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FACULTEIT GENEESKUNDE
FACULTY OF MEDICINE

LOGOPEDISCHE EN AUDIOLOGISCHE WETENSCHAPPEN
HERESTRAAT 49/721
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Katja De Meyer en Laura Stalmans

Verhandeling aangeboden tot het behalen van de graad van
Master in de Logopedische en Audiologische Wetenschappen

Promotor: Prof. Dr. Maaike Vandermosten
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Vermelding ethische goedkeuring.
De goedkeuring voor deze studie (MP022884) werd verleend door:
De Ethische commissie onderzoek : S60.007.

Dankwoord

Het schrijven van deze masterproef was een uitdagend, verrijkend en enorm leerrijk traject. We hebben ons hier beiden gedurende twee jaar op toegelegd, waardoor we alleen maar trots kunnen zijn op het resultaat. We willen graag de mensen rondom ons bedanken die een bijdrage hebben geleverd.

In de eerste plaats willen wij onze promotor Prof. Vandermosten en onze begeleider Drs. Pieter De Clercq uitdrukkelijk bedanken voor de sturing doorheen het traject. Twee jaar geleden hielpen zij ons op weg en ook doorheen het parcours konden wij bouwen op hun expertise en waardevolle feedback. Voor de dagelijkse begeleiding konden wij steeds rekenen op Drs. Pieter De Clercq. Hij stond steeds klaar met verhelderende antwoorden op onze vragen en constructieve opmerkingen. We willen hem dan ook heel graag oprecht bedanken voor de hulp, de feedback, het vertrouwen en de aanmoedigingen die hij ons zowel tijdens de vele meetings als ook daarbuiten gaf. Het was enorm interessant om kennis te maken met het onderzoeksveld binnen dit boeiende onderwerp. Verder willen wij ook alle deelnemers bedanken voor hun tijd en inzet. Hun deelname heeft dit onderzoek mee mogelijk gemaakt.

De weg naar een afgewerkte masterproef was niet zonder uitdagingen. We zijn dan ook erg blij dat we konden vertrekken vanuit een fijne samenwerking met elkaar, waarin ruimte was voor uitgebreid overleg en kritische reflecties, alsook voor steun en begrip. Hiervoor zijn we elkaar erg dankbaar. Ook willen wij beiden graag onze families, partners en vrienden bedanken om klaar te staan met een luisterend oor en bemoedigende woorden. Deze momenten van steun waren enorm waardevol om deze masterproef tot een mooi einde te brengen.

Katja De Meyer en Laura Stalmans

Samenvatting in het Engels

Background: Persons who have suffered a stroke develop aphasia in one-third of the cases. This acquired language impairment results in communication difficulties and is frequently accompanied by cognitive problems. In the (sub)acute phases of recovery, there is often considerable room for improvement, but this process may slow down or stabilize in the chronic phase. Numerous studies have investigated the potential compensatory mechanisms of the right hemisphere and the multiple demand (MD) network to support the left hemisphere language network. These studies often relied on group averages in neuroimaging. However, there is a need for more research specifically targeting individual activation patterns of post-stroke patients with chronic aphasia (PWA) using subject-specific fMRI methods.

Aim of the current study: Our research focuses on investigating the activation and potentially compensatory role of both the right-hemispheric regions of the language network and the domain-general MD network in PWA. For both networks, we examine absolute as well as relative activation (i.e., lateralization index; LI) in comparison to healthy controls, and we do this at the individual subject level. Additionally, we explore whether there is a correlation between the activation of these networks and the severity of language or cognitive deficits in PWA.

Method: We employed the single-subject approach with task-based fMRI to examine the involvement of the bilateral language regions and the MD network during language processing in chronic aphasia. Our participants consisted of 15 PWA and 13 age-matched healthy controls. We collected fMRI data during the performance of a listening and reading task (inducing language network activation) as well as a spatial working memory task (inducing MD network activation). Additionally, several standardized clinical language and cognitive assessments were administered. The individual activation patterns of the fMRI activations and the relative reliance on the left and right hemispheres (LIs) in both groups were compared, and the relationship with aphasia severity and cognitive deficit was explored through correlations with the behavioral tasks. The involvement of the MD network during language processing was examined by investigating language-task activity within subject-specific regions active during the MD task.

Results: We found a significant group difference for the language network activation in the left hemisphere, but not in the right hemisphere, during the language tasks, and no significant group difference for the MD activation during the MD task. Additionally, we did not find a significant link between language or MD network activation and aphasia severity or cognitive impairment. Concerning group differences in lateralization of the networks, PWA and healthy controls showed similar levels of lateralization of the language network during both language tasks, while PWA showed significantly less left-lateralized activation patterns in the MD network during the MD task. Concerning LI-correlations, no significant correlations were found between LIs of the language and MD network and aphasia severity, yet we did find a positive relation between stronger left-lateralized language activity during the reading task and cognitive performance. Lastly, we found no evidence for activation of the MD network during language processing.

Conclusion: We found no evidence for a compensatory mechanism of right-hemispheric regions in the language network in PWA. Furthermore, we found no evidence for a role of the MD network during passive, receptive language processing, offering compelling insight on a highly debated topic. For the correlations with the behavioral results, we suggest that the activation values in both the language and MD network may not provide conclusive insight into the severity of aphasia in the PWA group.

Samenvatting in het Nederlands

Achtergrond: Eén derde van de personen die een beroerte meemaken, ontwikkelt afasie. Deze verworven taalstoornis brengt moeilijkheden in de communicatie teweeg en gaat dikwijls samen met cognitieve problemen. Tijdens de (sub)acute fasen van het herstel is vaak veel verbetering mogelijk, maar dit proces vertraagt of stabiliseert tijdens de chronische fase. Talrijke studies hebben de potentieel compenserende mechanismen van de rechterhersenhelft en het 'multiple demand' (MD) netwerk ter ondersteuning van het taalnetwerk onderzocht. Deze studies maakten vaak gebruik van groepsgemiddelden bij hersenscans. Er is echter behoefte aan specifieker onderzoek gericht op individuele activatie patronen bij post-stroke patiënten met chronische afasie (PWA), a.d.h.v. subject-specifieke fMRI methoden.

Doel van de huidige studie: Wij richten ons op het onderzoeken van de activatie en rol van zowel de rechterhemisferische regio's van het taalnetwerk als het domein-overkoepelende MD netwerk in de chronische fase van afasie. Voor beide netwerken kijken we zowel naar absolute als naar relatieve activatie (lateralisatie-index; LI) in vergelijking met gezonde controles, en we doen dit op individueel-subjectniveau. Bovendien bestuderen we of er een verband bestaat tussen de activatie van deze netwerken en de ernst van taal- of cognitieve stoornissen bij PWA.

Methode: We gebruikten de "single-subject" methode met taakgerichte fMRI om de betrokkenheid van de taalregio's in de rechterhersenhelft en het MD netwerk tijdens taalverwerking bij chronische afasie te testen. Onze participanten bestonden uit 15 PWA en 13 leeftijdgematchte gezonde controles. We verzamelden fMRI-gegevens tijdens het uitvoeren van een luister- en leestaak (activeert taalnetwerk) evenals een ruimtelijke werkgeheugentaak (activeert MD netwerk). Verder werden er enkele gestandaardiseerde klinische taal- en cognitieve assessments afgenomen. De individuele activatiepatronen van de fMRI-activaties en de relatieve afhankelijkheid van de linker- en rechterhemisfeer (LIs) werden vergeleken tussen de groepen en de relatie met de ernst van afasie en cognitief deficit werd onderzocht a.d.h.v. correlaties met de gedragstaken. De betrokkenheid van het MD netwerk tijdens taalverwerking werd onderzocht door de taalactiviteit binnen subjectspecifieke regio's die actief zijn tijdens de MD taak te onderzoeken.

Resultaten: We vonden een significant groepsverschil voor de activiteit van het taalnetwerk in de linkerhersenhelft tijdens de taaltaken, maar niet voor de rechterhersenhelft, en geen significant groepsverschil voor MD activatie tijdens de MD taak. We vonden ook geen significant verband tussen de activatie van het taal- of MD netwerk en de ernst van afasie of cognitie. Met betrekking tot groepsverschillen in de lateralisatie van de netwerken, vertoonden PWA en gezonde controles vergelijkbare niveaus van lateralisatie van het taalnetwerk tijdens beide taaltaken, terwijl PWA significant minder links-gelateraliseerd activatiepatronen vertoonden in het MD netwerk tijdens de MD taak. Met betrekking tot LI-correlaties werden geen significante correlaties gevonden tussen LI's van het taal- en MD netwerk en de ernst van afasie, maar we vonden wel een positieve relatie tussen sterkere links-gelateraliseerde taalactiviteit tijdens de leestaak en cognitieve prestaties. Ten slotte vonden we geen bewijs voor activatie van het MD-netwerk tijdens taalverwerking.

Conclusie: We vonden geen bewijs voor een compensatiemechanisme t.h.v. de taalregio's in de rechterhersenhelft bij PWA. Verder vonden we geen bewijs voor een rol van het MD netwerk tijdens passieve, receptieve taalverwerking, wat interessante inzichten biedt in een sterk bediscussieerd onderwerp. Voor de correlaties met de gedragsresultaten suggereren we dat de activatiewaarden in zowel het taalnetwerk als het MD netwerk mogelijk geen doorslaggevend inzicht bieden in de ernst van afasie bij de PWA groep.

Inhoud

List of abbreviations and symbols

AAT: Akense Afasie Test

AF: arcuate fasciculus

AngG: angular gyrus

ANTAT: Amsterdam-Nijmegen Test voor Alledaagse Taalvaardigheden

AntPar: the anterior parietal cortex

AntTemp: anterior temporal cortex

BOLD signal: blood oxygen level-dependent signal

CAT-NL: Comprehensive Aphasia Test – Dutch version

CT: computerized tomography

CVA: cerebrovascular accident

(d)ACC: (dorsal) anterior cingulate cortex

EEG: electroencephalography

ERP: event-related potential

FDR: false discovery rate correction

(f)MRI: (functional) magnetic resonance imaging

(f)ROI: (functional) region of interest

GLM: general linear model

HRF: hemodynamic response function

IFG: inferior frontal gyrus

IFGop: opercular part of the inferior frontal gyrus

IFGorb: orbital part of the inferior frontal gyrus

LI: lateralization index

MCA: middle cerebral artery

MD network: multiple demand network

MFG: medial frontal gyrus

MFGorb: orbital part of the medial frontal gyrus

MidPar: the middle parietal cortex

mPFC: medial prefrontal cortex

MRI: magnetic resonance imaging

MTG: middle temporal gyrus

NBT: Nederlandse Benoem Test

OCS-NL: Oxford Cognitive Screen-NL

PCA: posterior cerebral artery

PostPar: the posterior parietal cortex

PostTemp: posterior temporal gyrus

PrecG: precentral gyrus

pre-SMA: pre-supplementary motor area

PWA: patient with aphasia

QoL: quality of life

rsfMRI: resting state functional magnetic resonance imaging

SAT: Semantic Association Task

SFG: superior frontal gyrus

SLT: speech and language therapy/therapist

SMA: supplementary motor area

spWM task: spatial working memory task

STG: superior temporal gyrus

STS: superior temporal sulcus

TBI: traumatic brain injury

Introduction

In Belgium, around 19.000 people suffer a stroke every year. Approximately 30% of all stroke survivors develop aphasia (De Cock et al., 2020; Le & Lui, 2022; Pulvermuller & Berthier, 2008). Aphasia is an acquired language disorder, affecting comprehension and/or production of language due to damage to the brain's language network. Research shows that the limitation of communication caused by aphasia greatly impacts quality of life (QoL) (Hilari et al., 2012; Lam & Wodchis, 2010). Recovery of the language function is possible to a certain extent, even in severe cases (Berthier, 2005), although aphasia is characterized by large heterogeneity in characteristics of the causal lesion, as well as recovery and outcome (Price et al., 2010).

Language recovery mostly takes place during the acute and subacute stages after the stroke and slows down after six months post-stroke in the chronic phase (Sheppard & Sebastian, 2021). This recovery is supported by both structural (Bae et al., 2022; Chang et al., 2021) and functional (Berthier et al., 2011; Saur et al., 2006) neural changes. These functional changes encapsulate neuroplasticity, a recovery process in which the brain adapts by engaging undamaged structures for language processing, like perilesional tissue and right-hemisphere homologue areas of the pre-existing language network, or by augmenting integration with the network for cognitive control (Berthier et al., 2011; Saur et al., 2006). Although these potential compensatory mechanisms have been suggested in literature, namely recruitment of the right-hemispheric language regions (e.g. Saur et al., 2006; Stockert et al., 2020) and recruitment of the domain-general multiple demand (MD) network (e.g. Geranmayeh et al., 2014), these findings are widely debated in the literature (for an overview, see Li et al. (2022); Wilson & Schneck, 2021).

Wilson & Schneck (2021) describe that the divergent and sometimes contradictory research findings may be, at least to some extent, attributed to methodological limitations of previous functional imaging studies, such as failure to adequately correct for multiple comparisons, difficulty interpreting task performance due to confounds (e.g. fatigue), inadequate contrast validity resulting in non-linguistic task demands influencing activation maps or the lack of a control group of healthy individuals, which is imperative for identifying compensatory mechanisms. Additionally, many previous studies use a group-averaging approach for fMRI data, in which fMRI data of each subject is spatially normalized to fit into a standard stereotactic representation of the human brain. However, this approach poses a major limitation, as it overlooks interindividual variations in the localization of functional brain regions and thereby reduces resolution and sensitivity to subtle activation (among other problems) (Fedorenko, 2021). To avoid these problems, Fedorenko et al. (2010) described a single-subject approach, which determines regions of interest based on functionality in each individual brain by using functional localization tasks, rather than based on structure.

The current study aims to investigate activation in the language and MD network in PWA in the chronic phase of recovery, using a single-subject approach. This is a relevant addition to the existing literature as most studies that investigated this population did not include a control group or used a group-averaging approach. Functional localizers were applied to identify the language network and the MD network. Based on this data, we explored activation patterns within the language network. Furthermore, we investigated

whether activation of the MD network acts as a compensatory mechanism during language processing in PWA. Previous research did not show involvement of the MD network in core language functions in healthy young populations (Diachek et al., 2020) and in naturalistic comprehension tasks (Shain et al., 2020). We aim to investigate whether this conclusion can be extended to language processing in PWA in the chronic phase of recovery.

Our master's thesis comprises four parts. The first chapter provides a comprehensive review of the relevant literature, aiming to establish a foundation of background knowledge and to further situate our study within the existing research field. We finish this part by enlisting our research questions. In the second chapter, we describe the methods used in this study. In the subsequent section, we present the results of our analyses. Finally, we critically discuss our results in the light of previous literature findings in order to support our conclusions. We describe limitations of this study and offer recommendations for future research.

1 Literature review

In this master's thesis, we investigate potential supporting or compensatory mechanisms for language processing in people with chronic post-stroke aphasia. Our study focuses on examining the activation and role of both the right-hemispheric regions of the language network and the domain-general multiple demand (MD) network within this population. Additionally, we explore whether there is an association between the activation of these networks and the severity of language or cognitive deficits in individuals with aphasia. This first chapter provides a comprehensive review of the relevant literature, aiming to establish a foundation of background knowledge and to situate our study within the existing research field.

1.1 Neural processing of language

1.1.1 Representation of language in the brain

1.1.1.1 Language models

When thinking about language and the brain, first of all one may wonder about the specific brain regions where language representations are located. Language can be categorized into two major functions, those being production and perception of language. For the motoric part of speech production, (pre)motor regions in the brain are relevant (Glanz et al., 2018; Pulvermüller et al., 2006; Tucker et al., 2021). For language perception, sensory input systems are needed, such as the auditory and the visual systems for hearing and reading. The neural processing of language, for example converting a message into sound before it is articulated (production) and vice versa, from sound to meaning (comprehension), requires support by multiple regions that are located in different parts of the brain. Since information is transferred between them, these regions work as a network (Friederici & Gierhan, 2013; Hagoort, 2017). Functional language representation in the brain varies significantly among individuals, with most showing strong left-hemisphere dominance (Bradshaw et al., 2017; Price, 2012; Springer et al., 1999). In some cases, language processing can be right-hemisphere dominant or bilateral, e.g. in approximately 22% of non-right-handed people. Still, in 78% of this population, language lateralization is left-hemispheric (Bolgina et al., 2022; Bradshaw et al., 2017; Carey & Johnstone, 2014; Szaflarski et al., 2002).

Over time, a high number of different models for the processing of language have been proposed. The classical model was originally based on the research of the French surgeon Paul Broca and the German neurobiologist Carl Wernicke in the late nineteenth century, but has since been expanded by other researchers to comply with more recent research findings based on more advanced techniques. In his research, Broca studied the association between the symptoms of patients who suffered from aphasia and the location of their brain lesions. In 1861, he was the first to assign the posterior two thirds of the inferior frontal gyrus (IFG) to the articulation of language, based on these lesion studies (Broca, 1865; Tremblay & Dick, 2016). In 1874, Wernicke found that auditory language

perception was strongly disturbed in patients with a lesion in the posterior part of the left superior temporal gyrus (STG), while their speech production remained fluent. Besides defining the location and function of Wernicke's area, he also was one of the first to develop a language model, in which he proposed that damage to different components of the model would lead to different, specific patterns of language deficits (O'Sullivan et al., 2019; Wernicke Carl, 1874). In 1885, German physician Ludwig Lichtheim elaborated on this model and illustrated it (Lichtheim, 1885). Revolutionary to his descriptions of the model was that he argued for functional specialization of certain brain regions, which was controversial at the time. Lichtheim also introduced the 'mental lexicon' to the model, which is a center, or multiple centers, in the brain, where concepts are formulated and stored (Lichtheim, 1885; O'Sullivan et al., 2019; Tremblay & Dick, 2016; Vandenborre et al., 2014). This highly influential Wernicke-Lichtheim model was later, in the 1960s, refined by American neurologist Norman Geschwind (Geschwind, 1965), whose adaptations constituted the best-known version of the classical model. Geschwind described that Wernicke's area, responsible for comprehension of language, and Broca's area, responsible for production of speech, are able to communicate mainly through the arcuate fasciculus (AF), a white-matter pathway that connects the two regions by passing dorsally under the parietal lobe (Ivanova et al., 2021). He also described the role of the angular gyrus in silent reading and the primary auditory cortex (Heschl's gyrus) in silent listening (Geschwind, 1965; Schevenels et al., 2020; Seghier, 2013). Even though the classical model, with all its adaptations, was very useful for starting to understand the neurological processing of language, more recent research has extensively shown that this model has multiple shortcomings and should therefore be considered to be outdated (Fedorenko & Blank, 2020; Tremblay & Dick, 2016). Due to the limitations of the available measurement tools in the 19th century, spatial and functional aspects of the network areas were deficiently determined (Fedorenko & Blank, 2020; Tremblay & Dick, 2016). Furthermore, the classical model implies two epicenters of language on the left-hemisphere cortex, mainly connected by the dorsal AF, while in reality the language network consists of widely distributed cortical and subcortical structures, which are connected by several pathways including more ventral pathways (Tremblay & Dick, 2016). In addition, multiple studies have shown that the strict distinction between language production and language comprehension in Broca's and Wernicke's area respectively, as described in the classical model, is not valid since these two aspects of language share neural resources (Menenti et al., 2011; Segaert et al., 2012; Stokes et al., 2019).

Many researchers have proposed alternatives for the classical model, one of which is the well-known 'dual-stream model' put forward by Hickok and Poeppel (Hickok, 2022; Hickok & Poeppel, 2000, 2004, 2007). This model draws on the concepts of a dorsal 'where' pathway and a ventral 'what' pathway in the visual system. According to this dual-stream model, early stages of speech perception involve auditory fields in the dorsal STG and mid-post superior temporal sulcus (STS) bilaterally, although asymmetrically. Afterwards, the cortical processing continues in two distinct processing streams. The ventral stream is involved in mapping sound onto meaning. Sensory representations of speech are projected ventro-laterally toward a temporal interface between sound-based phonological representations of speech and widely distributed conceptual representations. The dorsal stream is involved in mapping sound onto articulatory-based representations. It passes through a parietotemporal interface between sensory- and motor-based representations of speech, and then ultimately projects dorsally and posteriorly to the frontal lobe. The dorsal stream is strongly left-lateralized, whereas the ventral stream is left-dominant as well, but to a lesser degree (Hickok, 2022). Both pathways are bidirectional, which means they play a role in both perception and production of language (for an overview, see Hickok, 2022;

Saur & Hartwigsen, 2012). The model has been evaluated extensively in countless studies, expanding on the original framework (e.g. Friederici & Gierhan, 2013).

To conclude, the limitations of the classical model cannot be denied, but the terminology is still widely used. Authors such as Tremblay and Dick (2016) urge the neurobiological field to replace these vague terms of the classical model by more anatomically precise designations and a more comprehensive model of language. Including the interactions with other functional systems is an important step towards fully understanding human language and language disorders, such as aphasia. They suggest the dual-stream model as a possible alternative, which has also proven to be useful but incomplete. Some authors, such as Fedorenko, go further by pleading for a shift from anatomical descriptions of regions (location of brain areas) to functional divisions which delineate regions based on their shared function (Fedorenko, 2021; Fedorenko & Blank, 2020). Fedorenko argues that functional and anatomical regions do not always overlap completely and that, additionally, there is an important inter-individual variability in location of both macro-anatomical regions and finer anatomical subdivisions. Because of this, a functional division is more relevant than an anatomical one when looking to locate cognitive functions, such as language (Fedorenko, 2021; Fedorenko & Blank, 2020). Fedorenko et al. (2010) describe some relatively broad regions in which the language function is located in most participants, namely some frontal regions (IFG, orbital part of the IFG, medial frontal gyrus (MFG), superior frontal gyrus (SFG)), some posterior regions (anterior temporal gyrus, middle anterior temporal gyrus, middle posterior temporal gyrus, posterior temporal gyrus, angular gyrus), most of which are left lateralized. Several regions of the dual-stream model by Hickock and Poeppel (Hickok, 2022; Hickok & Poeppel, 2000, 2004, 2007) can be recognized in this list, such as the anterior and posterior temporal gyrus and different parts of the IFG (Friederici & Gierhan, 2013).

1.1.1.2 Language in the non-pathological aging brain

When examining language processing within the brain, it is of particular interest to focus on the neurological changes occurring in healthy individuals as they age. While aging is linked to particular deficits in language production, most language comprehension abilities remain unchanged as individuals age (Burke et al., 1991; Rossi & Diaz, 2016; Shafto & Tyler, 2014). This pattern of selective language impairments and preserved language functions contradicts ideas suggesting age-related declines in overall cognitive resources and predicting universal cognitive deterioration, including in language functions (Burke et al., 1991; Shafto & Tyler, 2014).

Typical aging involves changes in both gray and white matter in the brain, displaying notable regional variations in the timing and pace of deterioration (Good et al., 2001). Nevertheless, there is no direct correlation between the extent of neural changes and cognitive performance (Raz & Rodrigue, 2006). Part of the reason for this may be age-related compensatory neural recruitment: older adults who maintain relatively high performance in cognitive domains, such as episodic or working memory, exhibit increased neural activity, especially in prefrontal regions (Cabeza, 2002). This recruitment in older individuals frequently involves bilateral activation, whereas younger adults typically only activate the right hemisphere, indicating functional reorganization where regions in the left hemisphere take on processing functions typically associated with the right hemisphere (Shafto & Tyler, 2014).

There is considerable disagreement on the interpretation of behavioral studies with fMRI. In essence, the interpretation depends on the corresponding level of cognitive function or behavioral performance (Cabeza, 2002). When the increase in activation occurs with improved or preserved performance, this is usually interpreted as compensatory activity, which means that additional areas are recruited to supplement and compensate for structural or functional decline in core areas (Cabeza, 2002). However, when increases in brain activation correspond to decreases in performance, this is characterized as a sign of dedifferentiation - when cells grow from a fully differentiated state to a less differentiated state - or reduced efficiency of neural networks (D. C. Park et al., 2004; Yao & Wang, 2020). Another important note is that in fMRI studies, small but significant differences are more difficult to detect in older adults because often smaller samples are used here than in traditional behavioral studies, making the detection of significant results more difficult (Rossi & Diaz, 2016).

1.1.1.3 Functional neuroimaging methods

Multiple imaging methods have been developed for studying the brain's functionality. The most frequently used functional neuroimaging techniques are electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). Since EEG provides low spatial and high temporal resolution, whereas fMRI provides the opposite, these two techniques are considered to be complementary (Haufe et al., 2018). Given that we use fMRI in our study, we will not go into EEG in detail but will focus on fMRI.

MRI uses a strong magnetic field and radio pulses to generate detailed images of the brain (for an overview, see Lee et al., 2006). Within the MRI method, functional MRI (fMRI) can be distinguished, which looks at functionality rather than structure. To measure functionality, the blood oxygen level-dependent (BOLD) signal is tracked as a marker for activity. This hemodynamic response depicts changes in deoxyhemoglobin concentration. The BOLD signal depends on blood oxygenation, as well as on cerebral blood flow and volume. The more activity occurs in a certain region, the more oxygen that region requires (Glover, 2011; Logothetis, 2003). Conventional BOLD fMRI has a temporal resolution in the order of seconds and a spatial resolution of 1-6 mm (Tsvetanov et al., 2021; Xue et al., 2010). Some disadvantages are the long duration of the scan and the loud noise of the machine, which can make the experience uncomfortable. Furthermore, physiological factors, such as respiration or evolution in effort needed for performance of the task, cause an intra-individual test-retest variability (Li et al., 2022). The advantages, on the other hand, are that it is a non-invasive technique, with no use of ionizing radiation (A. Lee et al., 2006). The high spatial resolution in three dimensions renders this technique exceptionally valuable for obtaining detailed full-brain images. Due to these reasons this neuroimaging method was used for this master’s thesis.

An important distinction to make is that between task-based and resting-state fMRI (rsfMRI). During task-based fMRI, the subject completes a certain task, which allows the selected functional networks to be visualized. Important to note, is that different tasks may lead to different results. Furthermore, for some populations, such as patients who suffered a stroke, performing a task may be too difficult. During rsfMRI, the subjects are given no such tasks, and are rather instructed to lay still, but not sleep, and think of nothing in particular. In this resting state approach, brain areas that interact at rest are identified. This spontaneous, simultaneous activity in the brain indicates different functional networks, such as the language network (Mitchell et al., 2013). Even though rsfMRI avoids some of the disadvantages of task-based fMRI, the latter remains better suited to localize areas that

are involved in specific aspects of language processing (Branco et al., 2016; Smitha et al., 2019). This distinction is an important one to make, since the differences can influence the fMRI results greatly. The scans used for our master's thesis are based on task-based fMRI. The specifics of the used tasks will be discussed in the methods section of this thesis.

1.1.2 The Multiple Demand Network

The domain-general network is a network composed of the area posterior to the language-specific area within Broca's area, regions superior to those language specific areas, regions along the left inferior frontal sulcus and middle frontal gyrus, and inferior in the left anterior insula (Fedorenko et al., 2013; Fedorenko & Blank, 2020). These domain-general regions attend to diverse perceptual and cognitive tasks such as arithmetic processing, executive tasks and action observation. Stronger responses were observed to more effort-demanding conditions. The features seen in these domains are also found in another group of regions that make up the bilateral 'multiple demand' (MD) network. These regions include bilateral frontal, parietal, cingulate and insular areas. The functions of the MD network include attention, inhibition, working memory, fluid intelligence, goal-directed behavior and planning, and consciousness (Fedorenko & Blank, 2020).

1.2 Aphasia

1.2.1 Definition, causes, prevalence and quality of life

Aphasia refers to a condition in which comprehension or production of language is impaired, due to injury to the brain's language network. Damage to the brain can result from a range of pathological conditions including cerebrovascular accidents (CVAs), traumatic brain injuries (TBIs), brain masses, vascular dementia, or neurodegenerative diseases. CVA, also known as stroke, stands out as the leading cause of aphasia onset. A stroke can be ischemic (blood vessel occlusion, 80% of the CVA cases) or hemorrhagic (blood vessel rupture, 20% of the CVA cases) (Grysiewicz et al., 2008). In patients with a stroke, early confirmation of the diagnosis and cause are critical. Early treatment can save a substantial amount of brain tissue, given that, on average, patients lose around 1,9 million neurons every minute of acute reduction of perfusion (Saver, 2006). Both computerized tomography (CT) scan and MRI can be used in this process. Poststroke aphasia is possible in mixed stroke types and in both types separately, but in approximately 60% of all cases it is associated with ischemic stroke (Flowers et al., 2016). Location of the lesion can give some indication on the expected language deficits, although this is no precise predictor (Kasselimis et al., 2017). Aphasia does not arise as a consequence of motor or sensory function impairment, it is rather a deficit primarily affecting language abilities. The symptoms may vary from minor disruptions to total absence of one or more essential language components (Le & Lui, 2022). In addition to deficits in verbal communication other deficits can occur, such as deficits in writing, reading and nonverbal communication such as gesturing (Kagan & Simmons-Mackie, 2013).

