parietal network were associated with attention-switching to the "to be detected" phoneme, earlier in time for MoA and voicing (50-110 ms) and later in time for PoA (130-175 ms). Such a spatiotemporal integration of the different phonemic contrasts is important for successful phoneme discrimination and it would be interesting to investigate whether, to what degree and how this integration pattern is disturbed in aphasia with phonological input disorders, ideally by performing single-subject studies. However, larger patient studies first need to be performed in order to optimize the method of analysis and to detect possible patterns of spatiotemporal disintegration.

Based on the results of the different studies it can be concluded that during auditory phoneme discrimination a clear pattern of phonemic contrast sensitivity emerged, in which PoA appeared to be the most rigid and robust throughout life and voicing and MoA seemed to be more vulnerable, considering their greater susceptibility for aging effects and brain lesions. Taking together with the earlier auditory-acoustic activation for MoA/voicing and later auditory-motor integration for PoA, these patterns can potentially be explained from a developmental perspective, starting from the gestation period. Already in utero, the foetus is capable of hearing environmental sounds, considering that the auditory organ reaches its adult size by the twentieth week of gestation (Bibas, Xenellis, Michaels, Anagnostopoulou, Ferekidis & Wright, 2008). This is supported by the presence of auditory evoked responses in the foetal brain as measured with foetal magnetoencephalography (fMEG) (Sheridan, Matuz, Draganova, Eswaran & Preissl, 2010). Such auditory evoked magnetic fields

have proven that foetuses, mostly between 27 and 36 weeks gestational age, are capable of detecting tone-frequency changes (Draganova, Eswaran, Murphy, Huotilainen, Lowery & Preissl, 2005; Draganova, Eswaran, Murphy, Lowery & Preissl, 2007; Holst, Eswaran, Lowery, Murphy, Norton & Preissl, 2005; Huotilainen et al., 2004) and that neonates can process rapid temporal cues within 3 weeks after birth (Sheridan et al., 2010). Evidently, processing of sounds during foetal development and early infancy highly relies on acoustic-auditory features. It has even been established that prenatal auditory language stimulation induces neuronal changes in the foetal brain and indicates that shaping of the auditory central system begins well before birth (Partanen, Kujala, Näätänen, Liitola, Sambeth & Huotilainen, 2013). The phonemic contrasts voicing and MoA are highly acoustically founded and well-defined (temporal cue of voice onset time and F2 transition related to deep resonances, respectively) whereas PoA has a more elusive acoustic nature (lack of specific, invariant acoustic cues and presence of multiple acoustic variables; Sinnot & Gilmore, 2004) with a marked audio-visual, motor-phonetic component. The motor features are learned and related to auditory signals well after birth, when the infant starts babbling and receives tactile, proprioceptive and auditory feedback when producing sounds and sees and hears sounds being produced (Guenther et al., 2006). Because of the vague acoustic composition of PoA, an integrative perception strategy must be engaged based on auditory and motor features, whereas perception of voicing and MoA can be completed successfully based on auditory features only. With the aforementioned discussion in mind, we hypothesize that the early auditory-acoustic imprinting of voicing and MoA and the later auditory-motor integration for PoA during phoneme perception found in the last study might be a reflection of a very early, prenatal development of the central auditory system and a later, postnatal formation of the auditory-motor integration network.

But why does the later established phonemic contrast PoA remains the most stable with advancing age or after stroke and not the phonemic contrasts established earlier based on the acoustic features, such as voicing and MoA? Despite the early, prenatal auditory experiences with speech, acoustic features are highly variable, transient cues and are influenced by other factors like speech rate, speaker variability and noise, likely making them more vulnerable and susceptible for age- or stroke-related loss of grey matter (Möttönen & Watkins, 2009). Motor gestures, on the other hand, such as lip closing for /b/, are less variable and remain more stable, probably because of the more constant visuo-proprioceptive underpinning. In this way, motor gestures can provide a valuable complement to the faster declining acoustic features in difficult listening conditions, for example in noisy environments, but perhaps also with advancing age or stroke-related lesions (Möttönen, Dutton & Watkins, 2013; Tremblay, Dick & Small, 2013).

An intriguing observation throughout the normative studies and our patient study is the similar pattern of phonemic contrast sensitivity during phoneme discrimination in the context of non-pathological aging effects on the one hand and pathological stroke-related brain lesions on the other hand. This is also the case for word recognition, in which the P200 and N400 in response to the pseudowords were not influenced by advancing age or by stroke-related brain damage. Although remaining speculative at this point, it can be questioned whether a loss of grey matter and/or white matter connections associated with advancing age is comparable with stroke-related ischemic neuronal damage, in the framework of language decline or impairment. Both situations imply region-specific decreased activation of the cortical language network, for instance the temporal cortex, caused by a loss of neurons and their synaptic connections (Allen, Bruss, Kice Brown & Damasio, 2005; Sheppard, Wang & Wong, 2011; Tremblay et al., 2013). In healthy aging, this can be related to progressive cortical atrophy as a result of increased oxidative metabolism in neurons, glycation and dysregulation of intracellular calcium homeostasis, but also neurofibrillary tangles and granulovacuolar degeneration (Anderton, 2002; Esiri, 2007). On the other hand, stroke-related, acute ischemic neuronal loss, whether or not as a consequence of a brain haemorrhage, is caused by sudden intracranial circulatory arrest which induces oxygen and glucose deficits leading to metabolic dysfunctions (Lipton, 1999). Moreover, in analogy with the classical neurological compensation mechanisms observed in aphasic patients, such as recruitment of perilesional and contralesional areas, elderly subjects also show neuronal reorganization patterns in the form of reduced hemispheric asymmetry or enhanced recruitment of other regions not affected by age, such as the sensorimotor speech network (Cabeza, Anderson, Locantore & McIntosh, 2002; Tremblay et al., 2013). An increased reliance on the sensorimotor network might also explain the largely preserved discrimination of the PoA contrast in elderly subjects. So perhaps, when the age-related cortical atrophy reaches parts of the language network, similar (neurological) deterioration and compensation patterns in speech perception as with stroke-related damage can arise.

