Functional MRI of Language Processing and Recovery

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Para mi gran amigo Huaso,
Alejandro Barahona (1982-2009).

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Chapter 1

General Introduction

In recent years, insight into the cerebral representation of language processing has taken an enormous leap forward thanks to the increasing availability of advanced neuroimaging techniques. Functional Magnetic Resonance Imaging (fMRI) is currently one of the most preferred neuroimaging techniques for studying language processing. It has expanded the classical language models described by Broca, Wernicke and Lichtheim formulated in the 19th century[1], that were based on lesion studies and are still used for both patient care and clinical research.

Functional anatomical models of language

In the last two decades, a growing interest in cognitive neuroscience knowledge combined with the availability of fMRI has produced a profusion of data on many aspects of language processing. These data have led to a revision of classical language models, by demonstrating that in addition to the language functions being lateralized towards the left hemisphere[2], the right hemisphere[3] and the cerebellum[4] also play a role in certain language processes. Where language processing is increasingly unraveled by means of complex linguistics and psycholinguistic language tasks, from a clinical point of view, fMRI research of language can make an important contribution to the investigation of language disorders. Understanding the normal language organization in the brain, however, is mandatory for the interpretation of activation changes due to reorganizational mechanisms in patients with brain damage[5].

Presurgical evaluation of language dominance in brain tumor patients

In the presence of a brain tumor, the hemispheric dominance needs to be established as accurately as possible to reduce the risk of postoperative language deficits. Language localization in the brain varies among individuals, and specifically varies with handedness[6]. With specific language tasks, language activation can be explored not only in classical language areas localized in supratentorial regions of the brain, but also in the cerebellum. The cerebellar language activation is generally undisturbed by the tumor localized in or near the presumed classical language areas, thus it may be of interest as an additional diagnostic feature to determine language dominance in brain tumor patients.

Language recovery in patients with aphasia caused by stroke

Behavioral studies have widely assessed language disturbances in stroke patients with aphasia, characterizing their initial language profile and recovery process. Functional MRI offers a unique possibility to study the process of recovery on a neurophysiological level, by assessing the plasticity of the nervous system during the recovery process. Functional MRI studies of language recovery in aphasic patients can provide further insights into the way language activation changes during spontaneous recovery or in response to specific language therapy.

Aims and outline of this thesis

In this thesis I used fMRI to evaluate the neural substrates of language processing in healthy participants and in stroke patients with a specific focus on aphasia recovery.

Firstly, I describe the enormous leap in understanding of language processing that fMRI as a technique has made possible in Chapter 2. In this chapter, I discuss several considerations that need to be taken into account for implementing this technique for language research in patient care and clinical research. Additionally, I summarize the emerging models of language processing derived from functional neuroimaging studies.

Determining language dominance with fMRI is challenging in brain tumor patients, particularly in cases of suspected atypical language representation. Supratentorial activation patterns must be interpreted with great care when the tumor is in or near the presumed language areas, where tumor tissue or mass effect can lead to false negative fMRI results. The cerebellar language activation is generally undisturbed by the tumor localized in or near the presumed classical language areas. In Chapter 3, I assess cerebro-cerebellar language fMRI lateralization in healthy participants and in brain tumor patients with a focus on atypical language representation.

In Chapters 4 and 5 I investigate the normal neural mechanism of language functions that are commonly disrupted in aphasic patients, with a focus on aphasia recovery. In Chapter 4, I explore the neural mechanism underlying Melodic Intonation Therapy (MIT). This therapy uses the melodic elements of speech to improve language production in severe nonfluent aphasia. A crucial element of MIT is the melodically intoned auditory input: the patient listens to the therapist singing a target utterance. Such input of melodically intoned language is thought to facilitate production to a larger extent than that of spoken language. Using a sparse sampling fMRI sequence, I examine the differential auditory processing of spoken and melodically intoned language.

Phonological and semantic processing are two basic linguistic functions with direct implications for word finding in spoken language. Anomia is a word finding deficit frequently observed in aphasic patients. Previous fMRI studies of phonological and semantic processing used language paradigms that were mainly focused on language production, and mostly included young participants. In Chapter 5, I examine the neural substrate of phonological and semantic auditory, i.e. receptive, processing in healthy older adults, which is more applicable to patients with a severe aphasia. I specifically focus on the functional specialization within the left inferior frontal gyrus, given its proposed important role for compensation of language function in aphasia recovery.

Neuroimaging studies in aphasia research have primarily focused on whether stroke aphasic patients compensate for their functional loss by increasing the level of language-related brain activation in the left or the right hemisphere. A widely held interpretation of left hemisphere activation after stroke is that it reflects a better language recovery. According to this view, a persistent shift of language function to right hemisphere impedes post-stroke aphasia recovery. In Chapter 6 I explore the relationship between language lateralization and spontaneous language recovery, both at the level of language production and language comprehension, in chronic aphasia patients. In Chapter 7 we investigated whether intensive MIT produces a shift in language lateralization in sub-acute and chronic patients with aphasia

Finally, I will outline the main findings from these studies, together with the clinical implications and suggestions for future research, in Chapter 8, followed by a summary of the results of this thesis in Chapter 9.

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Chapter 2

Functional MRI of Language Processing: Basic Principles and Insights

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Introduction

In recent years, insight into the cerebral representation of language processing has taken an enormous leap forward thanks to the increasing availability of functional magnetic resonance imaging (fMRI) (Figure 1, 2). fMRI is now one of the most commonly used functional neuroimaging techniques for studying language processing and is increasingly being used for both patient care and clinical research. In the first section we provide a brief introduction into the basics of fMRI and task design. We then discuss current applications of fMRI in both clinical and research practice. The third section focuses on fMRI paradigms that are relevant for clinical applications. In the fourth section we will give an overview of the neuroanatomical models that have emerged from neuroimaging research so far. Finally, we look at future perspectives of new developments in fMRI techniques and analyses.

Figure 1. Patient being prepared for fMRI-tasks in the MRI scanner.

1. Basics of fMRI and task design

Functional neuroimaging methods

Functional MRI is currently the most frequently used neuroimaging technique in cognitive neuroscience. Since its emergence more than twenty years ago, its field has grown in usage, sophistication, range of applications, and impact.[1] Other commonly used neuroimaging techniques are Positron Emission Tomography (PET), Electroencephalography (EEG) and Magnetoencephalography (MEG). Although fMRI and PET (specifically H_2OPET) are different techniques, measuring changes in deoxyhaemoglobin and blood flow respectively, both measure neural activity indirectly by detecting the specific local changes in blood composition and blood flow that accompany such neural activity. Lately, fMRI has come to be preferred over PET, its closest counterpart, since it does not require the injection of a contrast agent and has no associated radiation exposure. These factors render it entirely non-invasive and widely applicable in studies involving

both patients and healthy volunteers. In addition, high quality anatomical images can be obtained together with functional imaging at relatively high temporal resolution, (i.e. seconds). This is far superior to that of PET, which has a temporal resolution in the range of 60 s and a spatial resolution of about 1.5 cm. fMR images are obtained using an MRI scanner with typical field strengths from 1.5 up to 7 Tesla. While EEG has a much higher temporal resolution (i.e. milliseconds) than fMRI, its spatial resolution is much lower. MEG is an imaging technique carried out in much the same way as EEG. The advantage of MEG over EEG is that signal localization is possible to a certain extent. Nevertheless, MEG is a costly technique and its ability to accurately detect events in deeper brain structures is until now limited. Table 1 summarizes for each technique the advantages and disadvantages mentioned above.

In light of the limitations and advantages of these neuroimaging techniques, their application for studying language depends on the aspect of language processing that is of interest in a particular study. Combinations of these techniques, such as fMRI with EEG, exploit their relative advantages and enable us to evaluate simultaneously when and where certain linguistic processes occur in the brain.

Table 1: Advantages and disadvantages of functional neuroimaging techniques

Technique	Advantages	Disadvantages
PET	Less sensitive to motion artifacts	Low spatial resolution Low temporal resolution Invasive Expensive
EEG	Low cost Excellent temporal resolution	Poor spatial resolution
MEG	High temporal resolution and good spatial resolution	Very expensive Limited resolution for deep structures
fMRI	Good spatial resolution Non-invasive Widely available	Relatively low temporal resolution

Functional MRI

One of the major requirements for successful imaging with fMRI is the need for participants to lie absolutely still in the scanner, as movement may induce unpredictable changes in the signal-to-noise ratio (SNR) and the magnetic field, leading to reduced image quality and reliability. Although participants need to lie still in the scanner, this does not restrict the possibility of performing a variety of tasks. Auditory stimuli can be delivered via MRI-compatible headphones, which also serve to attenuate the loud background scanner noise. Visual stimuli can be presented with MRI-compatible goggles, or projected on a screen placed inside or outside the MRI scanner, which are then visualized by means of a mirror placed on the head coil.

A further critical issue in fMRI is to ensure that the participant is actually performing the given task. This is of particular concern in clinical studies when patients' cooperation may be less certain.[2] Task performance can be monitored by using MRI-compatible devices, such as response buttons, and have the participant give his answer in multiple choice tasks. Both the type of response and the reaction time can thus be monitored.

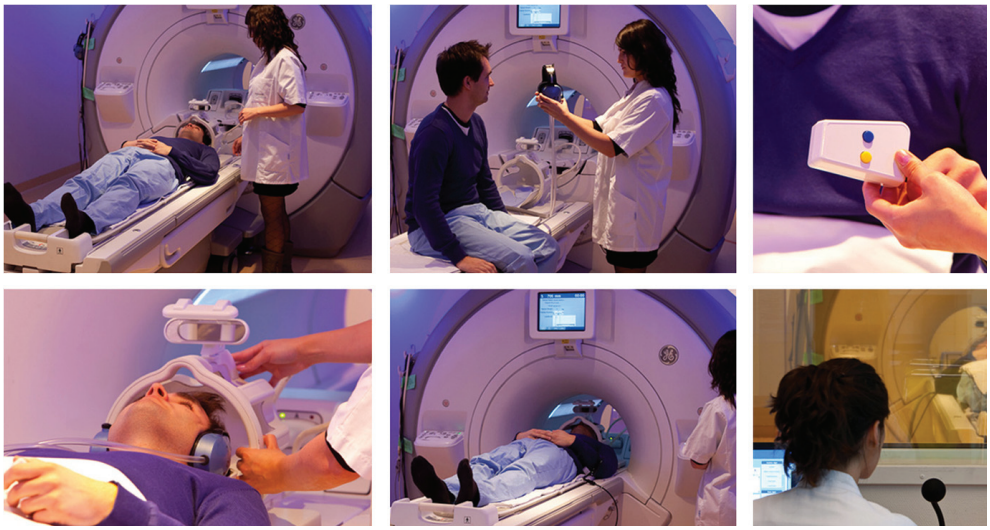

Figure 2. Functional MRI session

To monitor task performance more directly, some language tasks require verbal responses from participants. Although this seems the most obvious way of monitoring task performance, head motion almost invariably occurs with overt speech. Also, the movement of air through the oral and nasal cavities induces unpredictable susceptibility artifacts rendering the fMRI signal less reliable. This issue will be further addressed later in this section.

It is important to keep in mind that fMRI is not a direct measure of neuronal activation, but instead measures the consequences of metabolic processes associated with such activation. Blood oxygenation level dependent (BOLD) fMRI is the most commonly used functional neuroimaging technique. BOLD fMRI takes advantage of the tight link between local neuronal activity and blood flow (neurovascular coupling). [3,4] When neuronal activity increases locally, local blood flow also increases, leading to an increase in oxygenated blood that is disproportionate to the increased requirement for oxygen for neuronal activity. The resulting relative decrease in paramagnetic deoxygenated haemoglobin leads to an increase in the MR signal in those areas of the brain that are active. [2,5] The BOLD response follows a time course represented by the haemodynamic response function (HRF) proposed by Friston in 1995[6]. This BOLD response reaches a peak at an average of 6 seconds after the onset of neuronal activation. [6,7]

Both PET and fMRI visualize neuronal activity by using tasks or so-called paradigms, which typically consist of active and control conditions. This means that the pattern of brain activation observed in a study investigating language processes depends not only on the cognitive processes elicited by the active or experimental conditions (i.e. the language task), but also on the processes elicited (or not elicited) by the baseline conditions (also termed control or rest conditions). This technique is known as the subtraction-based method. One of the first functional imaging studies of language using PET was conducted in 1988 by Petersen [8], whose study explored the application of this subtraction-based method to language tasks by developing baseline conditions that engaged all but the linguistic processes. Such linguistic processes could thus be isolated from baseline conditions.

Later, Price [9] highlighted two critical limitations of the subtraction-based method with respect to language processing that should be taken into account when developing an fMRI paradigm: the first is that the language system is very responsive to seeing and hearing word-like stimuli. For example, it is hard to prevent word processing even when participants are not instructed to recognize or name a word or word-like stimulus during baseline conditions. This means that the selection of baseline conditions for language fMRI paradigms is challenging – it is difficult to find two conditions that differ only in the linguistic process of interest. The second limitation is that even when a particular process is thought to be engaged to the same degree during both experimental and baseline conditions, activation may vary depending on the demands of the conditions. As a consequence, non-linguistic regions, such as those involved in executive function, may still be engaged. For the design and interpretation of functional imaging studies we therefore need to carefully consider how linguistic processes as well executive and, potentially, other cognitive processes interact with sensory input and motor output.

Thus, based on the difference in MRI signal between two cognitive states, observed activation patterns are relative and strongly depend on both the experimental and baseline

conditions within a given task.[10] Even when the experimental and control conditions appear well matched based on theoretical psychological principles, subtle differences in task difficulty, response styles and strategies can easily affect the magnitude, spatial extent, and even the location of the brain regions activated during imaging experiments. [11] There have been several suggestions in the literature to account for these issues, such as designing the study such that experimental tasks are compared to simple baseline control conditions [6]; a parametric design [12] in which the condition of interest varies its level or load; and selective attention designs [13], in which subjects are shown identical or nearly identical stimuli but they selectively need to focus on one or another feature within the stimulus set.

Paradigm Design: General Principles

Paradigms can broadly be divided between those that are blocked and those that are event-related. [14] Blocked paradigms consist of alternating blocks of an active or control condition, each commonly lasting 20 to 40 seconds. A series of trial events of 1 condition is presented within each block. The signal acquired during blocks of the same condition is then compared with the other block(s) constituting a different condition. The advantage of blocked paradigms is that they are statistically robust, because a lot of signal is acquired for each condition. The disadvantage is that they are restrained, leaving not much room for unexpected or short stimuli, and subjects may develop cognitive strategies for responding to items within a block. Still, for patient-oriented language mapping or research, this type of design is generally preferred.[15] More complex cognitive tasks however may not be manageable by using a block design. An alternative model, unique for fMRI as opposed to PET experiments, is the single-trial or event-related (ER) design.[16] Within this design, it is possible to present short (pseudo) random stimuli, each representing a specific condition, in rapid succession. An event-related design therefore is very flexible, offering the possibility to present unexpected stimuli as well as many different conditions. It is however statistically less robust because the signal that is acquired per condition is generally low.

Another broad distinction between task designs can be made based on the modality of stimulus presentation. With visual stimulus presentation the advantage is that stimuli are not degraded by the loud scanner background noise, as is the case with auditorily presented stimuli. Additionally, hearing deficits, which are commonly present in the elderly population, are not an issue, while visual acuity deficits may be easily overcome with MR compatible glasses. When visual stimuli are presented, however, additional levels of processing are introduced that we may not necessarily be interested in and which may present an unnecessary additional challenge for patients. Therefore, selection of stimulus modality requires careful consideration when designing an fMRI task, especially for language paradigms. As an example, when phonologic processing is studied with

visually presented stimuli, grapheme to phoneme conversion is required in addition to phonological processing.

We further need to decide whether the task is performed covertly (silent) or overtly (spoken), and, relatedly, how in-scanner task performance is monitored. As said before, it is highly recommended to obtain in-scanner performance data not only to assure that the task is performed correctly, but also to be able to account for differences in task performance in post hoc analyses. Especially when designing studies in which patients undergo more than one fMRI session, task performance is essential to interpret differences both on a neurophysiological and a behavioral level across sessions. With covert task performance, responses can only be recorded indirectly, for instance by means of response buttons in judgment-oriented or multiple choice paradigms. Care needs to be taken that the additional activity unrelated to language processing (e.g., finger movement by pressing the button) is balanced out in the control condition. Furthermore, concurrent motor deficits which may be present after stroke or with a brain tumor need also be considered. These may for example be overcome by having the task consistently be performed with the non-dominant (and presumably non-affected) hand. Monitoring overt responses is relatively easy as overt responses can be registered and preferably recorded. Several disadvantages however render it less optimal than covert task performance. As mentioned, these are predominantly due to the movement of air in the paranasal sinuses and nasal and oral cavity during speech, leading to unpredictable susceptibility and distortion artefacts, and head motion. Head motion artefacts are not easily compensated for, because they are inherently response related and thus may severely reduce statistical power.[17] Excessive head motion may be reduced with training, but is rarely completely avoided. By using sparse sampling acquisition techniques (see below) or a hemodynamic delay design [18] overt responses can be given during the silent gaps interleaving the data acquisition. The slow paced design that allows sparse imaging (for example 4 s overt response and 2 s image acquisition) has been proposed to be appropriate for application to an older and impaired clinical population.[19] Such techniques however come at the cost of lower sensitivity and longer acquisition times and are therefore best reserved for those instances that overt responses are considered an absolute requirement.

Data Acquisition: Continuous Versus Sparse Sampling Acquisition

When using auditory stimuli, fMRI is particularly challenging due to an interaction between the experimental auditory stimuli and the extremely loud background scanner noise.[20-23] As well as being very loud (up to 110dB), the MRI scanner sound is an amplitude-modulated periodic sound with a complex spectrum that very likely interacts with the experimentally delivered stimuli. [23,24] Subjects may also be engaged in processes

different from auditory perception, because they have to extract the stimulus from the background MRI generated noise and will supposedly need to recruit more areas in the brain than strictly necessary for performing the task. This issue is most prominent when auditory comprehension and specific phonological processes are studied. With standard MRI compatible headphones, some attenuation (up to 30dB) of the background scanner noise can be achieved. Silent fMRI techniques, such as the BURST sequence, are very effective in reducing acoustic noise [25], but most tend to be too slow for fMRI studies.[26] Longer noise-free periods during acquisition—known as sparse temporal sampling—are also useful in reducing the amount of scanner-generated noise. Such sparse sampling techniques take advantage of the fact that the hemodynamic response to the increase in neuronal activity is delayed. It is therefore possible to acquire data at a delay after stimulus presentation, while the auditorily presented stimuli are not degraded by the scanner noise. They have been shown to improve fMRI activation of the auditory and language systems, but the amount of information acquired is usually decreased and acquisition times are long.[22, 24,27,28] A compromise can be found in the clustered volume acquisition technique. [29-31] This method has the advantage of a global increase in efficiency, while retaining sufficient silent gaps during which the subject can clearly perceive the auditory stimulus. We previously used this technique successfully in assessing auditory language processing, allowing for detection of fMRI activation without the need for very lengthy acquisition times.[32]

Acquisition time with clustered volume acquisition is still at least doubled compared with continuous scanning. This introduces the risk of motion artefacts, patient motivational and attentional issues, and a compromise in the number of language components that can be studied within a scanning session of a given duration. Additionally, and maybe even more importantly, sparse sampling techniques heavily rely on the hemodynamic delay after neuronal activity, with data being acquired at the assumed peak of the BOLD response. Assumptions about the HRF and related BOLD responses may not be valid in patients who suffered a stroke, and this may severely reduce BOLD sensitivity in sparse sampling acquisition techniques.