In Belgium, as in different countries such as the USA, approximately 30% of all stroke survivors develop aphasia (De Cock et al., 2020; Le & Lui, 2022; Pulvermuller & Berthier, 2008). The incidence of aphasia caused by CVA is the same for men and women (Hier et

al., 1994). The incidence of CVA in Belgium is estimated at 19.000 cases per year. Due to this high prevalence, language assessment is an indispensable part of poststroke care. As soon as possible, the patients should be assessed to determine presence and severity of aphasia (Rohde et al., 2018). Later assessment, in the subacute and chronic phase, is needed for follow-up and for adjusting language therapy to the specific needs of the person with aphasia (PWA) (Vandenborre et al., 2014). Communication is often deemed necessary for leading a fulfilling life (Preetha & Perumal, 2022). Research estimating the impact of many different diseases and diagnoses showed that aphasia has the largest negative influence on quality of life (QoL) (Lam & Wodchis, 2010). The QoL for PWA is influenced by the following factors: psychological distress, severity of the aphasia, physical health, and limitations in communication and daily activities (Hilari et al., 2012).

1.2.2 Classification

Aphasia is a broad condition, in which multiple subtypes can be recognized. Many classification systems have been described (for an overview, see Ardila, 2010). The most well-known classification system, namely the Boston Aphasia Classification System, was developed by Norman Geschwind, Edith Kaplan, Harold Goodglass, and Frank Benson in the 1960s. Their classification was based on the Wernicke-Lichtheim-Geschwind model. The system defines eight types of aphasia, each syndrome characterized by a specific set of language symptoms. Four of the subtypes have a perisylvian location (Broca's aphasia, Wernicke's aphasia, conduction aphasia and global aphasia), while the other four are pericentrally located (transcortical sensory aphasia, transcortical motor aphasia, transcortical mixed aphasia and anomic aphasia). Each subtype is linked to a specific brain area and can be defined as either fluent or nonfluent (Sheppard & Sebastian, 2021; Vandenborre et al., 2014). For all types of aphasia, the broader the affected area, the more severe or persistent the symptoms usually are (Kemmerer, 2015).

The first type of aphasia to be thoroughly described was Broca's aphasia, usually caused by a lesion in the left IFG. The following difficulties are typically linked with Broca's aphasia: difficulty with articulation, reduced prosody and speech rate, agrammatism, stereotypies, reduced comprehension of complex syntactic structures (Ardila, 2010; Kemmerer, 2015; Sheppard & Sebastian, 2021). In Wernicke's aphasia, lesions are usually found in the left STG or posterior middle temporal gyrus (MTG) (Kemmerer, 2015). Impairments, such as the following, are common in this type: impaired comprehension of words and sentences, disrupted naming, logorrhea (excessively fluent speech), paragrammatism (making syntactical errors), phonemic paraphasias (for an overview, see Ardila, 2010; Kemmerer, 2015). Patients are often unaware of their deficit. Anomia, a deficit in word-finding and naming, is to some degree present in each subtype, but not as prominently and persistently as in anomic aphasia. This subtype typically shows no other distinct deficits and is not as strongly linked to damage in a specific brain region as the other types (Kemmerer, 2015; Sheppard & Sebastian, 2021). Conduction aphasia is characterized by impaired repetition of sentences and in severe cases also words, and is caused by lesions in the white matter connection between Broca's and Wernicke's areas (Kemmerer, 2015). Transcortical aphasia syndromes are characterized by intact repetition and can additionally be subdivided into transcortical motor aphasia (impaired production), transcortical sensory aphasia (impaired comprehension) or mixed transcortical aphasia (impaired production and comprehension) (Kemmerer, 2015). Global aphasia is caused by large lesions encompassing most of the left perisylvian cortex and underlying white matter, leading to disruption of all or most components of language (Kemmerer, 2015; Sheppard & Sebastian,

2021). Often, speech production is limited to a few stereotypic utterances and comprehension only extends to a few highly familiar phrases or words.

In discussing the classification of aphasia subtypes, several considerations are to be made. First of all, a classification system such as the Boston Aphasia Classification System is too simplistic to cover all clinical cases of aphasia. Not all patients are classifiable into one of these types, but rather show symptoms of multiple types (Kemmerer, 2015). Secondly, the distinction into categories gives the impression that the patients therein form a homogeneous group. This, however, is not the case at all, since there is much variation possible concerning presence and degree of the symptoms within each subtype, depending on location and size of the lesion and exact location of the language areas in each patient (Bunker & Hillis, 2022; Kemmerer, 2015). Thirdly, the distinction between the aphasia types is based on concepts, such as Broca's area and Wernicke's area, that are insufficiently defined, as discussed before (Tremblay & Dick, 2016). A fourth limitation is that the description of the syndromes is based on general linguistic modalities, such as productive and receptive language, without taking more specified linguistic components such as semantics, lexicon, phonology, morphosyntax and pragmatics into account (Kemmerer, 2015). Fifth, each subtype, except for anomic aphasia, is linked to damage in a certain brain region. These lesion-to-syndrome correspondences, however, are not consistent, since many patients show damage to additional regions, no damage to the linked region, or have not developed aphasia despite damage to the linked brain region (Kasselimis et al., 2017). Lastly, a patient's aphasia symptoms may change over time, especially during the first three months poststroke, resulting in allocation to a different subtype (Kemmerer, 2015). During the transitioning process from one subtype to another, classification is extra challenging since some symptoms of both subtypes may be present. As an alternative to the Boston Aphasia Classification System, many researchers suggest a more individualized deficit-based approach, rather than a syndrome-based one to circumvent the limitations (Kasselimis et al., 2017; Sheppard & Sebastian, 2021). For example, many studies propose a data-driven approach to categorizing aphasia according to affected language components, e.g. semantics or phonology (Alyahya et al., 2020; Halai et al., 2017; Landrigan et al., 2021; Stefaniak et al., 2022).

1.2.3 Assessment

To deliver the required treatment, it is important to identify aphasia in stroke patients early on. An early start of intervention is widely assumed to be advantageous, although research is not conclusive about the precise effect (Nouwens et al., 2015). Speech and language therapists (SLTs) identify the potential aphasic patients by administering a language screening (for an overview, see Hachioui et al., 2017). This is a short test that requires only low effort from the patient, making it feasible for acute stroke patients. The result is dichotomic, as it presents the distinction between patients with no chance of having aphasia and patients that might have aphasia and should receive further assessment. For example, the ScreeLing (Visch-Brink et al., 2010) is a widely used screening test that is appropriate for mild to severe aphasia and should be applied as early after onset as possible (for an overview, see Berns et al., 2015).

Although a screening provides a good starting point, a more thorough comprehensive assessment is necessary to gain a complete understanding of the patient's language abilities (Hachioui et al., 2017). First of all, a notion of the patient's prestroke language skills, through interviewing the patient or a family member, can provide context for

interpreting the test results. Furthermore, all language components should be tested in both the expressive and receptive modality (Sheppard & Sebastian, 2021). One example of a broad language test is the Dutch version of the Comprehensive Aphasia Test (CAT-NL) (Swinburn et al., 2014). This test encapsulates most language components and can be used starting from more or less three weeks after the stroke (for an overview, see Berns et al., 2015). The Akense Afasie Test (AAT) (Graetz et al., 1992) contains six subtests, covering different language modalities and components (for an overview, see Jungen & van Engelen, 2018). Since the AAT is rather outdated, the CAT-NL should be considered the preferred assessment tool (Berns et al., 2015). These tests should be scored and interpreted carefully, with attention to performance on different subtests. If the broad assessment shows difficulties within a certain domain of language (i.e. semantics, pragmatics, …), it is important to conduct a more in-depth analysis of the found deficits with additional, more specialized tests to delineate the exact difficulties (Sheppard & Sebastian, 2021). Other tests that are often conducted are the Nederlandse Benoem Test (NBT) (Van Ewijk et al., 2020) for naming deficits, the Token Test, which is a subtest of the AAT (Graetz et al., 1992) for auditory comprehension, the Semantic Association Task (SAT) (Luzzatti et al., 2020) for verbal and visual semantics, and the Amsterdam-Nijmegen Test voor Alledaagse Taalvaardigheden (ANTAT) (Blomert et al., 1995) or Scenario Test (van der Meulen et al., 2008) for functional communication. Besides the formal tests, observation of the patient is essential in every step of the assessment process (Vandenborre et al., 2014).

Although these described assessment tools are widely used, there are some important limitations to take into consideration. First of all, the clinician conducting the tests should be adequately trained (Vogel et al., 2010). A lack of clinical skills may lead to suboptimal diagnosis, which may in turn result in poorly adapted therapy. Secondly, Rohde et al. (2018) take a more conservative stance towards published assessment tools, stating that the majority of these tools have not been definitively validated for distinguishing aphasic versus non-aphasic stroke patients. Several limiting factors diminish the conclusiveness of the conducted studies for diagnostic validation, such as the absence of a control group, the use of healthy controls instead of non-aphasic stroke patients and the inclusion of PWA due to different etiologies than stroke. A third limitation is the time-consuming nature of language tests, impacting both clinicians and patients (Berns et al., 2015). SLTs, on the one hand, do not only conduct the test but also invest time in scoring and interpreting the results. On the other hand, patients often undergo assessment in the acute phase of recovery, when the tests may form an imposition due to fatigue. This illustrates the importance of avoiding unnecessary testing and conducting only those tests needed for formulating an adjusted therapy plan. A fourth limitation is the frequent presence of comorbid impairments, such as cognitive deficits (Vogel et al., 2010), as cognitive abilities often are strongly interwoven in language assessment (i.e. many tasks require memory, attention and problem-solving skills) (Fonseca et al., 2017). Due to the high incidence of these comorbidities, it is important to be wary of misinterpreting poor results on language assessment. A fifth limitation in language assessment is that the described tests give no information on neural defects. The affected brain regions provide an indication, although not a conclusive one, of expected impairments and outcomes, and recovery of damaged areas is partially responsible for improvement of language abilities (Berthier et al., 2011). However, this recovery of brain tissue is not being followed up with the described assessment tools. A sixth limitation concerns the use of artificial tests instead of natural speaking situations in many of the widely used tests. These artificial tasks rely heavily on specific parts of the language network, while natural speech evokes a broader, less lateralized activation (Hamilton & Huth, 2020). This may be an advantage to patients who can compensate with other regions, or a disadvantage to patients who have relatively intact

language areas and damaged areas in this broader area of activation. Either way, testing with artificial stimuli is not representative for daily life communication. A final limitation lies in the fact that the majority of assessment tools do not take local dialects into account. Both the susceptibility to stroke (Grysiewicz et al., 2008) and the use of local dialects in Belgium increases with age. For this reason, it is important to keep in mind that a patient with post-stroke aphasia may formulate a response that is classified as wrong in the test manual, although the patient knows and understands the required concepts (Peña-Casanova et al., 2019). This limitation however is not restricted to language testing through behavioral measures, but extends to instrumental testing through neuroimaging, since the problem stems from the language use of the patient itself instead of administration or properties of the measuring tool.

1.2.4 Comorbidity with cognitive deficits

Cognitive skills allow one to process, store and use incoming info. The three components of cognition are attention, memory and executive functions, which is an umbrella term for inhibition, working memory, updating and switching (Murray, 2012; Schumacher et al., 2019). Only a limited amount of data regarding cognitive impairment in PWA is available, primarily due to the exclusion of PWA from many studies examining the prevalence of cognitive impairments after stroke, as their communication difficulties can disrupt conventional cognitive assessment procedures. El Hachioui et al. (2014) conducted a study and included aphasic stroke patients. They found that the majority of aphasic patients also had an impairment of at least one non-linguistic cognitive aspect, namely 88% at three months poststroke and 80% after one year (El Hachioui et al., 2014). Deficits in these cognitive abilities have been demonstrated to significantly influence aphasia recovery (Schumacher et al., 2019; Simic et al., 2019).

A narrative review (Abiodun Salako, 2017) analyzed qualitative studies on the operational mechanism of non-linguistic or cognitive modalities connected to language. In addition to the discussed study by El Hachioui et al (2014), this review also included nine other studies. A few findings of these studies were the following. Kalbe et al. (2005) found that the PWA in their sample all performed poorly in at least one of three cognitive domains (memory, attention and executive functions). Jefferies and Lambon Ralph (2006) found that limited executive functions may lead to deficits in word comprehension and production in PWA. Cognitive deficits and executive dysfunctions within the first three months post-stroke, predict future recovery in stroke in general (Y. H. Park et al., 2015) and in PWA (El Hachioui et al., 2014). Researchers found that higher pretreatment executive control level predicts better language therapy outcomes in the chronic stage of aphasia (Meier et al., 2022; Simic et al., 2019).

1.3 Neural recovery of stroke-related aphasia

1.3.1 Phases of neurostructural recovery

When suffering a stroke, brain tissue sustains damage from ischemic or hemorrhagic lesions. Afterwards, spontaneous recovery occurs, restoring brain tissue to some degree if supported by the required treatment, thereby often improving the functional deficits

(Murphy & Corbett, 2009). In ischemic strokes the changes are, partially, the result of reinstatement of cerebral blood flow in the ischemic penumbra. In the penumbra, which is the area bordering the center of the stroke, the blood flow has dropped but can still provide enough resources to prevent cell death for a certain period of time (Xing et al., 2012). Unlike the damage in the core of the stroke, the damage in the penumbra is reversible when perfusion is restored (Murphy & Corbett, 2009). In hemorrhagic stroke, bleeding and excessive pressure on the brain tissue should be stopped as soon as possible through intervention to prevent further damage (Montaño et al., 2021). Adjacent areas with diminished blood flow due to the bleeding may recover from restored blood flow, similar to the penumbra in ischemic stroke. Furthermore, research has shown an association between structural changes in the left hemisphere gray and white matter of the language network and language recovery in the subacute stages after a stroke (Bae et al., 2022; Chang et al., 2021). These structural changes only account for a part of the recovery, since functional neural changes have a great impact as well.

1.3.2 Phases of language recovery

Language recovery after stroke is a complex matter. Although not everyone may regain their prestroke language abilities, some recovery is possible for every subtype and severity of aphasia (Berthier, 2005). Factors such as age, pre-stroke language skills, lesion location, comorbidity (e.g. cognitive impairment), occupation and communication partners can contribute to aphasia severity and recovery, resulting in large heterogeneity across patients (Price, 2010). However, common phases can be identified in the process of recovery. Since some of the restorative mechanisms may occur in different phases, albeit to a different degree, these phases could be described as different but overlapping stages (Hillis & Heidler, 2002).

The acute phase, encapsulating roughly the first week after the stroke, is characterized by instability. When some areas of the language network are damaged by the stroke, the whole network becomes globally disturbed (Price et al., 2001). In the subacute phase, starting several days after the stroke up to around six months later, language recovery is usually the greatest (Sheppard & Sebastian, 2021). Most patients experience the greatest improvements of language in the first three months, but recovery continues strongly up to six months (El Hachioui et al., 2012; Sheppard & Sebastian, 2021). After about six months, the chronic phase starts, in which language recovery appears to be slower, although recovery may continue to a certain extent for years after the stroke in the chronic phase of aphasia, if supported by adequate language intervention (Berthier, 2005; Gerstenecker & Lazar, 2019; Murphy & Corbett, 2009; Saur & Hartwigsen, 2012).

One factor highly influencing the language recovery process is undergoing SLT. The exact influence this has on language outcome is still widely debated, however, the enhancement of recovery to some degree cannot be denied (Berns et al., 2015; Nouwens et al., 2015). Concerning the content of intervention, research shows that some brain regions linked to certain aspects of language (i.e. semantics, phonology, …), are more prone to show changes after focusing on that aspect in language therapy (Schevenels et al., 2020; Stefaniak et al., 2022). However, most observed brain regions displaying therapy-related changes were not linked to a specific type of language therapy, possibly because therapy often involves multiple aspects of language even when it focuses on just one (Schevenels et al., 2020). Furthermore, different researchers present varying results regarding recommended timing, intensity and duration of SLT. Regarding timing of treatment, it is

assumed that early intervention results in better outcome, although there is no conclusive evidence that supports this (Nouwens et al., 2015). Furthermore, early intervention may not always be feasible for patients in the acute stage after stroke. Another factor is intensity of treatment. Many studies state that more intensive therapy leads to better treatment outcomes (for an overview, see Brady et al. (2016)). However, other researchers such as Stahl et al. (2017) conclude that a ceiling effect occurs when offering more than two hours of practice per day, thus providing some counterweight to this statement. Rather, a two-week extension of treatment duration showed a significant positive influence. Additionally, more intensive treatment programs may induce a higher dropout rate (Brady et al., 2016). Taken together, evidence-based Belgian guidelines suggest an early start of intervention, an intensity of at least two hours per week or more if the patient can tolerate it, and a duration of at least six months to stimulate recovery in the best way possible (Berns et al., 2015).

Even though the current available research gives indications on the ideal form of language intervention, certain requirements should be met in research. First of all, because of the large heterogeneity in severity and treatment outcome across PWA, studies with large sample sizes are needed in order to produce generalizable results (Schevenels et al., 2020). Secondly, this variability causes a need for longitudinal follow-up within patients in research, instead of cross-sectional comparisons between patients (Schevenels et al., 2020). A longitudinal approach effectively tracks the evolution instead of comparing snapshots from highly variable timelines among different patients. Thirdly, since many studies use different patient populations (e.g. lesion size and location, severity of aphasia), intervention methods and outcome measures, it is not always possible to compare conducted studies and integrate their findings to formulate conclusions (Schevenels et al., 2020).

1.3.3 Neuroplasticity and the role of the right hemisphere

In aphasic stroke, the term neuroplasticity describes a recovery phenomenon that induces neural changes in reaction to the damage to language areas. This may encapsulate that the brain adapts by engaging undamaged structures for language processing, like perilesional tissue and homologue areas of the pre-existing language network, or by augmenting integration with the network for cognitive control (Berthier et al., 2011; Saur et al., 2006). The extent of involvement of these brain regions varies not only through morphological changes, but also through relocation of white matter connections, a process known as synaptogenesis (Berthier et al., 2011). Reorganization of brain functions occurs mostly in the subacute phase of recovery (Hillis & Heidler, 2002). Most of the compensating areas, recruited through neuroplasticity, are part of the pre-existing language processing network; there is little evidence for recruitment of previously unrelated areas (Saur & Hartwigsen, 2012; Stockert et al., 2020). Additionally, some research indicates a role of subcortical structures such as the basal ganglia in functional recovery of language (for a review, see Schevenels et al., 2020).

In their highly influential longitudinal study, Saur et al. (2006) describe the reorganization process through each phase of recovery. During the acute phase, activation in left-hemispheric language areas is minimal or not present, while right hemisphere activity is upregulated. A positive association has been found between language function and both retained activation in the left IFG and increased activity in the right IFG in the acute phase. This right hemisphere activity is most prominent in the subacute phase, when it is greater

than normal, whereas left-hemispheric language areas show a continuous and gradual increase in activation over time. In the chronic phase, activation patterns begin to normalize, meaning that right hemisphere activation during language tasks decreases while activation of left hemisphere language regions highly resembles that of healthy subjects in the chronic phase in most cases. A similar recovery pattern of early increase of right-hemisphere activity followed by normalization of the lateralization to the left-hemisphere language network is described in the longitudinal fMRI study of Nenert et al. (2018).

The precise role of right hemisphere activation in language recovery after stroke has been widely debated (for a review, see Li et al., 2022). Concerning the role of the right hemisphere, Saur et al. (2006) mention that, from a mechanistic point of view, the right IFG activation may indicate disinhibition. This view is supported by Price et al. (2005), who reviewed imaging studies on this subject and concluded that right hemisphere activation reflects disinhibition caused by damage of the homologue left hemisphere areas. In normal circumstances, these areas of the left hemisphere exert inhibition over their right hemisphere homologues. When these left hemisphere areas are damaged, their trans-hemispheric inhibition of right-sided activity gets disrupted. The right-sided activation therefore is not a sign of functionality according to the authors, but rather of a maladaptive strategy. As the left hemisphere language areas recover gradually, their inhibition results in the observed decrease of activation in their right hemisphere homologues. Arguments that support this standpoint are that the right hemisphere activation starts quickly after the stroke, when language is still highly diminished, and that the authors found no correlation between the activation and level of language production or comprehension recovery (Price et al, 2005). Another example of this line of research is the study of (Szaflarski et al., 2013), who found that an increased right-hemispheric shift was associated with lower language performance. They instead state that a normalization of the post-stroke language activation patterns is necessary for better language performance.

On the other hand, Saur et al. (2006) propose that the activation course in the frontal areas of the right hemisphere might be interpreted as attributing to functional recovery of language, since they found a strong correlation between improved function of language and increased activity in the right IFG in the acute stage. This view is supported by several task-based (Menke et al., 2009; Raboyeau et al., 2008) and resting-state (Xie et al., 2022) fMRI studies that found a link between activation in brain regions of the right hemisphere and language improvement. However, some studies only found this link in the acute stage (Saur et al., 2006) while other studies reported a facilitatory role of the right-hemisphere regions throughout the chronic phase, such as Elkana et al. (2013) and van Oers et al. (2010) (see Li et al., 2022 for an overview). Van Oers et al. (2010) describe that this engagement is indicative of task difficulty or learning, as it correlates with increased demands on working memory or executive control as tasks become more challenging.

Elkana et al. (2013) conducted a longitudinal fMRI study in young individuals with stroke-induced aphasia in the chronic phase of recovery. The authors advocate for expanding the recovery process described by Saur et al. (2006). Their research showed significant spontaneous progress of language function during the chronic phase of recovery, more than can be attributed to natural development. Also, this improvement in language was associated with increased activity in the right hemisphere. This result contradicts the generally accepted consensus that language recovery stagnates in the chronic phase of language recovery, due to the young age of the participants. This population demonstrates

a higher potential for neural reorganization than the older population where strokes are more prevalent (Elkana et al., 2013).

Stockert et al. (2020) conducted a longitudinal study, as a follow-up on the research of Saur et al. in 2006. The longitudinal study of Saur (2006) substantially advanced the understanding of the recovery process and the role of the right hemisphere, but it did not take lesion location into account. Therefore Stockert et al. (2020) explored the relation between lesion site and reorganizational mechanisms, resulting in compelling new insights. First of all, they observed that some activation patterns were present regardless of lesion location. For example, in the subacute phase, activation in perilesional areas and the bilateral domain-general network was linked to functional compensation, whereas reorganization in the chronic phase is mostly paralleled by increased activity in temporal areas of the left hemisphere. Secondly, the left hemisphere areas of the language network that remained intact showed an increase in activation. Namely, more frontal activation occurred when the lesion was located in the temporo-parietal region, and vice versa. Finally, activation of lesion-homologue areas in the right hemisphere can occur, but this was only observed in patients with a frontal lesion (Stockert et al., 2020). Lesion location shows to be an important factor in the reorganizational process. Another crucial factor is lesion size; however, this aspect is often insufficiently considered in studies (Schevenels et al., 2020).

To explore hemispheric dominance of the language functions, an interesting measurement is the lateralization index (LI). Rather than representing absolute activation, the LI measures the relative reliance on right-hemispheric regions compared to the dependence on left-hemispheric regions. LIs can range from 100 to -100. A positive LI indicates lateralization towards the left hemisphere, an LI of zero means symmetrical activation and a negative LI represents lateralization towards the right hemisphere. Although this measure can provide interesting insights due to the fact that it compares left- and right-sided activation, the use of LIs remains scarce in research. In their meta-analysis, Wilson & Schneck (2021) conclude that PWA often show lower LIs in comparison to controls. This may stem from direct damage to the left-hemispheric regions of interest (ROIs), or it may be an indirect effect through disruption of networks. In relation to language improvement in aphasia the findings surrounding the LI are inconclusive. Some authors find a correlation between improving language functionality and an initial decrease, followed by an increase of the LI (e.g. Nenert et al., 2018). Conversely, other authors, such as Dietz et al. (2016), did not find any link between LI and aphasia severity. A limitation of using the LIs according to Dietz et al. (2016) is that they introduce an inherent bias, since voxels that are damaged in the left hemisphere and therefore do not show any activation, may show activation in their right-sided homotopic areas. Therefore, the LI may decrease, simply because more voxels are activated in the right hemisphere, not because of their degree of activation. A possible solution for this limitation is to select a percentage of the most active voxels, so that the same number of voxels are included in the left and right hemisphere.

Recovering patterns are highly variable between subjects, due to differences in size and site of the lesion and the time since the stroke. Therefore, within-patient longitudinal follow-up is needed to capture the nature of the reorganizational processes after stroke in research. However, the majority of the available studies consist of cross-sectional designs. This underscores the value of the cited longitudinal studies of Saur et al. (2006) and Stockert et al. (2020), describing the recovery process from the acute to the chronic phase. A limitation of these studies, however, is their small sample sizes, with only 14 and 34 participating PWA, respectively. Even though many cross-sectional studies include more

participants, they yield highly variable and even contradicting findings, leading to an extensive debate surrounding the recovery process. The cause for these contradicting results is sometimes unclear, but might be attributed to differences in the description system of the anatomical areas, included patient population, task-based vs. resting-state fMRI, specific tasks, or, still, the use of small sample sizes (Schevenels et al., 2020). Rorden et al. (2012) describe the importance of taking lesion information into account, namely by masking or excluding the lesion when normalizing the brain onto a template to enable comparison between subjects, as the lesion may distort this process. Finally, Wilson & Schneck (2021) describe the importance of including a control group in research. For example, in PWA with a left-sided lesion, right hemisphere activity during language processing may be interpreted as compensatory activation. However, it is possible that this right hemisphere activity is not greater than in healthy controls, although it appears to be more prominent due to decreased left hemisphere activity. Alternatively, including healthy controls to the study allows for examining group differences, which is necessary for formulating correct conclusions.

1.3.4 Role of the MD network in language recovery

Similar to the activation of the right hemisphere, another potential compensatory mechanism for language recovery is activation of the MD network. As discussed previously, the MD network is a set of domain-general neural regions activated during a diverse range of executively demanding language and non-language cognitive tasks (Fedorenko et al., 2013; Stefaniak et al., 2021). These domain-general regions support the following functions: working memory, reasoning, attention, and executive functions (Fedorenko et al., 2013). Previous neuropsychological research has already suggested the involvement of domain-general brain regions in the recovery process of post-stroke aphasia (Fillingham et al., 2006; Fridriksson et al., 2006; Geranmayeh et al., 2017; Swinburn et al., 2004). For instance, Geranmayeh et al. (2017) found that the functionality of the relationship between the presupplementary motor area and the dorsal anterior cingulate region facilitates language recovery following a stroke. The presupplementary motor area/dorsal anterior cingulate region is frequently unaffected in cases of aphasic stroke (Geranmayeh et al., 2017). Functional neuroimaging has furnished evidence supporting the notion that language processes entail an interaction between brain regions specialized for language and domain-general brain regions. This interaction refers to the necessity of communication and coordination among different brain regions, including both those specialized in language processing and those with broader cognitive functions, to facilitate various aspects of language comprehension and production (Fedorenko & Thompson-Schill, 2014; Geranmayeh et al., 2017). An intriguing link between the MD network and the specific language network is that some linguistic manipulations can elicit a response in both the first language-specific and second domain-general MD areas. For example, regions in both networks have been shown to be sensitive to violations of linguistic structure under some task conditions, and also to manipulations of linguistic complexity in well-formed sentences (Fedorenko & Blank, 2020).

A particular component of the MD network has been proposed to facilitate the restoration of language function following a stroke. This specific part includes the dorsal anterior cingulate cortex (dACC), the nearby presupplementary motor area (preSMA) and the bilateral anterior insula with proximate IFG (Duncan, 2010; Fedorenko et al., 2013; Geranmayeh et al., 2017). The MD regions have previously been found to exhibit heightened activity during intentional modes of learning (Hampshire et al., 2016).

Geranmayeh et al. (2017) suggest that this segment of the MD network might present a promising target for experimental therapeutic interventions, including neurostimulation. The dACC and preSMA are specifically attractive targets, because they are frequently unaffected following aphasic stroke, particularly within the region of the left middle cerebral artery. Geranmayeh et al. (2017) discovered that boosting activity in the midline regions of the dACC and preSMA or enhancing connectivity within this segment of the MD network, could speed up language recovery. In a separate study, Sliwinska et al. (2017) reported that transcranial magnetic stimulation of the dACC and preSMA sped up the learning of a novel pseudo-language comprising pseudoword-picture pairs. Considering the extensive cognitive functions associated with this network, the authors suggest that the therapeutic possibilities might extend to recovery from diverse forms of brain injury (Geranmayeh et al., 2017).