Another interesting finding was the effect of a higher cognitive processing load during the active phoneme discrimination task, which negatively influenced the performance of both elderly subjects and aphasic patients. Especially the older subjects (>60 years) found it difficult to remain attentive and concentrated throughout the neurophysiological testing and aphasic patients sometimes had difficulty understanding the instructions. Despite the development of normative data for the P300 potential, elicited in the active phoneme discrimination task, they should always be used and interpreted with caution and by taking into account the behavioural performance of the subject. Nonetheless, the P300 amplitude and latency provide extra information on working memory and

sustained attention (Yurgil & Golob, 2013), and when compared with pre-attentive phoneme discrimination (the MMN) a complete picture of the subjects' cognitive capacities can be obtained.

Finally, while our single-case therapy study (Aerts et al., submitted) revealed encouraging and interesting results by implementing neurophysiological measures and concurred with two other studies reporting positive results using ERPs as an evaluation tool in chronic aphasic patients (Pulvermüller et al., 2005; Wilson et al., 2012), spontaneous recovery remains an issue when examining (intensive) therapy-related neurophysiological activation patterns in the acute stage of stroke. The first 3 to 4 months after stroke are the most critical for spontaneous recovery, encompassing organic healing processes, such as reduction of oedema and reperfusion of damaged cortical areas, but also behavioural language improvement and a better emotional and social state (Lendrem & Lincoln, 1985; Pulvermüller & Berthier, 2008). When delivering (intensive) therapy in that critical period, it is virtually impossible to unravel with 100% certainty whether neuronal reorganization can be ascribed to genuine therapeutic effects or spontaneous recovery of neuronal tissue (Pulvermüller & Berthier, 2008). A valid solution provided by Pulvermüller and Berthier (2008) is the inclusion of chronic aphasic patients (years after stroke), for whom any spontaneous restitution processes can be precluded. Despite this being a good option to investigate (intensive) treatment-related neuronal reorganization in general, it does not solve the question whether (intensive) aphasia therapy in the acute stage of stroke offers a benefit on top of the spontaneous recovery processes. At the behavioural level, recent studies yielded conflicting results on this matter or are still ongoing (Godecke, Hird, Lalor, Rai & Phillips, 2012; Laska, Kahan, Hellblom, Murray & von Arbin, 2011; Nouwens, Dippel, de Jong-Hagelstein, Visch-Brink, Koudstaal & de Lau, 2013). Usually, aphasic patients receiving specific language therapy are compared with patients not receiving therapy or another, non-linguistic therapy in a randomized controlled trial study design. However, this is a questionable study design to measure effects of therapy and certainly to draw conclusions about possible neuronal reorganization processes in a heterogeneous group of aphasic patients (Code, 2000). Performing more case-studies with a cross-over design as in our study (Aerts et al., submitted), in which a comparison is made between a therapy and therapy-free period in the same patient, provides a possible solution. However, the drawback in our study is that the therapy-free period occurred after the critical first 4 months post-stroke of spontaneous recovery. Ideally, in future research the cross-over design should be implemented in single-case studies within the first 4 months of stroke.

Some ***concerns or limitations*** throughout this doctoral thesis have to be considered. Firstly, we noticed that the signal-to-noise ratio of the pre-attentive ERPs sometimes was too low, which can

impede a proper interpretation at a single-subject level. This was the main reason to increase the number of stimuli in the pre-attentive phoneme discrimination task in the single-case therapy study (Aerts et al., submitted). However, this drastically enlarges the duration of the neurophysiological testing and can cause fatigue during the EEG registration, especially in acute aphasic patients with a poorer physical condition (keeping in mind that these patients are examined 3-5 days post-stroke). So, duration of the testing was the main reason to limit the number of stimuli of the paradigms, searching for a good balance between a shortest possible testing duration and including sufficient stimuli. In contrast to the phoneme discrimination paradigm, in which the amount of stimuli is easily increased, the word recognition paradigm is dependent on several lexical factors (word frequency, age of acquisition, number of syllables and phonemes) which must be taken into account when including more word and pseudoword stimuli. The current number of stimuli should definitely be tripled, obtaining 75 pseudowords and 300 real words, to achieve a more favourable signal-to-noise ratio for single-subject application.