Task Difficulty

It is crucial that the task difficulty is adapted to meet the patient's ability to perform the task, especially when studying patients with a neurological and/or cognitive deficit. When a task is too difficult this will lead to underperformance or dropout, resulting in decreased or absent activation. Brain activity will, however, also be low if no challenge is posed. Generally, we aim for a task performance level between 70% and 90%, which is established in pilot studies. In a relatively homogeneous patient population, a task with a fixed level of difficulty that all patients are expected to meet can be used. If patients are not too badly affected, one can use the same task both for patients and healthy

controls. To accommodate heterogeneity in the severity of disability, a task with several levels of difficulty can be applied in a so-called parametric design. Alternatively, the patient's performance prior to scanning can be tested and the task difficulty adjusted on an individual basis. This introduces a certain amount of heterogeneity with respect to the stimulus paradigms, but overall task performance is expected to be the same. It is important to train beforehand to ensure adequate task performance, but over-learning should be avoided.

In summary, functional neuroimaging provides a means to reveal the neuronal systems underlying language processing, with fMRI having several advantages over other neuroimaging techniques. Several important decisions must be made when designing an fMRI experiment and building an fMRI paradigm, especially when investigating language processing in patients, namely task design, stimulus modality and response mode (monitoring). A key issue in the design of an fMRI task is the control condition. Due to the subtraction method used in fMRI, the activation observed with fMRI is not the result of the active condition per se, but of the difference between at least two conditions.

Continuous data acquisition is generally preferred, as it allows sufficient data to be acquired in reasonable time, thereby increasing statistical power and decreasing the effects of motion artefacts. Silent gap acquisition may be used for imaging specific language processing components when it is important that auditory stimuli are not degraded by imager noise or when overt responses are required. Selection of data acquisition, stimulus modality, and active and baseline condition is highly dependent on the specific type of processing that is intended to be studied.

2. Functional MRI of language processing: application in clinical care and clinical research

Functional MRI has been shown to be a valuable technique for studying the cerebral representation of language processing and is increasingly being used for both clinical care and clinical research. In clinical care, fMRI of language is primarily used in the preoperative evaluation of hemispheric dominance. In clinical research, functional MRI is used to study language disorders due to neurologic disease and is generally aimed at language function recovery. Although fMRI cannot replace intraoperative electrocortical stimulation (ECS) in patients undergoing neurosurgery, it is a complementary technique useful for guiding surgical planning and mapping, thereby reducing the extent and duration of craniotomy.

fMRI in Clinical Practice

Functional MRI is now frequently used as part of the routine preoperative work-up of patients to establish the relationship of the lesion to eloquent brain regions, such as language representation. Identifying language areas purely on an anatomical basis is inexact due to considerable inter-individual anatomic and functional variability. Furthermore, in the presence of a lesion, functional areas may be displaced due to the lesion's mass effect, or function may have shifted to other areas in the brain due to plasticity. [33] Importantly, hemispheric dominance for language needs to be established preoperatively in both brain tumor patients and patients with temporal lobe epilepsy. Pre-operative fMRI of language provides information on the feasibility of surgery and allows adequate assessment of the risk of postoperative neurologic deficits.

Validity of fMRI for Preoperative Language Evaluation

In brain tumor patients, the aim of neurosurgery is to remove as much pathologic tissue as possible, which increases survival time, while at the same time minimizing the risk of postoperative neurologic deficits.[34] For optimal results, we need to establish the relationship between the tumor margins and the functionally important brain areas as accurately as possible.[35] The correlation between functional areas as established with functional MRI and intra- operative ECS has been studied for both motor and language function. A high correlation has been shown for the primary motor cortex, but results from language representation studies are conflicting and disappointing. The sensitivity of functional MRI in identifying critical language areas as established with ECS varied from 100% to as low as 22%.[33-38] Specificity was just as variable, ranging from 0% up to 100%. These results depend in part on the type and the number of tasks that were used, as well as on the statistical thresholds applied to the acquired images. [36.37] Because the aim of surgery is to remove as much pathological tissue as possible while sparing eloquent areas, both sensitivity and specificity of functional MRI need to be high. Unfortunately, this is not the case. An additional limitation of functional MRI is that it does not allow the distinction between regions that are essential for language processing, and modulatory brain regions, which may be resected without permanent deficit. Thus, functional MRI is not good enough to replace intraoperative ECS but is a complementary technique useful for guiding surgical planning and mapping, thereby reducing the duration and extent of craniotomy.

Despite the limitation of functional MRI for the localization of language representation, its validity in establishing hemispheric language dominance has been shown in a large number of patients and studies, with a greater than 90% agreement between the invasive Wada test and fMRI. [33, 35, 38-42] Consequently, functional MRI of language is currently being used as a substitute for the Wada test, because it is noninvasive and also gives information on the spatial relationship between language areas and the lesion. Care

still needs to be taken with large and/or high grade tumors in or near the presumed language areas, since these may interfere with the cerebrovascular haemodynamic autoregulation that the BOLD response in functional MRI depends on.[43, 44]

Clinical case: Brain tumor

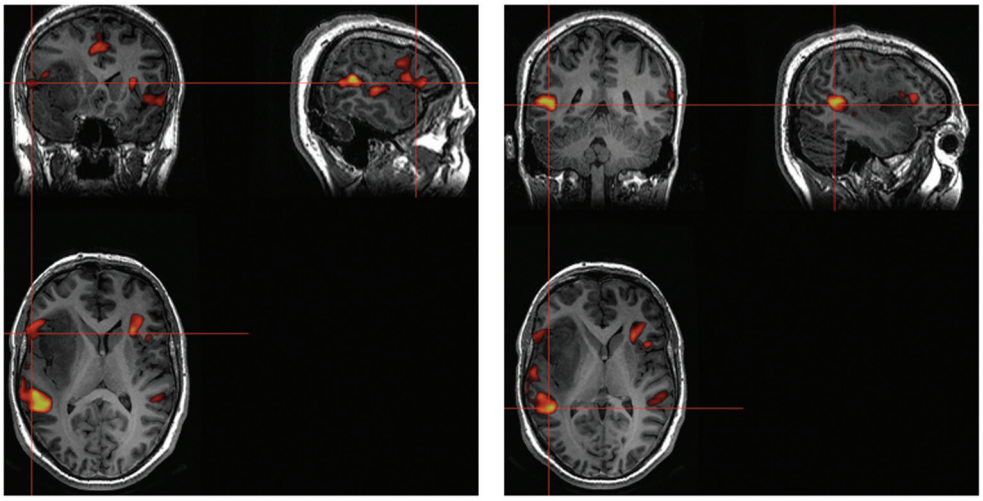

Figure 3. Left-handed patient with a brain tumor (right insula, frontal and temporal lobe).

Functional MRI in Clinical Research

Functional MRI can be used to study language processing in patients with aphasia due to stroke or other neurologic disorders, such as primary progressive aphasia, an unusual form of dementia. [45] The technique may also be used to study language function recovery and the effects of therapy (such as after aphasic stroke).

Recovery of language function

The recovery of language function after aphasic stroke is a dynamic process, with potentially different roles for the right and the left hemisphere at various stages of recovery.[46] The right hemisphere is thought to play an important role in language recovery, especially in the early stages, when homologous language areas in the right hemisphere take over the role of the damaged language areas in the left hemisphere.[47] Persistent right hemisphere involvement has however also been interpreted as a reflection of a maladaptive process, related to poor recovery of language function [48,49], suggesting that good recovery is only achieved when the language function is eventually taken back by the perilesional regions in the left hemisphere during the later stages of recovery.[46] The exact timing of such processes is as yet unknown. It is however postulated that lan-

guage therapies that match and accelerate such spontaneously occurring neuroplastic changes are optimally effective in language recovery.

Behavioral studies are used to assess the effect of timing and content of language therapy on recovery of language function clinically. Functional MRI offers the unique possibility to study the process of recovery on a neurophysiological level, assessing the plasticity of the nervous system in the recovery process. Studies examining the neural bases of either spontaneous or treatment-induced recovery are unfortunately still limited in number, poorly controlled and non-uniform. [47,50] To evaluate treatment effect it is necessary to use longitudinal designs with repeated assessments in the same individuals (e.g., before and after treatment). [51] It is also suggested that differences in reported activation changes may results from re-test effects due repeated task exposure, scanner related changes, in addition to or even instead of plasticity related changes. Therefore the replication and reliability of activation due to therapy effects is an issue of concern. Rapp et al[52], suggest that one way to overcome this issue is to conduct repeated baseline scans to ascertain any variability in activation.[53, 54] Another suggestion is to include tasks that reflect both impaired and unimpaired functions or items that participants can and cannot respond to correctly.[55,56] For further suggestions on how best to compare activation changes between sessions, see et al[51].Another issue that must be taken into account when conducting aphasia therapy studies is that selected language paradigms should measure the language processes that are targeted by therapy.

Additionally, the activation related to the selected language paradigm needs to be carefully assessed in healthy participants that are age and gender matched to the patient population, to obtain a reference of normal language processing.

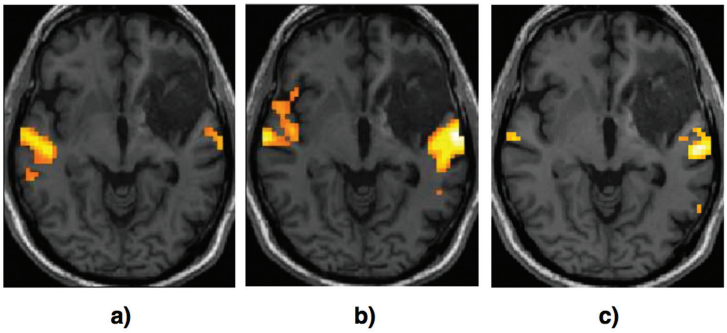

Figure 4: Language activation during a rhyme decision task in a chronic aphasia patient who followed intensive phonological and semantic treatment. a) before therapy, b) after therapy, c) 3 months after therapy.

Clinical case: Primary Progressive Aphasia

Figure 5 shows the areas of activation for semantic and phonologic language processing tasks in a right-handed 59-year-old patient with primary progressive aphasia. (a) T1-weighted MR images show cerebral atrophy, including atrophy of the temporal lobes. (b–c) T1-weighted MR images show superimposed activation in the frontal and

posterior parietotemporal language areas for both the semantic (b) and phonologic (c) tasks.

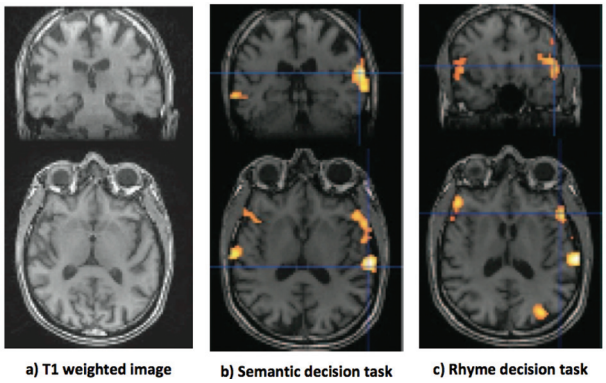

Figure 5: Language activation during phonological and semantic tasks in a patient with primary progressive aphasia

Considerations for imaging in clinical care and research

Neurovascular Changes

One of the major issues with functional MRI in stroke and tumor patients is the fact that BOLD functional MRI relies on the tight link between hemodynamic changes and neuronal activity. Neuronal activity is only measured indirectly: it is assumed to underlie the measured changes in blood oxygenation, which in turn are assumed to be the result of hemodynamic changes in response to neuronal activity. These assumptions may be justified in healthy, young volunteers, but they may be utterly invalid in the elderly patient population with neurovascular disease, such as the majority of stroke patients, or in the presence of a brain tumor.

In stroke patients the first problem arises from the assumption that the hemodynamic response after an increase in neuronal activity peaks at approximately 6 seconds. Typically, the stimulus paradigm is convolved with the HRF prior to general linear model analysis to take the assumed timing of the hemodynamic response into account. Studies of stroke patients, however, have shown that the HRF may actually peak much later, up to 20 seconds after stimulus presentation. [57,58] These findings are, at least in part, thought to be due to underlying age- and disease-related changes in the vascular bed, such as increased vascular tortuosity resulting in differences in the spatial organization of intracerebral arterioles, capillaries, and venules.[59] When a blocked stimulus paradigm is used this is not too problematic, because a blocked design is not very sensitive to temporal discrepancies between the modeled stimulus paradigm and measured signal changes. It becomes a real issue though when an event-related design is used, because this heavily relies on the exact modeling of stimulus and response timing convolved with the HRF.

The second problem is that, in the very early stages (first week) after stroke, the response of the local vasculature to ischemia is to dilate maximally, disrupting the normal neurovascular coupling response and resulting in a reduced or absent BOLD signal.[58,60] It is therefore, as well as for practical reasons, recommended to not perform BOLD functional MRI in the first week after stroke.

The third issue is that the hemodynamic compromise may exist beyond local changes in neurovascular response. Cerebrovascular stenotic or occlusive disease is a common cause of ischemic stroke, and may result in a hemodynamic compromise more extensive than in the ischemic brain tissue alone. Resulting compensatory hemodynamic changes consist of maximal vasodilatation in the affected brain region(s), which may lead to an inability of the local vasculature to respond to neuronal activity and consequently to reduced or absent BOLD sensitivity and false negative results. [57,59,61] The sensitivity to BOLD may roughly be assessed with breath hold functional MRI [62,63], while perfusion studies combined with a physiologic or pharmacologic challenge provide direct measures of the hemodynamic reserve.[64]

In brain tumor patients it has been shown that at the edge of the tumor, astrocytes and macrophages release nitric oxide. This increases the local perfusion, and may subsequently lead to a decrease of BOLD signal. [43] Additionally, high grade gliomas induce the proliferation of abnormal vessels in the adjacent brain parenchyma, that have been shown to lose auto-regulation and a reduced response to physiological stimuli.[65] The neurovascular coupling may be reduced both in high and in low grade gliomas by their infiltrative nature compromising the neuronal contacts with the capillary beds and astrocytes.[43] A final concern is that the mass effect of the tumor may have unpredictable effects on the BOLD signal. Due to compression of the venules and larger veins the outflow of deoxygenated blood from the area of activation may be accelerated, thereby reducing the BOLD signal.[65] Compression of the draining venules may on the other hand inhibit the outflow and cause pooling of deoxygenated blood in the tumor region, also reducing the BOLD signal.[66]

Reproducibility and validity

Validation studies of language functional MRI in brain tumor patients are relatively scarce, are generally performed in small patient populations, and suffer from differences in the validation methods used among the studies, disparities of brain lesions, and on the variety of the language tasks performed preoperatively and during intraoperative electrocortical mapping. When assessing changes in language activation as a function of spontaneous recovery and/or language therapy in stroke patients, the effect size needs to be greater than the intra-individual variability, i.e. variability between two scans. Fernandez et al[38] showed high intra-individual reproducibility in epilepsy

patients, across the hemispheres, resulting in highly reliable laterality indices, but not within each of the hemispheres, with significant variability in the location of particularly the temporo-parietal regions. Chen and Small[67] found that language activation was less reliable in stroke patients than in healthy controls, further affirming the need to assess and account for intra-individual variation of activation measured with functional MRI.

Functional MRI Data Analysis

Changes measured with functional MRI are small, and, especially when subtle effects are studied, may not even be detectable on an individual level. Therefore, typically, data are combined in group analyses to increase statistical power and to make inferences on a population level. In stroke patients conventional group analyses are problematic due to the large heterogeneity in lesion size, shape, and location. For instance, the perilesional region will vary from one patient to the other and will thus need to be defined on an individual level. The presence of a lesion also hinders the normalization to a standard brain template. Unified segmentation methods as well as masking the lesion prior to normalization may be required to improve inter-individual alignment of analogous brain areas and to avoid underestimation of the lesion.[68-70]

Instead of group analyses, the analysis of functional MRI data of stroke patients may thus often rely on a careful study of individuals.[47] Region of interest analyses, in which the known language areas and their homologues in the right hemisphere are identified in the individual patient, can be useful for group analyses. To this purpose, it is advisable to also image a neurologically intact, age and gender matched control group to identify task-specific language networks. The perilesional areas are identified on an individual patient level as additional regions of interest. On the basis of hypothesized underlying neurophysiologic processes of the aphasia therapy under study, further regions of interest may be considered. It is important to collect behavioral (performance) data and use these in the analyses to account for heterogeneity in severity of aphasia, degree of recovery, and task performance.

There are more advanced analyses techniques available than the commonly used model-based analyses, which include model-free and functional connectivity analyses.[71] In model-free analyses no assumptions need to be made regarding the underlying stimulus paradigm and timing of the HRF because they are data rather than model driven. This renders them an interesting alternative for the analysis of stroke patients with unpredictable HRF. With functional connectivity analyses brain regions are identified that are simultaneously active while spatially remote, thus implying a functional connection between these regions, although a causal relationship cannot be established.[71-75] Functional connectivity analyses allow for a more integral assessment of the language network, as shown in recent fMRI and PET studies. [76,77] In the latter study, for instance,

aphasic patients demonstrated selective disruption of the functional connection between the left and right anterolateral superior temporal cortices, the degree of which correlated negatively with the degree of recovery.