According to Saur et al. (2006), it might be possible that cognitive skills such as control and attention (supported by frontal regions) are barely needed for language in the acute stage of stroke-related aphasia, since the left hemisphere language activation is strongly diminished itself, and therefore the requirement for cognitive control of language performance from the right hemisphere is low. In the subacute phase however, the language areas are regaining their activation, but increased cognitive effort and therefore reliance on the domain-general network, is still strongly needed. This explains the additional peak of activation seen in the right frontal regions during this phase. In the chronic phase, the language network has regained most of its ability, resulting in a lesser need for cognitive control. Some patients may continue to rely on domain-general compensation, even in the chronic phase. This mostly occurs in cases where the lesion is of such significant size that the left hemisphere is not able to fully recover (Li et al., 2022).

This possible link between cognition and language processing is, however, strongly debated in the existing literature (Wilson & Schneck, 2021). Correlations have been observed by Fridriksson et al. (2010) between naming performances and activation in three brain regions, namely the left occipital lobe, the left orbital part of the IFG (IFGorb), and the left anterior cingulate cortex (ACC). They interpreted activation of the ACC as potential recruitment of a domain-general system related to attention or error monitoring. However, Wilson & Schneck (2021) argue in their meta-analysis that its precise location is ventral to the anterior cingulate regions linked with these functions (i.e., Fedorenko et al., 2013), indicating a stronger likelihood of it representing a semantic region rather than a MD network region as hypothesized by Fridriksson et al. (2010) (Binder et al., 2009). Two other brain regions identified as potential domain-general areas, demonstrating methodologically robust correlations between language performance and activation, are the dorsolateral prefrontal cortex and the supplementary motor area (SMA) (Allendorfer et al., 2012; Griffis et al., 2016). Wilson and Schneck (2021) analyzed these studies and found that two language tasks (a semantic decision task and a verb generation task) also recruited the same brain regions in the control group of the studies, which implies that the activation of these regions in PWA does not strongly suggest a compensatory role of the domain-general network.

In summary, the activation of the right hemisphere and the engagement of the MD network represents, according to some studies, potential compensatory mechanisms for language recovery following stroke-related aphasia. Previous studies have emphasized the importance of domain-general brain areas in language rehabilitation following a stroke, underscoring the necessity of communication and coordination between language-specialized and broader cognitive regions, although the debate about the precise role,

importance and relevance is still ongoing (Wilson & Schneck, 2021). As mentioned earlier, the importance of conducting studies using control groups also remains important here, to avoid misinterpretations of observed increased activation as a possible compensatory activation, as noted by Wilson & Schneck (2021).

1.4 Single-subject approach

1.4.1 Traditional approach

In the mid-1990's through 2000's, the group-averaging approach was the customary analytic approach of fMRI data (Fedorenko, 2021). In this method, the MRI data of each subject is spatially normalized to fit into a standard stereotactic representation of the human brain (Ashburner & Friston, 2000). This way, structural brain areas get positioned in such a way that they overlap in all participants. Afterwards, a voxel-wise statistical analysis is performed on this normalized data to find common activation patterns. A first challenge associated with this method is the problem of multiple comparisons. When searching for significantly active regions, all the voxels of the entire brain could be examined to determine in which ones the activation exceeds the significance threshold. However, in every statistical test there is a small chance of obtaining a false positive result, meaning that the activation appears significant while it is in fact not. In whole-brain analyses involving thousands of tests these small probabilities combine, significantly increasing the overall risk of false positive results. In addition to using a correctional factor in the statistical calculations, the number of comparisons can be limited by selecting regions of interest (ROIs) and solely assessing activation within those predefined areas, thereby eliminating the chance to find accidental results outside of the ROIs. These ROIs should be carefully selected based on previous whole-brain research, to avoid a detection bias. For example, selecting ROIs based on studies in healthy subjects could produce a bias towards areas of the language network, with too little attention going to potential compensatory activation in other areas (Schevenels et al., 2020). A second problem arising from the group-averaging approach, is that, although it addresses the 'where' question many researchers asked, it does not give conclusive information about underlying functionality of the found regions (Fedorenko, 2021). Since many cortical areas are highly heterogeneous in both structure and function, information on activity in a macroanatomical region is not sufficient to form conclusions on functional networks. Additionally, this variance of exact location of functional areas across subjects results in low sensitivity to subtle activation and blurring borders between functionally distinct areas (Fedorenko, 2021; Nieto-Castañón & Fedorenko, 2012).

1.4.2 Single-subject approach

In reaction to these problems, Fedorenko et al. (2010) proposed the single-subject approach. This method determines ROIs based on functionality in each individual brain, rather than based on structure, by using functional localization (which will be discussed in the next paragraph) (Fedorenko, 2021; Fedorenko et al., 2010). Afterwards, statistical inferences are made based on these individually defined ROIs, thereby circumventing the problem of excessive multiple comparisons as present in whole-brain analysis. As described by Fedorenko et al. (2021), the single-subject approach has many advantages

in comparison to group analyses. First of all, by administering functional localization, the single-subject approach enables the process of mapping functional networks. Secondly, the single-subject approach reaches higher levels of sensitivity to subtle activations and less blurring of borders between functionally distinct areas. Thirdly, the single-subject approach manages to produce a generalizable outcome, applicable to individuals outside of the testing sample, while still factoring in inter-individual differences in structure and function (Fedorenko, 2021).

1.4.3 Functional localizers

Functional localization is achieved through the implementation of functional localizer tasks. A functional localizer is a task performed during an fMRI scan that helps to identify a certain functional brain region or network instead of a structural one. Fedorenko et al. (2010) described a functional language localizer that contrasts normal existing sentences with sequences of pronounceable nonwords. Using rapid serial visual presentation, these stimuli are visually presented to the individual. The contrast between the standard sentences and sequences of pronounceable nonwords targets both processing at the level of individual words and higher-level processing of semantics and syntax in the brain. Furthermore, it is robust to changes in tasks. The baseline condition, comprising nonword lists, functions as a control to account for visual and/or acoustic processing, as well as phonological processing and grapheme-phoneme correspondence (Fedorenko et al., 2010; Fedorenko & Thompson-Schill, 2014).

However, this localizer has certain limitations. First of all, data-driven studies have proposed a classification system for aphasia including semantic vs phonological aphasia. However, as Fedorenko et al. (2010,2024) do not consider phonological processing to be a core aspect of language, it is not taken into account in this localizer task. This way, potentially valuable information may be overlooked. Furthermore, it is unsuitable for specific clinical populations or children. The visual variant of the localizer is not appropriate for individuals who are illiterate. Also in a broader sense, regardless of the presentation mode, processing single sentences is not particularly engaging. This can pose a challenge, particularly among populations with difficulties in sustaining attention, such as the elderly. The failure of keeping attention will likely lead to weaker activations within the brain. Moreover, rapid reading constitutes a rather cognitively demanding activity. This leads to potential confounding of language activation during rapid serial visual presentation between clinical populations (such as PWA) and typical healthy subjects, because of disproportionate difficulty of the task, which is unrelated to language processing (Scott et al., 2017).

Scott et al. (2017) presented in their research another version of a language localizer with three differences from the one just discussed: it uses auditory presentation that contrasts intact speech with degraded speech, it uses naturalistic materials and only asks passive listening from the patient. This functional localizer can also be adjusted for groups of diverse ages and speakers of different languages, by substituting the stimuli with another set that is more adapted to this patient (altered for age or language). This research compared this localizer to the functional localizer from Fedorenko et al. (2010) and discovered that the new localizer quickly and consistently detected the high-level language-processing regions on an individual subject basis. It is noteworthy that this study utilized healthy young individuals as their study population, and that this aspect has not yet been assessed in older adults or PWA.

1.5 Present study

The present study offers the opportunity to investigate on an individual level to what extent the MD network and the right-hemispheric homologue regions are involved in language processing in the chronic phase of aphasia, both in absolute and in relative (LI) terms. We propose three research questions: 1) 'Does the amount of activity of the language network and the MD network differ between PWA and healthy controls? Is there a correlation with behavioral test results?', 2) 'Is the activation of the right-hemispheric language regions relative to the activity in the left-hemispheric language regions, as measured by LIs, significantly different in PWA as compared to healthy controls, as a potential sign of compensation? Is there a correlation with behavioral test results?', and 3) 'Is there significant activation of the subject-specific MD network during language processing? If so, is there a significant group difference?'. In order to answer these questions, we will apply the single-subject approach with fMRI to circumvent some of the mentioned limitations of previous research.

Formulating hypotheses for these research questions forms a challenging task. For instance, the role of right-hemispheric homotopic regions as a compensatory mechanism is widely debated in the literature. Wilson and Schneck (2021) characterize the evidence on this matter as 'modest and equivocal'. According to them, these right hemisphere regions may be important in language recovery, although evidence lacks clarity to confirm significant reorganization. Li et al. (2022) further describe this ambiguity, noting three conflicting arguments in the literature regarding the contribution of right hemisphere activation to language recovery; which form our three hypotheses to our first research question: 1) activity of the right hemisphere regions supports language recovery in the chronic stage (e.g. Van Oers et al., 2010), 2) right hemisphere activity exerts a facilitatory role, but only in the earlier stages of recovery (e.g. Saur et al., 2006), and 3) right-sided activation represents a maladaptive mechanism, prohibiting optimal language recovery (Price et al., 2005). Concerning the activation of the left-hemispheric language regions, most research seems to indicate recovery has reached a plateau by the chronic phase, and that this restored activation supports language performance (Wilson & Schneck, 2021). Followingly, our second research question could be of particular interest, as LIs have been scarcely used in PWA in the literature. Therefore, however, the hypothesis can be based only on a limited amount of evidence. Based on Wilson & Schneck (2021) we expect lower LIs in PWA (i.e. less lateralization towards the left hemisphere) and according to Nenert et al. (2018) we would expect to see a positive correlation between LI and language function in the chronic stage of recovery. For our third research question, we hypothesize that there will be no significant activation of the subject-specific MD network during language processing. Diachek et al. (2020) demonstrated in their fMRI study, using the single-subject approach, that the MD activation is strongly dependent on the presence of a task, rather than on the need for language processing in healthy young subjects. MD activation was stronger for experimental tasks and tasks with individual words, whereas the language network showed stronger activation for tasks of passive listening and tasks with meaningful stimuli such as sentences (Diachek et al., 2020). Additionally, Shain et al. (2020) found no involvement of the MD network in naturalistic language processing. Wilson and Schneck (2021) analyzed several studies mentioned earlier (Allendorfer et al., 2012; Fridriksson et al., 2010; Griffis et al., 2016), concluding that the activation of the MD regions (mentioned in those studies) in PWA do not strongly suggest a compensatory role of the domain-general network (Wilson & Schneck, 2021).

The divergent and sometimes contradictory nature of these findings can be attributed, at least to some extent, to methodological issues of these previous studies. Firstly, most studies utilize the group-averaging approach, rather than employing the single-subject approach to identify the language network and MD network on an individual level. This exposes them to all limitations of the group-averaging method, including decreased sensitivity to subtle activation (Fedorenko et al, 2021). Furthermore, Wilson and Schneck (2021) describe three critical methodological issues contributing to diversity in research findings. A first limitation is the failure to adequately correct for multiple comparisons. The impact of this limitation can be mitigated when studies use ROIs, since the number of needed comparisons will thereby drastically decrease, although a correction is still required if more than one ROI is included. This was mentioned earlier as another advantage of the single-subject approach. Secondly, task performance confounds pose a moderate limitation. Factors typically caused by stroke such as difficulty with task-related cognitive processes, fatigue or frustration may influence task performance negatively, making it difficult to interpret lower scores in the patient group as a clear indication of reorganization. Thirdly, contrast validity poses a major limitation, as numerous studies utilize contrasts that were not equated for auditory, visual, motor, or other cognitive task demands. Consequently, these non-linguistic task demands may be reflected in the activation maps. Finally, both Wilson & Schneck (2021) and Li et al. (2022) state that the role of the MD network is still unclear, as some of the domain-general regions are also active in healthy controls during language processing (Wilson & Schneck, 2021) and that these regions also showed activity in stroke patients that suffered no damage to the language network (Li et al., 2022). This activity might therefore reflect cognitive control, but there is no strong evidence for a compensatory mechanism. This limitation underscores the importance of including an adequate control group to each study. The same is true for studying the role of the right hemisphere.

2 Methods

2.1 Participants

15 PWA (10 men, 5 women, 65 y/o ±16 years) who are in the chronic stages of recovery (≥ 12 months post-stroke) were included in our study. 12 of these patients were recruited from the stroke unit of UZ Leuven when they were in the acute post-stroke phase, and the remaining 3 subjects were enlisted through SLTs. Our control group consists of 13 neurologically healthy individuals (9 men, 4 women, 69 y/o ±7 years). These individuals were selected to match the age at the group level with the test subjects and to match the number of left-handed individuals with that of the test subjects, namely 2. This was determined by the Edinburgh Handedness Inventory (Oldfield, 1971). Using an unpaired Wilcoxon rank-sum test, no significant age difference was found between the two groups ($W=89.5$, $p=0.73$) and using a chi-squared test no significant sex difference was found between both groups ($\chi^2(1) = 0.021$, $p = 0{,}885$).

PWA were included based on the following criteria: (1) a stroke had occurred within the left hemisphere or bilaterally, (2) they were diagnosed with aphasia during the acute post-stroke phase through behavioral language assessments, and (3) they had no diagnosed psychiatric or neurodegenerative disorders. The paper of Kries et al. (2023), which includes 12 of our 15 PWA subjects, describes the diagnostic process during the acute post-stroke stage and the recruitment process in more detail. Among the 15 individuals with post-stroke aphasia, 11 presented with ischemic aphasia and 4 with hemorrhagic aphasia. Additionally, 13 exhibited a stroke in the left hemisphere, while 2 displayed bilateral brain damage. Moreover, 13 cases involved a stroke in the middle cerebral artery (MCA) blood vessel, whereas two were associated with the posterior cerebral artery (PCA) blood vessel. Furthermore, 13 participants underwent SLT, while 2 did not. Lastly, 13 were right-handed, and only 2 were left-handed. A comprehensive overview of the PWA subjects with additional demographic information and information about brain lesions can be found in Appendix A (Table A1). As for the exclusion criteria applied to both groups, individuals diagnosed with a hearing impairment were excluded from the study due to the auditory requirements of the listening task during the fMRI scans. All subjects provided written consent before their participation in the study. The study received approval from the ethics committee of UZ/KU Leuven (S60.007). The research was conducted in compliance with local legal regulations and with the fundamentals outlined in the Declaration of Helsinki (“World Medical Association Declaration of Helsinki”, 2013).

During the testing sessions, all participants underwent standardized clinical language assessments for aphasia. The first test administered was the NBT, also known as the Dutch Naming Test (Van Ewijk et al., 2020). The following assessment was the ScreeLing Test, a comprehensive aphasia battery assessing syntactic, phonological and semantic language skills (Visch-Brink et al., 2010; El Hachioui et al., 2017). Another language test was the verbal fluency task of the CAT-NL test (Swinburn et al., 2014). More specifically, we administered the semantic word fluency task, in which participants are asked to generate as many words as possible in 60 seconds within a certain semantic category, and the phonological word fluency task, in which participants are asked to generate as many words as possible in 60 seconds that begin with the same phoneme (Swinburn et al., 2014). These tasks do not only measure language functioning, but also cognitive functioning

(Bose et al., 2022). Additionally, we assessed cognitive functioning through a combined score of executive functions, attention and memory subscales, as measured by the Oxford Cognitive Screen-NL (OCS-NL) (Huygelier et al., 2020). No group differences were found in cognitive functioning (OCS-NL: W=86, p=0.61). The PWA group achieved significantly lower scores on all language assessments in comparison to the control group (NBT: W=15, $p < 0.001$; ScreeLing: W=23.5, $p < 0.001$; CAT-NL: W = 26.500, p = 0.006).

Table 1 provides an overview of the means and standard deviations for the continuous demographic information and the behavioral tests of the PWA participants and

Table 2 provides this for the control group.

Table 1. Descriptive statistics of demographics of the PWA group.

TOTAL	Age	Time since stroke	Lesion size (ml)	NBT	ScreeLing	CAT-NL total	OCS
Mean	64.667	37.667	53.362	247	63.600	26	94.622
Standard deviation	13.772	26.051	46.268	39.593	8.790	11.408	6.819

Table 2. Descriptive statistics of demographics of the control group.

TOTAL	Age	Time since stroke	Lesion size (ml)	NBT	ScreeLing	CAT-NL total	OCS
Mean	66.769	NA	NA	273.385	70.692	40.636	82.923
Standard deviation	8.633	NA	NA	2.694	1.932	11.448	36.851

2.2 MRI data acquisition

The MRI data collection consisted of subjects undergoing an MRI procedure including a T1-weighted anatomical brain scan, a T2-weighted FLAIR scan, and four functional tasks: an auditory listening localizer task, a visual reading localizer task, a spatial working memory (spWM) localizer task, and a natural story listening paradigm. However, in this study, the latter task is not further analyzed. The duration of the entire scan procedure was 50 to 60 minutes for each participant.

The MRI data were collected at the University Hospital Leuven on a 3-Tesla Philips scanner equipped with a 32-channel head coil. An anatomical brain image with a high resolution was obtained using a T1-weighted MPRAGE sequence (TR9.687ms, TE=4.6ms, 182 sagittal slices, flip angle=8°, voxel size=1 mm isotropic). Lesions were identified and segmented using the T2 FLAIR scan (TR4800ms, 200 sagittal slices). A T2*-weighted single-shot EPI sequence (TR1300ms, TE=29.8ms, 52 near-axial slices, flip angle=90°, voxel size=1.87x1.87x2.7mm) was used to capture functional images. For acquiring these functional images, the participants saw stimuli presented on a see-through screen, which

was positioned at the back of the magnet bore. The stimuli were visible for the subject through a mirror secured to the head coil.

2.3 Lesion segmentation

Lesion masks were outlined by hand on the T2-weighted FLAIR images of each patient with the use of MRIcron (v. 02092019, available via https://www.nitrc.org/project s/mricron), with reference to findings documented in the medical files of the patient, by a neurologist or neuroradiologist. Figure 1 illustrates a map showing the overlap of lesions within the PWA sample. The greatest overlap of lesions was identified in the left IFG and in the left insula (observed in 10 out of 15 participants).

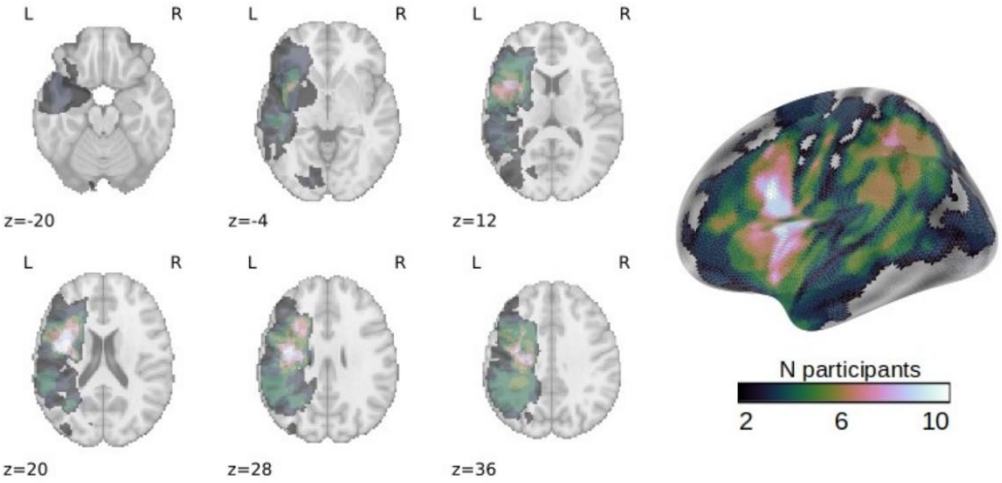

Figure 1. (adapted from De Clercq et al., 2024). *Lesion overlap image within the PWA sample. Axial slices with corresponding Z-coordinates are displayed in neurological orientation. On the right, a surface image is depicted.*

2.4 fMRI tasks

We administered an auditory listening task and a visual reading task, both aiming to identify the language network in the brain. Similarly, we conducted a visual spatial working memory task (spWM) in order to identify the MD network in the brain.

2.4.1 Listening localizer task

In this listening task, we utilized 20 segments from the folktale "The Little Mermaid", written by Hans Christian Andersen, narrated in Dutch ("De Kleine Zeemeermin") by a male native Flemish speaker, as employed by previous research conducted at the experimental Oto-Rhino-Laryngology lab of KU Leuven (Accou et al., 2021). The listening localizer followed the approach described by Scott et al. (2017), showing consistent identification of the language network in young and healthy subjects. We generated acoustically impaired variations of 10 segments to establish a control condition, ensuring similar spectral

characteristics but lacking speech comprehension and linguistic processing, by adding noise with a similar spectrum to the original versions, matched with the remaining 10 intact segments. The modulation for these stimuli was obtained from the speech envelope, computed as the absolute value of the Hilbert transform. Additionally, each segment ended with a gradual 2-second volume fade-out. Every segment was 18 seconds long. We also included eight resting blocks of each 12 seconds, following previous protocols (Malik-Moraleda et al., 2022; Scott et al., 2017), and the presentation order of conditions was randomized to avoid consecutive presentations of identical conditions.

The entire listening localizer task had a duration of seven minutes and 36 seconds. Subjects engaged in practice trials outside of the scanner to become familiar with the task and to confirm the clarity of the auditively presented stimuli through an fMRI practice scan before entering the scanner, where they were directed to attentively listen to all presented stimuli, this while visually fixating on a centrally displayed cross on a screen. After all participants completed the task, the contrast in activation between “intact” and “degraded” ("intact>degraded") was used to identify the language network, given that this comparison elicited more pronounced reactions in language-specific brain regions, consistent with prior findings (Scott et al., 2017; Malik-Moraleda et al., 2022). These regions are particularly implicated in interpreting word meanings in the brain and performing combinatorial semantic and syntactic tasks, which are not engaged when processing the presented impaired stimuli.

2.4.2 Reading localizer task

The reading localizer task comprised two main conditions: the passive reading of sentences and passive reading of non-word lists. The presented stimuli were designed based on previous studies (Fedorenko et al., 2010), with adjustments made to make the tasks easier to suit the targeted demographic (i.e., older adults and PWA). These adjustments included slower presentation and shorter presented sentences. The presented sentences featured straightforward syntax structures, combining individual word-level meanings to form larger cohesive phrases and sentence interpretations (e.g., "ALL EMPLOYEES RECEIVED A NICE BONUS LAST YEAR"). The non-word stimuli included articulable pseudowords of equivalent duration as the words in the sentence condition, created using the Wuggy pseudoword generator (Keuleers & Brysbaert, 2010).

Overall, the task lasted a total of seven minutes and 36 seconds. The subjects were directed to read the presented sentences and non-words in silence, while undergoing the fMRI scan. Beforehand they underwent task familiarization (i.e., practice trials of silent reading) and sentence readability was verified during an fMRI practice scan, and if needed adapted to the participants needs with the aid of MRI-proof plastic glasses. The task procedure is depicted in Figure 2 (A). Due to limited scanning time or discomfort (back pain from laying in the scanner), data from 2 healthy controls and 1 PWA were incomplete. The reading localization task was successfully completed by 14 PWA and 11 healthy controls.

Each trial comprised eight words/pseudowords presented for 1000 ms each, followed by a signal (a green check mark) indicating the end of the sentence for 1000ms. Each trial lasted for nine seconds, and each condition block contained two sequential trials of the identical condition (i.e., a total of 18 seconds). The reading localization task consisted of 10 blocks for each condition and eight resting blocks lasting 12 seconds each (during which subjects fixated on a presented cross). Blocks of trials were presented in a randomized sequence

ensuring that identical conditions never followed each other. The contrast in activation between “sentences” and “non-words” ("sentences > non-words") was used to identify the language network, as brain regions specialized in language typically tend to demonstrate more robust reaction to sentences with meaning, reflecting engagement in semantic and syntactic processes, unlike when reading non-words (Fedorenko et al., 2010).

2.4.3 Spatial working memory localizer task

Finally, a visual spatial working memory (spWM) task was conducted, differentiating a more challenging condition with an easier one, adhering to the methodology outlined in previous studies (Fedorenko et al., 2013). However, we adapted the method to accommodate our targeted demographic, employing a reduced tempo and reducing the quantity of presentations.

Overall, the task duration was five minutes and 48 seconds. Prior to the actual scan, subjects engaged in a pre-scanning training phase, and the visibility of stimuli was confirmed via an fMRI practice scan and adjusted if needed with the aid of MRI-proof plastic glasses. The task procedures are detailed in Figure 2 (B). One PWA was excluded from the analysis due to limited scanning time, leaving a total of 14 PWA and 13 healthy controls who completed the spWM localizer task successfully.

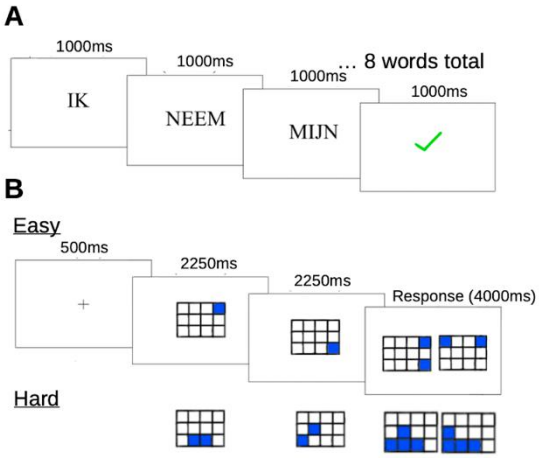

Figure 2. (adapted from De Clercq et al., 2024): *The localizer tasks. (A) illustrates the reading localizer task. (B) shows the spWM localizer task.*

Each trial lasted nine seconds, in which participants looked at a fixation cross for the duration of 500 ms, after which they looked at a grid (3x4) where either one or two locations on the grid were briefly displayed twice for 2250 ms. The presentation of one location corresponds to the easy condition, and the presentation of two locations corresponds to the hard conditions. The subjects mentally merged the presented locations afterwards and then had a window of 4000 ms to respond to a two-choice forced-selection paradigm. Participants were given a control with buttons in their left and right hands for answering. In cases of one-sided paralysis (N=2 PWA), these participants utilized a solitary control with one button with both options (left and right) for the subject to hold in one hand. Each condition block consisted of two successive trials featuring identical conditions, lasting a total of 18 seconds. The task consisted of eight blocks for each condition, interspersed with six rest blocks each lasting 12 seconds, where subjects maintained fixation on the centrally

presented cross. Also in this last task, the presentation order of the conditions was randomized to prevent consecutive occurrences of identical conditions. The differentiation between “hard” and “easy” ("hard>easy") was used as the critical contrast, formerly demonstrated to strongly activate the MD network (Fedorenko et al., 2013), related to its participation in cognitively and attentively challenging tasks and showing transferability to various other demanding cognitive activities (e.g., arithmetic operations; see Fedorenko et al., 2013).

2.5 fMRI data analysis

2.5.1 Preprocessing and first-level analysis

The analysis of the fMRI data was executed in SPM12 (Welcome Trust Centre for Neuroimaging, London, UK), running on Matlab 2021b (MathWorks, Massachusetts, USA). The raw fMRI data went through several steps of preprocessing prior to analysis. Preprocessing started with motion correction of the fMRI images through rigid realignment to the mean volume. This prevents distortions and artifacts in the data. Next, a slice-timing correction was conducted to compensate for the slight delay between the capturing of different slices of the brain. Then followed the coregistration of the functional images to the anatomical T1-weighted MRI image of each participant. The mean functional image was utilized to increase the alignment accuracy. To enable the comparison of activation between participants, the T1 image was then normalized to the template for older adults in MNI space, using the Clinical Toolbox (Rorden et al., 2012). To ensure an accurate anatomical representation despite the irregularities associated with stroke, the lesion and intact contralateral hemispheric brain regions were considered in the normalization process, as recommended by Rorden et al. (2012). To conclude preprocessing, functional images underwent Gaussian kernel smoothing with a 4 mm kernel size.

Following preprocessing, these volumes underwent first-level analyses. The experimental tasks presented to the participants during the fMRI scan were modeled by convolving their time courses with the canonical hemodynamic response function (HRF; Friston et al., 1994), which represents the typical pattern of neural activity and corresponding changes in blood oxygenation as observed in fMRI scans. This modeled information was represented by predictors in a general linear model (GLM) to estimate beta weights. Also, nuisance variables, which are not related to the experimental conditions but still might influence the fMRI findings, were included in the GLM. More specifically, six estimated head motion parameters encompassing both translations and rotations in the x, y and z axes were included. Using the obtained beta weights, critical contrasts were determined for each functional localizer to distinguish between relevant and irrelevant task-related activity. Contrasts were taken by comparing intact>degraded in the listening task, sentences>non-words in the reading task and hard>easy in the spWM task.