Secondly, 23 electrodes for source reconstruction is not optimal for fundamental research purposes and prohibits the unravelling of more detailed hypotheses in the current study, for instance on the spatiotemporal differentiation of the P300 or MMN *within* a phonemic contrast continuum (e.g. manner of articulation) (chapter nine). However, the ultimate goal is to perform this source reconstruction analysis in a group of acute aphasic patients, so we wanted to prevent a lengthy procedure when a large number of electrodes need to be applied. Aphasic patients in the acute stage of stroke easily get tired during a neurophysiological testing, especially in the first week, which can hinder a proper recording during the administration of the paradigms (and recording an EEG with 64 or more electrodes drastically increases the time for preparation). With this in mind, we chose to record the EEG with 23 electrodes. Moreover, we clustered the MNI coordinates to regions we believe are justifiable for a recording of 23 electrodes (average activity of inferior frontal cortex, sensorimotor cortex, inferior parietal cortex and superior temporal cortex), searching for a balance between an overestimation of localizations because of the less dense recording and underestimation when clustering to larger regions. Also, we did not state too specific hypotheses regarding spatial aligning of certain features inherent to the phonemic contrasts, due to the less dense recording.

Thirdly, it can be questioned why age and sex were not investigated together in one statistical analysis in light of investigating potential age-sex interactions. However, the original sample of 71 subjects was marked by an uneven distribution between men (n=23) and women (n=48), which created an unbalanced design and would bias the results in favour of the largest group, being the women. Therefore, it was chosen to separate the two variables and restrict the sample size for the sex study as a function of a more balanced men/women distribution while excluding age differences

between both sexes. This is a justified way of analysing, in line with Gur et al. (1999) who found no effect of age-corrected values on significant sex effects, most likely because there was no age difference between men and women. Moreover, in this way a more powerful regression analysis could be performed to measure aging effects.

Finally, an important issue not mentioned throughout this doctoral thesis and which is not scrutinized in the studies discussed above, is the influence of cognitive reserve (CoR) on stroke-related language disorders. CoR can be defined as a combination of protective factors, such as educational level, overall intelligence, literacy, socioeconomic status and (multi)language proficiency, which can mediate the risk of developing clinically expressed dementia (Bialystok, Craik, & Freedman, 2007; Robertson, 2014; Stern, 2009). For instance, it is possible that the same brain pathology can lead to different cognitive impairments and a different rate of recovery in an individual with higher CoR compared to an individual with lower CoR. With respect to stroke-induced language disorders, CoR can have an important protective effect as well. Higher levels of education have been related to less cognitive decline, less risk of post-stroke dementia and better preservation of language abilities after stroke (González-Fernández et al., 2011; Ojala-Oksala et al., 2012). Also, the presence and quality of social ties and emotional support before and during the stroke event predicts cognitive recovery (Glymour, Weuve, Fay, Glass, & Berkman, 2008). Moreover, as active bilingualism has shown to delay the onset of dementia and its progressive language impairments by as much as 5 years, independent of education (Alladi et al., 2013; Bialystok et al., 2007), it can be expected that bilingualism also has a beneficial effect in stroke-related language recovery (Kurland & Falcon, 2011). The underlying mechanism and neuronal network of CoR has recently been attributed to a set of processes which mediate the extent of CoR, namely arousal, sustained attention, novelty detection and awareness, sharing a similar right-lateralized fronto-parietal network (Robertson, 2014). Considering the clear overlap with neuronal circuitries important for language recovery and functioning early after stroke (Saur et al., 2006) and the effect of novelty detection and attention in an active oddball task as used in the current doctoral thesis (Friedman, Cycowicz, & Gaeta, 2001), it is clear that CoR is a clinical phenomenon that should not be disregarded. Hence, not accounting for CoR must be seen as a shortcoming of the above discussed studies.

In conclusion, age and sex have a significant impact on the neurophysiological correlates of auditory phoneme discrimination and word recognition, which justifies the classification into different age categories for the neurophysiological normative data of phonological input processes and the need to complement these data with more male subjects in view of distinguishing between men and women. Nevertheless, these preliminary normative data can already be used in clinical evaluation, considering the promising results demonstrated in the study with acute aphasic patients. As such,

the therapy study demonstrated the added value of ERPs, allowing more legitimate and well-founded decisions regarding therapy intensity and therapy content, which eventually led to more individualized language exercises. Moreover, the interesting and encouraging results obtained with the source reconstruction technique plea for try-outs in a patient population and fine-tuning of the analyses for potential implementation in the clinical evaluation of acute aphasic patients. In this way, functional spatiotemporal reorganization patterns during stroke recovery can be measured offline in a patient-friendly, non-invasive way.

10.2 Future perspectives

The present doctoral thesis unveiled new insights with respect to age- and sex-related neurophysiological correlates of phonological input processes and has led to the development of preliminary normative data for the Flemish population. Moreover, the ERP technique has demonstrated to be suitable for implementation in a diagnostic and therapeutic evaluation of aphasic patients. However, to obtain a complete, ready-to-use diagnostic- and treatment-related ERP protocol, further research is necessary.