3. Common fMRI tasks to investigate language comprehension and production

A great number of stimulus paradigms have been developed to assess language with fMRI, some of them using relatively complex tasks to investigate specific types of processing. To discuss all of them would be well beyond the scope of this chapter. Although it can be expected that normal language processing is increasingly unraveled by complex psycholinguistic paradigms, from a clinical point of view it makes more sense to approach fMRI research of language from the perspective of specific language deficits observed in patients, characterized in terms of linguistically relevant levels: semantics, phonology and syntax.[78] Here we will focus on paradigms probing these levels of language processing (emerged from neuropsychological and psycholinguistic research) and discuss those that are widely used in clinically orientated studies of language.

We will first review common fMRI tasks evaluating general modalities of language (speech comprehension and production): the passive listening and the naming tasks. Then we will focus on receptive and productive fMRI tasks evaluating the specific linguistic levels of semantic, phonological and syntactic processing. Finally, we will pay specific attention to the role of the inferior frontal gyrus (IFG) in both receptive and productive linguistic tasks as is being put forward in the current neuroimaging literature.

3.1 Auditory speech comprehension

Speech is an acoustically complex stimulus in which many aspects of language are engaged. Speech processing requires the listener to integrate several types of knowledge about the properties of speech, among which auditory speech perception (sub-lexical level), word recognition (lexical-semantic level), syntactic processing, and discourse coherence. Such analysis and integration mediated by this subset of processes are automatic and necessary to transform speech input into a meaningful representation.[79] To maintain these meaningful representations for sufficient time to allow the listener to combine meaningful sentences requires additional involvement of auditory short-term memory.[80]

It is worth to clarify the two main processes involved in auditory speech processing that tend to be confused in fMRI paradigms: speech perception and speech recognition. As

proposed by the neuroanatomical model of speech processing from Hickok and Poeppel[81] (see section 4), speech perception involves sub-lexical segments of speech being at an early stage in the process of auditory comprehension, and speech recognition involves a set of computations that transform acoustic signals into a representation that makes contact with a mental lexicon. Speech perception tasks do not need lexical access but to some extent require other task-specific operations such as executive control and working memory to allow the listener to maintain sub-lexical representations active during task performance.[82] Both processes have been described to recruit different neural systems not only restricted to Wernicke's area as proposed by the classical neurological model for speech comprehension.[83,84]

In the following section we will describe the widely used passive listening task for the evaluation of language comprehension which targets the processes involved in speech processing as discussed above.

Passive listening task

One of the most commonly used tasks in neuroimaging studies to investigate auditory comprehension, especially for patient populations, is passively listening to sentences or stories. Given that different linguistic processes simultaneously occur when hearing speech (phonology, semantic and syntax processing), a language network involving those processes can be identified. Therefore it has been a widely used paradigm for obtaining an overall activation measure of language comprehension processing in the brain (see figure 6).

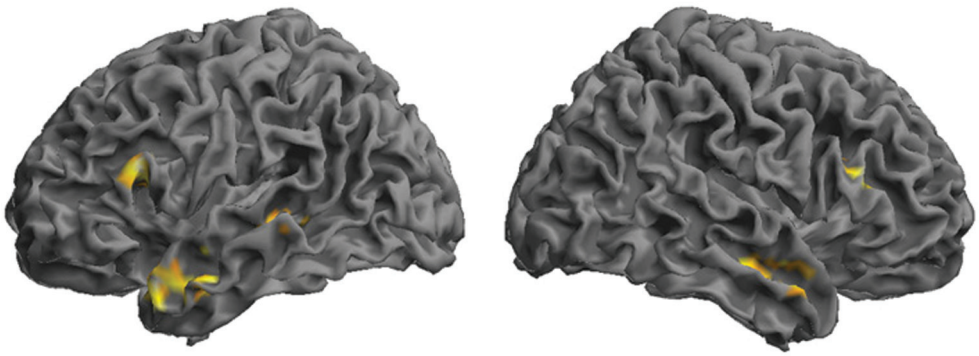

Figure 6. Combined activation of 10 healthy participants during a passive listening task.

Another advantage of the passive listening task is that it does not require active participation from the participant, and is therefore suitable for use in even severely aphasic patients or small children. [85,86] Nevertheless, a potential disadvantage is that task performance can not be monitored, which is a problem because no certainty is obtained that the task has been "performed" and there is the risk that subjects lose attention and that other cognitive processes interfere and activate brain regions that also are involved in speech comprehension and production.[87] One way to obtain a measure of task performance is to beforehand warn the participant about a comprehension questionnaire post-scan, directing the participant's attention to the stories before start scanning. Another option more suitable for pediatric population, is to implement active responses during scan acquisition with yes/no questions that can be answered by button response (see Vannest et al [86]).

The neural organization of speech processing is task dependent. Many fMRI studies have varied versions of the passive listening task to differentiate the processes involved in auditory comprehension by varying sentence complexity, manipulating text coherence, inducing grammatical and/or semantic errors. In addition, different control conditions have been explored in order to isolate areas responsible for speech perception, like tones, noises or speech-like sounds. Due to the tight connection between various levels of language processing for the performance of this task, it has been a challenge to tease apart the contribution of these levels involved in auditory comprehension. Furthermore, variance in neural activity during language comprehension tasks emerges from the internally-driven, information-seeking preferences of listeners independently when manipulating properties of the stimuli.[88]

Current fMRI literature using this task is consistent in reporting organization of speech recognition processes in the superior temporal lobe bilaterally [89, 90] although not symmetrically, the left hemisphere being more selective to speech.[83, 87] Additionally, the left STG has been described as being a shared region for auditory short term memory and speech comprehension.[91] Nevertheless, lateralization of language activation during passive listening tasks seems to depend on the control conditions used in passive listening paradigms. A consistent finding in paradigms using rest as control condition, listening to speech activates the STG bilaterally, including the dorsal STG and superior temporal sulcus (STS). However, some studies attempted to identify speech perception (prelinguistic auditory processing) more specifically by contrasting speech stimuli with various non-speech controls. Lowe et al[92] tested two different control conditions which gave different patterns of activation. Listening to forward text compared with ambient scanner noise resulted in bilateral activation of the primary and secondary auditory cortices and the left posterior temporal lobe (Wernicke's area). Listening to forward text compared to reversed text resulted in selective left posterior temporal lobe activation, the mid-superior temporal sulcus and the anterior superior and middle temporal gyri.

Tasks concerning passive listening consistently give rise to activation in temporal areas, but commonly also in the expressive speech areas in the inferior frontal gyrus (IFG) in the dominant hemisphere. [93]The role of this specific area in speech comprehension tasks, (not only specifically to passive listening task but also to other receptive tasks) will be discussed in a separate section dedicated to the IFG.

3.2 Word production

Picture naming and verbal fluency are the two main word retrieval tasks that have been widely used in both the field of clinical neuropsychology and in clinical neuroimaging studies to detect language processes involved in language production. In the picture naming task, similar to the well known Boston naming test, series of pictures (commonly line drawings) of objects are presented to the participants which they are required to name. This task engages central language processes including the retrieval of lexical information (i.e. retrieving the abstract linguistic representation of the object to be named), and phonological output [91] (figure 7). In verbal fluency tasks, participants are required to produce as many words as they can, starting with a given letter (phonological fluency), belonging to an specific category (semantic fluency) or producing a verb from a frequent noun (syntactic fluency). Since fluency tasks require specific linguistic demands, they will be discussed in detail below in the section of tasks investigating linguistics levels.

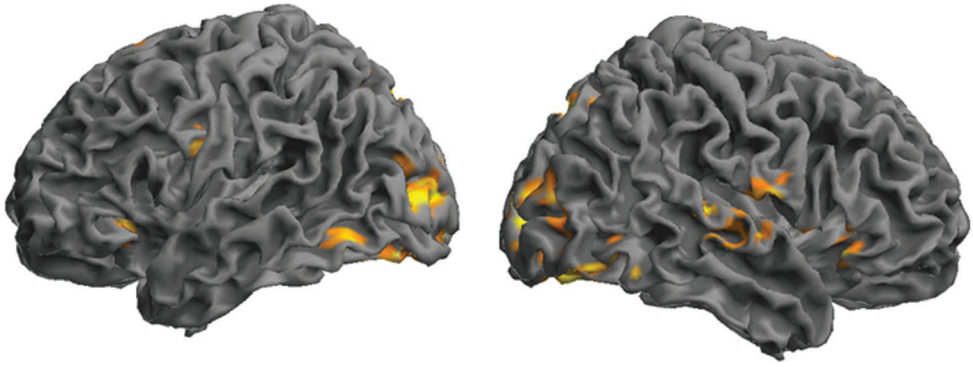

Figure 7: Combined activation of 10 healthy participants during an overt naming task using silent gap acquisition.

Initial word production fMRI studies required the subject to produce words silently (covert answers), since articulation may lead to distortion and motion artefacts during imagine acquisition. Unfortunately, covert paradigms have limited clinical application since participants performance can not be monitored, making interpretation of the imaging data difficult.[39] An acquisition methodology that overcomes these problems

allows for the stimulus presentation and/or response to occur in a silent period in between image acquisitions as previously discussed. This method has not only overcome the potential artefacts resulting from overt speech during image acquisition (increasing its applicability in clinical studies), it has also helped to implement this task in the same way as it is carried in electrophysiological studies (increasing the likelihood on proposed models of word production).[94] Moreover, in clinical fMRI language protocols, overt paradigms are also better to resemble the conditions during intraoperative language mapping.[15]

Word production tasks share a similiar linguistic route. As can seen in figure 8, picture naming and word generation differ only in their initial processes but share the whole cascade of word production components from lemma retrieval onward.[94] For picture naming tasks, visual object recognition is required compared to the other word production tasks. The subprocesses involved in these tasks can be grouped into semantic and phonological stages: During the semantic stage, the meaning of a picture or the concept of a word needs to be retrieved from a storage of word meanings. Conceptual representations must then be translated into word-level knowledge, by selection of the lexical entry that matches the picture or word representation. During the phonological stage, the abstract lexical unit receives a phonetic form, in which the phonological properties of the word are brought together for articulation. [95,96]

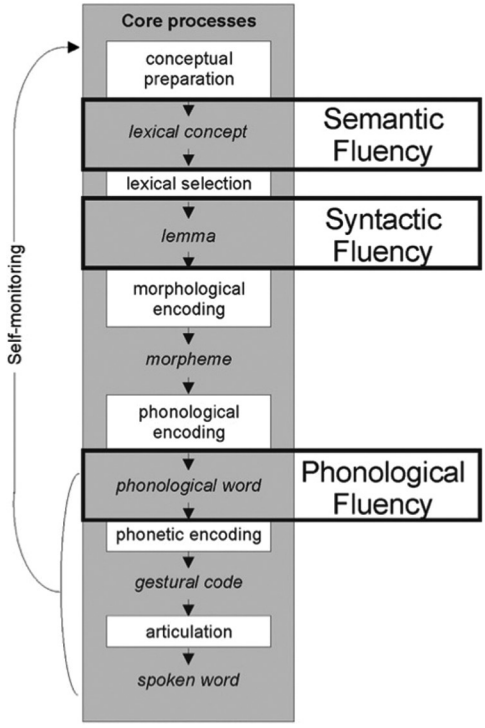

Figure 8: Model from Indefrey and Levelt 97 in Heim et al [98].

This model proposed by Indefrey levelt [97] (discussed in detail in section 4), provides anatomical locations for the subprocesses involved in word production tasks: lemma retrieval and selection in the middle temporal gyrus, phonological code retrieval in the posterior middle and superior temporal gyrus, syllabification in the posterior IFG, articulation in the inferior pre-central and post-central gyrus and self monitoring bilaterally in the superior temporal gyri, demonstrating that the semantic and phonological components of single word production engage different regions. Similar to what has already been mentioned on speech comprehension, for

language production tasks working memory has also been described to play an important role in maintaining and manipulating representations of speech sounds for short periods of time. By considering a meta-analysis of functional studies and lesion based symptom mapping from aphasia, Indefrey in 2011 [94] specified that besides picture naming and word production tasks might different linguistically at the lexical stage (specifically in the manner how the concepts are recalled), both task still share the same core word production components.

Picture naming

Picture naming is an elementary process in the use of language and requires the production of speech sounds associated with a visual stimulus. This task had been frequently used in neuroimaging studies but inconsistent results have yielded, either by selecting different response modalities (overt and covert) or by selecting different control tasks in picture naming paradigms (visual fixation, word repetition). For futher reference see Price et al. [99] A different explanation for this inconsistency explained by Kan et al[100] is that the magnitude of prefrontal activity during picture naming depends on the extent to which a given picture evokes a single reliable meaning. The authors investigated the prefrontal activity by asking the participants to name pictures with either high or low name agreement. In one experiment participants named black-and-white line drawings, either covertly or overtly. Across both modalities, the authors reported more left IFG activity when the subjects named low-agreement pictures than when they named high-agreement pictures. In the second experiment they replicated the effect of name agreement on left IFG activity during picture naming, using black-and-white photographs. This study provided support that the left IFG mediates selection among competing alternatives and suggest a means for understanding the naming deficits observed in nonfluent aphasic patients.

Some authors evaluating different paradigms used in the current neuroimaging literature [97,99] suggest a reliable naming network comprising the bilateral occipital gyri, left IFG, fusiform gyrus, right cerebellum, right insular and left superior temporal gyrus. Since overt performance of the picture naming task is preferred over covert performance due to reasons mentioned above, we will restrict this section to those studies requiring overt responses.

Current studies investigating the neural mechanism of picture naming focus on the decline of this function with age. Investigating changes in word retrieval in healthy elderly, Abrahams et al[19] implemented an overt picture naming task in middle aged to elderly adults. During the experimental condition the participants were presented with line drawings selected form the Boston Naming Test and were instructed to name the object. As a control condition the participants were presented with a meaningless fragmented

picture and were instructed to say the word "rest". Picture naming activated areas of the left IFG, middle and inferior occipital gyri and inferior temporal gyrus. The authors suggested that the activation found in the temporo-occipital regions represents semantic processing of visual information. This study successfully produced activation in cerebral regions corresponding to word retrieval processes and avoided the potential artefacts resulting from overt speech. Later work from Wierenga et al[101] also investigated differences in healthy young and older adults by requesting the participants to name gray scale photographs of three main categories: animals, tools and vehicles. In the control condition participants were requested to passively observe pixelated images. The main finding of this study was that older adults demonstrated a larger frontal network of activation during word retrieval than younger adults, as well as reduced left lateralization of activation. No activation differences between groups was reported in the temporal cortex (specifically in the fusiform gyrus), suggesting that the substrates for word retrieval but not for semantic knowledge change with ageing.

3.3 fMRI tasks for specific linguistic levels

As previously discussed, multiple linguistic stages are involved in tasks evaluating language comprehension and production (input and output systems respectively). A major effort of current research on language processing involves mapping the neural circuits that support these various linguistic levels and stages and understanding the relationship between input and output systems, as well as to related non-linguistic functions. In this section we will describe some of those fMRI paradigms designed to isolate these components, grouping them into three main linguistic levels: the phonological, semantic and syntactic level.

In receptive paradigms participants are commonly instructed to make semantic, phonological or syntactic decisions via button responses. The most common paradigms used to evaluate receptive semantic processing are category decisions between living and non-living nouns or decisions between abstract and concrete nouns. For phonology assessment lexical decision, word segmentation and rhyming decision tasks are commonly used. At the sentence level, syntactic tasks require decisions regarding presented sentences that are syntactically incorrect or correct.

In productive paradigms participants are requested to produce words (either covertly or overtly). To target the semantic level, category fluency tasks are used. For the phonological and syntactic levels, letter fluency and verb generation task are commonly used.

Most of such fMRI paradigms have been derived from commonly used linguistic and neuropsychological tests. Although it may be desirable to investigate in depth the neural representation of these linguistic levels in different modalities, fMRI paradigms can

not target all modalities that behavioral tests can do. For example, tasks involving writing can not be performed inside the scanner due to motion artefacts that induce hand movements. Tasks in which participants are instructed to view, read, or hear linguistic stimuli and produce single words are generally preferred in fMRI studies.

Table 2: Receptive and Productive tasks used to evaluate 3 main linguistic levels: phonology, semantics and syntax.

Technique	Advantages	Disadvantages
Semantics	- Semantic association - Category decision tasks: - living, non-living - concrete -abstract - Word-picture matching (subtest PALPA*)	- Category fluency (animals, professions, etcetera)
Phonology	- Auditory and Visual rhyming decision (subtest PALPA) - Auditory and Visual Lexical decision (Subtest PALPA) - Syllable segmentation	- Phonological verbal fluency (verbal fluency test using letters such as D,T,A) - Non-word repetition - Word repetition - Word stem completion - Overt rhyming
Syntax	- Semantic errors inside the sentence - Word order in the sentence	- Verb generation

Semantics

Receptive semantic tasks

Semantic processing comprises a subset of processes associated with the meaning of words and its functional anatomy has been a matter of debate across neuroimaging studies that either suggest involvement of the IFG or several regions within the temporal lobe. Many fMRI studies have been discussing whether the IFG subserves the retrieval of semantic knowledge. Chee et al[102]investigated semantic processing using different input modalities. Healthy participants were asked to determine whether visually or auditorily presented words were concrete or abstract by using a button press. The control tasks for the auditory task was syllable counting (phonological process) and the control condition for the written task was a case judgment task of words presented in upper or lower case. Both the visual and auditory semantic tasks activated the left inferior frontal, bilateral anterior prefrontal, and left premotor regions and anterior supplementary motor areas. Only during the auditory semantic task, left posterior temporal (middle temporal and fusiform gyrus) activation was observed.

In order to test whether IFG activation subserves retrieval of semantic knowledge or is related to selection of information among competing alternatives from semantic memory, Thompson-Schill et al [103] implemented two receptive semantic tasks (classification and comparison tasks) and a productive syntactic task (verb generation). They expected to modulate the degree of activation in de left IFG by manipulating the demands from these semantic tasks. They showed that activation in overlapping regions of the left IFG was dependent on selection demands in all three tasks. The authors therefore suggested that information and not retrieval of semantic knowledge drives activation of the left IFG.

To differentiate areas within the left inferior prefrontal cortex (IPFC), the superior, middle and inferior frontal gyrus, responsible for semantics and phonology Poldrak et al[104] had subjects perform a semantic decision task and a phonological decision task in comparison with a case judgment control task. Task requirements involved either making a case judgment (perceptual control task), counting the number of syllables (phonological task), or judging whether the words were concrete or abstract (semantic task). Performance of the semantic decision task resulted in extensive left IPFC activation compared to the perceptual control task. Phonological processing of words and pseudowords in the syllable counting task resulted in activation of the dorsal aspect of the left IFG near the inferior frontal sulcus compared to the perceptual control task, with greater activation for nonwords compared to words. In a direct comparison of the semantic and phonological decision tasks, semantic processing preferentially activated the ventral aspect of the left IFG. In short, they demonstrated distinct left prefrontal regions involved in semantic and phonological lexical processing.