2.5.2 Subject-specific network selection

The two-step method of identifying the functional ROIs (fROIs), namely subject-specific language and MD networks, was largely based on the methods described by Shain et al. (2020). Firstly, we applied group-level masks to the individual activation T-maps which were

derived from the beta weights (“parcels” available as downloadable content on *https://evlab.mit.edu/ 278 funcloc/download-parcels*). These masks delineate parcels in which most activity is expected during language tasks (six bilateral language parcels) and the spWM localizer task (ten bilateral MD parcels) (Shain et al., 2020), based on research in large samples of respectively 220 (Fedorenko et al., 2010) and 197 healthy, young individuals (Fedorenko et al., 2013). A visualization of these parcels, adapted from De Clercq et al., (2024), is shown in Figure 3. Language parcels include the inferior frontal gyrus (IFG), the orbital part of the IFG (IFGorb), the medial frontal gyrus (MFG), the anterior temporal cortex (AntTemp), the posterior temporal cortex (PostTemp), and the angular gyrus (AngG). The MD parcels include the superior (SFG) and medial (MFG) frontal gyrus, the orbital part of the MFG (MFGorb), the opercular part of the IFG (IFGop), the medial prefrontal cortex (mPFC), the precentral gyrus (PrecG), the insula (Insula), the anterior (AntPar), middle (MidPar) and the posterior (PostPar) parietal cortex. There is a small partial overlap between the language parcels and the MD parcels within certain regions of the MFG and IFG. These parcels are used as binary maps, meaning that only voxels within these parcels are considered in locating the subject-specific fROIs in the following step.

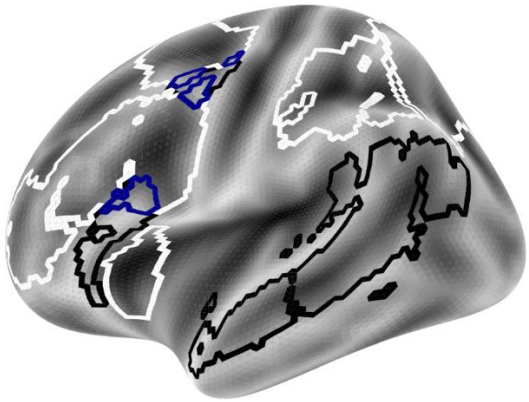

Figure 3. (adapted from De Clercq et al., 2024*). Visual representation of the parcels. Black outlines delineate language parcels. White outlines delineate MD parcels. Blue outlines delineate where language and MD parcels overlap.*

In the second step, we identified the top 10% most active voxels (highest T-scores) within each of these determined parcels per participant based on the unthresholded T-maps, as did Shain et al. (2020) in their paper. This approach enhances selection of only robustly responding voxels and ensures identical size of fROIs across all participants. We limited voxel selection for the language network to the language parcels and selection for the MD network to the MD parcels, since previous findings of De Clercq et al. (2024) indicate that most activity during the language localizer tasks was located in the language parcels and most activity during the spWM localizer task was observed in the MD parcels. In contrast to Shain et al. (2020), who applied a threshold of 0 for T-values, we did not administer any threshold, because negative T-values are relevant to our research question concerning significant activation of the MD network (i.e. whether T-value is greater than 0) during language processing. In order to maintain consistency across analyses, we used the same method for all of our research questions. The selected voxels constitute the ROIs for further analyses. This way, the ROIs are determined in a single-subject way, circumventing the limitations of the group-averaging approach as discussed in the literary review (Fedorenko et al., 2010). Results of individual parcels are included in the thesis’ appendix.

2.6 Statistical Analysis

In the following paragraph we discuss the conducted statistical analyses per research question. We used JASP (JASP team, 2024, version 0.18.3) and RStudio (Posit team, 2023) for all analyses and plots.

To decide whether to employ a parametric or non-parametric test for our research questions, the unthresholded activation data underwent a Shapiro-Wilk test for each specific research question. This yielded both significant and non-significant outcomes. Given these results, in combination with the limited size of our sample population, we opted to utilize non-parametric tests for all our analyses. We performed a false discovery rate correction (FDR-correction) on the p-values for the main analyses of our research questions, namely for the mean language networks and mean MD networks, using RStudio (Posit team, 2023), but not for the individual parcels, nor for any correlations with behavioral results.

Research question 1: Does the amount of activity of the language network and MD network differ between PWA and healthy controls? Is there a correlation with behavioral test results?

To determine whether to use a parametric or a non-parametric test, the unthresholded activation data per group underwent a Shapiro-Wilk test, showing significant results for the mean activity of the left hemisphere in the aphasia group during the listening task and for both hemispheres in the healthy controls during the reading task (see Appendix B for detailed test results and Q-Q plots). This indicates a non-normal distribution of the data. Taken together with our small sample size, we concluded that non-parametric tests would best fit for further analyses on this data. To test whether there were significant group differences in activity level in the language network and the MD network, we conducted Wilcoxon rank-sum tests for four parcels. More specifically we compared the mean T-values of the language and MD parcels, left and right. Given previous findings of De Clercq et al. (2024) indicating that most activity during the language localizer tasks is located in the language parcels and most activity during the spWM localizer task is found in the MD parcels, we restricted the analyses of these parcels to their respective tasks. In order to allow later calculation of LIs (second research question), we set all negative mean activations per parcel (top 10% most active voxels) in the language network and MD network (during spWM task) activation data to a value of zero. We did not, however, do this for the activation of the subject-specific MD network during language tasks (third research question). P-values of the main analyses (not analyses of individual parcels) were corrected for multiple comparisons (FDR-correction), using RStudio (Posit team, 2023). Main analyses will be presented in the main text, while analyses of the individual parcels are shown in Appendix C. Next, we investigated whether there was a significant correlation between activation strength and the score on the NBT, fluency tasks of the CAT-NL, ScreeLing and OCS-NL, using partial Spearman rank correlations. We corrected for the following covariants: age, time since stroke and lesion size. Correlations with the mean activity of the language and MD networks are described in the main text, while results for individual parcels are added in Appendix D. We did not correct for multiple comparisons in these analyses, because of their exploratory nature.

Research question 2: Is the activation of the right-hemispheric language regions relative to the activity in the left-hemispheric language regions, as measured by LIs, significantly

different in PWA as compared to healthy controls, as a potential sign of compensation? Is there a correlation with behavioral test results?

To investigate the relative reliance on the right hemisphere, we first calculated LIs, comparing the mean T-values of left-hemispheric and of the right-hemispheric top 10% most active voxels in both the language as the MD parcels. LIs were calculated as follows: $\frac{T_{LH} - T_{RH}}{T_{LH} + T_{RH}} * 100$. As mentioned before, we set all negative mean activations per parcel (top 10% most active voxels) in the language network and MD network (during spWM task) activation data to a value of zero, in order to allow calculation of LIs using the given formula. Subsequently, we administered a Wilcoxon rank-sum test (non-parametric test, due to significant results in Shapiro-Wilk test for LIs of some parcels as shown in Appendix E and due to the small sample size) to compare LIs in PWA and healthy controls in order to investigate potential significant group differences. FDR-correction was administered on the main analyses, not on analyses of individual parcels. Again, we looked for correlations with behavioral test results using partial Spearman rank correlations (covariants: age, time since stroke, lesion size; no correction for multiple comparisons). The group comparisons and correlation results of the LIs of mean activity are presented in the main text, while analyses of the individual parcels can be found in Appendix F and G.

Research question 3: Is there significant activation of the subject-specific MD network during language processing? If so, is there a significant group difference?

To define the subject-specific MD network for each participant, we selected the top 10% most active voxels in all MD parcels during the spWM task. To answer the research question, these regions were used as ROIs as we investigated their activity during the two language localizer tasks. Based on some significant results on the Shapiro-Wilk test administered on this unthresholded data (see Appendix H), we used a one-sided Wilcoxon signed-rank test to determine whether their activation was significantly greater than 0. Group comparisons are only made (Wilcoxon rank-sum tests, FDR-correction of p-values for multiple comparisons) when the first analysis of the third research question showed significant activation. In case of meaningful results, we also administer partial Spearman rank correlations to look for associations between activity levels and performance on behavioral tests (no correction for multiple comparisons). See Appendix I for the results of analyses on the individual parcels; results of mean activity are presented in the main text. No correction for multiple comparisons was used for analyses on individual parcels.

3 Results

3.1 Results for research question 1

Our first research question consists of two parts. Firstly, we investigated whether there is a difference in the activation values within the language network and the MD network between PWA and healthy controls. Secondly, we investigated whether there is a correlation with the results of behavioral tests of PWA.

3.1.1 Comparison of activity of the language network and MD network between PWA and control group

We opted for the Wilcoxon rank-sum test, performed for 4 groups of parcels (as discussed in the method section). These four groups are the language network in the left and right hemisphere, and the MD network in the left and right hemisphere. The tests were conducted per network (language network and MD network), and per individual parcel.

3.1.1.1 Listening localizer task

The test showed significant higher values for controls for the listening localizer task for the mean language activation in the left hemisphere (W = 45.000, p = 0.030 FDR-corrected) and no significant group difference was found for the mean language activation in the right hemisphere (W = 63.000, p = 0.118 FDR-corrected). A visual representation in the form of boxplots can be found in Figure 4 below. Additionally, some significant higher values for controls were found in the individual language parcels, namely in the left anterior temporal parcel (W = 49.000, p = 0.025), the left posterior temporal parcel (W = 44.000, p = 0.013), and the right (W = 48.000, p = 0.022) and left (W = 45.000, p = 0.015) MFG (see Appendix C for details and boxplots).

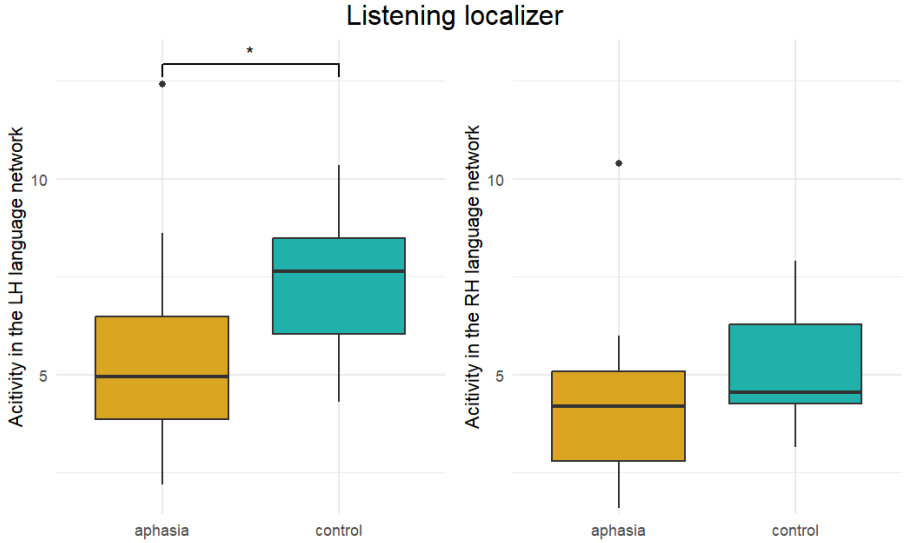

Figure 4. *Boxplots of the mean language network activity during the listening localizer task in the left hemisphere (left figure) and in the right hemisphere (right figure) for the PWA group and control group.*

3.1.1.2 Reading localizer task

The test showed significant higher values for controls for the reading localizer task for the mean language activation in the left hemisphere (W = 39.000, p = 0.076 FDR-corrected) and no significant group differences for the right hemisphere (W = 76.000, p = 0.979 FDR-corrected). A visual representation in the form of a boxplot can be found in Figure 5 below. Additionally, some significantly higher values for controls were found in the individual language parcels, more specifically in the left posterior temporal parcel (W = 37.000, p = 0.029) and the left angular gyrus (W = 34.000, p = 0.018) (see Appendix C for details and boxplots).

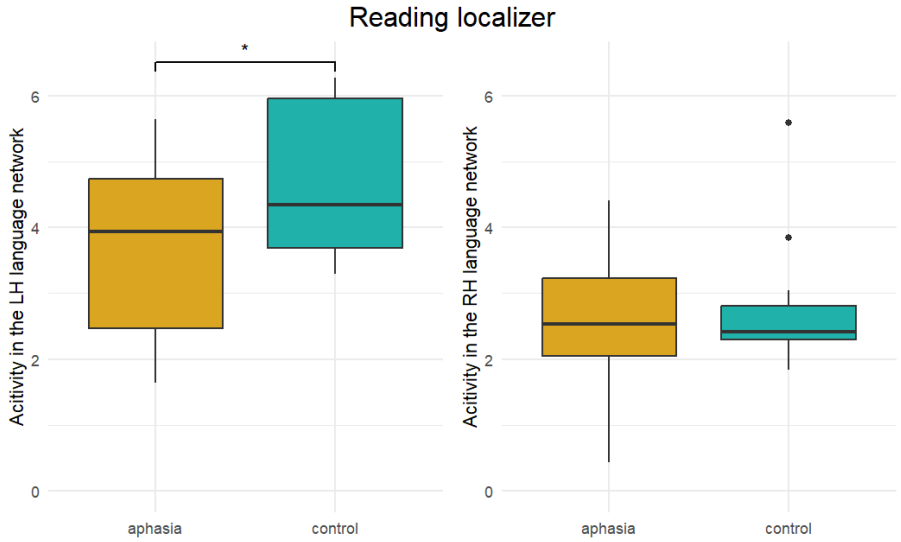

Figure 5. *Boxplots of the mean language network activity during the reading localizer task in the left hemisphere (left figure) and in the right hemisphere (right figure) for the PWA group and the control group.*

3.1.1.3 spWM task

The test showed no significant difference in activation between both groups in the MD network for the spWM task, both for the MD network in the left hemisphere (W = 61.000, p = 0.310 FDR-corrected) and for the MD network in the right hemisphere (W = 89.000, p = 0.943 FDR-corrected). A visual representation in the form of a boxplot can be found in Figure 6 below. Additionally, some significant higher activation values were found for the control group in the individual language parcels, more specifically in the left insula (W = 42.000, p = 0.017), the left precentral gyrus (W = 48.000, p = 0.038) and the left anterior parietal parcel (W = 37.000, p = 0.008) (see Appendix C for details and boxplots).

Figure 6. *Boxplots of the mean MD network activity during the spWM task in the left hemisphere (left figure) and in the right hemisphere (right figure) for the PWA group and the control group.*

3.1.2 Correlations with behavioral test results

For this research question, we aim to determine whether the activation values provide insight into the severity of aphasia in PWA. Therefore, we will not report correlations in control groups, as this almost always yields a ceiling effect due to the high performance of healthy older adults on those tests. The test used to calculate the correlations was the Partial Spearman rank correlations test, including age, lesion size and time since the stroke as covariants.

3.1.2.1 Listening localizer task

For the listening localizer task, the test showed no significant correlations between the behavioral tasks and the mean language network in the left (correlation with NBT: ρ = -0.033, p = 0.918; ScreeLing: ρ = 0.253, p = 0.427; CAT-NL: ρ = 0.222, p = 0.512; OCS: ρ = 0.211, p = 0.510) or right hemispheres (correlation with NBT: ρ = 0.003, p = 0.993; ScreeLing: ρ = 0.133, p = 0.681; CAT-NL: ρ = - 0.168, p = 0.621; OCS: ρ = 0.229, p = 0.473). A visual representation in the form of scatterplots can be found in Figure 7 below. Nor were there correlations found in the individual parcels for the left and right hemispheres (see Appendix D for details).

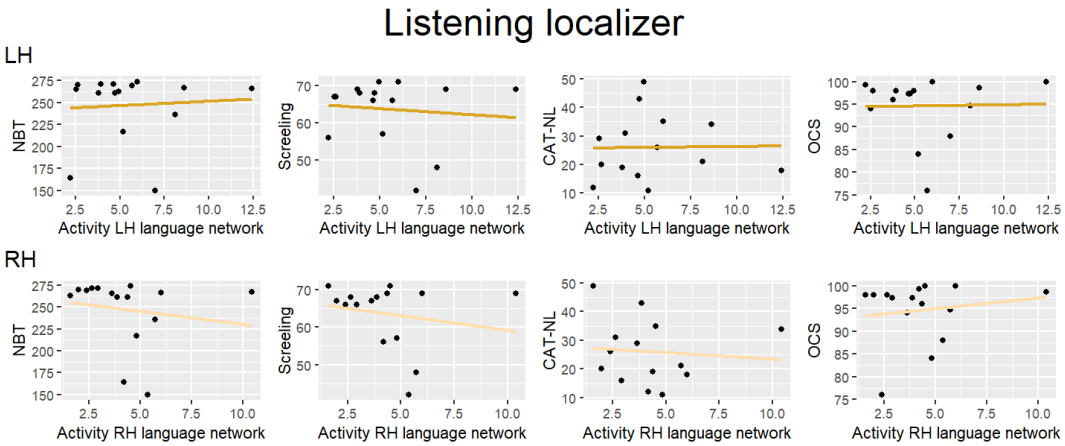

Figure 7. *Scatterplots for the raw correlations (without adjustment for confounding variables) between the behavioral tasks and the mean language network in the left hemisphere (top row) and in the right hemisphere (bottom row) in PWA for the listening localizer task.*

3.1.2.2 Reading localizer task

For the reading localizer task there were no significant correlations for the mean language network in the left (correlation with NBT: ρ = - 0.076, p = 0.886; ScreeLing: ρ = 0.485, p = 0.330; CAT-NL: ρ = 0.375, p = 0.531; OCS: ρ = 0.375, p = 0.464) or right hemisphere (correlation with NBT: ρ = - 0.174, p = 0.630; ScreeLing: ρ = - 0.306, p = 0.390; CAT-NL: ρ = - 0.361, p = 0.339; OCS: ρ = - 0.369, p = 0.294), as represented in Figure 8, but one correlation appeared to be significant in the individual parcels, namely between the right orbital part of the IFG and the CAT-NL (ρ = - 0.775, p = 0.014) (see Appendix D for details).

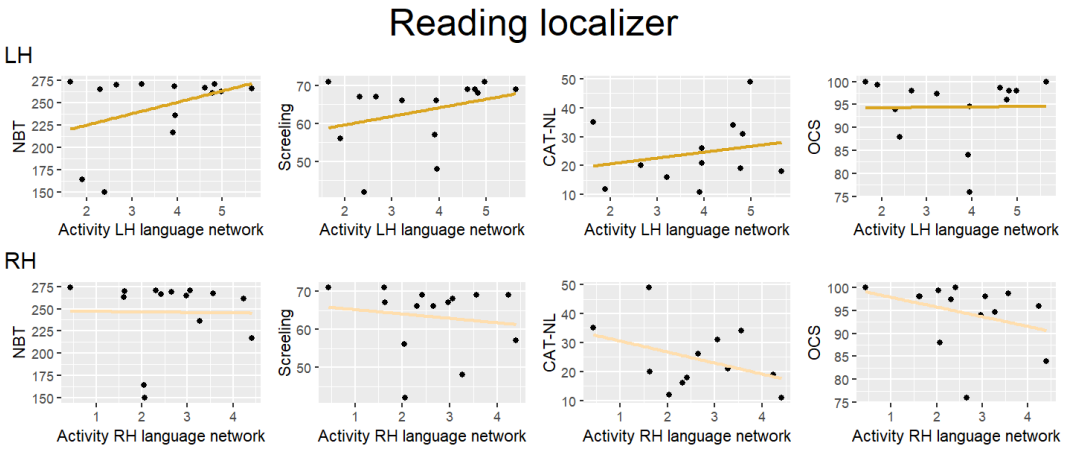

Figure 8. *Scatterplots for the raw correlations (without adjustment for confounding variables) between the behavioral tasks and the mean language network in the left hemisphere (top row) and in the right hemisphere (bottom row) in PWA for the reading localizer task.*

3.1.2.3 spWM task

For the spWM task, no significant correlations were found between the mean MD network in the left (correlation with NBT: ρ = 0.116, p = 0.734; ScreeLing: ρ = 0.218, p = 0.519;

CAT-NL: ρ = - 0.156, p = 0.666; OCS: ρ = 0.302, p = 0.366) or right hemispheres (correlation with NBT: ρ = 0.090, p = 0.792; ScreeLing: ρ = 0.326, p = 0.328; CAT-NL: ρ = 0.204, p = 0.573; OCS: ρ = 0.185, p = 0.587) and the behavioral tasks. A visual representation in the form of scatterplots can be found in Figure 9 below. Nor were there correlations found in the individual parcels left and right (see Appendix D for details).

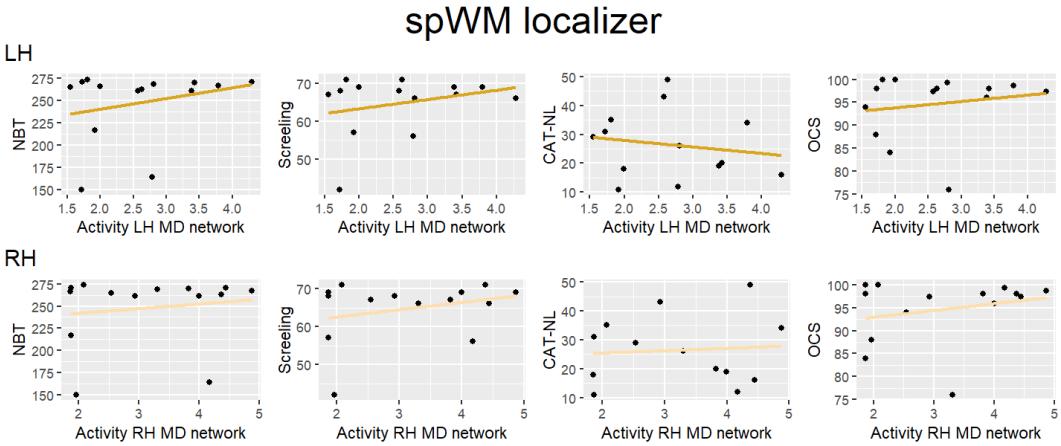

Figure 9. *Scatterplots for the raw correlations (without adjustment for confounding variables) between the behavioral tasks and the mean MD network in the left hemisphere (top row) and in the right hemisphere (bottom row) in PWA for the spWM task.*

3.2 Results for research question 2

3.2.1 Group comparisons of LIs

For our second research question, we investigated whether PWA relied on their right hemisphere to a different extent than healthy controls. To this end, we calculated the LIs, allowing us to look at relative reliance, as discussed before. We opted for the non-parametric Wilcoxon rank-sum test to investigate group differences.

3.2.1.1 Listening localizer task

No significant group difference was found for the LI of the mean activity of the language parcels in the listening localizer task (W = 78.000, p = 0.387 FDR-corrected) (Figure 10), nor for the individual language parcels either (see Appendix F for details).

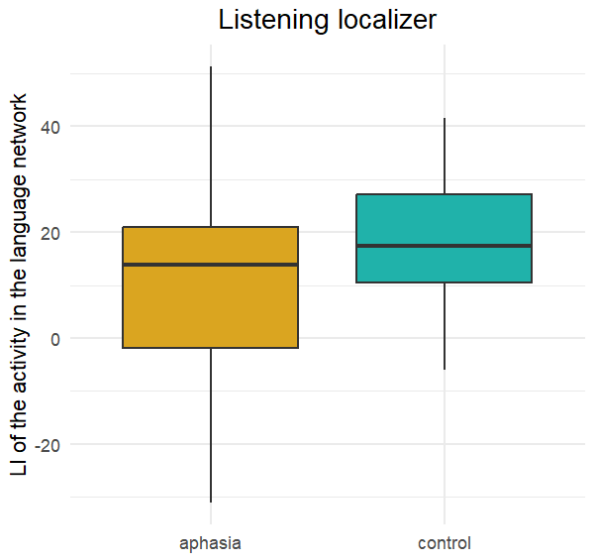

Figure 10. *Boxplot representing the LIs of language activity of both groups during the listening localizer task.*

3.2.1.2 Reading localizer task

No significant group differences of mean activity of the language parcels were found in the reading localizer task (W = 53.000, p = 0.202 FDR-corrected) (Figure 11). Additionally, none of the individual parcels showed significant group differences (see Appendix F for details).

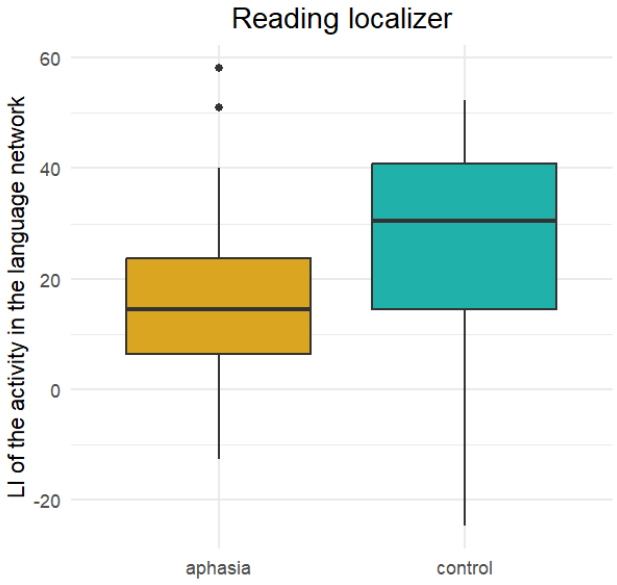

Figure 11. *Boxplot representing the LIs of language activity of both groups during the reading localizer task.*

3.2.1.3 spWM localizer task

In the spWM task, the LI of the mean activity of the MD network was significantly lower in the aphasia group (W = 39.000, p = 0.011 FDR-corrected) (Figure 12). Significantly lower LIs for the aphasia group were also found for some of the individual MD parcels, namely the medial frontal gyrus (W = 33.000, p = 0.004), the anterior parietal gyrus (W = 31.000, p = 0.003) and the superior frontal gyrus (W = 45.000, p = 0.025) (see Appendix F for details).

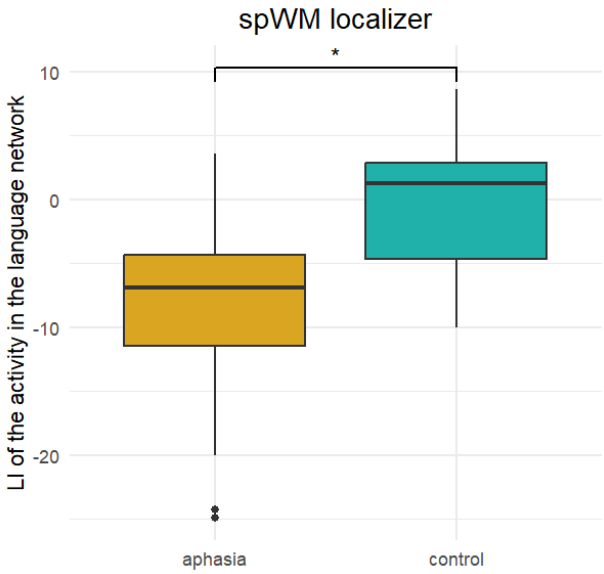

Figure 12. *Boxplot representing the LIs of activity in the MD network of both groups during the spWM localizer task*.

3.2.2 Correlations with behavioral test results

In order to explore potential associations between relative reliance on one or the other hemisphere and language or cognitive performance, we investigated the correlation between the LIs and behavioral test results for the aphasia group. In line with the previous research question, correlations with scores of the control group are not considered, since no significant correlations are expected due to a ceiling effect on the test scores. We administered partial Spearman rank correlations (Spearman's rho) in each localizer task for the LI of the mean activity in the language parcels (listening task, reading task) or the MD parcels (spWM task), including age, lesion size and time since stroke as covariants. Important to note is that no correction for multiple comparisons was applied on the analyses of the mean activity or on the analyses of separate parcels, due to their exploratory nature. Results for the individual parcels can be consulted in more detail in Appendix G.

3.2.2.1 Listening localizer task

In the listening localizer task, no correlations were found between any of the behavioral tests and the LI of the mean language activity (correlation with NBT: ρ = -0.028, p = 0.931; ScreeLing: ρ = 0.177, p = 0.582; CAT-NL: ρ = 0.225, p = 0.507; OCS-NL: ρ = 0.339, p = 0.281) (Figure 13). None of the correlations in separate parcels reached significance.