10.2.1 Extend present normative data

The existing normative data have to be extended in order to obtain a database with enough healthy controls in every age group and an equal distribution of men and women. Ideally, a total of 50 to 75 subjects should be included in every age group with a 1:1 ratio between men and women (Bridges & Holler, 2007). This means that in total at least 25 men and 25 women should be recruited for every age group. Consequently, a minimum grand total of 300 healthy subjects should be anticipated. Further statistical analyses should point out whether the currently implemented age categories have to be maintained or if perhaps larger categories can be created, e.g. 20-40, 40-60 and 60+ or even <60 and >60. Also, at this point, years of education were not taken into account, mostly to restrict the number of variables in the statistical analysis. Nonetheless, in the context of CoR, this is a factor that can have an important effect on the normative data, together with overall intelligence, socioeconomic status and language proficiency. Therefore, when expanding the existing normative data, years of education is definitely a factor to be taken into account, but also intelligence, occupational status and multilingualism should be included.

10.2.2 Develop aphasic normative data

The group of acute aphasic patients should be extended as well to ascertain whether the current established neurophysiological effects during phonological input processes can be confirmed at a larger scale. Ultimately, normative data for aphasic patients should be developed with coverage of

the main aphasic classifications, such as Broca's and Wernicke's aphasia, global aphasia, anomic aphasia, and the transcortical aphasias, but also according to site of lesion. This would make it possible to compare an aphasic patient with normative data of the same age group and sex and normative aphasic group of the same symptomology and lesional character. Ideally, the above mentioned factors involved in CoR should also be inquired in the aphasic group and included in the aphasic normative data.

10.2.3 Develop normative data for other language processes

The present work only focused on phonological input processes, which covers only a small portion of the entire language network. Other stages of auditory language processing can also be examined neurophysiologically with specific ERPs, such as phonological output processes during spoken word production (Geva, Jones, Crinion, Price, Baron & Warburton, 2012; McArdle, Mari, Pursley, Schulz & Braun, 2009), visual word recognition (Hauk, Davis, Ford, Pulvermüller & Marslen-Wilson, 2006) and semantic and syntactic processes at word and sentence level (Kotz & Friederici, 2003). During the present doctoral research, phonological output tasks were also developed and administered with the same normative group as the perception tasks. These tasks are also based on the speech processing model by Ellis and Young (1996) and comprise the phonological output lexicon (spoken word form) and the phonological assemblybuffer (individual phonemes of a word). In a following research project, the results of these tasks should be analysed and worked out to ultimately develop normative data as well.

10.2.4 Validate source reconstruction method in aphasic patients

The currently used source reconstruction method unravelled an interesting spatiotemporal pattern during the auditory phoneme discrimination task. Future research should focus on validating the source reconstruction analyses during the same phoneme discrimination task in aphasic patients in the acute stage of stroke and in follow-up (therapy) studies. Moreover, source reconstruction should also be performed on the auditory word recognition task, after some fine-tuning as discussed in the limitations. In this way, it can be determined whether this technique can be implemented at single-subject level for clinical purposes as a function of exploring potential neurological reorganization patterns during phonological input processes at a non-intensive, non-invasive manner.

10.2.5 More case studies on effect therapy and therapy intensity

A final recommendation for further research is to perform more case studies with respect to the influence of intensity within an impairment-based therapy in order to create a case-series study. From a wealth of literature and our last study, it has become clear that therapy intensity (minimum 2 hours per session) might be an important, influencing factor on language treatment effect. Although

randomized controlled trials are highly appreciated, they have the major disadvantage of summating effects of a very heterogeneous group of aphasic patients. Collecting a large number of single-subject studies and merging them in a case-series study design will strengthen possible outcomes regarding therapy effect. Considering that at present the "Rijksinstituut voor Ziekte- en Invaliditeitsverzekering" (RIZIV) only covers reimbursement for a maximum of 1 hour per session, such studies can be useful for enforcing potential adjustments to the current system of reimbursement of speech- and language therapy in the context of neurological disorders.

10.3 References

Aerts, A., van Mierlo, P., Hartsuiker, R. J., Hallez, H., Santens, P. & De Letter, M. (2013). Neurophysiological investigation of phonological input: Aging effects and development of normative data. *Brain and Language, 125*(3), 253-263.

Aerts, A., van Mierlo, P., Hartsuiker, R. J., Santens, P. & De Letter, M. (under review). Sex differences in neurophysiological activation patterns during phonological processing: An influential factor for normative data. *Archives of Sexual Behavior*

Aerts, A., Batens, K., Santens, P., van Mierlo, P., Huysman, E., Hartsuiker, R.J., Hemelsoet, D., Duyck, W., Raedt, R., Van Roost, D. & De Letter, M. (under review). Therapy-related language improvement in an aphasic patient evidenced by behavioural and neurophysiological measures: A 1-year follow-up after stroke. *Aphasiology*

Alladi, S., Bak, T.H., Duggirala, V., Surampudi, B., Shailaja, M., Shukla, A., et al. (2013). Bilingualism delays age at onset of dementia, independent of education and immigration status. *Neurology, 81* (22), 1938-1944.

Allen, J.S., Bruss, J., Kice Brown, C. & Damasio, H. (2005). Normal neuroanatomical variation due to age: The major lobes and a parcellation of the temporal region. *Neurobiology of Aging, 26*, 1245-1260.