With the aim of investigating the effect of using different control conditions for word comprehension paradigms, Binder et al[105]implemented three different paradigms of an auditory semantic decision task using rest, tone decision and phoneme decision as a control condition tasks in 26 healthy participants. In the semantic decision versus rest, bilateral STG activation was found presumably due to auditory processing, as well as widespread prefrontal, anterior cingulate, anterior insular, and subcortical activation bilaterally, which was attributed to general tasks performance processes that are not specific to language. Semantic decision versus tone decision showed extensive left lateralized activation on the angular gyrus, dorsal prefrontal cortex and ventral temporal lobe that was not observed when the same active condition was contrasted against the previously described rest control condition. The authors proposed that this network was responsible for storing and retrieving conceptual knowledge that underlies word meaning. To isolate comprehension processes related to the retrieval of word meaning, they contrasted the semantic task to a phoneme decision task. With this phonological contrast, strong leftward activation was found in the angular gyrus, ventral temporal lobe, dorsal prefrontal cortex, pars orbitalis of the IFG, orbitofrontal cortex and posterior cingulate gyrus. Compared to the previous semantic versus tone decision contrast, the

semantic versus phoneme decision contrast produced less extensive activation either due to the fact that in this contrast activation is related to pre-semantic speech perception processes or due to the nature of the phoneme decision stimuli which worked as a partial masking of the lexical-semantic system. The authors concluded that the semantic-tone decision contrast gives consistent and a strongly left-lateralized activation, identifying not only differences related to pre-semantic phoneme perception but also differences in the degree of semantic processing.

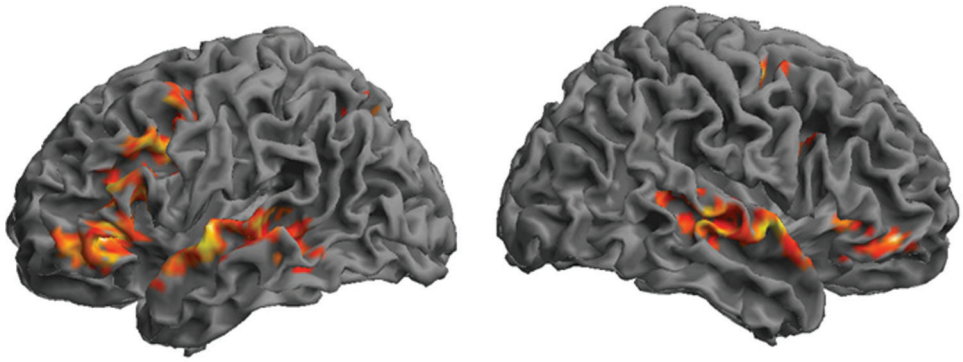

Figure 9: Combined activation of 10 healthy participants performing an auditory semantic association decision task.

Productive semantic tasks

One of the classic behavioral tests to evaluate semantic processing is the semantic fluency test which is widely used by neuropsychologists and clinical linguistics. In this verbal fluency task, participants are required to produce as many words as they can belonging to a specific category (category fluency). Birn et al[106] investigated the behavioral and neurofunctional effects of response pacing and covert versus overt speech in semantic category-driven word generation task. Four conditions were considered: paced-overt, paced-covert, unpaced-overt, and unpaced-covert category word production. Word generation overall showed left hemispheric activation in the IFG, premotor cortex, cingulate gyrus, thalamus, and basal ganglia. Direct comparison of generation modes revealed significantly greater activation for the paced compared to unpaced conditions in the right superior temporal, bilateral middle frontal, and bilateral anterior cingulate gyrus, which includes regions associated with sustained attention, motor planning, and response inhibition. Covert compared to overt conditions showed significantly greater activation in the right parietal lobe and anterior cingulate, as well as left middle temporal and superior frontal regions. The authors concluded that paced overt paradigms are useful adaptations of conventional semantic fluency in fMRI. However, response pacing is associated with additional non-linguistic effects related to response inhibition, motor preparation, and sustained attention.

Phonology

Receptive phonological tasks

Phonological processing comprises a set of cognitive processes related to the processing of speech sounds. In speech perception, phonological processing involves the mapping of acoustic features onto linguistic representations, both at the level of single phonemes and at the level of whole words.[107] Commonly used tasks implemented in fMRI studies involve lexical decision, syllable segmentation and rhyming that mainly require phonological processing. Although lexical decision tasks may also require semantic processing, we will consider it as a mainly phonological task.

Since written stimuli may induce orthographic processing, which would not occur with auditory stimuli, several studies have investigated the effect of input modality for phonological processing. Booth et al[108] investigated modality-specific substrates of phonological processing by implementing both visual and auditory phonological rhyming tasks. Each task modality used a different control condition. The control condition for the visual rhyming task consisted of deciding whether a pair of lines was in the same orientation as the previously presented stimulus. The control condition for the auditory rhyming task consisted of deciding whether presented pairs of tones were similar or different in frequency. Visual rhyming compared to the visual control condition showed activation in the left superior and inferior frontal gyrus, middle occipital gyrus, putamen and fusiform gyrus. To a lesser extent, right hemispheric activation was also observed in the IFG and middle occipital gyrus. Auditory rhyming versus the auditory control condition showed left lateralized activation in the medial and inferior frontal gyrus, STG and fusiform gyrus. Right hemispheric activation was also seen in the STG and to a lesser extent in the transverse temporal gyrus of Heschl. In a more recent study, Heim et al [109] investigated the activation patterns in participants performing a lexical decision task with visually and auditorily presented real words and pseudo-words. Independent of input modality, the left IFG pars opercularis was activated. Using a similar lexical decision task, Kotz et al[110] compared spoken words and pseudo-words which were primed with a rhyming or non-rhyming word or pseudo-word. The aim of the study was to investigate whether the role of the left IFG is purely phonological or rather lexical in nature. Rhyming pseudo-words compared to rhyming words increased activation bilaterally in the STG, whereas rhyming words compared to rhyming pseudo-words increased activation in the frontal and parietal regions. Left IFG activation at the level of the left pars orbitalis and triangularis was found to be greater for words than pseudo-words. This study demonstrated that the left IFG plays a significant role in speech perception strongly linked to the lexicality of a stimulus.

Lurito et al[111] compared activation patterns of a rhyme decision task of visually presented words to covert word generation from visually presented letters. Both tasks were contrasted to line drawn crosses as a baseline condition. Overall, both tasks showed similar robust perisylvian language area activation, including the IFG, the posterior superior tem-

poral lobe, and the fusiform gyrus. The rhyme decision task activated the left hemisphere cortical regions more selectively than the word generation task, but showed less activation than the word generation task in areas typically not considered specifically related to language function, such as the dorsolateral prefrontal cortex and anterior cingulate.

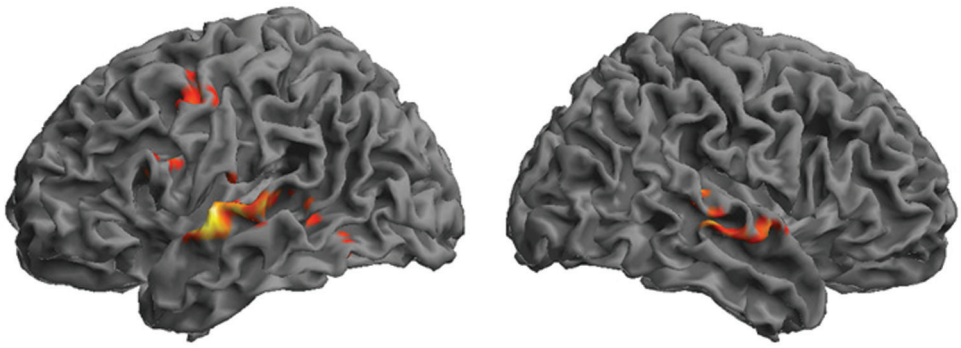

Figure 10: Combined activation of 10 healthy participants performing an auditory rhyme decision task.

Productive phonological tasks

As with the category fluency tasks, phonological fluency is also widely used in neuropsychological research and translated to functional neuroimaging studies. In such a verbal fluency task, participants are required to produce as many words as they can starting with a given letter. Abraham et al[19] implemented a paced-letter based task in which the participant was presented with an auditory cue of a letter and was required to respond overtly. During the baseline condition the participant was cued by auditory presentation of the word "rest" which he was required to repeat. The areas of significant activation during the phonological fluency condition included extensive regions of the left middle frontal gyrus, IFG, anterior cingulate gyrus and medial prefrontal cortex (BA 6).

Using several different production tasks, Buckner et al[112] investigated whether left IFG involvement was dependent on task demand and input modality. Participants performed a visual and an auditory word stem completion task in which several word stems were presented from which complete words needed to be generated by the participant. These stems were repeated throughout the fMRI task to detect activation due to stimulus familiarization (priming effect). A syntactic task was also performed in which participants had to generate a verb from a visually presented noun to identify those brain regions that were not specific to phonological processing. This study demonstrated selective reduction of activation in repeated word generation for both input modalities in the left IFG and inferior temporal regions. These implemented tasks activated a common language network including the anterior ventral and posterior dorsal regions of the left IFG involved in maintaining verbal representations.

Another well known neuropsychological test which has been translated to functional neuroimaging studies evaluating phonological processing is the non-word repetition task. Investigating phonological syllable representation, an early step during phonological processing in production tasks, Papoutsi et al[113] used a pseudoword repetition task proposing that syllabification should be sensitive to the amount of material to be inserted into syllables (i.e., pseudoword length) but not to the frequency of co-occurrence of phonemes in the language (biphone frequency), whereas both variables should affect phonetic encoding and articulation stages. Their results showed a dissociation between one dorsal region in the left IFG that was only sensitive to word length but not biphone frequency and, hence, compatible with a role in syllabification, and another more ventral region that was sensitive to both variables and thus probably involved in a phonetic processing stage. Similar results by Ghosh et a[114] confirmed a stronger activation of the pars opercularis of the left IFG for the production of bisyllables compared to monosyllables. Sahin et al[115] reported a word length effect in the pars triangularis of the left IFG. In summary, effects of manipulation of (pseudo)word length are compatible with phonological encoding and later processing stages.

Kircher et al[116] implemented an overt rhyming fluency task. In this study participants were instructed to perform two tasks: letter verbal fluency in which participants were instructed to overtly articulate as many words as possible to a given initial letter and a rhyming verbal fluency in which participants had to generate words that rhymed with pseudo-word stimuli. Generating novel rhyme words was mainly mediated by the left inferior parietal lobe, a region associated with meta-phonological as well as sub-lexical linguistic processes.[116] Both tasks activated a language network encompassing the left IFG and the middle and superior temporal gyri. Rhyming verbal fluency demonstrated significantly stronger activation of the left inferior parietal region compared to a semantic verbal fluency task also evaluated in this study.

Syntax

Receptive syntactic tasks

Compared to the previously discussed receptive phonological and semantic tasks, receptive syntactic tasks are not that commonly used in clinical studies. They have mainly been used in psycholinguistic studies with the aim to disentangle syntactic processing from semantic processing. Dapretto et al[13] is one of the first fMRI studies investigating the neural substrate of sentence comprehension using a selective attention paradigm task. In this paradigm semantic and syntactic information was manipulated without varying the complexity of the sentences. Participants were instructed to decide whether the meaning of two sentences differed. In the semantic condition, each pair of sentences was identical in all aspects except for one word that was replaced with either a

synonym or a different word. In the syntactic condition, the sentences in each pair were either cast in a different form (i.e., in the active versus the passive voice) or used a different word order (i.e., preposed versus postposed prepositional phrases). This paradigm was specifically designed to unequivocally disentangle syntactic from lexico-semantic aspects of sentence processing. Their findings indicated that a part of the left IFG area (pars opercularis) is critically implicated in processing syntactic information, whereas the pars orbitalis of the left IFG is selectively involved in processing the semantic aspects of a sentence.

Syntactic processing has also been investigated by comparing sentences with and without grammatical errors, sentences with more versus less syntactically complex structures, and sentences with semantic violations. In all these paradigms, the demands on syntactic processing are confounded by the differing demands on semantics because both grammatical errors and complex sentences make it more difficult to extract the meaning of a sentence.[84] As summarized by Price[84], the left pars opercularis was more activated for sentences with implausible versus plausible meanings and are also for sentences with grammatical errors or complex structures. For example, left ventral pars opercularis activation has been reported by Friederici et al[117]when sentences had syntactic errors, and by Raettig et al[118] when there were violations in verb–argument structure.

Productive syntactic tasks

Similar to the phonological and semantic fluency tasks described above, in syntactic fluency task participants are required to produce a verb in relation to a frequent noun. Although this task also requires semantic processing, the core processing is syntax. The verb is the center of sentences requiring an object. So the nouns surrounding the verbs are the arguments which together with the verbs trigger the sentence structure.

Investigating changes in the IFG by modifying verb generation demands, Thompson-Schill et al[119] suggested that verb generation should show more activation in the primed condition relative to unprimed because the irrelevant information should increase the selection demands. They found a small increase in activation for primed versus unprimed conditions.

Summary

Taken together, the properties of applied language tasks are such that no single task allows for the identification of neural correlates of all components that have been psycholinguistically identified.[94] We can see that currently reported results are strongly

dependent on how a linguistic task is implemented, which control tasks are used to isolate the single processing in interest, which input modality is selected to present the stimuli, and the type of required response (targeting productive or receptive language processing). Without a doubt, functional neuroimaging data identify many areas that are involved in task performance, but do not inform us on which areas are critical for such performance. Lesion data may be helpful in this respect, as well as techniques that manipulate brain function, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). For a further overview of these techniques see Naeser et al[120]and Holland et al[121].

3.4 The role of the IFG in language processing

Current fMRI studies have shown that different receptive and productive tasks recruit different regions of the left IFG and it has been a matter of debate whether this activation is due to specific word retrieval or to central executive demands (such as working memory) or stimulus expectancy.[122]

Considering studies that modify the content of the sentences in passive listening tasks, Price[84] summarizes that when semantic content of sentences is difficult to extract, activation increases in the left and right pars opercularis and orbitalis. In parallel, it has been suggested that this frontal activation may be due to the subject's covertly rehearsing the heard text with coarticulation.[123] Current discussion about such reported frontal activation across fMRI studies, especially in premotor areas, has suggested that it is to simply modulate auditory speech recognition systems, while not playing a crucial role for speech comprehension.[124,125]

There are two more hypotheses about the functional organization of the left IFG in relation to fluency tasks, One hypothesis suggests an anatomical differentiation for phonological and semantic operations within the left IFG. [10,126,127] The second hypothesis proposes that both processes are encompassed within a more general "supramodal executive function" (selecting task-relevant information among competing alternatives within the left IFG).[128] In a systematic review of the fMRI studies using phonological and semantic fluency tasks (mainly studies requiring covert response) Costafreda et al[129] tested both theories. Their results were in accordance with the anatomical differentiation theory showing that semantic fluency tasks tended to activate the anterior ventral portion of the IFG (BA45) whereas the phonological fluency activated a more posterior dorsal portion of the IFG (BA44).

In a more recent study however, Heim et al[98] challenged the anatomical differentiation hypothesis. By using a sparse imaging technique, the same group of participants were

ask to perform a paced semantic (category based), phonological (letter based) and syntactic fluency task. A closely matched baseline task was use to control for word retrieval and articulation in which participants had to generate any noun without a predefined criterion. A rest period was added as a loosely matched control task. The results of this study were partially in line with the previously mentioned meta-analysis. Compared to rest, all language tasks activated well known language areas including both critical regions of the left IFG, with the same pattern of activation for the semantic (anterior ventral portion of the IFG: BA45) and phonological fluency (posterior portion of the IFG: BA44). Semantic fluency showed more activation than phonological fluency in the left middle frontal gyrus and the left fusiform gyrus. More activation for phonological than for semantic fluency in the left inferior parietal lobule was reported, which according to the authors was due to deactivation in the semantic rather than activation in the phonological condition. However, phonological fluency activated the posterior portion of the left IFG more strongly than semantic or syntactic fluency. Contrary to what it was expected, semantic fluency did not elicit higher activation than the phonological fluency task in any part of left IFG. No differences were found between syntactic and semantic fluency. Considering that task performance was equal in all tasks, the authors concluded that the activation in the anterior portion of the left IFG observed during verbal fluency tasks seems to be not restricted to semantic processing as previously suggested, but instead different parts of the left IFG support task-specific and more general processes in verbal fluency. Furthermore, activation in the left IFG depends more on the general demands on the selection of entries from the mental lexicon rather than the particular linguistic domain (semantic or phonological).

Implementing a different paradigm in which performance and brain activity could be evaluated under conditions that more closely mirror standard behavioral test demands, Birn et al[106] investigated overt verbal fluency (category and letter based) incorporating both a task switching manipulation and an automatic speech condition in order to modulate executive function demand. In the experimental condition participants were presented with a single letter or category cue and they had to generate as many words as they could think of starting with that letter or category. When two letters or two categories cues were presented, participants were required to generate one word corresponding to one of the letters (or categories), then switch to the other letter (or category), and continue to alternate between the two cues (e.g. when presented with the cue "colour/fruit" subjects would generate "blue, apple, red, banana..."). During the control condition participants were instructed to name the months of the year in chronological order. The study showed activation in the left precentral and inferior frontal gyrus for letter fluency, and greater activation more anteriorly in the left middle frontal gyrus as well as in the left fusiform gyrus for category fluency. Moreover they showed greater activation of the left occipito-temporal sulcus/posterior fusiform gyrus during word retrieval to letter than to category fluency. These findings provide converging evidence that letter and category fluency performance is dependent on partially distinct neural

circuitry, again in line with the anatomical differentiation hypothesis.