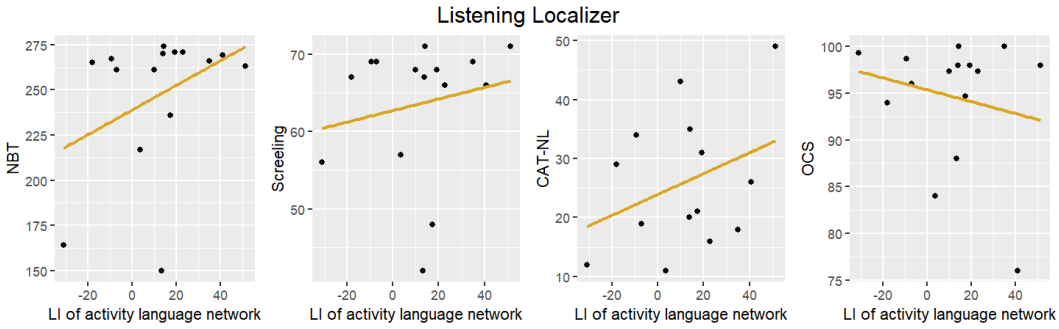

Figure 13. *Scatterplots for the raw correlations (without adjustment for confounding variables) between the behavioral tasks and the LIs of the mean language network in PWA for the listening localizer task.*

3.2.2.2 Reading localizer task

In the reading localizer task, there were significant positive correlations between the LI of the mean language activity and the score on the OCS-NL (ρ = 0.780, p = 0.008) but not for the NBT (ρ = 0.480, p = 0.160), ScreeLing (ρ = 0.609, p = 0.062) and CAT-NL (ρ = 0.393, p = 0.295) (Figure 14). Several analyses in the individual parcels showed significant results, namely the LI of the anterior temporal region with the OCS-NL (ρ = 0.685, p = 0.029), the LI of the orbital IFG with the CAT-NL (ρ = 0.746, p = 0.034), the LI of the posterior temporal region with the NBT (ρ = 0.682, p = 0.0.030), ScreeLing (ρ = 0.854, p = 0.002) and OCS-NL (ρ = 0.717, p = 0.020), the LI of the angular gyrus with the ScreeLing (ρ = 0.830, p = 0.003) and the LI of the MFG with the OCS-NL (ρ = 0.814, p = 0.004).

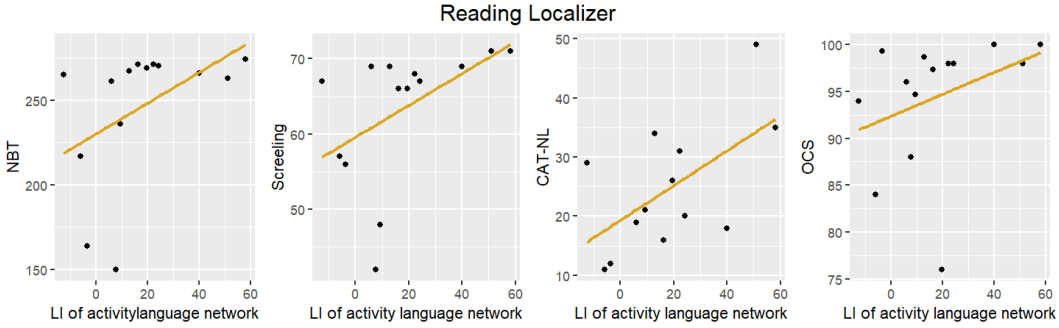

Figure 14. *Scatterplots for the raw correlations (without adjustment for confounding variables) between the behavioral tasks and the LIs of the mean language network in PWA for the reading localizer task.*

3.2.2.3 spWM localizer task

Finally, in the spWM task, no significant correlations were found between the LIs of the mean activity in the MD regions and any of the behavioral tests assessing language (NBT: ρ = 0.008, p = 0.982; ScreeLing: ρ = -0.315, p = 0.345). Also, no correlation was found with the OCS-NL, testing cognition (ρ = 0.157, p = 0.645). Finally, the CAT-NL (language and cognition) did not show a significant correlation either (ρ = - 0.571, p = 0.085) (Figure 15). In the individual parcels, only the correlation between the orbital part of the MFG and the CAT-NL score was significant (ρ = - 0.711; p = 0.021).

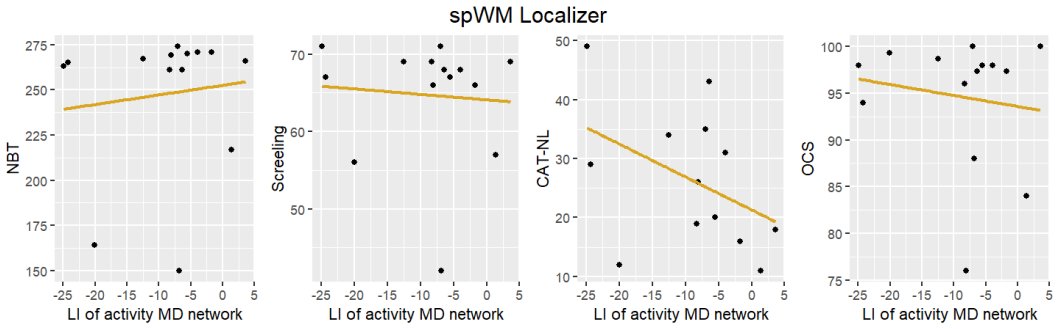

Figure 15. *Scatterplots for the raw correlations (without adjustment for confounding variables) between the behavioral tasks and the LIs of the mean MD network in PWA for the spWM localizer task.*

3.3 Results for research question 3

3.3.1 Activity in the subject-specific MD network during language tasks

The third research question addresses whether the activity in the subject-specific MD network during language processing is significant. To assess this, we used a one-sided Wilcoxon signed-rank test.

3.3.1.1 Listening localizer task

The aphasia group showed no significant activation of the subject-specific MD network in the left (V = 26.000, p = 0.955 FDR-corrected) or right hemisphere (V = 41.000, p = 0.955 FDR-corrected) (Figure 16), nor in any of the individual parcels (see Appendix I). Similarly, the control group did not show any significant activity in the left (V = 69.000, p = 0.190 FDR-corrected) or right (V = 65.000, p = 0.190 FDR-corrected) hemispheric MD network (Figure 16), however, significant activity was found in some individual parcels, namely the insula in the left (V = 87.000, p < 0.001) and right (V = 91.000, p < 0.001) hemisphere, the precentral gyrus in the left (V = 84.000, p = 0.002) and right (V = 79.000, p = 0.009) hemisphere and the opercular part of the IFG in the left (V = 84.000, p = 0.002) and right (V = 75.000, p = 0.020) hemispheres (see Appendix I for more details).

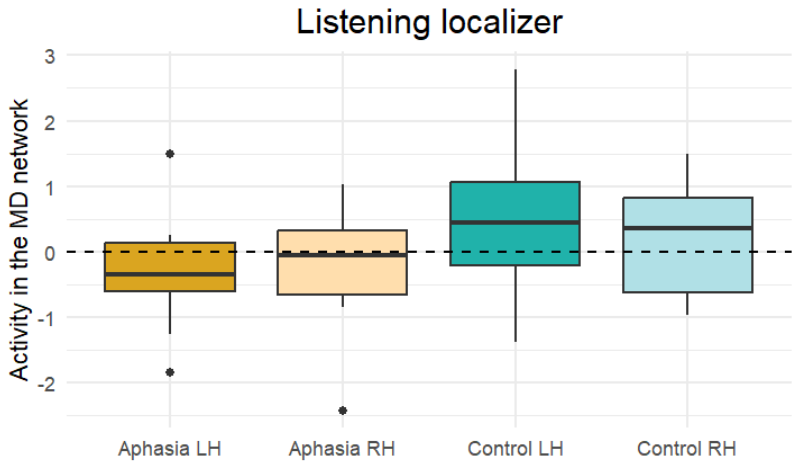

Figure 16. *Boxplots showing the activity of the subject-specific MD network during the listening localizer task for both hemispheres in each group.*

3.3.1.2 Reading localizer task

In the reading localizer task, no significant activity of the MD network was found in any of the analyses on mean activity per hemisphere (aphasia left hemisphere: V = 14.000, p = 1 FDR-corrected; right hemisphere: V = 13.000, p = 1 FDR-corrected; controls left hemisphere: V = 1.000, p = 1 FDR-corrected; right hemisphere: V = 3.000, p = 1 FDR-corrected) (Figure 17) or in separate parcels (see Appendix I). Since no significant activity was found, no group comparisons were made and we did not look for correlations with aphasia severity (behavioral tests).

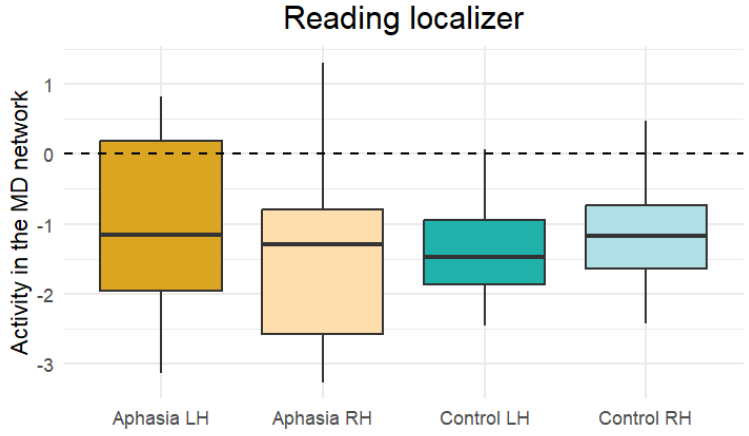

Figure 17. *Boxplots showing the activity of the subject-specific MD network during the reading localizer task for both hemispheres in each group.*

4 Discussion

4.1 Discussion of research question 1

4.1.1 Comparison of activity of the language network and MD network between aphasia and control group

Our results showed that the mean language activation in the left hemisphere was lower for the aphasia group in comparison to the control group for both language localizer tasks. For the spWM task, no significant group differences for activation values of the mean MD network were found in either hemisphere. All three localizer tasks showed some significant findings in the individual parcels.

The mean language activation in the left hemisphere was lower for the aphasia group in comparison to the control group for both the listening and the reading localizer task. These results are in line with Wilson & Schneck (2021) and Li et al. (2022), who described a reduced language activation in the left hemisphere in PWA compared to healthy controls. Indeed, aphasia following a stroke most commonly results from injury to the left hemisphere language regions (Fridriksson et al., 2018; Turkeltaub, 2015; Tyler et al., 2011), which are therefore partially or even completely destroyed. However, Saur et al. (2006) found that left hemisphere activation normalizes in the chronic phase. This seems contradictory to our results, although based on our cross-sectional results we do not know whether our aphasia participants are still recovering or have reached a plateau.

Furthermore, the language localizers revealed a decreased activation in some individual language parcels. This is in line with our findings of the mean language activity in the left hemisphere: the left posterior temporal regions during both language tasks, both the left and right MFG (only for the listening localizer), the left anterior temporal regions (only for the listening localizer) and the left angular gyrus (only for the reading localizer). Previous literature has identified these regions as part of the language network (Binder et al., 2011; Gohel et al., 2019; Kim et al., 2022; Vasileiadi et al., 2023; Wong & Gallate, 2012), although Fedorenko et al. (2024) do not consider the angular gyrus to be part of this network. The left anterior temporal region showed significantly lower activation in the aphasia group compared to the control group during the listening task only. Previous studies (Friederici et al., 2000; Humphries et al., 2005, 2006) have linked this region to listening tasks involving whole sentences, like the listening localizer in our study. This difference indicates that this region may not be completely restored in the chronic phase of aphasia. Moreover, we did not find significantly different activation values in this left anterior temporal region between both groups for the reading localizer task. According to Stowe et al. (1999), the left anterior temporal region is indeed involved in reading sentences, therefore suggesting that the activation in chronic aphasia is better restored during reading than during listening. However, reading is often experienced as more difficult than listening for PWA (DeDe, 2013). Furthermore, Gohel et al. (2019) state that the MFG plays a role in nuances of language expression such as semantics, grammar and syntax, verbal fluency, and verbal working memory as well as other cognitive functions, including attention orientation. Since both listening and reading are entailed under these functions, we found no explanation for why only the listening, and not the reading, localizer task showed lower activation values

for the aphasia group in comparison to the control group. Additionally, the activation values of the left angular gyrus were significantly lower for the aphasia group in comparison to the control group only specifically during the reading localizer task. Some studies state that the left angular gyrus plays an important role in silent reading (Geschwind, 1965; Seghier, 2013). However, silent reading, which encompasses phonological processing, is filtered out by the reading localizer task, as both the sentences and non-word lists require grapheme-to-phoneme conversion. Fedorenko et al. (2010) constructed this reading localizer to not include phonological information, because they view it as a lower-order language function (Fedorenko et al., 2024). Yet, Seghier (2013) suggests that the angular gyrus is also involved in semantic processing of written language, which may offer an explanation for our findings. However, it is important to keep in mind that this is uncertain due to a lack of correction for multiple comparisons and our small sample size and since none of the PWA showed prominent difficulties with reading during behavioral testing. Finally, we would have expected to find group differences for the left IFG, as this parcel was damaged in 10 out of the 15 PWA (see Figure 1). This was not the case, indicating that the top 10% most active voxels within this parcel could still reach a level of activation similar to that of healthy controls.

Concerning the possible compensatory role of the right hemisphere, we did not find significant differences between both groups for the mean language activity of the language network in the right hemisphere. Yet, we found one significantly higher activation value for the control group in the right MFG parcel. This deviates from the expected direction, because in case of a compensatory mechanism, we would expect more activity in the aphasia group rather than in the control group. Taken together, we found no evidence for a compensatory mechanism of the right hemisphere in PWA. This is in line with Wilson and Schneck (2021), who argue that evidence for compensatory mechanisms of the right hemisphere in PWA is only modest. Studies such as Saur et al. (2006) suggest that right hemisphere activation normalizes in the chronic phase, which is also consistent with our findings. Several studies suggest that the role of the right hemisphere in aphasia recovery may depend on various variables, such as traits of the brain lesion, age of the person, location of the brain lesion, individual recovery trajectories in patients, types of rehabilitation and particular language components tested during the scanning process (Cocquyt et al., 2017; Crinion & Price, 2005; De Clercq et al., 2024; Jarso et al., 2013; Li et al., 2022; Newport et al., 2022; Sebastian et al., 2016; Stefaniak et al., 2022; Stockert et al., 2020). For instance, Newport et al. (2022) found that children who suffer an injury in the left language network at a young age due to a perinatal stroke, appear to show significant compensation from the right hemisphere, resulting in normal language functionality.

For the spWM task, no significantly different activation values were found between both groups for the mean MD network activity in the left or right hemispheres. Because the MD network plays a role in cognitive tasks (Fedorenko & Blank, 2020), and cognition is often a problem in PWA (El Hachioui et al., 2014), we could potentially expect to see group differences in the mean activation values of the MD network here. However, our aphasia group and control group also showed no significant differences during the cognitive test OCS-NL, so our findings here align with what we expected based on those cognitive test results. A few significantly higher activity values were found for the control group in comparison to the aphasia group for some individual parcels, which have been described in previous literature as part of the MD network: the left precentral gyrus and the left anterior parietal cortex (Duncan, 2010) and the left insula (Duncan, 2010; Stiers et al., 2010). This group difference in the left insula is not unexpected, since this parcel was damaged in 10 out of the 15 PWA (Figure 1). However, caution is advised when interpreting these group

differences in the individual parcels. The small sample size and absence of correction for multiple comparisons, increase the likelihood of false positive results.

In conclusion of this first part of our first research question, we can state that there are indeed significant differences between the aphasia group and the control group for the mean amount of activity of the language network in the left hemisphere during the language localizer tasks, and in some individual parcels of the language network, left and right. However, we did not find evidence for a compensation mechanism of right hemisphere activation. Further, there are no significant differences found for the mean activity of the MD network during the spWM task (only for a few individual parcels).

4.1.2 Correlations with behavioral test results

For both language localizer tasks, we found no significant correlations between the severity of the aphasia and the activation of the mean language network in the left or right hemispheres, nor in the individual parcels for the left and right hemispheres. However, some non-significant positive and negative trends were found. For the spWM localizer task, no significant correlations were found between the activation of the mean MD network in the left or right hemispheres and the severity of aphasia, nor for cognition.

None of the correlations between the mean activity in the left or right hemisphere during either language task and the severity of aphasia or cognitive deficit reached significance. In both localizers, there were some non-significant positive correlations for the individual parcels in the left hemisphere. Concerning the role of the left hemisphere, the meta-analysis by Wilson & Schneck (2020) described 86 task-related fMRI studies in PWA and found positive correlations between better language function and activation in preserved left hemisphere language regions. These findings are in line with the observed positive trends in our study, indicating that undamaged areas in the left hemisphere play an important role in language recovery in PWA.

Remarkably, the correlations for individual parcels of the right hemisphere showed non-significant positive trends for the listening localizer task, while the reading localizer revealed some negative trends for right-hemispheric activation. The difference in outcomes between the tasks may be explained by the fact that reading evokes stronger left-lateralized activation of the language network in healthy young individuals, while listening relies more on bilateral language activation (Berl et al., 2010; Buchweitz et al., 2009). Therefore, higher right-hemispheric activity might lead to better listening comprehension, but not in reading, as these regions are normally more involved in listening than in reading comprehension.

Concerning the role of the right hemisphere, one negative correlation appeared to be significant in the individual parcels, namely between the right orbital part of the IFG and the CAT-NL assessment. This implies that a higher activity in the right orbital part of the IFG during the reading localizer task is correlated with a lower score on the CAT-NL tasks. A lower score on these CAT-NL subtasks is considered indicative of worse cognitive ability in the domains of verbal fluency and language production (Swinburn et al., 2004). Saur et al. (2006) reported improvement of language throughout recovery and normalized activity of the right IFG in the chronic phase. They state that, in accordance with Naeser et al. (2005), heightened activity of this region in the chronic phase is the result of extensive damage to the left hemisphere, thereby limiting the potential left-hemispheric recovery. This would lead to suboptimal language functioning, which is in line with our findings. However,

the significant result that we found in this individual parcel should be interpreted carefully, because of our small sample size and the lack of correction for multiple comparisons. Similarly, Postman-Caucheteux et al. (2010) found in their study with a picture-naming task, that naming errors were associated with activation in the right hemisphere, more specifically in the right IFG/MFG, and described this as an indication for dysfunction of the language function. This perspective is supported by many other studies (e.g. Rosen et al., 2000; Szaflarski et al., 2013). However, another line of research suggests a facilitating role of right hemisphere activation in aphasia recovery, with some studies demonstrating a positive correlation between right hemisphere activation and language performance (Griffis et al., 2017; Robson et al., 2014; van Oers et al., 2010). These mixed findings suggest that different mechanisms may account for right hemisphere activation in individuals with aphasia, which is strongly influenced by individual differences (e.g., lesion size, time since symptom onset) (Li et al. 2022). For instance, the association between brain activation and language performance may depend on lesion size. (Griffis et al., 2017) observed in their study that in right hemisphere areas (particularly the right SMA), there was a positive correlation between increased activation and semantic fluency in patients with larger lesions. Conversely, this activation in the right hemisphere in patients with smaller lesions showed a significant negative correlation (Wilson & Schneck, 2020). However, it should be noted that we do correct for lesion size, therefore this finding does not apply to our results. In addition to cortical areas, right hemisphere white matter tracts may also play a role in language recovery according to Sihvonen et al. (2023), and different pathways play a maladaptive or supportive role in this, which could be interesting to further investigate in future research.

For the spWM localizer task, no significant correlations were found between the activation of the mean MD network in the left or right hemispheres and the severity of aphasia, nor for cognition (OCS-NL), although we would expect better scores on the OCS-NL to have a correlation with more activation values in the MD network. Neither did we find significant correlations in the individual parcels left and right (some non-significant positive trends are to be seen in the left and right hemisphere). This does not support what has been demonstrated in previous studies, namely that cognition, as well as working memory, are often impaired in aphasia and thus potentially influence language recovery (El Hachioui et al., 2014; Fedorenko & Blank, 2020). However, other studies have indicated that these additional cognitive issues are often specific to the individual patient and may also depend on the task's modality (Kasselimis et al., 2017). It is also important to note that the language and MD networks are located close to each other in the brain according to Fedorenko et al. (2012), thus making it highly likely that the MD network may be damaged in PWA, depending on the individual characteristics of the lesion. This does not appear to be the case in our study, as no group differences were found within the MD network.

To conclude the second part of our first research question we can state that there is in general no correlation between the activation strength during the language and MD localizer tasks in the language and MD networks and the behavioral language and cognition test results and thus the severity of aphasia or cognitive deficits, with exception of one significant negative correlation between the right pars orbitalis of the IFG and the CAT-NL tasks, during the reading localizer task. We suggest that the activation values in both the language and MD network may not provide conclusive insight into the severity of aphasia in the aphasia group, but this should be interpreted carefully since our sample was small.

4.2 Discussion of research question 2

4.2.1 Group comparisons of LIs

Concerning the group comparisons of LIs, PWA and healthy controls show similar levels of lateralization of the mean language network during both language localizers, while PWA showed a significantly less left-lateralized activation pattern in the mean MD network during the spWM localizer.

As discussed, in our first research question we observed significantly higher mean activity for the language network in the left hemisphere during the listening localizer task in healthy controls compared to PWA, but not for the right hemisphere. However, these findings represent average group differences in absolute activation levels and do therefore not lead directly to significantly different LIs. These average values do not apply for each individual participant, and they do not represent a one-to-one relation between activity in the left and right hemisphere for an individual participant. Therefore, a participant with aphasia who exhibits, for example, high activation in the left hemisphere may show either high or low activity in the right hemisphere. This relationship cannot be inferred from group comparisons of absolute activity, but can be examined through the relative reliance on the left and right hemisphere within each participant through LIs.

Analyzing LIs in both PWA and healthy controls renders insight in the relative reliance on left- and right-hemispheric activity. A positive LI indicates lateralization towards the left hemisphere, an LI of zero means symmetrical activation and a negative LI represents lateralization towards the right hemisphere. According to the results of our analysis, neither group showed significantly different LIs for the language network in the listening or reading localizer task, nor in any individual language parcels. As the LI only shows relative activity, these findings might indicate that the aphasia group exhibit lower activation in both the left and the right hemisphere. This interpretation is supported by the findings of our first research question, where we found significantly lower activation levels for PWA compared to controls in the left hemisphere and non-significant trends in the same direction in the right hemisphere (during the listening localizer task; see Figure 4 and Figure C1). Alternatively, visual inspection of these boxplots (see Figure 10, Figure 11, Figure F1, Figure F2) show a trend towards lower LIs in PWA. Possibly, this trend did not reach significance due to the small sample size. Based on the results of the first research question, this pattern would best be explained by the reduced left-hemispheric activation, rather than heightened activation of the right hemisphere. Still, the findings of Wilson & Schneck (2020), namely that PWA show lower LIs than healthy controls, are not conclusively replicated by our findings. Nenert et al. (2018) described that LIs initially decrease after a stroke due to increased right-sided activity, but normalize when activation becomes more left-dominant again, which could be true for the PWA in our study since they are in the chronic stage of recovery. The recovery process can however not be derived from our cross-sectional study.

Overall, LIs of both groups were relatively close to zero in both the listening (control group: mean 19, PWA: mean 12) and reading tasks (control group: mean 26, PWA: mean 17), suggesting no strong lateralization of activity. This is in line with findings of a systematic review of Bradshaw et al. (2017), reporting overall low LIs for studies using passive language tasks in healthy subjects, indicating bilateral activation of the language network rather than strong left lateralized activation. This may be due to the fact that these tasks

require use of many components of language in comparison to a more specific task, which often elicit more strongly lateralized activation, namely higher LIs (e.g. semantic task; Wilson et al., 2018; Bradshaw et al., 2017). However, Fedorenko et al. (2024) describe that left-lateralization of the language network is an important and relatively stable feature of the language network across individuals, which is even already in place at the age of three years (Hiersche et al., 2023). Alternatively, the observed reduced asymmetry of language activity might be caused by the age of the participants. Functional neuroimaging studies have described increasing lateralization towards the left throughout development (Olulade et al., 2020), followed by similar changes towards symmetric activation in healthy elderly people (Cabeza, 2002), which is in line with our findings. Furthermore, when visually comparing LIs of the activity of the mean language network with the LIs of activity of individual parcels (see Figure 10, Figure 11, Figure F1, Figure F2), we see a slight trend towards higher LIs within the separate parcels in both healthy participants and PWA. Bradshaw et al. (2017) also described this pattern in their systematic review, stating that regional LIs are generally stronger than more global LIs.

In contrast to the language lateralization, the group comparison of the LI of the mean MD network during the spWM localizer task did reach significance, showing lower (and mostly negative) LIs for the aphasia group. MD activation therefore seems to be slightly right lateralized in PWA, in contrast to the rather symmetrical activation in the control group. In PWA, left-sided MD regions may have been damaged by the stroke, which could explain larger relative reliance on the right hemisphere in PWA. Fedorenko et al. (2013) localized the regions belonging to the MD network and described them as each being bilaterally involved. This is visible in the LIs close to zero in the control group.

Finally, upon visual inspection of the boxplots showing the LIs in the specific parcels, as depicted in Appendix F, we observed that the distribution of LIs frequently exhibits larger variability in the aphasia group compared to the control group. This indicates a certain heterogeneity within the aphasia group that seems to be larger than in the control group. This is no unexpected observation, since the substantial heterogeneity among PWA has been widely accepted in literature (e.g. Saur & Hartwigsen, 2012; Sheppard & Sebastian, 2021).

To conclude, PWA and healthy controls exhibited similar levels of lateralization of the mean language network during both language localizers. In the mean MD network, however, PWA displayed a significantly less left-lateralized activation pattern during the spWM localizer.

4.2.2 Correlations with behavioral test results

To investigate the influence of the LI on language and cognitive performance in PWA, correlations between these values were examined. No significant correlations were found between language network LIs and aphasia severity in both language localizers, though a positive trend was observed. However, stronger left-lateralized activity during the reading localizer was positively related to cognitive performance. Additionally, no significant correlations were found between MD network LIs and any behavioral parameters.

The results varied between the two language localizer tasks. In the listening localizer, no significant correlations were found. In the reading localizer, however, the LI of mean language activity showed a significant positive correlation with the results of the OCS-NL.

This indicates that stronger left-lateralized language activation is related to better cognitive performance, which is unexpected. None of the correlations with the language tests reached significance, although the positive correlation with the ScreeLing showed an effect in the same direction (with p-value < 0.10). Besides the LI of the mean language activity, significant positive correlations with the OCS-NL score were found as well for several of the separate language parcels in the reading localizer task, namely in the anterior temporal parcel, the posterior temporal parcel and the MFG. Left lateralized language activity during the reading localizer task might therefore support cognitive functioning as measured by the OCS-NL, although interpretations require caution due to the small sample size. For example, Gohel et al. (2019) described that MFG supports cognitive functions such as attention in addition to different aspects of language, which might explain this correlation. However, positive correlations between LIs of the language network and cognitive performance could be influenced by the fact that the OCS-NL included tasks in which, for example, the participant was asked to read and retain a sentence. If the participant could not fully rely on their left lateralized language network, e.g. due to incomplete recovery, and therefore had to rely relatively more on the language regions in the right hemisphere than healthy controls, this may have led to suboptimal reading, which might influence both results of the reading localizer task and performance on a cognitive task that relies on reading skills.

Moreover, besides the correlations with the OCS-NL score, we also found significant correlations and non-significant trends in the same direction between LIs of separate parcels and test scores on language tests. Important to note is that there is a collinearity between performance on behavioral tests for language and cognition, as poor performance on cognitive tasks is associated with poor performance on language or communication tasks (Murray, 2012). The collinearity between language and cognitive tests, taken together with the high chance of comorbid deficits (El Hachioui et al., 2014), complicates interpretation of either task (Murray et al., 2012; Rohde et al., 2018). In literature, the relation between LIs and aphasia severity is unclear. Our results seem to generally support the findings of Dietz et al. (2016), who found no link between language improvement and LIs, although we found non-significant trends towards positive correlations between left-lateralized language activity and performance on language tasks, which is in line with the findings of Nenert et al. (2018). The different results for both localizers could be explained by the fact that the reading localizer task typically emphasizes semantic and syntactic functioning, whereas the listening localizer requires focus on phonology (Bradshaw et al., 2017). Less relative reliance on the left hemisphere during only the reading localizer might indicate that processing of phonology has returned to a normal lateralization level, while language components such as semantics or syntax still show a disturbed lateralization pattern in the chronic phase of aphasia recovery. Further, a systematic review of Bradshaw et al. (2017) found that verbal fluency tasks elicit higher LIs than many other language tasks in healthy participants. Interestingly, we only found one significant correlation with the CAT-NL fluency tasks, namely for the LI of the orbital part of the IFG during the reading localizer, although the other correlations were in the same direction.