Anderton, B.H. (2002). Ageing of the brain. *Mechanisms of Ageing and Development, 123*, 811-817.

Bialystok, E., Craik, F.I.M, & Freedman, M. (2007). Bilingualism as a protection against the onset of symptoms of dementia. *Neuropsychologia, 45*, 459-464.

Bibas, A.G., Xenellis, J., Michaels, L., Anagnostopoulou, S., Ferekidis, E. & Wright, A. (2008). Temporal bone study of development of the organ of Corti: correlation between auditory function and anatomical structure. *The Journal of Laryngology and Otology, 122*(4), 336-342.

Breier, J. I., Maher, L. M., Schmadeke, S., Hasan, K. M., & Papanicolaou, A. C. (2007). Changes in language-specific brain activation after therapy for aphasia using magnetoencephalography: A case study. *Neurocase, 13*(3), 169-177.

Bridges, A.J. & Holler, K.A. (2007). How many is enough? Determining optimal sample sizes for normative studies in pediatric neuropsychology. *Child Neuropsychology, 13*, 528-538.

Cabeza, R., Anderson, N.D., Locantore, J.K., McIntosh, A.R., (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *NeuroImage, 17*, 1394-1402.

Code, C. (2000). The problem with RCTs. RCSLT Bulletin, 574, 14-15

Dickey, L., Kagan, A., Lindsay, P., Fang, J., Rowland, A., & Black, S. (2010). Incidence and Profile of Inpatient Stroke-Induced Aphasia in Ontario, Canada. *Archives of Physical Medicine and Rehabilitation, 91*, 196-202.

Draganova, R., Eswaran, H., Murphy, P., Lowery, C. & Preissl, H. (2007). Serial magnetoencephalographic study of fetal and newborn auditory discriminative evoked responses. *Early Human Development, 83*, 199-207.

Draganova, R., Eswaran, H., Murphy, P., Huotilainen, M., Lowery, C. & Preissl, H. (2005). Sound frequency change detection in fetuses and newborns, a magnetoencephalographic study. *NeuroImage, 28*, 354-361.

Ellis, A.W., & Young, A.W (1996). *Human Cognitive Neuropsychology: A Textbook with Readings* (augmented edition). Hove, UK: Psychology Press.

Esiri, M.M. (2007). Ageing and the brain. *Journal of Pathology, 211*, 181-187.

Friedman, D., Cycowicz, Y.M., & Gaeta, H. (2001). The novelty P3: an event-related brain potential (ERP) sign of the brain's evaluation of novelty. *Neuroscience and Biobehavioral Reviews, 25*, 355-373.

Friston, K., Harrison, L., Daunizeau, J., Kiebel, S., Phillips, C., Trujillo-Barreto, N., et al. (2008). Multiple sparse priors for the M/EEG inverse problem. *NeuroImage, 39*, 1104-1120.

Geva, S., Jones, P.S., Crinion, J.T., Price, C.J., Baron, J.C. & Warburton, E.A. (2012). The Effect of Aging on the Neural Correlates of Phonological Word Retrieval. *Journal of Cognitive Neuroscience, 24*(11), 2135-2146.

Glymour, M.M., Weuve, J., Fay, M.E., Glass, T., & Berkman, L.F. (2008). Social Ties and Cognitive Recovery after Stroke: Does Social Integration Promote Cognitive Resilience? *Neuroepidemiology, 31*, 10-20.

Godecke, E., Hird, K., Lalor, E. E., Rai, T., & Phillips, M. R. (2012). Very early poststroke aphasia therapy: a pilot randomized controlled efficacy trial. *International Journal of Stroke, 7*(8), 635-644.

González-Fernández, M., Davis, C., Molitoris, J.J., Newhart, M., Leigh, R., & Hillis, A.E. (2011). Formal Education, Socioeconomic Status, and the Severity of Aphasia After Stroke. *Archives of Physical and Medical Rehabilitation, 92* (11), 1809-1813.

Guenther, F.H., Ghosh, S.S. & Tourville, J.A. (2006). Neural modeling and imaging of the cortical interactions underlying syllable production. *Brain and Language, 96*, 280-301.

Gur, R.C., Turetsky, B.I., Matsui, M., Yan, M., Bilker, W., Hughett, P., et al. (1999). Sex differences in brain gray and white matter in healthy young adults: Correlations with cognitive performance. *The Journal of Neuroscience, 19*(10), 4065-4072.

Hauk, O., Davis, M.H., Ford, M., Pulvermüller, F. & Marslen-Wilson, W.D. (2006). The time course of visual word recognition as revealed by linear regression analysis of ERP data. *NeuroImage, 30*, 1383-1400.

Hickok, G., Houde, J. & Rong, F. (2011). Sensorimotor integration in speech processing: computational basis and neural organization. *Neuron, 69*, 407-422.

Holst, M., Eswaran, H., Lowery, C., Murphy, P., Norton, J. & Preissl, H. (2005). Development of auditory evoked fields in human fetuses and newborns: A longitudinal MEG study. *Clinical Neurophysiology, 116*, 1949-1955.

Huotilainen, M., Kujala, A., Hotakainen, M., Parkkonenm, L., Taulu, S., Simola, J., et al. (2004). Short-term memory functions of the human fetus recorded with magnetoencephalography. *NeuroReport, 16*(1), 81-84.