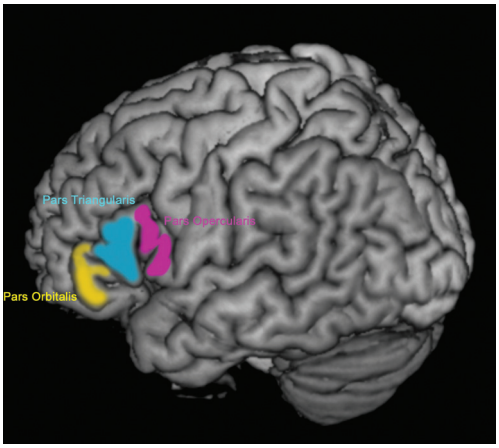

Figure 11: Subdivision of the left inferior frontal gyrus

Investigating the underlying neural substrate of word-finding difficulties in elderly adults, Meinzer et al[130] implemented an overt verbal fluency (category and letter based) task in healthy elderly and young adults. During letter fluency tasks, both groups had similar performance and left lateralized frontal activation. However, a significantly lower performance during the semantic task in the older group was accompanied by additional right (inferior and middle) frontal activity, which was negatively correlated with performance. In the younger group, semantic fluency versus baseline showed peak activity centered at the junction of the left anterior STG (BA 22) and the IFG (BA 9). A similar pattern of activation was observed during the phonological fluency task but a larger anterior cluster was activated in the left hemisphere that included the left STG and IFG (BA 22/9) and also encompassed the pars triangularis (BA 45). Moreover, the younger group recruited different subportions of the left IFG for phonological and semantic fluency, showing more pronounced activation for the phonological versus semantic fluency in anterior ventral and posterior dorsal left IFG while the older participants failed to show this distinction.

Summary

Current reviews of fMRI studies suggest that the anterior and mid-portions of the IFG, the middle and inferior temporal gyri, and the angular gyrus of the parietal lobe are associated with semantic processing.[10, 131] Phonological processing has implicated the posterior portion of the IFG, the STG and the supramarginal gyrus of the parietal lobe.[10,90,97] The pars opercularis of the IFG is dedicated to syntactic processing and in the posterior part of the ST,G a region selectively activated by sentence and text processing. It is hypothesized that different working memory perception-actions loops are identifiable for the different language components. [132]4. Functional neuroanatomical models of language processing

In the past decade, several neuroscientists have tried to summarize data from neuroimaging studies in order to provide a complete overview of the neural mechanism of language processing. This is an ambitious body of work that is necessary to evaluate

what neuroimaging studies can tell us so far about language processing. In the following section we will discuss functional neuroanatomical models of language which have updated the role of Broca and Wernicke in language processing, describing at the same time the postulated role of other cortical areas.

4.1 Complementing classical and cognitive models of language processing with functional neuroimaging

The classical model of language simply considers two language areas localized in the left hemisphere: Broca's area in the IFG and Wernicke's area in the posterior parieto-temporal region. The regions are interconnected by a white matter tract, the arcuate fasciculus. This model, formulated in the 19th century and based on lesion studies, is still popular among clinicians due to its simplicity and clinical applicability. With the increasing interest of different disciplines investigating language processing, however, we know that the classical model is not sufficient to fully explain the complexity of language.

The 20th Century Ccgnitive scientists have primarily emphasized the complexity of linguistic functions rather than focusing on their anatomical locations. Based on behavioral tests they developed highly sophisticated models (Morton[133], Pattersson & Shewell[134]; Levelt[95]) describing many different types of operations involved in language processing. In these modularity models the language system is divided into many interacting subcomponents and devised information processing models comprised of boxes and arrows. Figure 13 shows the classic word processing model proposed by Patterson & Shewell[134].

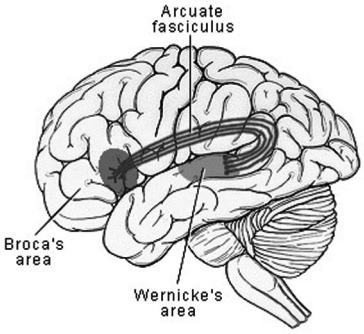

Figure 12: Classical representation of the arcuate fasciculus connecting Broca's and Wernicke's regions.

Following this proposal, many other models expanded this initial model to explain sentence processing and bilingualism. [135,136] Later connectionist models reduced these modularity models by highlighting the interaction between such subcomponents.[137] The current goal of the neuroscience of language involves the anatomical mapping of neural circuits that support these linguistic stages and their interactions, redefining models of normal and abnormal language processing, searching not only for the relation between production and comprehension systems, but also trying to explain the role of non-linguistic cognitive functions such as memory and attention.

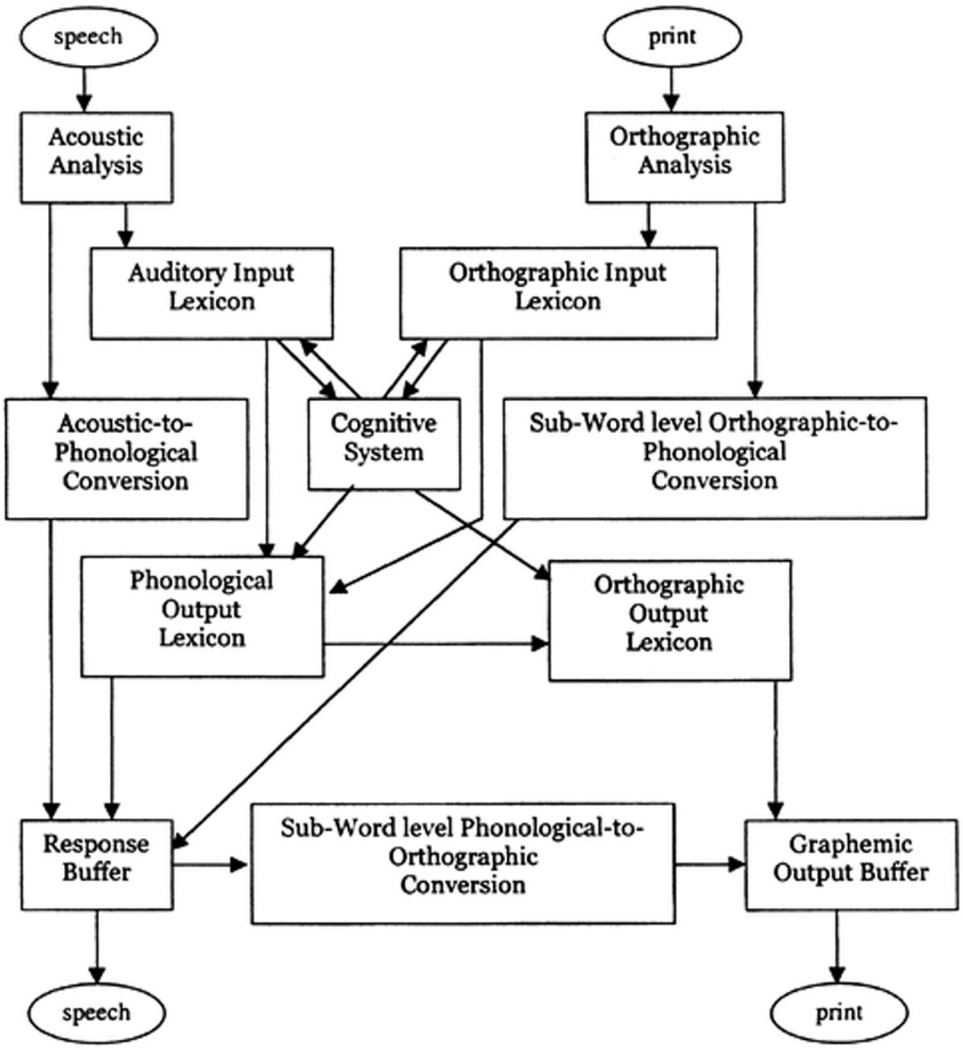

Figure 13: The classic word processing model proposed by Patterson & Shewel [134].

Recently, there has been substantial progress in the development of large-scale models of functional neuroanatomy of language by integrating data from functional imaging studies. Using information from cognitive-linguistic models, a multitude of highly detailed aspects of language processing have been artificially manipulated to create a variety of paradigms which allow a parceled exploration of the separate levels of language processing, such as phonological, semantic and syntactic processing.

Many of the anatomical and neurolinguistic assumptions from the 19th and 20th Century models are currently being reconsidered with the advance of functional neuro-

imaging techniques. Current neuroscientists transform these classical ideas into new theoretical positions, openly challenging fundamental long-held notions of language organization. Resulting functional neuroanatomical models of language processing have merged language processing concepts from the current literature with functional imaging findings.

The first model to complement neuroimaging findings from fMRI and PET studies with the classical neurological and cognitive models was described by Price[9]. By collecting functional neuroimaging data from different authors investigating auditory and visual word processing [134,137], Price[9] matched the findings of these studies with the subprocesses described in cognitive models, comparing at the same time similarities and discrepancies with the classical neurological model. Auditory processing of heard words is conducted in the superior temporal cortex whereas processing of written words takes place in the posterior inferior temporal and temporo-occipital cortex. Activation in the left posterior superior temporal sulcus for both tasks is consistent with the neurological model and may correspond to the non-semantic word retrieval suggested by connectionist cognitive models, in which they try to reveal a network for language processing rather than finding different neural backgrounds per linguistic level. The semantic system is subserved by a network that includes the angular gyrus and the anterior inferior temporal cortex. Price highlights that the activation observed in frontal areas during semantic tasks may be related to non-linguistic processes. For reading of words, two routes are described for phonological-lexical retrieval: a non-semantic route, through the posterior superior temporal cortex, and a semantic route, through the posterior inferior temporal cortex. This model further specifies that the acoustic-phonetic (prelexical) analysis of words is conducted in the superior temporal sulcus rather than in the superior temporal gyrus as proposed by the neurological model. Finally, the articulatory planning of speech is proposed to be conducted in the anterior insula, the so-called "Dronker's area" rather than in Broca's area as previously suggested by the classical model of language. More recently, in 2010, Price provided an update of the anatomy of language considering 120 published fMRI studies investigating speech comprehension and production in the healthy adult brain. [84] In this more recent review, the focus is not only on the neural basis at the word but also at sentence level.

Moving from word to sentence level, Friederici[126] proposed a neurocognitive model of sentence comprehension, explaining its time course and neuroanatomy based on electrophysiological (event related potentials: ERPs) and neuroimaging data (PET and fMRI).

This model departs from the focus on word level processing by identifying mainly semantic and syntactic interactions during sentence comprehension. It also highlights the role of prosody, a suprasegmental phonological feature which influences syntactic processes. With respect to the time course of sentence comprehension, the model explains that syntactic processing precedes, and is in many aspects independent of, semantic

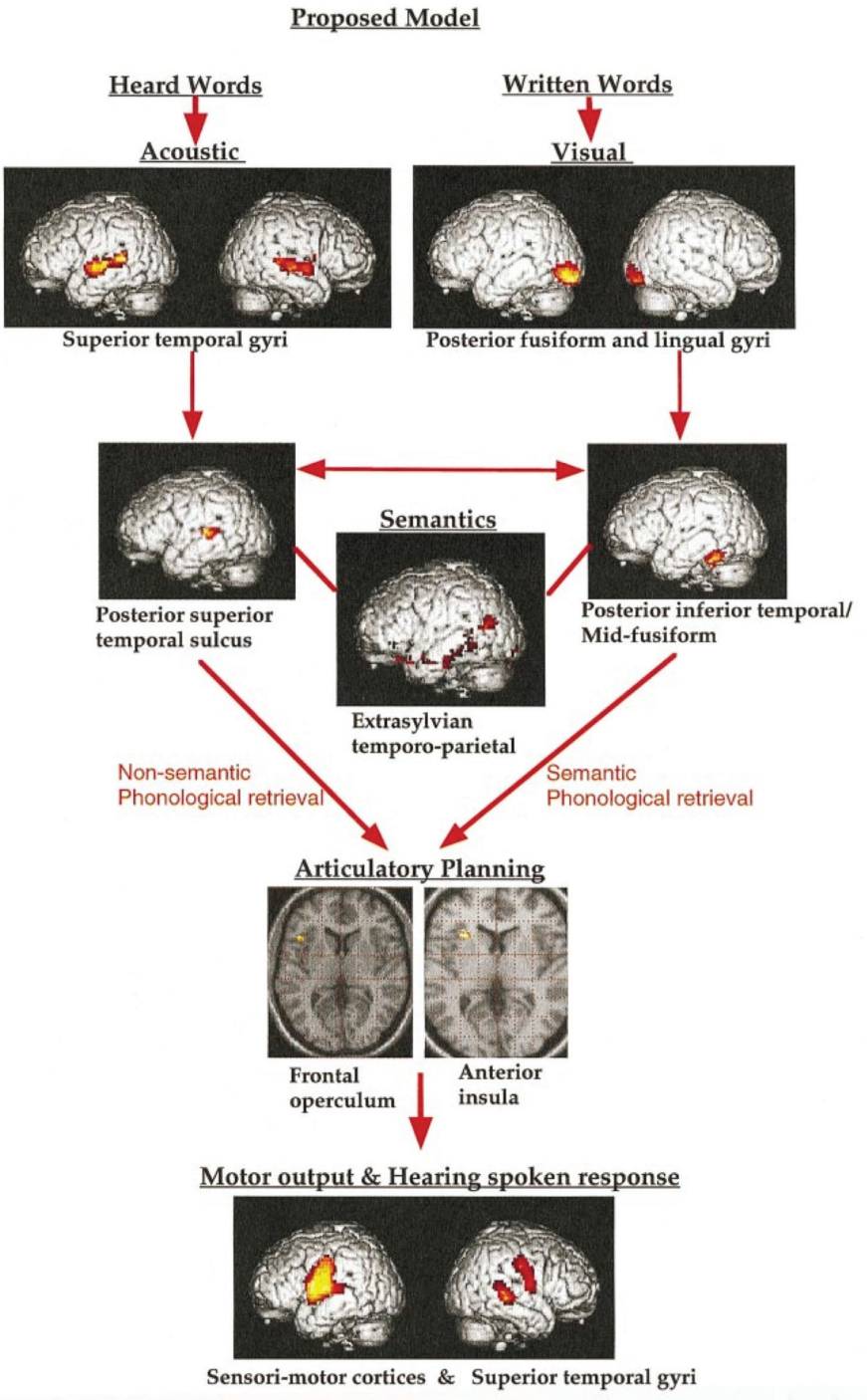

Figure 14: Functional language model as proposed by Price[9].

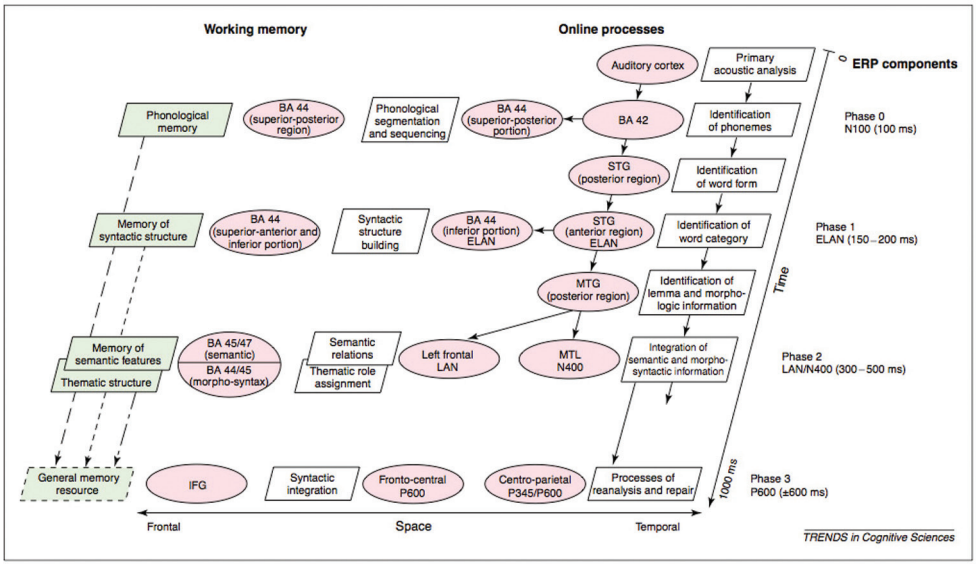

Figure 15: Functional language model as proposed by Friederici[126].

processing. Nevertheless, both processes may interact only during later stages for thematic-relationships, during integration of semantic and morpho-syntactic information. On the other hand, the functional neuroanatomy of auditory language comprehension is described as a bilateral temporo–frontal network, in which the left temporal regions support processes that identify phonetic, lexical elements and the frontal cortex is involved with sequencing and the formation of structural semantic and thematic relationships. Nevertheless, linguistics features, syntactic and semantic information are processed predominately by the left hemisphere, while processing of prosodic information occurs predominantly in the right hemisphere. Temporal regions support identification, with syntactic processes involving the left anterior superior temporal gyrus, semantic processes recruiting the left medial temporal gyrus and prosodic processes involving the right posterior superior temporal gyrus. Frontal regions support the formation of relationships, with syntactic relationships involving opercular areas of the IFG (BA 44), and semantic relationships recruiting pars triangularis and orbitalis of the IFG (BA 45/47 respectively).

From a different perspective to group the results from neuroimaging studies Hagoort[127] proposed a psychologically orientated model that connects psycholinguistic models to a neurobiological account of language which distinguishes three functional components of language processing: memory, unification and control (MUC). The memory component relates to different types of language information stored in long-term memory, as well as to retrieval operations. The unification component refers to operations that take place in parallel with the semantic, syntactic and phonological levels of processing. The control component relates language to action, such as when the correct

target language needs to be selected (in the case of bilingualism), or to handle turn taking during conversation. This MUC model applies to both language production and language comprehension. According to this model the temporal cortex is critical for retrieving the information for language from our memory. This concerns the tone and other aspects of words in the STG, the meaning of words (the inferior part of the temporal cortex), and the grammatical properties of words (the middle part of the temporal cortex).

Based on the language production model described by Levelt[138], a model on the interaction of word production and perception was proposed by Indefrey and Levelt[97], based on a comprehensive meta-analysis of different neuroimaging techniques (PET, SPECT, fMRI, MEG, TMS) combined with information on the time course of word production provided by behavioral and EEG studies. In this model, five core processes are identified for word production with the following areas being involved: lemma retrieval and selection in the middle temporal gyrus, phonological code retrieval in the posterior middle and superior temporal gyrus, syllabification in the posterior IFG, articulation in the inferior pre-central and post-central gyrus and self monitoring bilaterally in the STG. By comparing activated regions during auditory word perception to regions that were reliably found in word production tasks (studies both requiring overt and covert answers) they identified overlapping areas as being involved in three subsequent stages of the word production pathway: lexical selection, lexical phonological code retrieval, and post-lexical syllabification. This anatomical overlap between the neural correlates of word production and perception processes is not incompatible with the psycholinguistic evidence suggesting points of contact between the word production and perception pathways at these three levels. The model was later updated by Indefrey[94] by including the role of the left IFG and inferior parietal cortex in word production as described in the previous section.

With the same aim to find an overlap in areas responsible for language comprehension and production, Hickok and Poeppel[81] attempted to describe and apply their model to interpret the complex symptomatology of several classical aphasia syndromes. Compared to the previously discussed models, this model provides a context to interpret the neural basis not only of traditional language functions (such as speech perception, auditory comprehension, and speech production), but also provides a natural account of verbal working memory. The model postulates two cortical - ventral and dorsal - streams (analogous to visual processing).