Finally, the LIs of the MD network activation during the spWM localizer task were not significantly correlated with any of the behavioral language or cognition tasks, indicating that the relative reliance on left- and right-hemispheric MD network does not influence language performance or cognitive performance. Only one separate parcel showed a significant correlation; the orbital part of the MFG showed a significant negative correlation with performance on the CAT-NL, meaning that the less left lateralized the MD activation was, the higher the score on the CAT-NL. The selected tasks from the CAT-NL were the

phonological and semantic fluency tasks, which, according to Bose et al. (2022), do not only measure language functioning, but also executive functioning. This could explain why a correlation was found with activity in an MD parcel. Furthermore, Stefaniak et al. (2022) reported a positive correlation between activation change in the bilateral MFG and the fluency task of the CAT-NL at 2 weeks to 4 months post-stroke. However, their results showed a positive association, whereas our results (negative correlation) indicate that less left-lateralized activation would be beneficial for performance on this task.

In conclusion, in both language localizers no significant correlations were found between LIs of the mean language network and aphasia severity, although we noticed a positive trend. Yet, we did find a positive relation between stronger left-lateralized language activity during the reading localizer and cognitive performance. Furthermore, no significant correlations were found between LIs of the mean MD network and any of these behavioral parameters.

4.3 Discussion of research question 3

4.3.1 Activity in the subject-specific MD network during language tasks

To answer our third research question about the involvement of the MD network during language processing, we analyzed the activation level of the subject-specific MD network, as located with the spWM localizer task, during the language localizer tasks. These analyses showed no evidence for mean activation of the MD network for the aphasia group, nor for the control group, during either of the two language localizer tasks.

During the reading task, no individual parcels showed significant activity levels in either group. During the listening task, however, some specific parcels did show significant activity among the control group, but not among the aphasia group; namely the bilateral insula, the bilateral precentral gyrus and the bilateral orbital part of the IFG. Interestingly, some of these parcels have previously been described as involved in language processing in the literature (e.g. Oh et al., 2014, Kaestner et al., 2021). These findings should, however, be interpreted with the utmost caution since the sample was small and no correction for multiple comparisons was administered on the analyses of individual parcels. The insula showed significant activity in both hemispheres in the control group during the listening localizer. According to a meta-analysis of fMRI studies conducted by Oh et al. (2014), the insula is involved in language comprehension through engaging in several processes such as phonological processing. Additionally, due to its direct anatomical and reciprocal functional links with the IFG, the insula is believed to support the phonological, semantic and syntactic processing (Oh et al., 2014). Furthermore, the precentral gyrus (left and right hemisphere) also showed significant activation during the listening task in the control group. There is some evidence in the literature for a role of the precentral gyrus in language processing, but mostly in phonology through grapheme-to-phoneme conversion during silent reading (Kaestner et al., 2021). Based on this literature, we would expect to find a significant activation during the reading task rather than during the listening task, although the reading localizer task, containing a control condition of non-word lists, leaves out phoneme-level information. Finally, significant activation was found for the parcel containing the pars opercularis of the IFG. The opercular part of the IFG is typically known as part of Broca's area, which plays an important role in language processing (Broca, 1865;

Kemmerer, 2015). However, since the voxels were subject-specifically selected based on the results of the spWM task, they are in fact part of the subject-specific MD network, and therefore rather represents the functionally distinct MD region within this area as described by Fedorenko and Blank (2020). The unexpected significant activation in both the precentral gyrus and opercular IFG may be explained by the lack of correction for multiple comparisons, since this leads to a higher chance of false positive results. Alternatively, they contradict a potential compensatory function of the MD network in aphasia, since we only found significant results in the control group.

Overall, we found no evidence for activation of the MD network during language processing. Therefore, this study seems to corroborate the findings of Diachek et al. (2020), stating that based on their subject-specific fMRI study the MD network does not support core aspects of language comprehension in healthy young subjects. Our study offers interesting new insights, as we can extend this argument for healthy elderly, which is a population that has not often been described in literature on this topic, and for PWA in the chronic stage of recovery, although our findings are based on passive listening and reading tasks. It is conceivable that the language network may require additional support in case of a more cognitively challenging language task (Diachek et al., 2020), such as active/productive tasks or natural conversation (Lee et al., 2017), although Shain et al. (2020) found no evidence for engagement of the MD network during naturalistic language comprehension in a sample of healthy subjects. Moreover, it remains possible that the MD network assumes a compensatory or supportive role during the acute or subacute stages of recovery (Saur et al., 2006) or in case of damage to certain locations (Stockert et al., 2020) but we cannot make any statements based solely on our cross-sectional study in which we did not take lesion location into account. In conclusion, similar to the findings of Li et al. (2022) and Wilson and Schneck (2021), we did not find strong evidence for a compensatory MD mechanism, at least in the chronic phase of aphasia. Longitudinal subject-specific research, including patients with more acute cases of aphasia and additionally differentiating between different lesion locations, is needed to gain more comprehensive insight in the recovery process. A potential obstacle for identifying the MD network in acute post-stroke aphasia patients, however, is the large prevalence of cognitive impairments in this population (El Hachioui et al., 2014), as the spWM task used to localize the MD network is highly cognitively demanding.

Despite this corroboration with some research, our findings contradict many other studies that state that the MD network does play a compensatory role in aphasia (e.g. Geranmayeh, 2017; for an overview see Wilson & Schneck, 2021 and Li et al., 2022). These findings however could be influenced by the limitations of these studies, as described in our literature review. Oftentimes, these studies did not include a healthy control group and as a result, observed activation in the MD network was sometimes interpreted as compensatory activity. However, without information on whether this activation pattern might be similar in healthy controls, it remains uncertain whether it represents compensation rather than normal processing. Furthermore, many studies failed to consider interindividual heterogeneity in the functionality of anatomical brain regions as they applied the traditional group-based approach, rather than the individual-subject approach. This leads to decreased sensitivity and accuracy in localizing the precise brain regions belonging to a certain network (Fedorenko et al., 2021, Nieto-Castañón & Fedorenko, 2012). Given that the present study included a control group of healthy participants and employed the single-subject approach, we believe that our results offer a valuable contrast to these prior studies.

4.4 Limitations of this study and directions for future research

We would like to emphasize that our findings should be nuanced by taking the limitations of this study into account. First of all, the small sample size (15 PWA, 13 healthy controls) might reduce the statistical power, resulting in a higher chance of false negative results. A larger sample size would be more ideal; however, this may be difficult to achieve in research with PWA. Similarly, this limitation applies to many previous studies, such as Saur et al. (2006) who included 14 PWA or Stockert et al. (2020) who included 17 PWA with a frontal lesion and 17 PWA with a temporo-parietal lesion, in contrast to studies examining healthy subjects such as Shain et al. (2020) who included 78 participants or Diachek et al. (2020) who included 481 subjects. Wilson and Schneck (2021) describe that 37% of the included studies in their systematic review and meta-analysis included less than 12 participants, which they consider to be the minimum for fMRI research, and only 17% included 24 or more participants. Future research on these topics should aim to include larger samples, as most effects in neuroplasticity are likely subtle and complex (Wilson & Schneck, 2021). Another limitation in our statistical analyses is that we did not apply a correction for multiple comparisons to the test results for individual parcels, due to the explorative nature of these analyses. Statistically significant findings should therefore be interpreted with caution, since the chance of getting false positive results is high. We did, however, correct for multiple comparisons (FDR-correction) in all our main analyses.

Furthermore, we only tested people in the chronic phase of aphasia recovery and only cross-sectionally. Because of this restriction, we cannot deduct any conclusions on activation levels in the language and MD network in the acute or subacute stage, nor on recovery of aphasia over time. It is possible that activation patterns of people in a more acute stage of aphasia would differ to a greater extent from the control group, as their language impairment might still be more prominently present. However, this was not the purpose of the current study. In contrast, none of the included PWA in our study scored below the cut-off on any of the behavioral tests, therefore showing no highly prominent impairments. Additionally, we only administered receptive language tasks, namely passive listening or reading without additional cognitive demands. As the MD network in healthy young subjects did show activation related to cognitive task demands (Diachek et al., 2020), it is conceivable that the MD network may engage or take on a compensatory role in PWA during more active and complex language tasks. An interesting direction for future research might be to test this population of PWA in the chronic stage of recovery with more challenging language tasks during the fMRI scan and behavioral testing, such as active language production and natural language use (e.g. conversation, noisy environment), which require more cognitive control than the more artificial language stimuli we used. This might lead to more ecologically valid results, through detecting more subtle remaining impairments, which might still influence communication in daily life.

Additionally, PWA form a very heterogeneous group, including varying degrees of severity and several subtypes, all associated with different lesion locations and impairments. Taking these factors into account would provide interesting additional insights, but would also lead to more selectivity in included PWA, leading to even smaller sample sizes. For example, the study of Stockert et al. (2020) found that right-sided homologues of the language areas in the left hemisphere only showed activation in people with post-stroke aphasia with a frontal lesion, not in people with a temporo-parietal lesion. Lesion location is therefore proven to be an important factor in activation patterns, which we did not take into account in the current study. However, dividing our aphasia group according to lesion site, would further reduce our sample. A related limitation, is that the used reading localizer task does

not provide information on phonological processing. Yet, many people with aphasia have difficulties with this aspect, which is reflected in the fact that data-driven studies have proposed a classification system for aphasia including phonological aphasia (Alyahya et al., 2020; Halai et al., 2017; Landrigan et al., 2021; Stefaniak et al., 2022). Fedorenko et al. (2010,2024) do not consider phonological processing to be a core aspect of language, but rather of speech perception. Therefore, it is not taken into account in this localizer task, potentially leading to overlooking valuable information.

A returning remark in the literature is the large heterogeneity in research findings. This could partly be a result of the lack of use of an individualized functional localization approach in determining ROIs of both the language and the MD network, as we did in the current study. Since the topic neuroplasticity and potential compensatory mechanisms is highly complex and may be influenced by many factors, such as pre-stroke network organization or lesion characteristics, interindividual differences should be treated as valuable information, rather than noise (Seghier & Price, 2018). As described in the literature review, this single-subject approach yields many advantages as compared to the group-averaging approach. However, there are two notable limitations to this approach as we administered it. To select the voxels that should be included in the left- or right-hemispheric language or MD network, we selected the top 10% most active voxels of each isolated language or MD parcel in that hemisphere, as did Shain et al. (2020) in their research. For our analyses of the activation of a network per hemisphere, we calculated the mean activity (mean T-level) across all parcels within that network and hemisphere. A first shortcoming of this method is its inherent incapability of allowing spatial overlap between the language network and the MD network, since it looks for each network in spatially dissociated parcels. Secondly, because we set no threshold for activity when selecting the top 10% most active voxels, the present stroke-related lesions may have affected our outcomes. For instance, when the damaged area would encompass 90% of a certain parcel, our approach would select the remaining 10% as the 10% most active voxels, even if they exhibited no language activation or only noise. However, De Clercq et al. (2024), who investigated our first and third research question, took a different, “union” approach. They, instead, selected the top 10% most active voxels across the union of all, both language and MD, parcels. This approach successfully addresses the aforementioned limitations, as it does not restrict voxel selection to either the language or MD parcels, and additionally offers interesting insights in the relative engagement of each parcel to its network. We nonetheless believe that these limitations do not greatly affect our research findings, as our approach yielded patterns of significance very similar to those found by De Clercq et al. (2024).

Finally, another limitation can be found in our operationalization of the single-subject approach. We use the single-subject approach to allow for interindividual variation of how functions are distributed across anatomical brain structures. However, we still search for activity within delineated areas, namely the parcels. Although these parcels were determined based on research including large samples of participants (Fedorenko et al., 2010; Fedorenko et al., 2013), and therefore likely encompass most targeted activation, this is still to a certain degree less sensitive to individual variations than a whole-brain approach. However, a whole-brain approach would result in an enormous amount of comparisons, which would make it close to impossible to find significant results after correction for multiple comparisons, which justifies limiting the selection of voxels within group-constrained subject-specific fROIs (Fedorenko et al., 2010).

Conclusion

In this master thesis, we applied a single-subject approach to investigate activation of both the language and MD network in people with chronic post-stroke aphasia and age-matched controls during task-based fMRI. Overall, our results are in line with findings of previous research. In the language network, we found reduced activation in the left hemisphere in PWA compared to healthy controls, but similar right-hemispheric activity. Furthermore, we found trends, although not conclusive, indicating that normalization of left-hemispheric activity contributes to functional language performance in the chronic phase (in accordance with Wilson & Scheck, 2021; Li et al. 2022). On the other hand, we found an interesting, but non-conclusive, relation between right hemisphere activation and worse language performance in PWA. Taken together, we found no clear evidence for a compensatory role of the right hemisphere in chronic aphasia. In the existing literature, there is an ongoing debate surrounding this topic, as many studies show contradicting results. However, our findings are in line with the conclusion of Wilson & Schneck (2021) stating that conclusive evidence for a compensatory right-hemispheric mechanism in adults is lacking. Research surrounding potential influential factors, such as lesion size or time post onset, is needed to clarify the ambiguity surrounding this topic (Li et al., 2022).

Despite observing trends towards less left-lateralized activation in the language network of PWA, which is in line with Wilson & Schenck (2021), these trends did not reach statistical significance. This suggests a degree of normalization in language activation patterns within the chronic phase of aphasia recovery, with PWA demonstrating similar levels of lateralization to healthy controls. Our results seem to generally support the findings of Dietz et al. (2016), who found no link between aphasia severity and LIs, although we found non-significant trends towards positive correlations between left-lateralized language activity and performance on language tasks, which is in line with the findings of Nenert et al. (2018). Higher LIs were associated with a higher OCS-score, but only during the reading task. Furthermore, MD activation during the spWM task was slightly right-lateralized in PWA, in contrast to the rather symmetrical activation in the control group, possibly due to the left-hemispheric damage. We found no clear associations with language or cognitive impairment.

Concerning the potential compensatory role of the MD network during language processing, we found no evidence for such a mechanism in people with chronic aphasia, nor did we find any evidence for MD activation during language processing in healthy elderly. This is in line with previous research in healthy young populations (Diachek et al., 2020) and with naturalistic comprehension tasks (Shain et al., 2020). Nonetheless, there are many studies that did report evidence for such a compensatory role (e.g. Geranmayeh et al., 2017; for an overview see Wilson & Schneck, 2021 and Li et al., 2022). On this topic, Wilson & Schneck (2021) describe how shortcomings of these studies contribute to the ongoing ambiguity in the literature concerning this potential compensatory mechanism in post-stroke aphasia. Consequently, both Wilson & Schneck (2021) and Li et al. (2022) state that the role of the MD network in language processing is still unclear.

The current study has some limiting characteristics, such as (among others) the small sample size, only including people in the chronic phase of aphasia, only applying passive, receptive language tasks, no inclusion of information on lesion location, and the cross-sectional research design. Despite these constraints, we believe that our study provides

compelling insights due to its innovative characteristics, namely investigating potential compensatory mechanisms in PWA by using the single-subject approach and the inclusion of a control group of healthy elderly.

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Appendix

Appendix A

Table A1. Demographic information, lesion information and behavioral test results of the PWA subjects (adapted from De Clercq et al., 2024).

Subject	Age	Sex	Time since stroke (months)	Lesion size (ml)	NBT	ScreeLing	CAT-NL	OCS
sub-007	72	m	47	80.79	261	68	43	97.33
sub-008	43	m	39	6.91	274	71	35	100
sub-010	62	f	45	6.55	263	71	49	98
sub-011	70	m	45	46.99	261	69	19	96
sub-013	80	m	28	10.84	269	69	26	76
sub-014	70	m	22	98.72	265	67	29	94
sub-015	73	f	47	0.81	271	68	31	98
sub-017	41	f	13	78.25	267	69	34	98.67
sub-018	69	m	18	3.95	270	67	20	98
sub-020	51	m	31	45.63	217	57	11	84
sub-022	74	m	121	58.59	266	69	18	100
sub-024	80	f	26	88.60	236	48	21	94.67
sub-025	74	m	17	30.81	271	66	16	97.33
sub-027	70	m	21	76.67	150	42	NA	88
sub-031	41	f	45	166.32	164	56	12	99.33

Appendix B

Listening localizer task

Table B1. Results of the Shapiro-Wilk test for the listening localizer task for the mean language activity and individual parcels in both right and left hemispheres.

		W	p
gem_RH_taal	**aphasia**	**0.876**	**0.042****
	healthy	0.928	0.318
gem_LH_taal	aphasia	0.910	0.135
	healthy	0.964	0.820
RH-AngG_mean	aphasia	0.884	0.055*
	healthy	0.948	0.563
LH-AngG_mean	**aphasia**	**0.878**	**0.044****
	healthy	0.885	0.083*
RH-AntTemp_mean	aphasia	0.901	0.099*
	healthy	0.898	0.126
LH-AntTemp_mean	aphasia	0.973	0.903
	healthy	0.974	0.936
RH-IFG_mean	aphasia	0.909	0.129
	healthy	0.931	0.346
LH-IFG_mean	**aphasia**	**0.839**	**0.012*****
	healthy	0.966	0.837
RH-IFGorb_mean	aphasia	0.982	0.983
	healthy	**0.750**	**0.002*****
LH-IFGorb_mean	**aphasia**	**0.804**	**0.006*****
	healthy	0.906	0.163
RH-MFG_mean	**aphasia**	**0.799**	**0.004*****
	healthy	0.929	0.332
LH-MFG_mean	aphasia	0.915	0.164
	healthy	**0.849**	**0.028****
RH-PostTemp_mean	**aphasia**	**0.827**	**0.008*****
	healthy	0.904	0.154
LH-PostTemp_mean	aphasia	0.938	0.358
	healthy	0.958	0.730

* = $p < 0.10$, ** = $p < 0.05$, *** = $p < 0.01$

Note. Significant results suggest a deviation from normality.

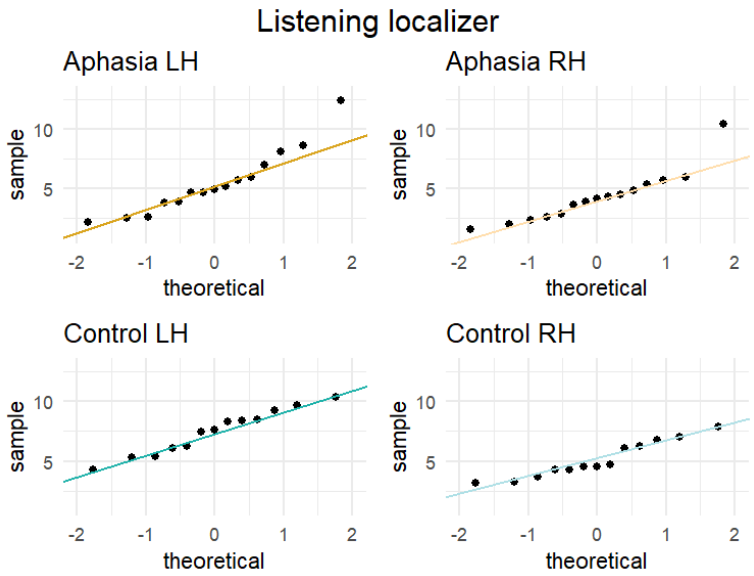

Figure B1. *Q-Q plots of the mean activity of the language network in both left and right hemisphere during the listening localizer task.*

Reading localizer task

Table B2. Results of the Shapiro-Wilk test for the mean language activity and individual parcels in both right and left hemispheres during the reading localizer task.

		W	p
gem_RH_taal	aphasia	0.979	0.968
	healthy	**0.756**	**0.002*** **
gem_LH_taal	aphasia	0.942	0.446
	healthy	**0.834**	**0.027** **
RH-AngG_mean	aphasia	0.971	0.894
	healthy	0.864	0.065*
LH-AngG_mean	aphasia	0.974	0.926
	healthy	0.932	0.431
RH-AntTemp_mean	aphasia	0.930	0.310
	healthy	**0.695**	**< .001*** **
LH-AntTemp_mean	aphasia	0.982	0.985
	healthy	0.868	0.074
RH-IFG_mean	aphasia	0.956	0.658
	healthy	**0.840**	**0.032** **
LH-IFG_mean	aphasia	0.946	0.502
	healthy	0.856	0.051*
RH-IFGorb_mean	aphasia	0.963	0.766
	healthy	**0.844**	**0.036** **
LH-IFGorb_mean	aphasia	0.932	0.365
	healthy	0.858	0.054*
RH-MFG_mean	aphasia	0.925	0.261
	healthy	0.966	0.840
LH-MFG_mean	aphasia	0.950	0.556
	healthy	0.937	0.481
RH-PostTemp_mean	aphasia	0.945	0.483
	healthy	0.861	0.058*
LH-PostTemp_mean	aphasia	0.936	0.373
	healthy	0.992	0.999

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

Note. Significant results suggest a deviation from normality.

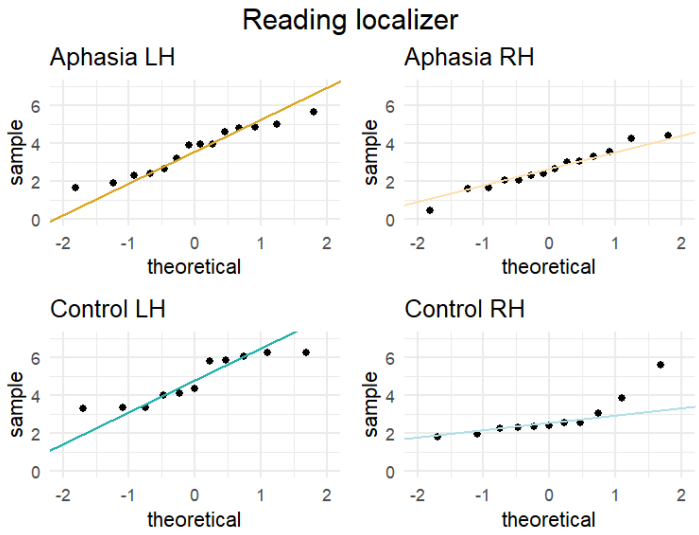

Figure B2. *Q-Q plots of the mean activity of the language network in both left and right hemisphere during the reading localizer task.*

spWM localizer task

Table B3. Results of the Shapiro-Wilk test for the mean MD activity and individual parcels in both right and left hemispheres during the spWM localizer task.

		W	p
gem_RH_md	aphasia	0.881	0.061*
	healthy	0.963	0.800
gem_LH_md	aphasia	0.922	0.239
	healthy	0.921	0.262
RH-AntPar_mean	aphasia	0.884	0.067*
	healthy	0.926	0.306
LH-AntPar_mean	aphasia	0.927	0.277
	healthy	0.960	0.747
RH-IFGop_mean	aphasia	0.941	0.433
	healthy	0.925	0.290
LH-IFGop_mean	aphasia	0.926	0.270
	healthy	0.971	0.904
RH-Insula_mean	aphasia	0.949	0.548
	healthy	0.962	0.791
LH-Insula_mean	aphasia	0.895	0.097*
	healthy	0.963	0.799
RH-MFG(md)_mean	aphasia	0.891	0.083*
	healthy	0.938	0.430
LH-MFG(md)_mean	aphasia	0.962	0.762
	healthy	0.920	0.251
RH-MFGorb_mean	aphasia	0.934	0.349
	healthy	0.949	0.579
LH-MFGorb_mean	aphasia	0.917	0.201
	healthy	0.980	0.980
RH-MidPar_mean	aphasia	0.881	0.060*
	healthy	0.940	0.451
LH-MidPar_mean	aphasia	0.939	0.410
	healthy	0.946	0.533
RH-mPFC_mean	aphasia	0.908	0.149
	healthy	0.958	0.724
LH-mPFC_mean	aphasia	0.921	0.224
	healthy	0.950	0.601
RH-PostPar_mean	aphasia	0.898	0.106
	healthy	0.919	0.242
LH-PostPar_mean	**aphasia**	**0.871**	**0.044****
	healthy	0.919	0.244
RH-PrecG_mean	aphasia	0.924	0.249
	healthy	0.955	0.677
LH-PrecG_mean	aphasia	0.961	0.734
	healthy	0.904	0.149
RH-SFG_mean	aphasia	0.945	0.491
	healthy	0.933	0.377
LH-SFG_mean	aphasia	0.896	0.100
	healthy	0.933	0.376

* = $p < 0.10$, ** = $p < 0.05$, *** = $p < 0.01$

Note. Significant results suggest a deviation from normality.

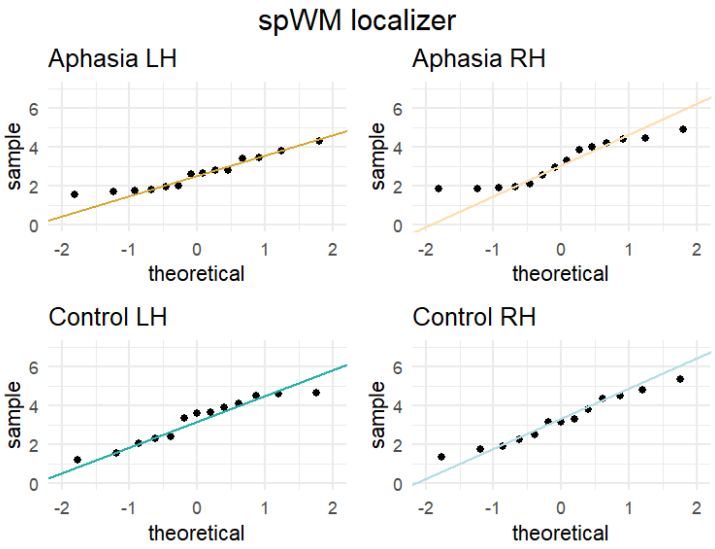

Figure B3. *Q-Q plots of the mean activity of the mean MD network in both left and right hemisphere during the spWM localizer task.*

Appendix C

Listening localizer task

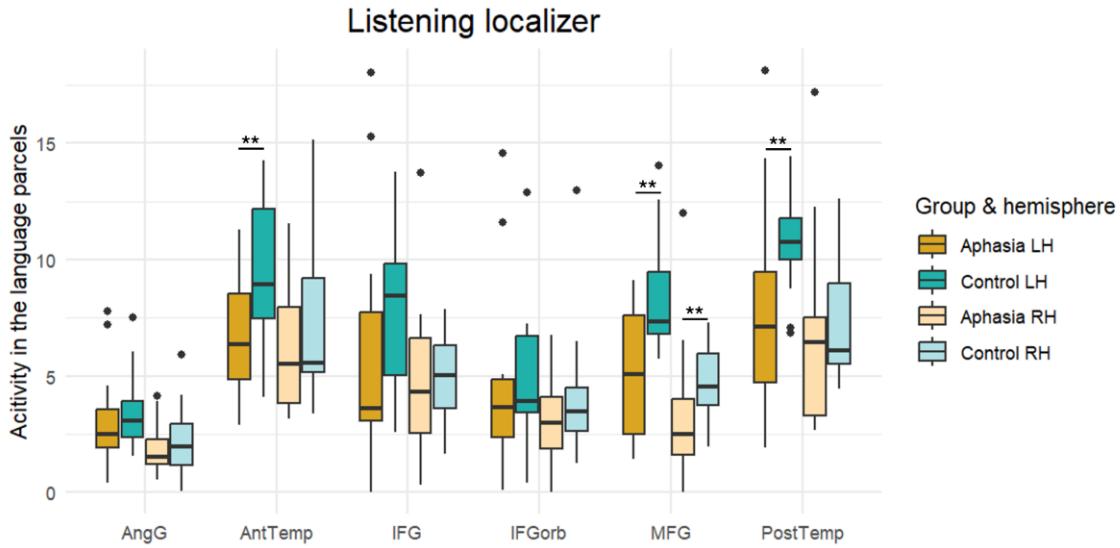

Figure C1. *Boxplots of activity in the individual language parcels during the listening localizer task in left and right hemisphere in the aphasia and control group.*

Table C1. Results of the Wilcoxon rank-sum test for activity in the individual language parcels in both right and left hemispheres during the listening localizer task.