Kauhanena, M.-L., Korpelainena, J.T., Hiltunenb, P., Määttäa, R., Mononena, H., Brusinc, E. et al. (2000). Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. *Cerebrovascular Diseases, 10*, 455–461.

Kay, J., Lesser, R., & Coltheart, M. (1992). *PALPA: Psycholinguistic Assessments of Language Processing in Aphasia*. Hove, UK: Psychology Press.

Kelly H., Brady, M.C. & Enderby, P. (2010). Speech and language therapy for aphasia following stroke. *Cochrane Database of Systematic Reviews, 5*, CD000425.

Kotz, S.A. & Friederici, A.D. (2003). Electrophysiology of normal and pathological language processing. *Journal of Neurolinguistics, 16*, 43-58.

Kurland, J. & Falcon, M. (2011). Effects of cognate status and language of therapy during intensive semantic naming treatment in a case of severe nonfluent bilingual aphasia. *Clinical Linguistics & Phonetics, 25* (6-7), 584-600.

Laska, A. C., Kahan, T., Hellblom, A., Murray, V., & von Arbin, M. (2011). A randomized controlled trial on very early speech and language therapy in acute stroke patients with aphasia. *Cerebrovascular Disease Extra, 1*(1), 667-4.

Lendrem, W. & Lincoln, N.B. (1985). Spontaneous recovery of language in patients with aphasia between 4 and 34 weeks after stroke. *Journal of Neurology, Neurosurgery, and Psychiatry, 48*, 743-748.

Lipton, P. (1999). Ischemic Cell Death in Brain Neurons. Physiological Reviews, 79, 1431-1568.

McArdle, J.J., Mari, Z., Pursley, R.H., Schulz, G.M. & Braun, A.R. (2009). Electrophysiological evidence of functional integration between the language and motor systems in the brain: A study of the speech Bereitschaftspotential. *Clinical Neurophysiology, 120*, 275-284.

Meinzer, M., Rodriguez, A.D., & Rothi, L.J.G. (2012). First Decade of Research on Constrained-Induced Treatment Approaches for Aphasia Rehabilitation. *Archives of Physical Medicine and Rehabilitation, 93*(1), S35-S45.

Mottonen, R. & Watkins, K.E. (2009). Motor Representations of Articulators Contribute to Categorical Perception of Speech Sounds. *The Journal of Neuroscience, 29*(31), 9819-9825.

Mottonen, R., Dutton, R. & Watkins, K.E. (2013). Auditory-Motor Processing of Speech Sounds. *Cerebral Cortex, 23*, 1190-1197.

Nouwens, F., Dippel, D.W.J., de Jong-Hagelstein, M., Visch-Brink, E.G., Koudstaal, P.J. & de Lau, L.M.L. (2013). Rotterdam Aphasia Therapy Study (RATS) – 3: "The efficacy of intensive cognitive-linguistic therapy in the acute stage of aphasia"; design of a randomised controlled trial. *Trials, 14*, 24.

Ojala-Oksala, J., Jokinen, H., Kopsi, V., Lehtonen, K., Luukkonen, L., Paukkunen, A., et al., (2012). Educational History Is an Independent Predictor of Cognitive Deficits and Long-Term Survival in Postacute Patients With Mild to Moderate Ischemic Stroke. *Stroke, 43*, 2931-2935.

Partanen, E., Kujala, T., Näätänen, R., Liitola, A., Sambeth, A. & Huotilainen, M. (2013). Learning-induced neural plasticity of speech processing before birth.

Pulvermuller, F., & Berthier, M.L. (2008). Aphasia therapy on a neuroscience basis. *Aphasiology, 22*(6), 563-599.

Pulvermuller, F., Hauk, O., Zohsel, K., Neininger, B., & Mohr, B. (2005). Therapy-related reorganization of language in both hemispheres of patients with chronic aphasia. *NeuroImage, 28*(2), 481-489.

Robertson, I.H. (2014). A right hemisphere role in cognitive reserve. *Neurobiology of Aging, 35*, 1375-1385.

Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., et al. (2006). Dynamics of language reorganization after stroke. *Brain, 129*(6), 1371-1384.

Sheppard, J.P., Wang, J.-P. & Wong, P.C.M. (2011). Large-Scale Cortical Functional Organization and Speech Perception across the Lifespan. *PLoS ONE 6*(1), e16510.

Sheridan, C.J., Matuz, T., Draganova, R., Eswaran, H. & Preissl, H. (2010). Fetal Magnetoencephalography - Achievements and Challenges in the Study of Prenatal and Early Postnatal Brain Responses: A Review. *Infant and Child Development, 19*, 80-93.

Sheridan, C., Draganova, R., Ware, M., Murphy, P., Govindan, R., Siegel, E.R., et al. (2010). Early development of brain responses to rapidly presented auditory stimulation: A magnetoencephalographic study. *Brain & Development, 32*, 642-657.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*, 2015-2028.

Sinnot, J.M. & Gilmore, C.S. (2004). Perception of place-of-articulation information in natural speech by monkeys versus humans. *Perception & Psychophysics, 66*(8), 1341-1350.