The ventral stream is involved with auditory recognition, i.e. mapping sound onto meaning. The dorsal stream, which projects from the core auditory cortex to the parietal and frontal lobes, is the interface between auditory and motor processing, i.e. maps sound onto articulatory representation. This proposal is later updated by the authors in 2007 [83] to a model in which the streams are extensively subdivided. It further assumes that the

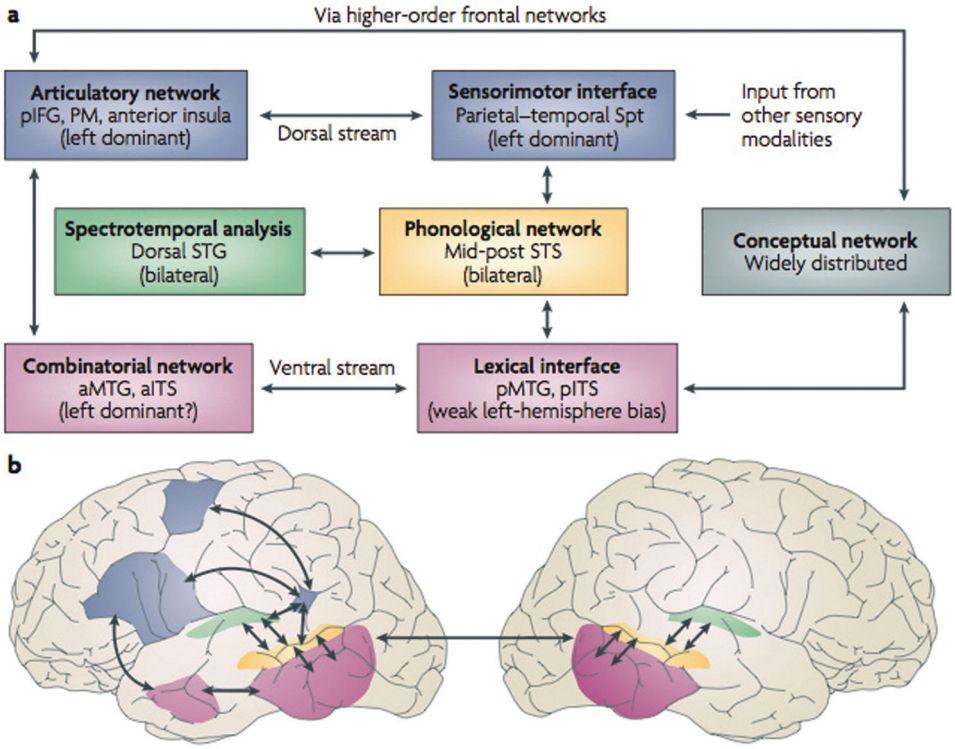

Figure 16: Dorsal and Ventral stream language model proposed by Hickok and Poeppel[83].

ventral stream is largely bilaterally organized, with important computational differences between the left and right hemispheric systems. The dorsal stream is assumed to be left-hemispheric dominant. This hypothesis was further complemented by Saur et al[139] by combining fMRI and diffusion tensor imaging-based tractography in healthy participants (Figure 17). This study identified the most probable anatomical pathways connecting brain regions preferentially associated with auditory comprehension (semantic) and repetition (phonology), respectively. The authors demonstrated that temporo-frontal interactions are subserved by 2 distinct fiber bundles. The repetition of nonwords is subserved by a dorsal stream connecting the superior temporal lobe and premotor areas in the frontal lobe (including pars opercularis of the IFG) via the arcuate and superior longitudinal fascicles. In contrast, higher-level language comprehension such as the passive listening task is mediated by a ventral pathway connecting the middle temporal lobe and the ventrolateral prefrontal cortex via the extreme capsule. The impact of these anatomical pathways for language processing is now widely discussed. [90,125]

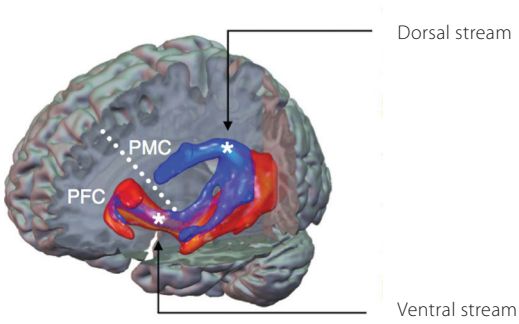

Figure 17: Dual pathway network for language described by Saur et al[139]. Composite fiber network for repetition (blue) and comprehension (red). Three-dimensional tractography renderings visualize the spatial orientation of both networks to each other. Dashed white line illustrates the bisection of the frontal lobe into a ventral part, which is connected to the postrolandic brain via the ventral pathway and a dorsal part, which is connected to the postrolandic brain via the dorsal pathway.

A final neuroanatomy model of language processing?

In summary, in the last decade a multitude of models has been proposed, each with a specific approach and focus (on generally a single domain) with subsequent great diversity of regions involved, but all aiming to converge linguistic and anatomical findings to describe the neurobiology of language from an integrated functional neuroanatomical perspective. Although each of the models recognizes to a greater or lesser extent the importance of the classical language areas in the left hemisphere, it is clear that several other brain regions are involved as a partially distributed network interconnected processing areas. [140] Moreover, it seems that brain regions are highly subdivided for specific components of language and not just responsible for one particular type of processing.

Current effort of language fMRI studies are aiming to investigate whether the three linguistics levels, semantics, phonology and syntactic processes, recruit either different or the same anatomical areas in both receptive and productive modality. Due to the variety of paradigms used across the fMRI literature, it seems difficult to replicate and compare results. Some recent studies are testing reproducibility by keeping paradigms constant, without varying demands to prevent involvement of other cognitive functions as executive system, and using same input modality (visual or auditory).

5. Future perspectives

There is no doubt that current neuroimaging studies have been providing valuable insights into the functional organization of language system. The complexity of language processing however poses a multitude of challenges that become apparent from the great diversity of models and functional neuroimaging studies at hand.

Exciting new developments in the field of fMRI will in the near future enable neuroscientists to dig deeper into language processing than was possible until now. From

a data acquisition point of view, imaging at high field strength (7 Tesla and higher) allows for great anatomical detail and selective sensitivity to the capillary bed of functionally active brain parenchyma. Combination of fMRI with other modalities such as TMS and tDCS will provide us with the ability to distinguish critical from non-critical areas, whereas combined fMRI and PET imaging is now possible with hybrid PET-MRI scanners, allowing simultaneous acquisition of functional, anatomical and metabolic information. Finally, new data analysis tools in the form of multivoxel pattern analysis (MVPA) are already put forward as having the ability to read the mind and being sensitive to subtle and complex brain activation patterns. Such developments overcome to a large extent the simplification imposed on current fMRI research and may undoubtedly bring us closer to a deeper understanding of language processing.

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Chapter 3

Crossed Cerebro-Cerebellar Language Lateralization: an Additional Diagnostic Feature for Assessing Atypical Language Representation in Presurgical Functional MR Imaging

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Abstract

Background and Purpose: Determining language dominance with fMRI is challenging in brain tumor patients, particularly in cases of suspected atypical language representation. Supratentorial activation patterns must be interpreted with great care when the tumor is in or near the presumed language areas, where tumor tissue or mass effect can lead to false negative fMRI results. In this study we assessed cerebro-cerebellar language fMRI lateralization in healthy participants and in brain tumors patients with a focus on atypical language representation.

Materials and methods: Twenty healthy participants and 38 patients with a brain tumor underwent fMRI with a verb generation task. Cerebral and cerebellar language lateralization were separately classified as left-sided, right-sided or symmetrical. Electrocortical stimulation (ECS) was performed in 19 patients. With McNemar's test we evaluated the dependency between language lateralization in the cerebrum and cerebellum, and with Pearson correlation analysis the relationship between the cerebral and cerebellar lateralization indices (LIs).

Results: There was a significant dependency between cerebral and cerebellar language activation, with moderate negative correlation (Pearson's r= - 0.69). Crossed cerebro-cerebellar language activation was present in both healthy participants and patients, irrespective of handedness, or typical or atypical language representation. There were no discordant findings between fMRI and ECS.

Conclusion: Language lateralization in the cerebellum can be considered as an additional diagnostic feature to determine language dominance in brain tumor patients. This is particularly useful in cases of uncertainty, such as the interference of the brain tumor with cerebral language activation on fMRI, and atypical language representation.

Introduction

Functional MRI is a feasible diagnostic neuroimaging tool for determining hemispheric language dominance in brain tumor patients preoperatively.[1] Nevertheless, it has important limitations to take into account when evaluating language lateralization, particularly in brain tumor patient.[1-3] Activation patterns must be interpreted with great care when the tumor is in or near the presumed language areas, where tumor tissue or mass effect can lead to false negative fMRI results.[2]

Determining language dominance is additionally challenging in left-handed brain tumor patients. Left-handers are known to have less well defined language lateralization patterns, with more atypical right-sided language lateralization compared to right-handers.[4-6] In brain tumor patients, the ability of fMRI to confirm Wada-established language lateralization was significantly more specific for right than for left-handed or ambidextrous patients, presumably due to their higher rate of typical, left lateralized language representation.[7] In a study evaluating the role of fMRI confirming language dominance in patients with epilepsy, this technique showed higher post-test probability for language dominance in patients with typical language representation than in patients with atypical language representation.[8]

Thus far, studies assessing language lateralization have focused on the supratentorial brain.

Prior fMRI studies have shown activation not only in the cerebral hemispheres but also in the cerebellum while performing specific language tasks.[9-11] An example is the verb generation (VG) task, which is preferred to localize language areas in tumor patients[11-14] and has been properly validated with Electro Cortical Stimulation (ECS).[15] In persons with left hemispheric language dominance, this task has shown to activate the right cerebellum.[9] Some further studies have provided evidence for a so-called crossed cerebro-cerebellar language lateralization pattern in healthy persons, both with typical, left-sided and with atypical, right-sided language lateralization.[10, 16] This crossed cerebro-cerebellar language lateralization may serve as a useful additional diagnostic feature in determining language hemispheric dominance in brain tumor patients, because the cerebellar language activation is generally undisturbed by the tumor localized in or near the presumed supratentorial language areas. Such an additional diagnostic feature may be especially helpful in patients with potentially atypical language representation, namely left-handers.

The purpose of our study was to assess cerebro-cerebellar language fMRI lateralization in healthy participants and in brain tumors patients with a focus on atypical language representation.

Methods

Study participants

We included 20 healthy participants (HPs) whose functional data were reported in a previous study[17] which investigated the relationship between cerebral functional language lateralization and structural asymmetry of the arcuate fasciculus, and 38 brain tumor patients. Institutional Review Board (IRB) approval was obtained for the inclusion of HPs as well as for the retrospective use of anonymized patient data. We included more left than right-handed HPs to increase the probability of finding atypical - right lateralized or symmetrical - language representation. Handedness in healthy participants was assessed with the Oldfield's Edinburgh Handedness Inventory (EHI)[18]. Written informed consent was obtained from all HPs before participation in this study. The IRB waived the requirement to obtain written informed consent from patients. Patients were selected from our database of 205 patients referred for preoperative fMRI by the neurosurgery department at our institution between May 2004 and September 2013. From this database we selected all left-handed patients (19 patients) who had performed an fMRI language task. We then matched these with 19 right-handed patients for gender, age and tumor location. Handedness in all patients was assessed by the neurosurgeon at presurgical neurological examination. All patients were able to perform the language task and were native Dutch speakers except for one native German speaker, who was fluent in Dutch after learning this language at the age of 37 years. Nineteen patients (9 left-handed) were operated in an awake setting. In the awake setting, direct ECS was performed to identify language functions (biphasic pulse, 50 Hz frequency, 1 ms duration, 6–12 mA).

Data acquisition and preprocessing

Participants performed a VG task.[12] They were instructed to think of a verb related to an auditorily presented noun and in the control condition they listened to high (2000 Hz) and low (400 Hz) tones.

Participants were scanned at 1.5T or 3.0T with an 8-channel head coil. Functional and structural sequences are specified in the supplemental material (Table 1). Imaging data were analyzed using SPM8 (Statistical Parametric Mapping, London, UK). Functional images were manually aligned to the anterior commissure, realigned to correct for motion, co-registered with the individual's T1-weighed image[19], and smoothed with a 3D Gaussian Full Width Half Maximum filter of 6x6x6 mm^3.[20]

Anatomical images of the HPs were segmented and normalized together with the functional images to the Montreal Neurological Institute standard brain space using affine and nonlinear registration. This resulted in resampled voxel sizes of 3x3x3 mm^3 for the

functional and 1x1x1 mm^3 for the anatomical images. Patient data were not normalized, in line with routine presurgical analysis, but resliced with preservation of the acquired voxel size.

Data analysis

Statistical activation maps were generated with a general linear model, using a box-car function convolved with a hemodynamic response function, corrected for temporal autocorrelation and filtered with a high-pass filter of 128 s cut-off. Motion parameters were included as regressors of no interest to reduce potential confounding effects of motion. Individual t-contrast images of language activation (VG>tones) were generated for all participants. Differently to the analysis performed with the HPs in our previous study[17], individual lateralization indices (LI) were determined ROIs known to be involved in language processing: inferior frontal gyrus, superior temporal gyrus and middle temporal gyrus, angular and supramarginal gyrus, and the cerebellum. Furthermore, in this study the number of activated voxels within these ROIs was calculated using a threshold independent method.[21, 22] The LI was defined as: (LH-RH)/(LH+RH), where LH and RH are the number of activated voxels in the left and right hemisphere respectively. Activation was classified for the cerebrum and cerebellum separately as left lateralized for LI values between 0.1 and 1.0, right lateralized for LI values between -0.1 and -1.0, or symmetrical for LI values between or equal to -0.1 and 0.1.[21]

Patients' individual t-contrast images, thresholded individually but at a minimum t-value of 3.2, were assessed qualitatively by a neuroradiologist with 11 years' experience in presurgical fMRI who was blinded for the handedness of the patients and ECS findings. Language activation was assessed in the same predetermined language areas as those quantitatively assessed in the HPs. For each region activation was categorized as left lateralized, right lateralized, symmetrical, or no activation, on the basis of which an overall assessment supratentorial language representation was made. Cerebellar activation was not taken into account when determining overall language lateralization.

For both HPs and patients, when functional language activation in the cerebrum was left lateralized, we defined this as typical language representation. When cerebral language activation was right lateralized or symmetrical, we defined this as atypical language representation. Furthermore, when activation patterns were observed in the left cerebrum and right cerebellum, or viceversa, we defined this relationship as crossed cerebro-cerebellar language activation.[23]

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (v20, IBM Corporation, New York, USA). Age differences between left and right-handed participants were examined using an independent samples t-test. Gender differences between both groups of patients were examined using Fisher's Exact test. To test whether the lateralization in the cerebrum and in the cerebellum were independent of each other, a McNemar's test was performed in HPs and patient data. In HPs the possible relationship between the LIs of the cerebrum and of the cerebellum was investigated with a scatterplot, and tested with Pearson correlation analysis. We used a significance level of $\alpha = 0.05$ for all analyses.

Results

Participant characteristics

From the 20 HPs included in the study (mean age: 32.8 years, range: 25-54 years, 9 male) 13 were classified[18] as left-handed and 7 as right-handed (Table 1). There were no significant differences between the left and right-handed HPs for age ($t(18)= -0.416$, $p=0.682$) or gender ($p=0.374$, Fisher exact test). Patient characteristics are shown in Table 2. There were no significant differences between the left and right-handed patients for age ($t(36)= -0.723$, $p=0.474$) or gender ($p=0.728$, Fisher exact test). In 24 patients tumors were reported as low-grade and in 13 patients as high-grade upon histopathological examination. Thirty-two of the 38 patients underwent surgery. ECS was performed in 19 of these and language regions were identified in 5.

Table 1: Healthy participant demographics and lateralization indices (LIs)

Age (years)	Gender	EHI score	LI cerebrum	LI cerebellum	Lateralization cerebrum	Lateralization cerebellum
25	M	-100	0.42	-0.36	L	R
30	M	-100	-0.44	0.34	R	L
33	F	-100	-0.27	0.03	R	S
27	F	-100	0.34	-0.41	L	R
28	F	-100	0.02	-0.43	S	R
35	F	-100	0.24	-0.19	L	R
53	M	-90	-0.18	0.13	R	L
36	F	-90	-0.28	0.07	R	S
30	M	-80	0.13	-0.22	L	R
29	M	-78	0.32	-0.40	L	R
28	F	-20	-0.04	-0.13	S	R
31	M	-20	0.48	0.00	L	S

43	M	0	-0.18	0.00	R	S
30	F	100	0.21	-0.30	L	R
34	F	100	0.16	-0.04	L	S
34	M	100	0.32	-0.12	L	R
34	F	100	0.31	-0.46	L	R
29	F	100	0.42	-0.30	L	R
32	M	100	0.33	-0.09	L	S
28	F	100	0.43	-0.25	L	R

Note. – M: male; F: female; Handedness was assessed with the Oldfield's Edinburgh Handedness Inventory (EHI); LI: lateralization index; L: left-sided; R: right-sided; S: symmetrical.