	W	p
RH-AngG_mean	87.000	0.650
LH-AngG_mean	75.000	0.316
RH-AntTemp_mean	76.000	0.339
LH-AntTemp_mean	**49.000**	**0.025****
RH-IFG_mean	87.000	0.650
LH-IFG_mean	59.000	0.080*
RH-IFGorb_mean	76.000	0.339
LH-IFGorb_mean	74.000	0.430
RH-MFG_mean	**48.000**	**0.022****
LH-MFG_mean	**45.000**	**0.015****
RH-PostTemp_mean	69.000	0.201
LH-PostTemp_mean	**44.000**	**0.013****

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

Reading localizer task

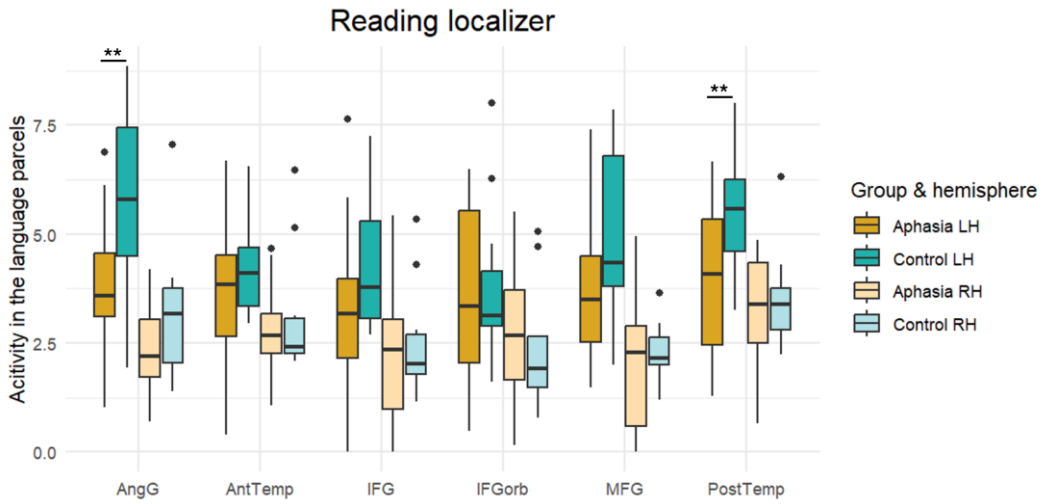

Figure C2. *Boxplots of activity in the individual language parcels during the reading localizer task in left and right hemisphere in the aphasia and control group.*

Table C2. Results of the Wilcoxon rank-sum test for activity in the individual language parcels in both right and left hemispheres during the reading localizer task.

	W	p
RH-AntTemp_mean	75.000	0.936
LH-AntTemp_mean	61.000	0.403
RH-IFGorb_mean	93.000	0.403
LH-IFGorb_mean	65.000	0.733
RH-PostTemp_mean	76.000	0.979
LH-PostTemp_mean	**37.000**	**0.029****
RH-IFG_mean	76.000	0.979
LH-IFG_mean	51.000	0.166
RH-AngG_mean	53.000	0.202
LH-AngG_mean	**34.000**	**0.018****
RH-MFG_mean	72.000	0.809
LH-MFG_mean	44.000	0.075*

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

spWM task

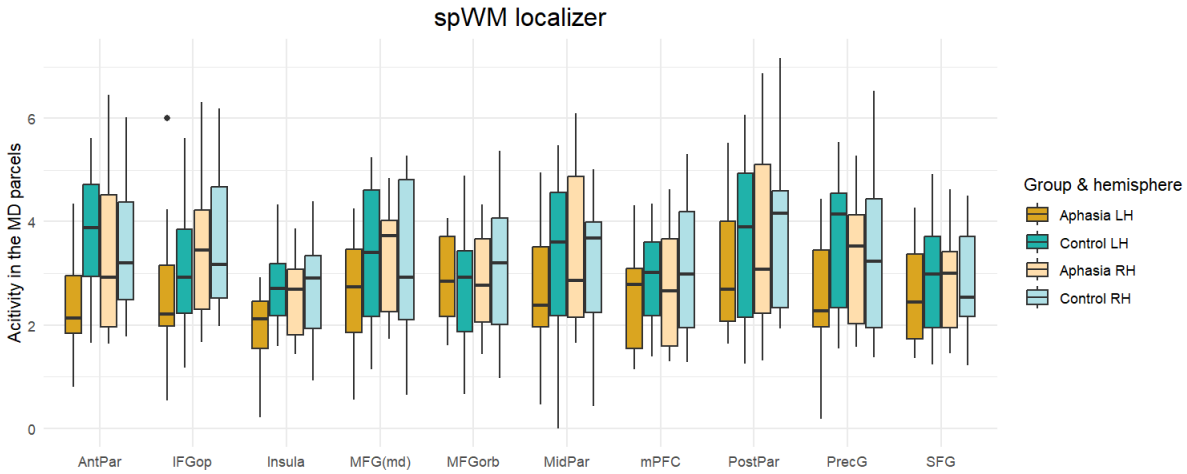

Figure C3. *Boxplots of activity in the individual MD parcels during the spWM localizer task in left and right hemisphere in the aphasia and control group.*

Table C3. Results of the Wilcoxon rank-sum test for the activity in the individual parcels in both right and left hemispheres during the spWM localizer task.

	W	p
RH-AntPar_mean	78.000	0.550
LH-AntPar_mean	**37.000**	**0.008*** **
RH-IFGop_mean	83.000	0.720
LH-IFGop_mean	67.000	0.259
RH-Insula_mean	80.000	0.616
LH-Insula_mean	**42.000**	**0.017****
RH-MFG(md)_mean	93.000	0.943
LH-MFG(md)_mean	63.000	0.185
RH-MFGorb_mean	81.000	0.650
LH-MFGorb_mean	95.000	0.867
RH-MidPar_mean	92.000	0.981
LH-MidPar_mean	68.000	0.280
RH-mPFC_mean	78.000	0.550
LH-mPFC_mean	69.000	0.302
RH-PostPar_mean	81.000	0.650
LH-PostPar_mean	75.000	0.458
RH-PrecG_mean	91.000	1.000
LH-PrecG_mean	**48.000**	**0.038****
RH-SFG_mean	91.000	1.000
LH-SFG_mean	81.000	0.650

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

Appendix D

Listening localizer task

Table D1. Partial Spearman rank correlations between activity of the right-hemispheric language parcels during the listening localizer and behavioral test results (covariants: age, lesion size, time since stroke).

		Spearman's rho	p
RH-AngG_mean	- NBT	-0.044	0.893
RH-AngG_mean	- ScreeLing	-0.202	0.528
RH-AngG_mean	- CAT-NL	-0.052	0.879
RH-AngG_mean	- OCS	0.103	0.751
RH-AntTemp_mean	- NBT	0.358	0.254
RH-AntTemp_mean	- ScreeLing	0.224	0.483
RH-AntTemp_mean	- CAT-NL	0.186	0.584
RH-AntTemp_mean	- OCS	0.159	0.622
RH-IFG_mean	- NBT	0.151	0.639
RH-IFG_mean	- ScreeLing	0.228	0.475
RH-IFG_mean	- CAT-NL	-0.328	0.325
RH-IFG_mean	- OCS	0.562	0.057*
RH-IFGorb_mean	- NBT	0.038	0.907
RH-IFGorb_mean	- ScreeLing	0.276	0.385
RH-IFGorb_mean	- CAT-NL	-0.120	0.725
RH-IFGorb_mean	- OCS	0.140	0.664
RH-MFG_mean	- NBT	-0.008	0.981
RH-MFG_mean	- ScreeLing	0.233	0.466
RH-MFG_mean	- CAT-NL	0.165	0.628
RH-MFG_mean	- OCS	-0.173	0.590
RH-PostTemp_mean	- NBT	-0.217	0.498
RH-PostTemp_mean	- ScreeLing	0.194	0.545
RH-PostTemp_mean	- CAT-NL	-0.167	0.623
RH-PostTemp_mean	- OCS	0.149	0.643

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

Table D2. Partial Spearman rank correlations between activity of the left-hemispheric language parcels during the listening localizer and behavioral test results (covariants: age, lesion size, time since stroke).

		Spearman's rho	p
LH-AngG_mean	- NBT	0.140	0.665
LH-AngG_mean	- ScreeLing	0.342	0.276
LH-AngG_mean	- CAT-NL	0.445	0.170
LH-AngG_mean	- OCS	0.152	0.638
LH-AntTemp_mean	- NBT	-0.067	0.836
LH-AntTemp_mean	- ScreeLing	0.104	0.749
LH-AntTemp_mean	- CAT-NL	0.217	0.522
LH-AntTemp_mean	- OCS	0.266	0.403
LH-IFG_mean	- NBT	-0.083	0.798
LH-IFG_mean	- ScreeLing	0.146	0.650
LH-IFG_mean	- CAT-NL	-0.099	0.773
LH-IFG_mean	- OCS	0.284	0.370
LH-IFGorb_mean	- NBT	0.179	0.599
LH-IFGorb_mean	- ScreeLing	0.035	0.918
LH-IFGorb_mean	- CAT-NL	-0.331	0.351
LH-IFGorb_mean	- OCS	0.255	0.449
LH-MFG_mean	- NBT	-0.065	0.840
LH-MFG_mean	- ScreeLing	0.293	0.356
LH-MFG_mean	- CAT-NL	0.340	0.306
LH-MFG_mean	- OCS	0.086	0.790
LH-PostTemp_mean	- NBT	-0.055	0.865
LH-PostTemp_mean	- ScreeLing	0.345	0.271
LH-PostTemp_mean	- CAT-NL	0.178	0.601
LH-PostTemp_mean	- OCS	-0.010	0.976

* = $p < 0.10$, ** = $p < 0.05$, *** = $p < 0.01$

Reading localizer task

Table D3. Partial Spearman rank correlations between activity of the right-hemispheric language parcels during the reading localizer and behavioral test results (covariants: age, lesion size, time since stroke).

		Spearman's rho	p
RH-AngG_mean	- NBT	-0.354	0.316
RH-AngG_mean	- ScreeLing	-0.458	0.183
RH-AngG_mean	- CAT-NL	0.140	0.720
RH-AngG_mean	- OCS	-0.626	0.053*
RH-AntTemp_mean	- NBT	0.058	0.873
RH-AntTemp_mean	- ScreeLing	-0.038	0.917
RH-AntTemp_mean	- CAT-NL	-0.373	0.322
RH-AntTemp_mean	- OCS	-0.210	0.561
RH-IFG_mean	- NBT	-0.203	0.574
RH-IFG_mean	- ScreeLing	-0.315	0.375
RH-IFG_mean	- CAT-NL	-0.353	0.352
RH-IFG_mean	- OCS	-0.327	0.356
RH-IFGorb_mean	- NBT	-0.260	0.467
RH-IFGorb_mean	- ScreeLing	-0.281	0.431
RH-IFGorb_mean	**- CAT-NL**	**-0.775**	**0.014****
RH-IFGorb_mean	- OCS	-0.185	0.608
RH-MFG_mean	- NBT	-0.260	0.469
RH-MFG_mean	- ScreeLing	-0.254	0.479
RH-MFG_mean	- CAT-NL	-0.200	0.605
RH-MFG_mean	- OCS	-0.628	0.052*
RH-PostTemp_mean	- NBT	-0.069	0.850
RH-PostTemp_mean	- ScreeLing	-0.166	0.647
RH-PostTemp_mean	- CAT-NL	-0.375	0.320
RH-PostTemp_mean	- OCS	-0.196	0.587

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

Table D4. Partial Spearman rank correlations between activity of the left-hemispheric language parcels during the reading localizer and behavioral test results (covariants: age, lesion size, time since stroke).

		Spearman's rho	p
LH-AngG_mean	- NBT	0.011	0.975
LH-AngG_mean	- ScreeLing	0.519	0.124
LH-AngG_mean	- CAT-NL	0.609	0.082*
LH-AngG_mean	- OCS	0.194	0.591
LH-AntTemp_mean	- NBT	-0.351	0.320
LH-AntTemp_mean	- ScreeLing	-0.030	0.934
LH-AntTemp_mean	- CAT-NL	-0.309	0.419
LH-AntTemp_mean	- OCS	0.049	0.893
LH-IFG_mean	- NBT	-0.138	0.704
LH-IFG_mean	- ScreeLing	0.186	0.608
LH-IFG_mean	- CAT-NL	0.172	0.657
LH-IFG_mean	- OCS	0.270	0.450
LH-IFGorb_mean	- NBT	-0.234	0.545
LH-IFGorb_mean	- ScreeLing	-0.072	0.853
LH-IFGorb_mean	- CAT-NL	-0.167	0.692
LH-IFGorb_mean	- OCS	-0.098	0.802
LH-MFG_mean	- NBT	-0.006	0.987
LH-MFG_mean	- ScreeLing	0.365	0.300
LH-MFG_mean	- CAT-NL	-0.039	0.921
LH-MFG_mean	- OCS	0.068	0.853
LH-PostTemp_mean	- NBT	0.173	0.632
LH-PostTemp_mean	- ScreeLing	0.354	0.316
LH-PostTemp_mean	- CAT-NL	0.062	0.875
LH-PostTemp_mean	- OCS	0.206	0.567

* = $p < 0.10$, ** = $p < 0.05$, *** = $p < 0.01$

spWM task

Table D5. Partial Spearman rank correlations between activity of the right-hemispheric MD parcels during the spWM localizer and behavioral test results (covariants: age, lesion size, time since stroke).

		Spearman's rho	p
RH-AntPar_mean	- NBT	0.193	0.570
RH-AntPar_mean	- ScreeLing	0.353	0.287
RH-AntPar_mean	- CAT-NL	0.093	0.797
RH-AntPar_mean	- OCS	0.367	0.266
RH-IFGop_mean	- NBT	-0.056	0.871
RH-IFGop_mean	- ScreeLing	0.248	0.462
RH-IFGop_mean	- CAT-NL	0.221	0.539
RH-IFGop_mean	- OCS	0.092	0.788
RH-Insula_mean	- NBT	-0.005	0.989
RH-Insula_mean	- ScreeLing	0.442	0.174
RH-Insula_mean	- CAT-NL	0.540	0.107
RH-Insula_mean	- OCS	-0.166	0.626
RH-MFG(md)_mean	- NBT	-0.029	0.933
RH-MFG(md)_mean	- ScreeLing	0.275	0.412
RH-MFG(md)_mean	- CAT-NL	0.301	0.398
RH-MFG(md)_mean	- OCS	-0.022	0.948
RH-MFGorb_mean	- NBT	-0.027	0.937
RH-MFGorb_mean	- ScreeLing	0.297	0.375
RH-MFGorb_mean	- CAT-NL	0.102	0.779
RH-MFGorb_mean	- OCS	-0.021	0.952
RH-MidPar_mean	- NBT	0.141	0.680
RH-MidPar_mean	- ScreeLing	0.285	0.396
RH-MidPar_mean	- CAT-NL	0.018	0.962
RH-MidPar_mean	- OCS	0.325	0.329
RH-mPFC_mean	- NBT	0.230	0.497
RH-mPFC_mean	- ScreeLing	0.523	0.099*
RH-mPFC_mean	- CAT-NL	0.318	0.370
RH-mPFC_mean	- OCS	0.242	0.474
RH-PostPar_mean	- NBT	-0.013	0.969
RH-PostPar_mean	- ScreeLing	0.114	0.739
RH-PostPar_mean	- CAT-NL	-0.173	0.633
RH-PostPar_mean	- OCS	0.443	0.172
RH-PrecG_mean	- NBT	0.048	0.888
RH-PrecG_mean	- ScreeLing	0.181	0.593
RH-PrecG_mean	- CAT-NL	0.191	0.597
RH-PrecG_mean	- OCS	0.039	0.910
RH-SFG_mean	- NBT	0.099	0.772
RH-SFG_mean	- ScreeLing	0.045	0.896
RH-SFG_mean	- CAT-NL	-0.247	0.491
RH-SFG_mean	- OCS	0.121	0.723

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

Table D6. Partial Spearman rank correlations between activity of the left-hemispheric MD parcels during the spWM localizer and behavioral test results (covariants: age, lesion size, time since stroke).

		Spearman's rho	p
LH-AntPar_mean	- NBT	0.104	0.762
LH-AntPar_mean	- ScreeLing	0.381	0.247
LH-AntPar_mean	- CAT-NL	-0.168	0.643
LH-AntPar_mean	- OCS	0.332	0.319
LH-IFGop_mean	- NBT	-0.095	0.782
LH-IFGop_mean	- ScreeLing	0.266	0.429
LH-IFGop_mean	- CAT-NL	0.137	0.705
LH-IFGop_mean	- OCS	0.252	0.454
LH-Insula_mean	- NBT	-0.265	0.431
LH-Insula_mean	- ScreeLing	-0.353	0.286
LH-Insula_mean	- CAT-NL	-0.303	0.396
LH-Insula_mean	- OCS	-0.046	0.893
LH-MFG(md)_mean	- NBT	0.028	0.935
LH-MFG(md)_mean	- ScreeLing	0.222	0.512
LH-MFG(md)_mean	- CAT-NL	-0.035	0.925
LH-MFG(md)_mean	- OCS	0.201	0.554
LH-MFGorb_mean	- NBT	-0.289	0.389
LH-MFGorb_mean	- ScreeLing	-0.166	0.626
LH-MFGorb_mean	- CAT-NL	-0.461	0.180
LH-MFGorb_mean	- OCS	-0.252	0.454
LH-MidPar_mean	- NBT	0.292	0.384
LH-MidPar_mean	- ScreeLing	0.485	0.130
LH-MidPar_mean	- CAT-NL	0.191	0.597
LH-MidPar_mean	- OCS	0.319	0.339
LH-mPFC_mean	- NBT	0.099	0.772
LH-mPFC_mean	- ScreeLing	0.344	0.300
LH-mPFC_mean	- CAT-NL	0.333	0.346
LH-mPFC_mean	- OCS	0.100	0.770
LH-PostPar_mean	- NBT	0.187	0.582
LH-PostPar_mean	- ScreeLing	0.345	0.298
LH-PostPar_mean	- CAT-NL	-0.042	0.907
LH-PostPar_mean	- OCS	0.344	0.300
LH-PrecG_mean	- NBT	-0.011	0.975
LH-PrecG_mean	- ScreeLing	0.309	0.354
LH-PrecG_mean	- CAT-NL	0.081	0.823
LH-PrecG_mean	- OCS	0.153	0.654
LH-SFG_mean	- NBT	0.303	0.365
LH-SFG_mean	- ScreeLing	0.154	0.652
LH-SFG_mean	- CAT-NL	-0.168	0.642
LH-SFG_mean	- OCS	0.218	0.520

* = $p < 0.10$, ** = $p < 0.05$, *** = $p < 0.01$

Appendix E

Listening localizer

Table E1. Results of the Shapiro-Wilk test for the LIs of the mean language network and individual parcels in right and left hemisphere during the listening localizer task.

		W	p
Lateralisatie-index taal	aphasia	0.979	0.964
	healthy	0.987	0.998
AngG_LI	aphasia	0.924	0.223
	healthy	0.982	0.989
AntTemp_LI	aphasia	0.885	0.057*
	healthy	0.909	0.177
IFG_LI	aphasia	0.915	0.163
	healthy	0.972	0.922
IFGorb_LI	aphasia	0.945	0.490
	healthy	0.980	0.981
MFG_LI	aphasia	0.983	0.986
	healthy	0.982	0.986
PostTemp_LI	aphasia	0.909	0.133
	healthy	0.871	0.055*

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

Note. Significant results suggest a deviation from normality.

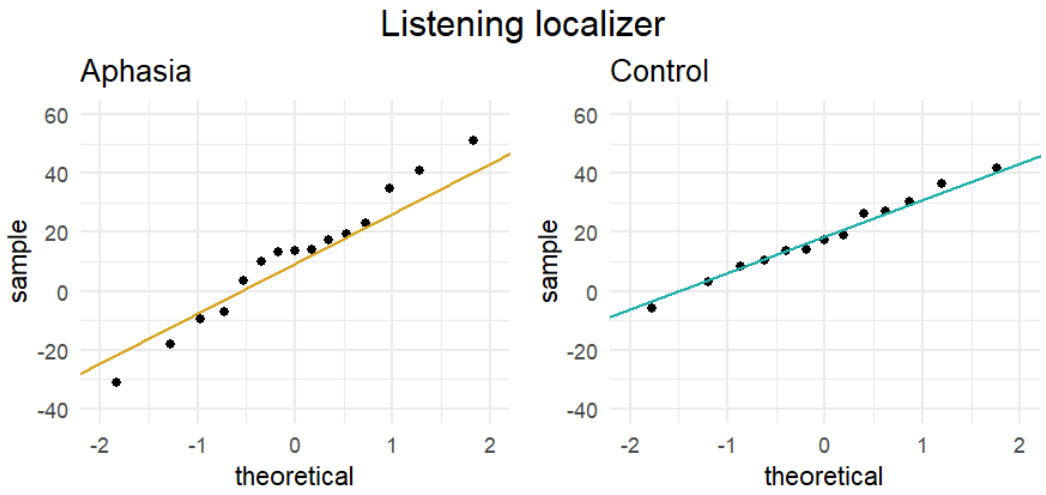

Figure E1. *Q-Q plots of the LIs of the mean language network during the listening localizer task.*

Reading localizer

Table E2. Results of the Shapiro-Wilk test for the LIs of the mean language network and individual parcels in right and left hemisphere during the reading localizer task.

		W	p
Lateralisatie-index taal	aphasia	0.948	0.526
	healthy	0.893	0.151
AngG_LI	aphasia	0.937	0.385
	healthy	0.899	0.178
AntTemp_LI	**aphasia**	**0.767**	**0.002*****
	healthy	**0.755**	**0.002*****
IFG_LI	aphasia	0.957	0.667
	healthy	0.926	0.368
IFGorb_LI	aphasia	0.959	0.742
	healthy	0.951	0.662
MFG_LI	aphasia	0.946	0.503
	healthy	0.933	0.440
PostTemp_LI	aphasia	0.963	0.779
	healthy	0.885	0.122

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

Note. Significant results suggest a deviation from normality.

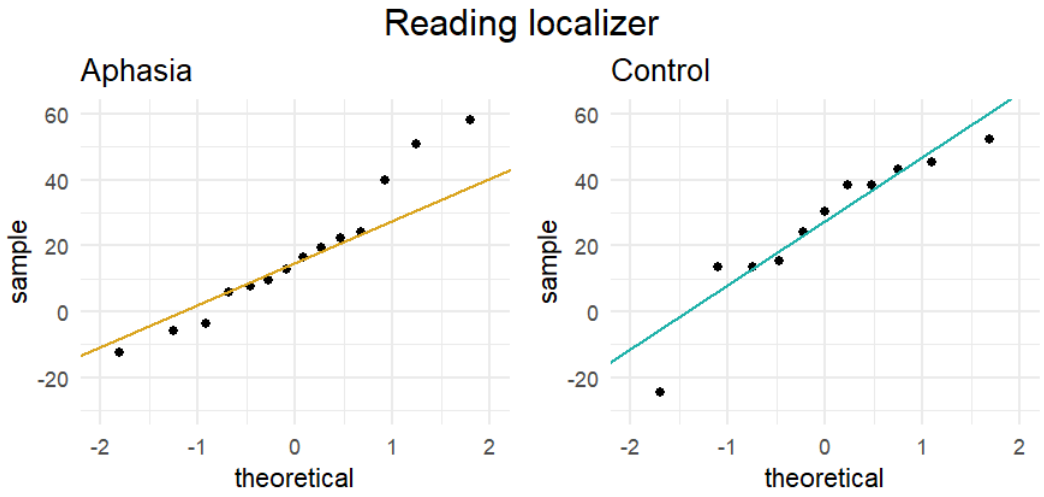

Figure E2. *Q-Q plots of the LIs of the mean language network during the reading localizer task.*

spWM localizer

Table E3. Results of the Shapiro-Wilk test for the spWM localizer task for the LIs of the mean MD network and individual parcels in right and left hemisphere.

		W	p
Lateralisatie-index md	aphasia	0.905	0.133
	healthy	0.967	0.850
AntPar_LI	aphasia	0.942	0.448
	healthy	0.954	0.653
IFGop_LI	aphasia	0.947	0.522
	healthy	0.990	1.000
Insula_LI	**aphasia**	**0.812**	**0.007*** **
	healthy	0.940	0.456
MFG(md)_LI	**aphasia**	**0.813**	**0.007*** **
	healthy	0.984	0.994
MFGorb_LI	aphasia	0.878	0.055*
	healthy	0.947	0.553
MidPar_LI	aphasia	0.938	0.398
	healthy	**0.663**	**< .001*** **
mPFC_LI	aphasia	0.977	0.955
	healthy	0.958	0.723
PostPar_LI	aphasia	0.965	0.801
	healthy	0.959	0.742
PrecG_LI	**aphasia**	**0.870**	**0.042** **
	healthy	0.937	0.421
SFG_LI	aphasia	0.909	0.154
	healthy	0.936	0.412

* = p < 0.10, ** = p < 0.05, *** = p < 0.01
Note. Significant results suggest a deviation from normality.

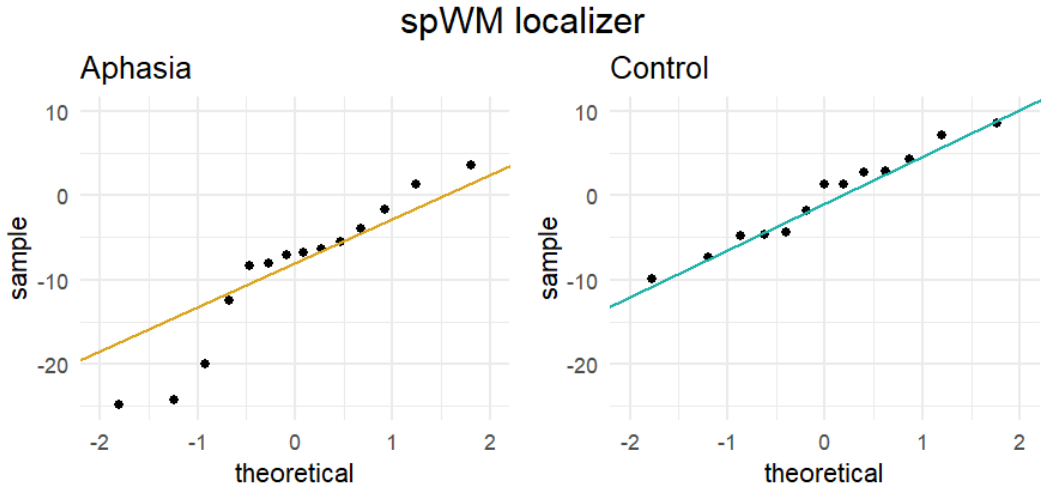

Figure E3. *Q-Q plots of the LIs of the mean MD network during the spWM localizer task.*

Appendix F

Listening localizer

Table F1. Results of Wilcoxon rank-sum test for the group comparison of LIs for individual language parcels during the listening localizer task.

	W	p
AngG_LI	80.000	0.440
AntTemp_LI	83.000	0.525
IFG_LI	70.000	0.217
IFGorb_LI	114.000	0.280
MFG_LI	91.000	0.786
PostTemp_LI	75.000	0.316

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

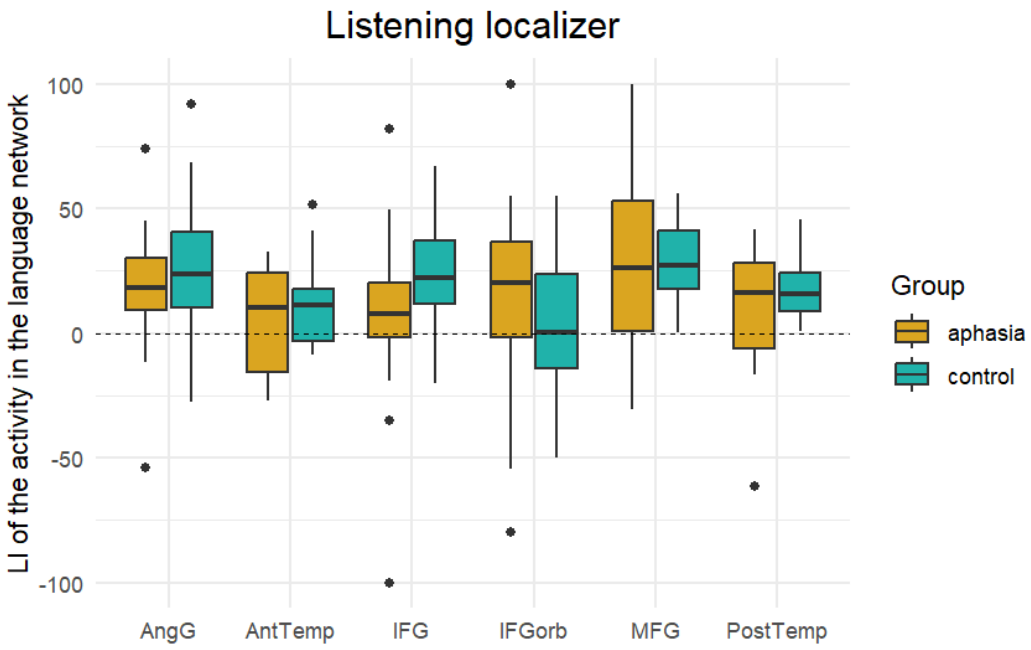

Figure F1. *Boxplots representing the LIs of activity in the language parcels of both groups during the listening localizer task.*

Reading localizer

Table F2. Results of Wilcoxon rank-sum test for the group comparison of LIs for individual language parcels during the reading localizer task.