Sommer, I.E.C., Aleman, A., Bouma, A. & Kahn, R.S. (2004). Do women really have more bilateral language representation than men? A meta-analysis of functional imaging studies. *Brain, 127*, 1845-1852.

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L. & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience, 6*(3), 309-315.

Sowell, E.R., Peterson, B.S., Kan, E., Woods, R.P., Yoshii, J., Bansal, R., et al. (2007). Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. *Cerebral Cortex, 17*, 1550-1560.

Tremblay, P., Dick, A.S., Small, S.L. (2013). Functional and structural aging of the speech sensorimotor neural system: functional magnetic resonance imaging evidence. *Neurobiology of Aging, 34*, 1935-1951.

Wilson, K. R., O'Rourke, H., Wozniak, L. A., Kostopoulos, E., Marchand, Y., & Newman, A. J. (2012). Changes in N400 topography following intensive speech language therapy for individuals with aphasia. *Brain and Language, 123*(2), 94-103.

Yurgil, K. A., & Golob, E. J. (2013). Cortical potentials in an auditory oddball task reflect individual differences in working memory capacity. *Psychophysiology, 50*(12), 1263-1274.

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FULL LIST OF PUBLICATIONS

AND CONFERENCE PROCEEDINGS

International peer-reviewed journals – A1 (7)

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Hallez, H., Santens, P. & De Letter, M. (2013). Neurophysiological investigation of phonological input: Aging effects and development of normative data. *Brain and Language, 125* (3), 253-263. (impact factor 2013: 3.31)

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Santens, P. & De Letter, M. (revised). Sex differences in neurophysiological activation patterns during phonological processing: An influencing factor for normative data. *Archives of Sexual Behavior.* (impact factor 2013: 2.78)

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Santens, P. & De Letter, M. (under review). Neurophysiological sensitivity for impaired phonological processing in the acute stage of aphasia. *Brain and Language.* (impact factor 2013: 3.31)

Aerts, A., Batens, K., Santens, P., van Mierlo, P., Huysman, E., Hartsuiker, R.J., Hemelsoet, D., Duyck, W., Raedt, R., Van Roost, D. & De Letter, M. (revised). Therapy-related language improvement in an aphasic patient evidenced by behavioural and neurophysiological measures: A 1-year follow-up after stroke. *Aphasiology.* (impact factor 2013: 1.73)

Aerts, A., Strobbe, G., van Mierlo, P., Hartsuiker, R.J., Corthals, P., Santens, P. & De Letter, M. (submitted). Spatio-temporal differentiation of neural activity in auditory and motor regions during pre-attentive and attentive phoneme discrimination. *Behavioural Brain Research.* (impact factor 2013: 3.39)

De Letter, M., **Aerts, A.**, Van Borsel, J., Vanhoutte, S., Raedt, R., Van Mierlo, P., Boon, P., Van Roost, D. & Santens, P. (accepted for publication). Direct electrophysiological registration of phonological perception in the human subthalamic nucleus. *Brain and Language.* (impact factor 2013: 3.31)

De Letter, M., Vanhoutte, S., **Aerts, A.**, Santens, P., Vermeersch, H., Roche, N., Stillaert, F., Blondeel, P. & Van Lierde, K. (revised). Cortico-muscular recovery in a patient with facial allotransplantation: a 22 months follow-up study. *Psychophysiology*. (impact factor 2013: 3.18)

National peer-reviewed journals – A2 (1)

Aerts, A., Vinck, L., Wilssens, I., Wackenier, P. & Mariën, P. (2012). Therapy effect of Constraint Induced Aphasia Therapy in children with SLI: An exploratory study. *Logopedie, 25* (5), 29-38.

Conference proceedings – C3 (24)

PUBLISHED (5)

Presentations (1)

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Hallez, H., Santens, P. & De Letter, M. (14 December 2012). Neurophysiological investigation of phonological input: Dutch norms and influence of aging processes. *Stem-, Spraak- en Taalpathologie, 17* (4), VII – VII.
(Annual Conference of the Dutch Association for Voice, Speech and Language Pathology, Utrecht, The Netherlands)

Posters (4)

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Santens, P. & De Letter, M. (20-25 September 2013). Gender differences in neurophysiological activation patterns during phonological input processing: A contributory factor for developing normative data. *Stem-, Spraak- en Taalpathologie, 18* (S01), 13 – 15.
(14th International Science of Aphasia conference, Brussels, Belgium)

De Letter, M., **Aerts, A.**, Vanhoutte, S., Raedt, R., Van Borsel, J., Van Roost, D. & Santens, P. (20-25 September 2013). Phonological and semantic registration of the subthalamic nucleus. *Stem-, Spraak- en Taalpathologie, 18* (S01), 29 – 30.
(14th International Science of Aphasia conference, Brussels, Belgium)

Batens, K., De Letter, M., Raedt, R., **Aerts, A.**, Duyck, W., Van Roost, D. & Santens, P. (20-25 September 2013). Clinical use of event-related potentials in diagnostic and therapeutic evaluation of

phonological input processes in the acute stage of aphasia: A case study. *Stem-, Spraak- en Taalpathologie, 18* (S01), 19 – 21.
(14th International Science of Aphasia conference, Brussels, Belgium)