Table 2: Patient and tumor characteristics and language lateralization

A /G/H	Diagnosis / WHO grade / Tumor location	Lateraliza cerebrum	Lateraliza cerebellum	ECS findings
23/F/L	Oligoastrocytoma / II / Right frontoparietal	L	R	Not performed
23/F/R	Astrocytoma /II / Right frontal	L	R	Not performed
31/F/L	Oligodendroglioma / II / Left temporoparietal	L	R	Language not found
31/F/R	Glioblastoma / IV / Left temporoparietal	S	S	Language not found
25/F/L	n.a/n.a/ Left parietal	L	R	Not performed
27/F/R	Astrocytoma / II / Left insula, temporal	L	R	Language left
59/F/L	Oligodendroglioma / III / Left frontal	S	n.a.	Language not found
60/F/R	Oligoastrocytoma / II / Left frontal	L	R	Language left
52/F/L	Oligodendroglioma / II / Right frontal	L	R	Language not found
55/F/R	Oligoastrocytoma / III / Right insula, frontoparietotemporal	L	R	Language not found
26/M/L	Astrocytoma / II / Right temporal	S	n.a.	Not performed
29/M/R	Oligodendroglioma / II / Right temporal	L	R	Language not found
52/M/L	Astrocytoma / III / Right insula, temporoparietal	L	R	Not performed
52/M/R	Glioblastoma / IV / Right insula frontotemporal	L	R	Not performed
40/M/L	Oligodendroglioma / III / Right insula frontoparietal	R	S	Language not found

44/M/R	Astrocytoma / II / Right temporoparietal	R	L	Not performed
27/M/L	Astrocytoma / II / Right insula, frontotemporal	S	S	Language right
31/M/R	Astrocytoma / II / Right insula, temporoparietal	L	R	Not performed
30/M/L	Oligodendroglioma / II / Right frontoparietal	L	R	Not performed
31/M/R	Astrocytoma / II / Right insula, frontotemporal	L	R	Language not found
44/M/L	Glioblastoma / IV / Right frontoparietal	L	n.a.	Language not found
46/M/R	Glioblastoma /IV / Left temporal	L	R	Language not found
26/M/L	Oligodendroglioma / III / Left and right frontal	S	S	Language not found
28/M/R	Astrocytoma / III / Left frontoparietal	L	R	Not performed
41/M/L	Oligodendroglioma / II / Right insula, frontal	L	R	Not performed
50/M/R	Oligodendroglioma / II / Right frontal	L	R	Language not found
14/M/L	Astrocytoma / I / Left temporoparietal	L	R	Not performed
25/M/R	Ganglioglioma / I / Left temporoparietal	L	R	Language not found
26/M/L	Astrocytoma / II / Left insula, frontal	L	R	Language left
28/M/R	Oligoastrocytoma / II / Left frontoparietal	L	R	Not performed
36/M/L	Glioblastoma / IV / Right temporoparietal	L	R	Not performed
41/F/R	Oligodendroglioma / II / Right temporal	L	R	Not performed
48/M/L	Astrocytoma / III / Right insula, frontotemporal	L	R	Not performed
59/M/R	Astrocytoma / II / Right insula, frontal	L	R	Not performed
43/M/L	Oligoastrocytoma / II / Left frontal	S	R	Language not found
41/M/R	Astrocytoma / II / Left frontal	L	R	Language left
38/M/L	Astrocytoma / II / Right insula, frontotemporal	L	R	Not performed
31/F/R	Oligodendroglioma / III / Right frontal	L	n.a.	Not performed

Note. – A: age in years, M: male; F: female; G: gender, H: Handedness was assessed by the neurosurgeon during the presurgical neurological examination; L: left-handed; R: right-handed; WHO: world health organization. L: left lateralized activation; R: right lateralized activation; n.a: not assessable.

Cerebro-cerebellar language lateralization in HPs

The cerebral and cerebellar language lateralization and LIs in HPs are presented in Figure 1 and Table 1. We found a crossed cerebro-cerebellar activation in 60% (12/20) of HPs. None of the participants showed language lateralization towards the same hemisphere in both the cerebrum and cerebellum. Of the 13 left-handed participants, 6 showed typical, and 7 atypical language representation: right lateralized cerebral activation in 5, and symmetrical cerebral activation in 2 participants. Crossed cerebro-cerebellar language activation was observed in 7 left-handed participants (5/6 with typical and 2/7 with atypical language representation). Of the remaining 6 participants, cerebellar activation was symmetrical in 4 and right lateralized in 2. All 7 right-handed participants showed typical language representation of whom 5 showed a crossed cerebro-cerebellar language activation. The remaining 2 participants showed symmetrical activation in the cerebellum.

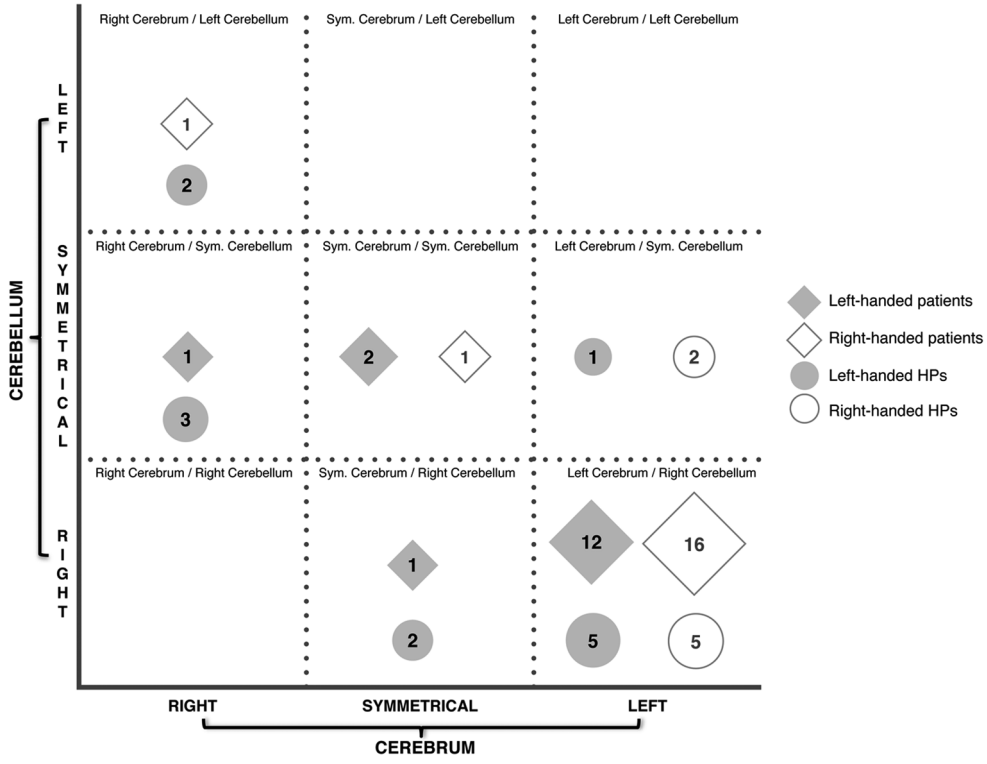

Figure 1. Cerebro-cerebellar language representation in healthy participants and patients. The four patients with no activation in the cerebellum (as described in Table 2) are not represented in this figure. Sym. = symmetrical; HP = healthy participant.

There was a significant dependency between the cerebral and cerebellar language lateralization patterns with X^2 (3, N = 20) = 8.533, p=0.036. The scatterplot (Figure 2) indi-

cated a negative direction of this dependency, with a moderate negative correlation between the LIs of the cerebrum and the cerebellum, Pearson's r(20) = -0.69, p=0.001.

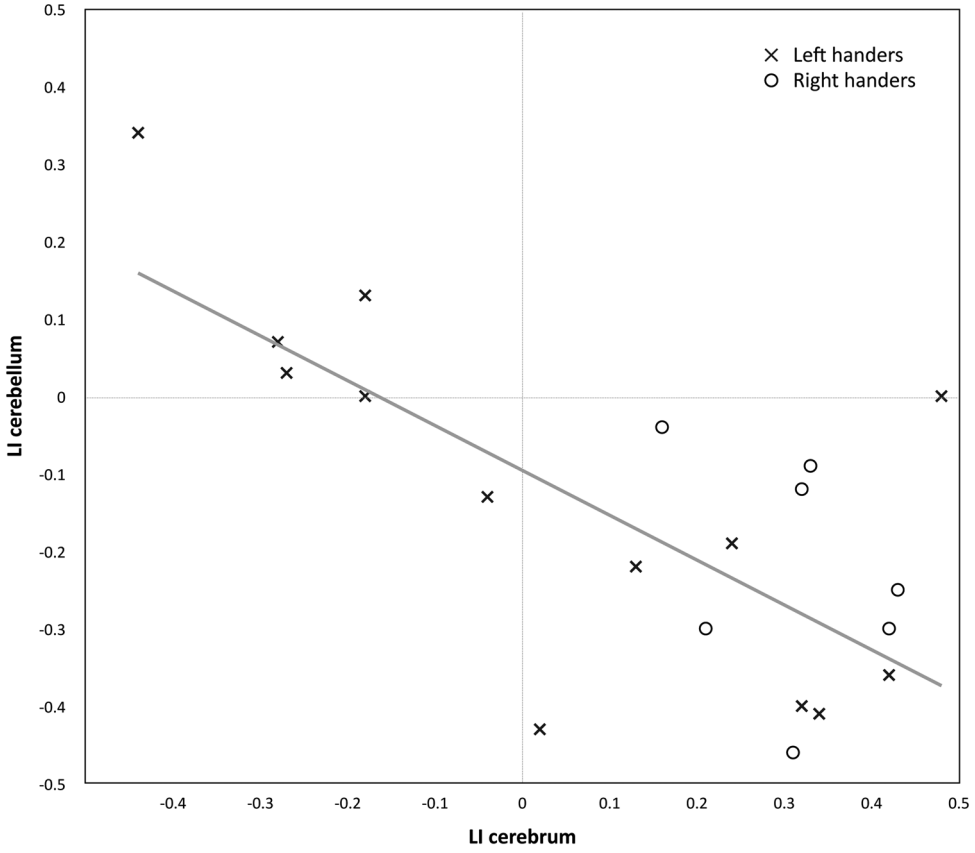

Figure 2. Scatterplot of the healthy participants' lateralization indices (LIs) of the cerebrum and cerebellum.

Cerebro-cerebellar lateralization in tumor patients

The cerebral and cerebellar language lateralization in patients is presented in Figure 1 and in Table 2. We found crossed cerebro-cerebellar activation in 76% (29/38) of patients. None of the patients showed language lateralization towards the same side in both the cerebrum and cerebellum.

Out of the 19 left-handed patients, 13 showed typical, and 6 atypical language representation. Crossed cerebro-cerebellar language activation was observed in 12/13 of left-handed patients with typical language representation. Of the 6 patients with atypical language representation, cerebral language activation was right lateralized in 1 and

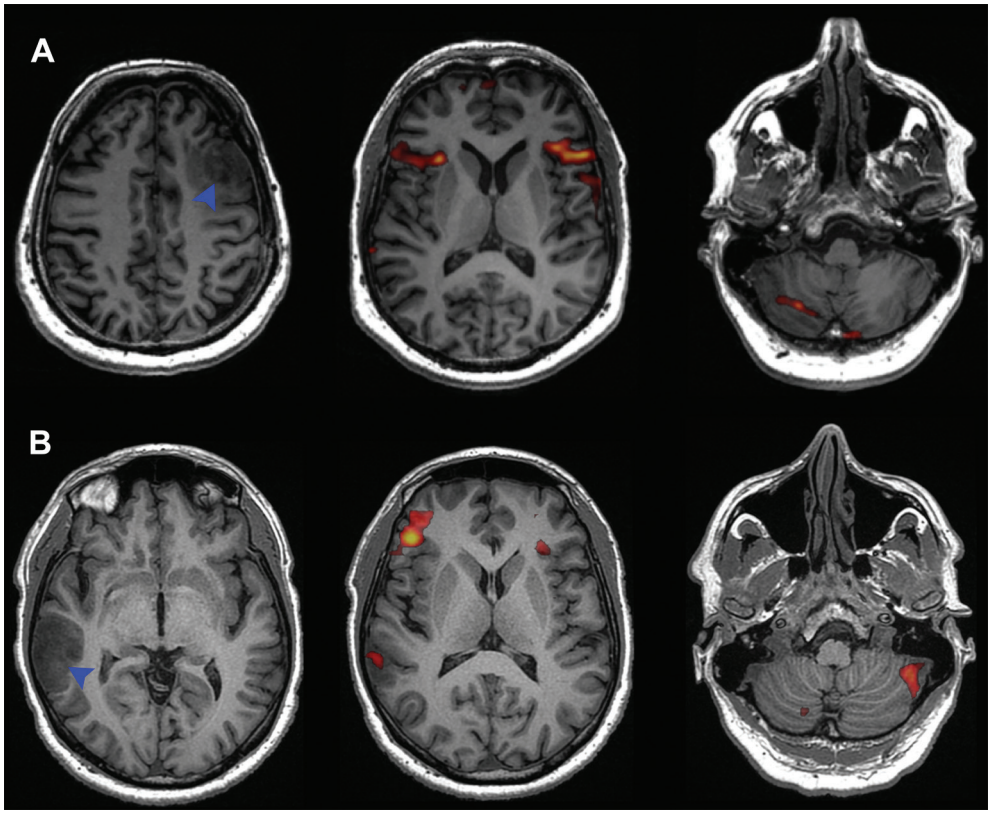

Figure 3. A. Language activation of a left-handed, bilingual patient, with tumor in the left middle frontal gyrus (blue arrowhead), showing symmetrical cerebral activation and right lateralized cerebellar activation, B. Language activation of a right-handed patient, with tumor in the right middle temporal and angular gyri (blue arrowhead), showing atypical, right lateralized cerebral activation and crossed cerebellar lateralization.

symmetrical in 5. Of these, one patient with symmetrical cerebral language activation showed right lateralized activation in the cerebellum (Figure 3A). His tumor was localized in the presumed language areas in the left hemisphere, which could have reduced language activation in the left hemisphere, resulting in a – potentially false – symmetrical language activation pattern. In addition, this patient was a bilingual speaker whose mother tongue was German. Although he was fluent in Dutch, he performed the VG task in his mother tongue while the task was presented in Dutch. It is known that language activation in bilingual patients may be more symmetrical [24], and him performing the task with the interference of both languages may have contributed to the unexpected language activation pattern we observed. The other patients showed symmetrical (3 patients) or no activation (1 patient) in the cerebellum.

Out of the 19 right-handed patients, 17 showed typical, and 2 atypical language representation. Crossed cerebro-cerebellar language activation was observed in 16 out of

the 17 patients with typical language representation. Of the 2 patients with atypical language representation, 1 showed right lateralized cerebral activation with crossed cerebro-cerebellar language representation (Figure 3B). The other patient showed symmetrical cerebral and cerebellar language activation.

There was a significant dependency between the lateralization in the cerebrum and in the cerebellum, X^2 (6, N = 38) = 42.06, p= 0.000.

There were no discordant findings between fMRI and ECS, which positively identified language representation in the same hemisphere in 5 patients. In one of these patients, fMRI language activation was found to be present in both hemispheres, whereas it was only identified on the operated side with ECS (the contralateral hemisphere not having been assessed with ECS).

Discussion

We found a significant dependency between language lateralization in the cerebrum and in the cerebellum, both in HPs and in brain tumor patients, in line with previous studies in healthy left and right-handers with typical language representation.[10, 23] Furthermore, we found a moderate inverse correlation of cerebro-cerebellar lateralization; in other words, the more strongly language was lateralized towards a cerebral hemisphere, the more strongly it was lateralized to the contralateral cerebellar hemisphere. In almost all cases where activation in the cerebellum was lateralized, there was a crossed cerebro-cerebellar lateralization pattern, irrespective of whether language representation was typical or atypical. This means that, as a rule of thumb, in cases of clear cerebellar lateralization cerebral language lateralization can be assumed to be contralateral. Language lateralization in the cerebellum may thus serve as an additional diagnostic feature for determining hemispheric language dominance in people with either typical or atypical language representation. Cerebellar activation was found to be symmetrical in a minority of HPs and patients. In these cases, there was no clear correlation with cerebral language representation; in some cerebral language was also symmetrical, but in others cerebral activation was clearly lateralized. In cases where assessment of cerebral lateralization is hindered by tumor effects and cerebellar activation is symmetrical, another examinations such as the Wada test ECS is thus still required to determine language dominance.[1, 8]

Neuroimaging studies of the VG task indicated that the cerebellum is involved in generating or maintaining articulatory representation[25], even though no speech motor output was required. Both lesion and functional neuroimaging studies suggest that the cerebellum contributes to diverse cognitive language components and aspects of

language production[25, 26], and cerebellar activation has been reported not only in productive tasks but also in speech comprehension tasks.[27] The mechanism underlying the observed crossed cerebro-cerebellar activation remains to be elucidated. Connectome analyses could be used to attempt to find white matter pathways that may be responsible for these findings.

Irrespective of handedness or the side of lateralization, crossed cerebro-cerebellar activation was observed in the vast majority of cases, and particularly in all patients but 1 bilingual, where cerebellar activation was lateralized. This finding is of particular clinical use in cases where hemispheric language dominance cannot be assessed due to the interference of language activation due to tumor interference[2, 28], and in left-handed patients in whom diagnostic uncertainty is greater due to the increased prevalence of atypical language representation.

To the best of our knowledge this is the first study confirming crossed cerebro-cerebellar activation in a large group of HPs and brain tumor patients with a high prevalence of atypical language representation. To assess the correlation between cerebral and cerebellar lateralization quantitatively, we used a threshold independent method, which is less prone to within-subject variability than threshold dependent LI calculation, and generates LIs that are more in agreement with clinical findings[21]. For the assessment of language lateralization in brain tumor patients, we chose to assess language lateralization qualitatively to remain as close to the clinical routine as possible. Studies comparing quantitative with qualitative assessment of language lateralization have shown that visual inspection by an experienced rater is reliable for presurgical assessment of language lateralization[29-31]. This qualitative approach provided a clinically applicable assessment of the cerebro-cerebellar relationship in tumor patients.

The main limitation of our study, as in many studies assessing functional language lateralization presurgically[1, 32], is the relative lack of a gold standard. Next to techniques as the Wada test and ECS that are commonly considered as a gold standard, Transcranial Magnetic Stimulation[33], Magentoencefalography[34] and fMRI are currently being used as presurgical method to evaluate language lateralization. In our study, in combination with fMRI, ECS was performed in the majority of our patients, but in many no language area was identified. ECS assessment is limited to the brain region just surrounding the tumor, and language areas at some distance from the tumor are thus not identified. Even when a language area is identified, we cannot know for certain whether this is the sole, dominant hemisphere: bilateral language representation can not be assessed with certainty. While we found no discordance between ECS and fMRI, the number of patients in whom this could be assessed with certainty was small. A minor limitation of our study is that patients were scanned at several scanners. This is consistent with daily clinical practice. Nevertheless, we used a standardized imaging protocol for presurgical fMRI evaluations, maintaining similar image resolution across our MRI systems, and

standardized image analysis. Another minor limitation was the difference in assessment of handedness: in healthy participants the standardized EHI was used while in patients handedness information was obtained from the preoperative neurosurgical evaluation. Finally, patients with both high and low grade glioma were included in this study. Neurovascular decoupling is a potential limitation of fMRI in high grade tumors. Our study population was too small to allow for a formal comparison or a distinction between these tumor grades.

Conclusion

Cerebellar activation may provide an additional diagnostic feature to assess hemispheric language dominance, both in typical and in atypical language representation. This is particularly useful in left-handed brain tumor patients, in whom language representation is commonly atypical, resulting in diagnostic uncertainty especially when there is potential interference of the tumor with language activation. When cerebellar activation is found to be lateralized, we can as a rule of thumb assume that there is contralateral hemispheric language dominance. This crossed cerebro-cerebellar pattern of activation could be included as a diagnostic tool in future guidelines of clinical fMRI examinations, which should further specify that a language task is used which is known to involve the cerebellum.