	W	p
Lateralisatie-index taal	53.000	0.202
AntTemp_LI	67.000	0.609
IFGorb_LI	67.000	0.820
PostTemp_LI	47.000	0.107
IFG_LI	65.000	0.536
AngG_LI	65.000	0.536
MFG_LI	72.000	0.809

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

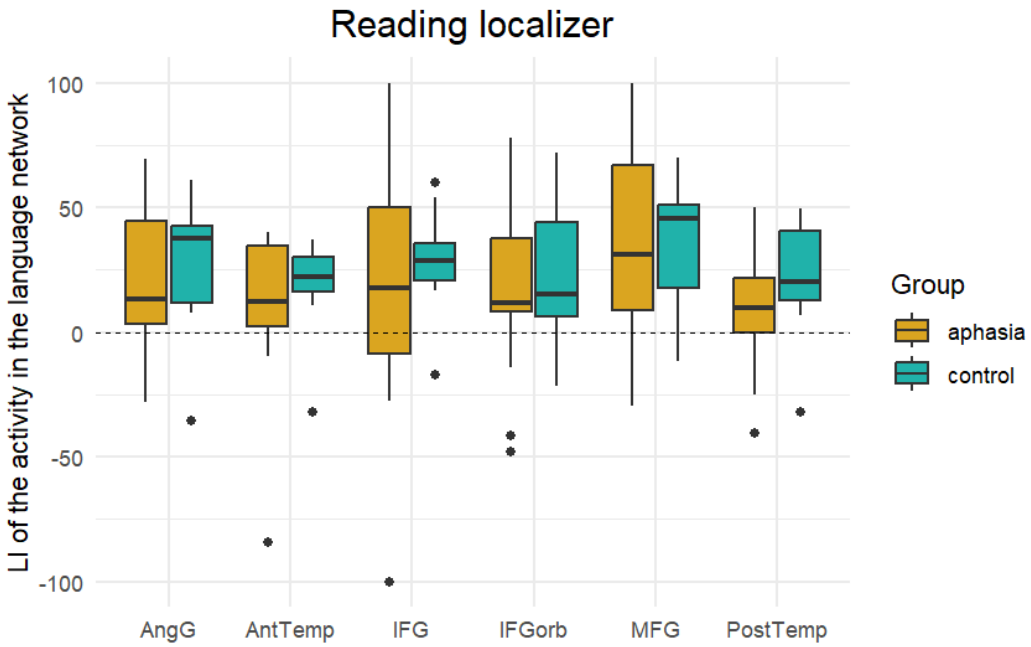

Figure F2. *Boxplots representing the LIs of activity in the language parcels of both groups during the reading localizer task.*

spWM localizer

Table F3. Results of Wilcoxon rank-sum test for the group comparison of LIs for individual MD parcels during the spWM localizer task.

	W	p
AntPar_LI	**31.000**	**0.003*** **
IFGop_LI	70.000	0.325
Insula_LI	51.000	0.054*
MFG(md)_LI	**33.000**	**0.004*** **
MFGorb_LI	102.000	0.616
MidPar_LI	64.000	0.202
mPFC_LI	76.000	0.488
PostPar_LI	83.000	0.720
PrecG_LI	58.000	0.116
SFG_LI	**45.000**	**0.025** **

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

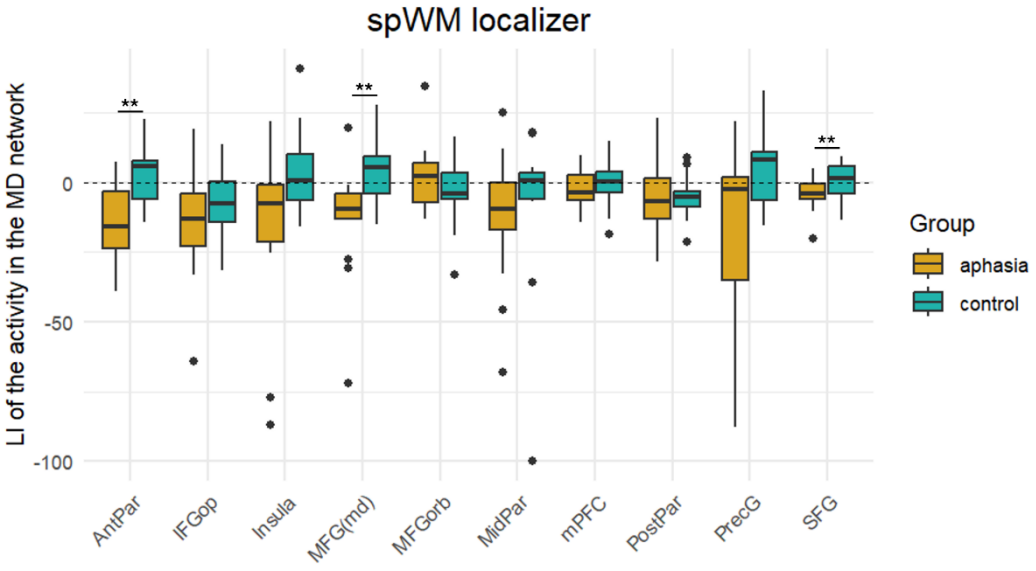

Figure F3. *Boxplots representing the LIs of activity in the MD parcels of both groups during the spWM localizer task.*

Appendix G

Listening localizer

Table G1. Partial Spearman rank correlations between LIs of language parcels during the listening localizer and behavioral test results (covariants: age, lesion size, time since stroke).

		Spearman's rho	p
AngG_LI	- NBT	0.282	0.374
AngG_LI	- ScreeLing	0.537	0.072*
AngG_LI	- CAT-NL	0.510	0.109
AngG_LI	- OCS	0.111	0.731
AntTemp_LI	- NBT	-0.392	0.207
AntTemp_LI	- ScreeLing	-0.039	0.904
AntTemp_LI	- CAT-NL	0.136	0.689
AntTemp_LI	- OCS	0.061	0.849
IFG_LI	- NBT	-0.280	0.378
IFG_LI	- ScreeLing	-0.027	0.934
IFG_LI	- CAT-NL	0.295	0.378
IFG_LI	- OCS	-0.063	0.847
IFGorb_LI	- NBT	-0.105	0.758
IFGorb_LI	- ScreeLing	0.011	0.974
IFGorb_LI	- CAT-NL	-0.091	0.802
IFGorb_LI	- OCS	0.290	0.388
MFG_LI	- NBT	-0.118	0.716
MFG_LI	- ScreeLing	0.261	0.413
MFG_LI	- CAT-NL	0.333	0.317
MFG_LI	- OCS	0.279	0.380
PostTemp_LI	- NBT	0.220	0.493
PostTemp_LI	- ScreeLing	0.138	0.669
PostTemp_LI	- CAT-NL	0.161	0.635
PostTemp_LI	- OCS	-0.051	0.875

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

Reading localizer

Table G2. Partial Spearman rank correlations between LIs of language parcels during the reading localizer and behavioral test results (covariants: age, lesion size, time since stroke).

		Spearman's rho	p
AngG_LI	- NBT	0.536	0.110
AngG_LI	**- ScreeLing**	**0.830**	**0.003*** **
AngG_LI	- CAT-NL	0.580	0.102
AngG_LI	- OCS	0.622	0.055
AntTemp_LI	- NBT	0.334	0.346
AntTemp_LI	- ScreeLing	0.521	0.123
AntTemp_LI	- CAT-NL	0.397	0.290
AntTemp_LI	**- OCS**	**0.685**	**0.029****
IFG_LI	- NBT	0.215	0.550
IFG_LI	- ScreeLing	0.400	0.252
IFG_LI	- CAT-NL	0.205	0.597
IFG_LI	- OCS	0.541	0.106
IFGorb_LI	- NBT	0.267	0.488
IFGorb_LI	- ScreeLing	0.318	0.405
IFGorb_LI	**- CAT-NL**	**0.746**	**0.034****
IFGorb_LI	- OCS	0.079	0.840
MFG_LI	- NBT	0.480	0.160
MFG_LI	- ScreeLing	0.585	0.076*
MFG_LI	- CAT-NL	-0.026	0.947
MFG_LI	**- OCS**	**0.814**	**0.004*** **
PostTemp_LI	**- NBT**	**0.682**	**0.030****
PostTemp_LI	**- ScreeLing**	**0.854**	**0.002*** **
PostTemp_LI	- CAT-NL	0.496	0.175
PostTemp_LI	**- OCS**	**0.717**	**0.020****

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

spWM localizer

Table G3. Partial Spearman rank correlations between LIs of MD parcels during the spWM localizer and behavioral test results (covariants: age, lesion size, time since stroke).

		Spearman's rho	p
AntPar_LI	- NBT	0.129	0.706
AntPar_LI	- ScreeLing	0.044	0.898
AntPar_LI	- CAT-NL	-0.156	0.667
AntPar_LI	- OCS	-0.134	0.695
IFGop_LI	- NBT	0.158	0.642
IFGop_LI	- ScreeLing	0.082	0.812
IFGop_LI	- CAT-NL	-0.266	0.457
IFGop_LI	- OCS	0.567	0.069*
Insula_LI	- NBT	-0.202	0.551
Insula_LI	- ScreeLing	-0.549	0.080*
Insula_LI	- CAT-NL	-0.608	0.062*
Insula_LI	- OCS	0.027	0.938
MFG(md)_LI	- NBT	0.073	0.832
MFG(md)_LI	- ScreeLing	0.074	0.829
MFG(md)_LI	- CAT-NL	-0.353	0.317
MFG(md)_LI	- OCS	0.251	0.457
MFGorb_LI	- NBT	0.176	0.604
MFGorb_LI	- ScreeLing	-0.472	0.143
MFGorb_LI	**- CAT-NL**	**-0.711**	**0.021****
MFGorb_LI	- OCS	0.233	0.491
MidPar_LI	- NBT	0.066	0.847
MidPar_LI	- ScreeLing	0.069	0.841
MidPar_LI	- CAT-NL	-0.234	0.516
MidPar_LI	- OCS	-0.078	0.819
mPFC_LI	- NBT	-0.038	0.912
mPFC_LI	- ScreeLing	-0.233	0.491
mPFC_LI	- CAT-NL	0.290	0.417
mPFC_LI	- OCS	-0.222	0.513
PostPar_LI	- NBT	0.363	0.273
PostPar_LI	- ScreeLing	0.190	0.575
PostPar_LI	- CAT-NL	0.162	0.654
PostPar_LI	- OCS	-0.253	0.453
PrecG_LI	- NBT	0.080	0.816
PrecG_LI	- ScreeLing	0.010	0.978
PrecG_LI	- CAT-NL	-0.031	0.932
PrecG_LI	- OCS	0.478	0.137
SFG_LI	- NBT	0.287	0.393
SFG_LI	- ScreeLing	0.187	0.582
SFG_LI	- CAT-NL	-0.050	0.890
SFG_LI	- OCS	0.166	0.627

* = $p < 0.10$, ** = $p < 0.05$, *** = $p < 0.01$

Appendix H

Listening localizer

Table H1. Results of the Shapiro-Wilk test for the activity of the MD network and individual MD parcels in both right and left hemispheres during the listening localizer.

		W	p
gem_RH_md	aphasia	0.907	0.140
	healthy	0.916	0.224
gem_LH_md	aphasia	0.957	0.674
	healthy	0.980	0.979
RH-AntPar_mean	aphasia	0.954	0.619
	healthy	0.868	0.050*
LH-AntPar_mean	aphasia	0.986	0.995
	healthy	0.991	1.000
RH-IFGop_mean	aphasia	0.944	0.468
	healthy	**0.863**	**0.043****
LH-IFGop_mean	aphasia	0.894	0.092*
	healthy	0.933	0.374
RH-Insula_mean	aphasia	0.901	0.116
	healthy	0.952	0.623
LH-Insula_mean	aphasia	0.949	0.539
	healthy	0.956	0.698
RH-MFG(md)_mean	aphasia	0.945	0.482
	healthy	0.928	0.324
LH-MFG(md)_mean	aphasia	0.936	0.372
	healthy	**0.817**	**0.011****
RH-MFGorb_mean	**aphasia**	**0.864**	**0.035****
	healthy	0.971	0.905
LH-MFGorb_mean	aphasia	0.888	0.076*
	healthy	0.972	0.913
RH-MidPar_mean	aphasia	0.952	0.592
	healthy	0.904	0.152
LH-MidPar_mean	aphasia	0.918	0.207
	healthy	0.949	0.583
RH-mPFC_mean	aphasia	0.956	0.659
	healthy	0.961	0.762
LH-mPFC_mean	aphasia	0.920	0.223
	healthy	0.896	0.117
RH-PostPar_mean	aphasia	0.964	0.786
	healthy	0.958	0.716
LH-PostPar_mean	aphasia	0.941	0.435
	healthy	0.960	0.756
RH-PrecG_mean	aphasia	0.971	0.893
	healthy	0.944	0.512
LH-PrecG_mean	**aphasia**	**0.770**	**0.002*****
	healthy	0.935	0.398
RH-SFG_mean	aphasia	0.934	0.345
	healthy	0.915	0.216

		W	p
LH-SFG_mean	aphasia	0.930	0.306
	healthy	0.941	0.467

* = p < 0.10, ** = p < 0.05, *** = p < 0.01
Note. Significant results suggest a deviation from normality.

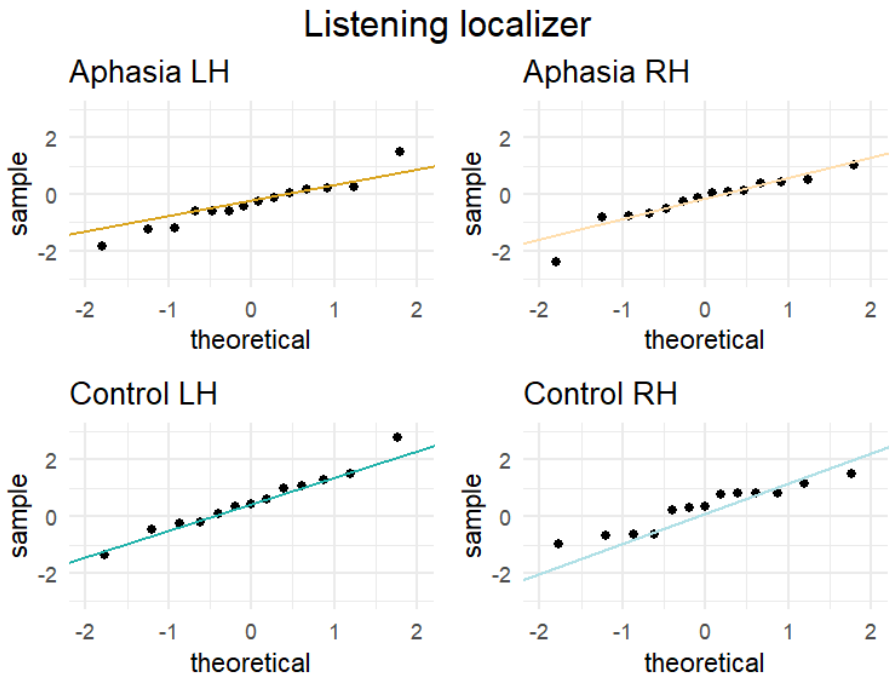

Figure H1. *Q-Q plots of the activity of the MD network in both right and left hemispheres during the listening localizer task.*

Reading localizer

Table H2. Results of the Shapiro-Wilk test for the activity of the MD network and individual MD parcels in both right and left hemispheres during the reading localizer.

		W	p
gem_RH_md	aphasia	0.922	0.265
	healthy	0.965	0.829
gem_LH_md	aphasia	0.957	0.702
	healthy	0.964	0.816
RH-AntPar_mean	aphasia	0.895	0.115
	healthy	0.941	0.537
LH-AntPar_mean	aphasia	0.923	0.274
	healthy	0.916	0.287
RH-IFGop_mean	aphasia	0.961	0.763
	healthy	0.947	0.608
LH-IFGop_mean	aphasia	0.964	0.811
	healthy	0.952	0.673
RH-Insula_mean	**aphasia**	**0.854**	**0.032****
	healthy	0.955	0.712
LH-Insula_mean	aphasia	0.940	0.461
	healthy	0.945	0.584
RH-MFG(md)_mean	aphasia	0.904	0.153
	healthy	0.952	0.671
LH-MFG(md)_mean	aphasia	0.927	0.314
	healthy	0.926	0.371
RH-MFGorb_mean	aphasia	0.984	0.995
	healthy	0.955	0.709
LH-MFGorb_mean	aphasia	0.952	0.635
	healthy	0.953	0.688
RH-MidPar_mean	aphasia	0.963	0.800
	healthy	0.959	0.757
LH-MidPar_mean	aphasia	0.911	0.191
	healthy	0.876	0.092*
RH-mPFC_mean	aphasia	0.966	0.836
	healthy	0.912	0.254
LH-mPFC_mean	aphasia	0.956	0.688
	healthy	0.890	0.138
RH-PostPar_mean	aphasia	0.947	0.551
	healthy	0.923	0.341
LH-PostPar_mean	aphasia	0.955	0.670
	healthy	**0.852**	**0.045****
RH-PrecG_mean	aphasia	0.977	0.963
	healthy	0.971	0.900
LH-PrecG_mean	aphasia	0.932	0.357
	healthy	**0.849**	**0.042****
RH-SFG_mean	aphasia	0.974	0.936
	healthy	0.914	0.272
LH-SFG_mean	aphasia	0.973	0.926
	healthy	0.932	0.432

* = $p < 0.10$, ** = $p < 0.05$, *** = $p < 0.01$

Note. Significant results suggest a deviation from normality.

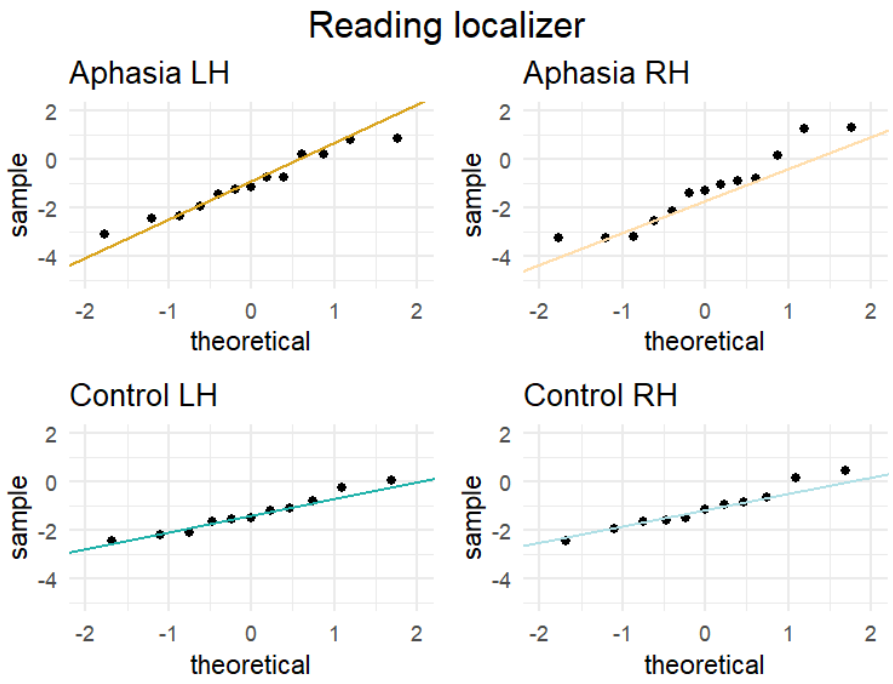

Figure H2. *Q-Q plots of the activity of the mean MD network in both right and left hemispheres during the reading localizer task.*

Appendix I

Listening localizer

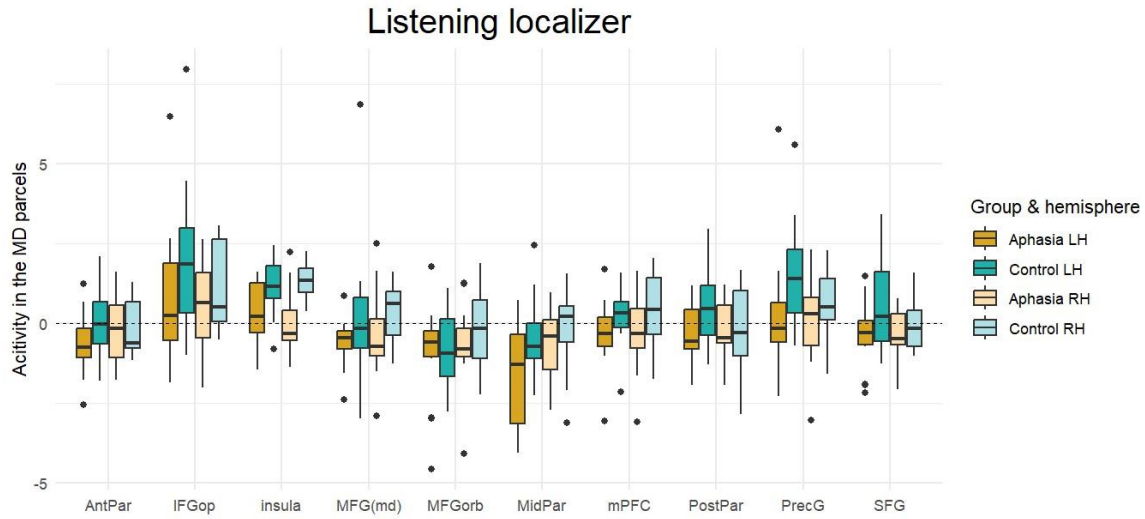

Figure I1. *Activity of the subject-specific MD parcels during the listening localizer task for both hemispheres in aphasia and control group.*

Aphasia

Table I1. Results of Wilcoxon signed-rank test for activation of subject-specific MD parcels during the listening localizer task in the aphasia group.

	V	p
RH-AntPar_mean	41.000	0.768
LH-AntPar_mean	20.000	0.982
RH-IFGop_mean	72.000	0.121
LH-IFGop_mean	73.000	0.108
RH-Insula_mean	45.000	0.687
LH-Insula_mean	69.000	0.163
RH-MFG(md)_mean	33.000	0.892
LH-MFG(md)_mean	11.000	0.997
RH-MFGorb_mean	27.000	0.948
LH-MFGorb_mean	14.000	0.995
RH-MidPar_mean	25.000	0.961
LH-MidPar_mean	8.000	0.999
RH-mPFC_mean	35.000	0.866
LH-mPFC_mean	36.000	0.852
RH-PostPar_mean	43.000	0.729
LH-PostPar_mean	32.000	0.903
RH-PrecG_mean	57.000	0.404
LH-PrecG_mean	50.000	0.572
RH-SFG_mean	35.000	0.866
LH-SFG_mean	33.000	0.892

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

Note. Wilcoxon signed-rank test; the alternative hypothesis specifies that the median is greater than 0.

Control

Table I2. Results of Wilcoxon signed-rank test for activation of subject-specific MD parcels during the listening localizer task in the control group.

	V	p
RH-AntPar_mean	39.000	0.682
LH-AntPar_mean	45.000	0.527
RH-IFGop_mean	**75.000**	**0.020****
LH-IFGop_mean	**84.000**	**0.002*****
RH-Insula_mean	**91.000**	**< .001*****
LH-Insula_mean	**87.000**	**< .001*****
RH-MFG(md)_mean	64.000	0.108
LH-MFG(md)_mean	45.000	0.527
RH-MFGorb_mean	36.000	0.751
LH-MFGorb_mean	15.000	0.987
RH-MidPar_mean	43.000	0.580
LH-MidPar_mean	28.000	0.892
RH-mPFC_mean	63.000	0.122
LH-mPFC_mean	67.000	0.073*
RH-PostPar_mean	40.000	0.658
LH-PostPar_mean	61.000	0.153
RH-PrecG_mean	**79.000**	**0.009*****
LH-PrecG_mean	**84.000**	**0.002*****
RH-SFG_mean	42.000	0.607
LH-SFG_mean	62.000	0.137

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

Note. Wilcoxon singed-rank test, the alternative hypothesis specifies that the median is greater than 0.

Reading localizer

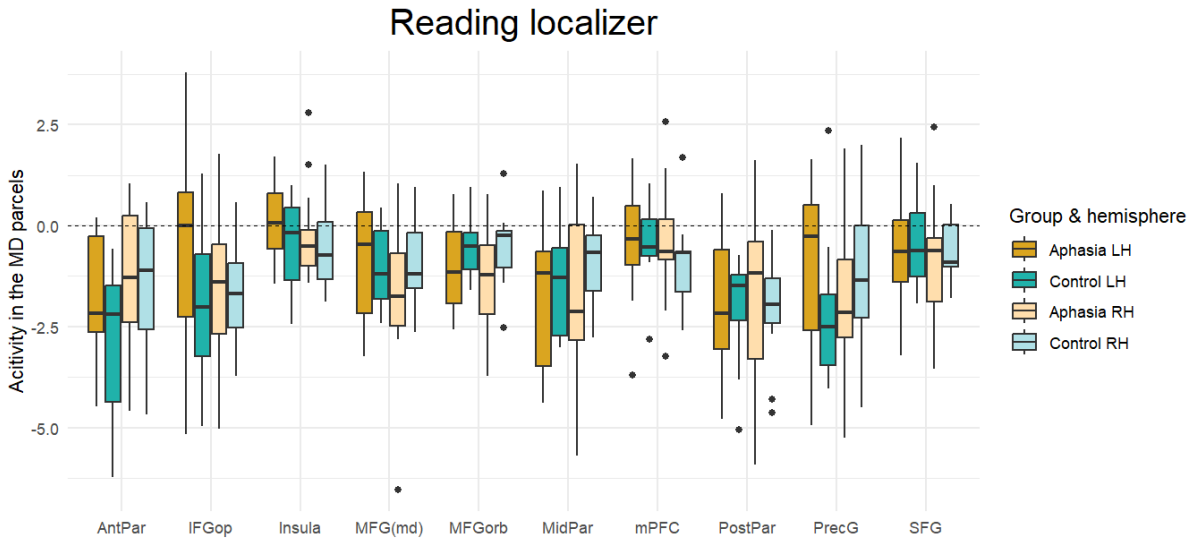

Figure I2. *Activity of the subject-specific MD parcels during the reading localizer task for both hemispheres in aphasia and control group.*

Aphasia

Table I3. Results of Wilcoxon signed-rank test for activation of subject-specific defined MD parcels during the reading localizer task in the aphasia group.

	V	p
RH-AntPar_mean	16.000	0.984
LH-AntPar_mean	2.000	1.000
RH-IFGop_mean	13.000	0.991
LH-IFGop_mean	34.000	0.793
RH-Insula_mean	30.000	0.863
LH-Insula_mean	50.000	0.393
RH-MFG(md)_mean	7.000	0.998
LH-MFG(md)_mean	23.000	0.945
RH-MFGorb_mean	8.000	0.998
LH-MFGorb_mean	11.000	0.995
RH-MidPar_mean	12.000	0.993
LH-MidPar_mean	4.000	0.999
RH-mPFC_mean	31.000	0.847
LH-mPFC_mean	34.000	0.793
RH-PostPar_mean	9.000	0.997
LH-PostPar_mean	5.000	0.999
RH-PrecG_mean	7.000	0.998
LH-PrecG_mean	26.000	0.916
RH-SFG_mean	19.000	0.971
LH-SFG_mean	24.000	0.936

* = p < 0.10, ** = p < 0.05, *** = p < 0.01

Note. Wilcoxon signed-rank test, the alternative hypothesis specifies that the median is greater than 0.

Control

Table I4. Results of Wilcoxon signed-rank test for activation of subject-specific defined MD parcels during the reading localizer task in the control group.

	V	p
RH-AntPar_mean	8.000	0.991
LH-AntPar_mean	0.000	1.000
RH-IFGop_mean	3.000	0.999
LH-IFGop_mean	5.000	0.997
RH-Insula_mean	15.000	0.949
LH-Insula_mean	18.000	0.913
RH-MFG(md)_mean	9.000	0.988
LH-MFG(md)_mean	7.000	0.993
RH-MFGorb_mean	11.000	0.979
LH-MFGorb_mean	12.000	0.973
RH-MidPar_mean	9.000	0.988
LH-MidPar_mean	7.000	0.993
RH-mPFC_mean	8.000	0.991
LH-mPFC_mean	21.000	0.861
RH-PostPar_mean	0.000	1.000
LH-PostPar_mean	0.000	1.000
RH-PrecG_mean	11.000	0.979
LH-PrecG_mean	4.000	0.998
RH-SFG_mean	15.000	0.949
LH-SFG_mean	18.000	0.913

* = $p < 0.10$, ** = $p < 0.05$, *** = $p < 0.01$

Note. Wilcoxon signed-rank test, the alternative hypothesis specifies that the median is greater than 0.

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