De Letter, M., **Aerts, A.**, Vanhoutte, S., Van Borsel, J., Raedt, R., De Taeye, L., van Mierlo, P., Boon, P., Van Roost, D. & Santens, P. (4 October 2014). Direct electrophysiological registration of phonological and semantic perception in the human subthalamic nucleus. *Frontiers in Human Neuroscience*, doi: 10.3389/conf.fnhum.2014.214.00023 (impact factor 2013: 2.89)
(5th Belgian Brain Congress, Ghent, Belgium)

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Presentations (9)

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Hallez, H., Santens, P. & De Letter, M. (8 February 2013). Electrophysiological analysis of phonology in logopaedic practice: Influence of aging and development of Flemish norms.
(6th Symposium Neurosciences of Speech and Language, Ghent, Belgium)

Aerts, A., Santens, P. & De Letter, M. (7 March 2013). Neurophysiology and phonological input processes.
(Weekly meeting department of Neurology UZ Gent, Ghent, Belgium)

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Hallez, H., Santens, P. & De Letter, M. (13 March 2013). Neurophysiological investigation of phonological input: Aging effects and development of normative data.
(Science Day UGent, Ghent, Belgium)

Aerts, A., Santens, P. & De Letter, M. (25 April 2013). Neurophysiology of phonological input processes.
(Neuroscience forum Institute of Neuroscience, Ghent, Belgium)

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Hallez, H., Santens, P. & De Letter, M. (6-7 June 2013). Electrophysiology of phonological input processes.
(AfasieNet Jongerendagen, Groningen, The Netherlands)

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Hallez, H., Santens, P. & De Letter, M. (11-12 October 2013). Neurophysiological investigation of phonological input: Influence of age and gender and the development of Flemish normative data.
(2nd Aphasia Conference 2013, Zeist, The Netherlands)

Batens, K., **Aerts, A.** & De Letter, M. (28 February 2014). Short-term follow-up of a reading problem after stroke.
(7th Symposium Neurosciences of Speech and Language, Ghent, Belgium)

Aerts, A., Batens, K. & De Letter, M. (28 February 2014). Long-term follow-up after stroke: The added value of neurophysiology.
(7th Symposium Neurosciences of Speech and Language, Ghent, Belgium)

De Letter, M., **Aerts, A.,** Vanhoutte, S., Van Borsel, J., Raedt, R., De Taeye, L., van Mierlo, P., Boon, P., Van Roost, D. & Santens, P. (14 March 2014). Cortico-subcortical interactions for semantic and phonological perception in Parkinson's disease.
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Posters (10)

Aerts, A., Santens, P., Hartsuiker, R.J., Hallez, H. & De Letter, M. (9 December 2011). Electrophysiological Correlates of Phonological Processing in Aphasia: A case report.
(33th Conference of the Flemish Association for Speech and Language Pathologists, Elewijt, Belgium)

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Hallez, H., Santens, P. & De Letter, M. (15 March 2013). Neurophysiological investigation of phonological input: Aging effects and development of normative data.
(34th Conference of the Flemish Association for Speech and Language Pathologists, Berchem, Belgium)

Vinck, L., **Aerts, A.**, Wilssens, I., Wackenier, P. & Mariën, P. (15 March 2013). Therapy effect of Constraint Induced Aphasia Therapy in children with SLI: An exploratory study.
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Aerts, A., van Mierlo, P., Hartsuiker, R.J., Hallez, H., Santens, P. & De Letter, M. (22 April 2013). Neurophysiological investigation of phonological input: Aging effects and development of normative data.
(Student Research Symposium (SOS) UGent, Ghent, Belgium)

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Santens, P. & De Letter, M. (11-12 October 2013). Gender differences in neurophysiological activation patterns during phonological input processing: A contributory factor for developing normative data.
(2nd Aphasia Conference 2013, Zeist, The Netherlands)

Aerts, A., Strobbe, G., van Mierlo, P., Hartsuiker, R.J., Santens, P. & De Letter, M. (6-8 November 2013). Interplay between auditory and motor areas during phoneme and word processing investigated on a millisecond time basis.
(5th Annual Meeting of the Society for the Neurobiology of Language, San Diego, California, USA)

Aerts, A., van Mierlo, P., Hartsuiker, R. J., Santens, P. & De Letter, M. (14 March 2014). Neurophysiological sensitivity for impaired phonological processing in the acute stage of aphasia.
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Batens, K., De Letter, M., **Aerts, A.,** Raedt, R., Duyck, W., Van Roost, D. & Santens, P. (14 March 2014). Clinical use of event-related potentials in diagnostic and therapeutic evaluation of phonological input processes: A one year follow-up case study.
(35th Conference of the Flemish Association for Speech and Language Pathologists, Berchem, Belgium)

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Santens, P. & De Letter, M. (27-29 August 2014). Neurophysiological alterations during phoneme and word processing in the acute stage of aphasia.
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De Letter, M., **Aerts, A.**, Vanhoutte, S., Van Borsel, J., Raedt, R., De Taeye, L., van Mierlo, P., Boon, P., Van Roost, D. & Santens, P. (27-29 August 2014). Direct electrophysiological registration of phonological and semantic perception in the human subthalamic nucleus.
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