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Supplemental Table 1: Scanner specific parameters of the 3D T1w and T2*w sequences

A: 3D T1w acquisition parameters				
Parameters	Discovery 750 (3.0T)	Signa HDx (3.0T)	Discovery 450 (1.5T)	Signa HD (1.5T)
TR	8.2ms	12ms	9.2ms	10.1ms
TE	3.2ms	3.8ms	4.2ms	2.0ms
TI	450ms	300ms	450ms	400ms
FA	12°	18°	12°	20°
FOV	240x240mm	250x175mm	240x180mm	240x240mm
Acquisition matrix	240x240	416x256	256x224	320x224
Slice thickness/ overlap	1.0/0.0mm	1.6/0.8mm	1.6/0.8mm	1.6/0mm
Resolution	1.0 x 1.0 x 1.0mm^3	0.6 x 0.7 x 0.8mm^3	0.9 x 0.8 x 0.8mm^3	0.8 x 1.1 x 1.6mm^3
B: T2*w acquisition parameters				
Parameters	Discovery 750 (3.0T)	Signa HDx (3.0T)	Discovery 450 (1.5T)	Signa HD (1.5T)
TR	3000ms	3000ms	3000ms	3000ms
TE	30ms	30ms	35ms	40ms
FA	90°	75°	75°	60°
FOV	240x180mm	220x220mm	220x220mm	240x240mm
Acquisition matrix	96x64	96x64	96x64	96x64
Number of slices	39	39	39	35
Slice thickness/ gap	2.2/0.3mm	3.5/0.0mm	3.5/0.0mm	3.5/0.0mm
Resolution	2.5 x 2.8 x 2.2mm^3	2.3 x 3.4 x 3.5mm^3	2.3 x 3.4 x 3.5mm^3	2.5 x 3.8 x 3.5mm^3

Note: - All healthy participants were scanned on a 1.5T scanner (Signa HD, GE Healthcare, Wisconsin, USA). Fifteen patients were scanned on a 1.5T scanner (Discovery 450/Signa HD, GE Healthcare, Wisconsin, USA) and 23 patients were scanned on a 3.0T scanner (Discovery 750/Signa HDx, GE Healthcare, Wisconsin, USA). TR= repetition time; TE=echo time; TI=inversion time; FA=Flip angle; FOV= field of view

Chapter 4

Insight into the Neurophysiological Processes of Melodically Intoned Language with Functional MRI

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Abstract

Background and Purpose: Melodic Intonation Therapy (MIT) uses the melodic elements of speech to improve language production in severe nonfluent aphasia. A crucial element of MIT is the melodically intoned auditory input: the patient listens to the therapist singing a target utterance. Such input of melodically intoned language facilitates production, whereas auditory input of spoken language does not.

Methods: Using a sparse sampling fMRI sequence, we examined the differential auditory processing of spoken and melodically intoned language. Nineteen right-handed healthy volunteers performed an auditory lexical decision task in an event related design consisting of spoken and melodically intoned meaningful and meaningless items. The control conditions consisted of neutral utterances, either melodically intoned or spoken.

Results: Irrespective of whether the items were normally spoken or melodically intoned, meaningful items showed greater activation in the supramarginal gyrus and inferior parietal lobule, predominantly in the left hemisphere. Melodically intoned language activated both temporal lobes rather symmetrically, as well as the right frontal lobe cortices, indicating that these regions are engaged in the acoustic complexity of melodically intoned stimuli. Compared to spoken language, melodically intoned language activated sensory motor regions and articulatory language networks in the left hemisphere, but only when meaningful language was used.

Discussion: Our results suggest that the facilitatory effect of MIT may – in part – depend on an auditory input which combines melody and meaning. As such, they provide a sound basis for the further investigation of melodic language processing in aphasic patients, and eventually the neurophysiological processes underlying MIT.

Introduction

Aphasia is a severe language disorder that affects language comprehension and production at different degrees, compromising both spoken and written modalities. The most common cause of aphasia is stroke, in which a neurovascular event damages the language areas localized in the left hemisphere. A common treatment to restore spoken language in severe nonfluent aphasic patients is Melodic Intonation Therapy (MIT)[1]. This form of therapy has recently received much press attention after the successful recovery of U.S. congresswoman Gabrielle Giffords[2]. In a stepwise procedure, MIT uses musical elements of speech such as melody and rhythm[3] to help the patient to initiate language production. In the first steps, the speech and language therapist (SLT) shows the patient how to produce a specific target utterance by "singing" the utterance, i.e. accentuating its melody and the rhythm. This is accompanied by tapping with the left hand. Such melodically intoned auditory input is thought to play a crucial role in facilitating language production, by priming the patient's inner rehearsal of the target utterance[3]. MIT's critical elements, intonation and left-hand tapping, are both thought to be related to right hemisphere activation. Intonation targets the potential role of this hemisphere in processing spectral information, musical features and prosody, while left-hand tapping engages the right hemisphere sensorimotor network that controls hand and mouth movements[3]. Although it is not yet clear whether it is melody, rhythm or their combination used in MIT that specifically aid speech production[4, 5], the treatment has been associated with functional[6] and also structural changes in the right hemisphere[7]. The positive effect of this treatment, hypothetically aiding the reorganization of language representation in the damaged brain, has triggered interest in understanding how the musical elements, that are used in MIT, are processed in the brain.

Neuroimaging studies investigating the differences between spoken and melodic language in healthy volunteers have thus far focused primarily on production (i.e. speaking and singing)[8-11]. Despite the methodological diversity of these studies, in general they report a lateralization effect for singing to the right, and speech to the left hemisphere. Thus, encouraging the aphasic patients to use melody during their speech production may target areas in the undamaged right hemisphere, but the question remains what the role is of the melodically intoned auditory input, that is offered intensively during MIT and that probably plays a crucial role in the initial facilitation of language production.

From this point of view, i.e. reception instead of production, Meyer et al[12] investigated the perceptual differences in processing spoken normal sentences, spoken delexicalized sentences and prosodic speech (speech utterance reduced to speech melody). Melody (pitch variations in speech) is a component of prosody among several others such as rhythm and loudness[13]. Their results suggest that right hemispheric activation observed while processing normal speech stimuli mainly comes from the underlying processing

of prosody. Later studies have focused on the perception of spoken and sung language and have shown differences in hemispheric lateralization[14, 15]. Speech prosody patterns are similar to the musical features in singing such as melody, rhythm and loudness, but they exhibit differences regarding their acoustic features. Callan et al[14] found right lateralized activation of the anterior superior temporal gyrus (STG) for sung language, and a strongly left-lateralized activity pattern for spoken language. Schön et al[15] suggested that linguistic and musical processing have a different hemispheric specialization. Brain activation patterns for sung versus spoken words showed more extended activations in the right temporal lobe, whereas the processing of linguistic aspects in singing versus vocalization showed a predominance in the left temporal lobe. A recent study of Merril et al[16] found that listening to song and speech activated the temporal lobe rather symmetrically. However, substantial nonoverlap was also found: activation in the inferior frontal gyrus (IFG) was left lateralized for spoken words as well as for processing pitch in speech, while right-sided lateralization was found for pitch in song.

The brain regions involved in the auditory perception of melodically intoned language, a simplified version of singing, have not, to our knowledge, been reported. No more than three to four tones are used to exaggerate speech prosody[17, 18]. Melodically intoned language is a key feature in MIT and for a greater insight into its neurophysiological processes, this feature needs to be examined. The aim of the present study is to investigate the differential perceptual processing of spoken and melodically intoned language using functional MRI. We furthermore assessed whether there was an effect of lexical-semantic content, since it is meaningful language that MIT uses to improve everyday communication in aphasic patients. A sparse temporal sampling design was employed for acquisition of the functional imaging data to ensure that scanner noise would not interfere with the auditory stimuli, thus being maximally sensitive to differences between the different types of language stimuli.

Methods

Participants

Twenty right-handed volunteers (median age: 23 years, range: 21-51 years, 15 females) with no neurological or psychiatric history, participated in this study. None of the participants had any particular musical education. They did not use any prescription medication except oral contraception. Handedness was determined with the Edinburgh Handedness Inventory[19] indicating 100% right-handedness in all participants. The study was approved by the institutional review board and all participants gave written informed consent prior to participation. Due to technical failure during data acquisition, one participant (female, aged 21 years) was excluded from the analysis.

Experimental stimuli and paradigm

The experiment consisted of 2 conditions of spoken and melodically intoned stimuli. Each condition contained 3 categories of 30 items each: 1) 30 *meaningful* items (17 real words and 13 short noun, prepositional or verb phrases); 2) 30 *meaningless* items without lexical-semantic information (17 pseudowords and 13 short phrases containing pseudowords); 3) 30 *neutral utterances*, consisting of a repetitive consonant vocal combination ("Nana"). (Figure 1; sample stimuli (in Dutch) can be provided upon request). Within and across both conditions, stimuli were matched across the 3 categories for the number of syllables (range: 2-6), for intonation and stress patterns (for spoken stimuli), melodic contour (for melodically intoned stimuli), semantic content and syntactic structure of the phrases. We chose to use different words as spoken and melodically intoned stimuli to prevent our participants from becoming familiarized with the words, thus avoiding unwanted and unpredictable effects such as habituation, memory and learning. Representative examples of the stimuli from both conditions are given in figure 1, indicating the very minor differences in semantic content between stimuli of a given category such as *"goede morgen"* (good morning) in the spoken condition and *"goede middag"* (good afternoon) in the melodically intoned condition.

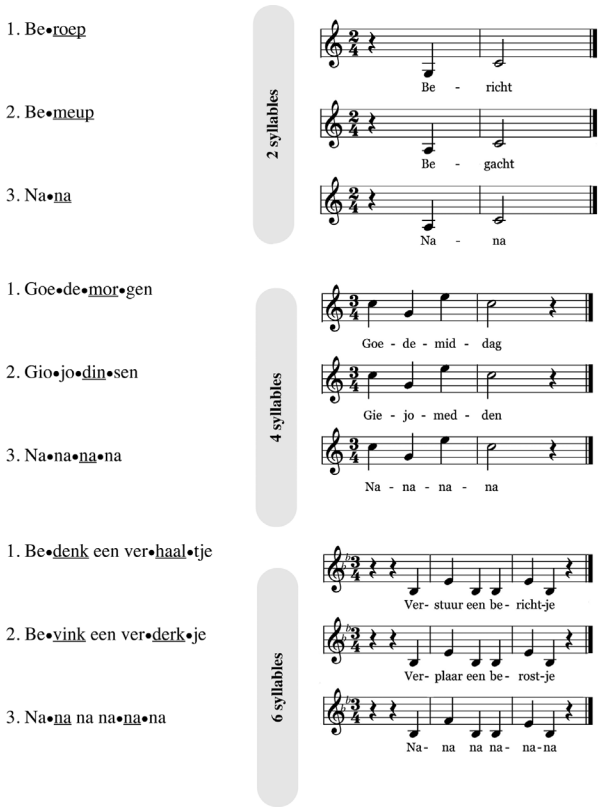

Figure 1. Stimulus examples (in Dutch) of the two experimental conditions. Spoken stimuli (left side of the figure): words are separated into syllables with a black dot. Syllables that are underlined are stressed. Melodically intoned stimuli (right side of the figure): musical notation of the stimulus. In each condition there are three types of stimuli: (1) meaningful, (2) meaningless, and (3) neutral utterances. Provided are examples of words with two and four syllables, and of short phrases of six syllables. Approximately ♩ = 120.

The items were selected by a clinical linguist specialized in MIT and were recorded by a female therapist. Spoken stimuli were recorded with a natural intonation and were not stressed rhythmically in order to keep them as natural as possible. Melodically intoned stimuli were recorded with the same prosodic patterns as those used in MIT. All recorded items had a maximum duration of 3 s. Melodically intoned items were on average longer than the spoken items (2.24 s versus 1.23 s respectively; 2-sample t-test $p<0.0001$).

The experiment was conducted in an event related design consisting of 4 experimental conditions and 2 control conditions. The stimuli in the experimental conditions consisted of 30 melodically intoned meaningful items ("melodic-sense"), 30 spoken meaningful items ("spoken-sense"), 30 melodically intoned meaningless items ("melodic-nonsense"), and 30 spoken meaningless items ("spoken-nonsense"). The 2 control conditions consisted of the neutral utterances, either melodically -intoned (n=30; "melodic-neutral") or spoken (n=30; "spoken-neutral"). The task was presented binaurally through an MR compatible headphone system. Participants were required to press the response button upon hearing a meaningful item by pressing the response pad held in the left hand.

Stimuli were pseudo-randomized using the genetic algorithm toolbox Optimize Design 11[20] and implemented in Matlab version 6.5.1 (The Mathworks Sherborn, MA, US), with optimization for the contrast between melodically intoned versus spoken language primarily (which we will refer to as acoustic information), and for the contrast between meaningful and meaningless language secondarily (lexical-semantic information).

The task was presented using Presentation v13.0 software (Neurobehavioral Systems Inc. Albany, CA, US) installed on a desktop PC, which was dedicated for stimulus presentation. External triggering by the MR system ensured synchronization of the stimulus paradigm with the imaging data acquisition and precise recording of task performance and response times through a fiber optic button response pad.

Participants were familiarized with the task prior to scanning with a sample set of representative items. Behavioral data (responses and reaction times) were collected during scanning. Differences in performance between melodically intoned and spoken items were assessed with a 2 sample t-test.

fMRI image analysis

Imaging acquisition and preprocessing

Scanning was performed on a 3T MR system (HD platform, GE Healthcare, Milwaukee, WI, US). An 8-channel head coil was used for reception of the signal.

For anatomical reference, a high-resolution 3 dimensional (3D) Inversion Recovery (IR) Fast Spoiled Gradient Echo (FSPGR) T1-weighed sequence was used, with the following pulse sequence parameters: repetition time (TR)/echo time (TE)/inversion time (TI) 10.5/2.1/300 ms; flip angle 18°; acquisition matrix 416×256; field of view (FOV) 250×175 mm^2; 172 slices with a slice thickness of 1.6 mm and 0.8 mm overlap; acquisition time 4:40 min.

For functional imaging, a sparse temporal sampling design was employed for acquisition of the functional imaging data, using a single shot T2*-weighted gradient echo echo-planar imaging (EPI) sequence sensitive to blood oxygenation level dependent (BOLD) contrast (TE 30 ms; flip angle 75°; acquisition matrix 64×96; FOV 220×220 mm^2; slice thickness 3.5 mm with no gap; 39 slices with full brain coverage). TR was 6000 ms and acquisition time 3000 ms resulting in a 3000 ms silent gap which was used for presentation of the auditory stimulus. Total duration was 18:30 min.

The functional imaging data acquisition included 5 dummy scans that were discarded from further analysis. Imaging analysis was performed using SPM8 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, UK). Images were manually reoriented to the anterior commissure and subsequently all T2*-weighed functional images were realigned to correct for the participant's motion during data acquisition and were co-registered with the individual's high-resolution T1-weighed anatomical image[21]. The functional and anatomical images were normalized to the standard brain space defined by the Montreal Neurological Institute (MNI) as provided within SPM8, using affine and nonlinear registration. This resulted in resampled voxel sizes of 3x3x3 mm^3 for the functional and 1x1x1 mm^3 for the anatomical images. The normalized functional images were smoothed with a 3D Gaussian Full Width Half Maximum (FWHM) filter of 6x6x6 mm^3 to increase the signal-to-noise ratio, correct for inter-individual anatomical variation and to normalize the data[22].

Statistical analysis of fMRI data

All fMRI data were analyzed within the context of the General Linear Model (GLM), by modeling the experimental conditions convolved with the hemodynamic response function (HRF), corrected for temporal autocorrelation and filtered with a high-pass filter of 128 s cut-off. The neutral conditions were not modeled and served as an implicit baseline. To account for the sparse sampling acquisition, we defined the micro time resolution and onset based on the time bin that corresponded to the middle of the actual acquisition time (1500 ms). Motion parameters were included in the model as regressors of no interest to reduce potential confounding effects due to motion. Because of the significantly longer duration of the melodically intoned versus the spoken stimuli, stimulus duration was modeled as an additional regressor of no interest to ac-

count for confounding stimulus duration effects. The individual t-contrast images for spoken-sense, spoken-nonsense, melodic-sense and melodic-nonsense were used to perform a full-factorial ANOVA group analysis (n=19 participants). The 2 within-subject factors, prosody and lexical-semantic information (equal variance, levels not independent), were entered in this analysis. Main effects as well as the interaction between these factors were investigated. The following contrasts were created to evaluate the main effects of lexical-semantic information: sense>nonsense and nonsense>sense; and of acoustic information: spoken>melodic and melodic>spoken. Interaction effects for acoustic information with lexical-semantic information were explored with the following contrasts: spoken-sense versus spoken-nonsense, melodic-sense versus melodic-nonsense, spoken-sense versus melodic-sense and spoken-nonsense versus melodic-nonsense. The threshold for significance was set at $p<0.05$ family wise error (FWE) corrected for multiple comparisons.

Anatomical labeling of significantly activated clusters was performed using the Automated Anatomical Labeling map [23] software extension to SPM8, using the extended local maxima labeling option. Figures were created with the SPM render function.

Results

Task performance

Participants performed well in both conditions with an average accuracy of 96% (SD: 3%). Performance was equally high in both conditions (p=0.486).

fMRI activation results

Lexical-semantic information: main effect and interactions

We found a main effect for the lexical-semantic information factor ($F(1,72) = 26.27$ $p_{FWE\ corrected} < 0.05$). Post-hoc analysis revealed no increased activation for the meaningless items compared to meaningful items (nonsense>sense). For the meaningful items compared to meaningless items (sense>nonsense) increased activation was seen left lateralized in the supramarginal gyrus (SMG) and inferior parietal lobule (IPL). Increased bilateral activation was seen in the rolandic operculum, insula, supplementary and cingulate motor area. Right sided activation was observed in the pre- and postcentral gyrus at the level of the hand motor area, presumably due to the button presses (Figure 2A; Table 1).

Table 1. Anatomical location, cluster sizes (k, number of voxels), MNI coordinates and statistical T-values of areas of significant activation for the contrast sense>nonsense ($p_{FWE\ corrected}$<.05, k≥10). The percentages reflect the proportion of the activated cluster localized in each anatomical region.

Anatomical location	Side	Cluster size	MNI			T-value
			x	y	z	
Inferior parietal lobule (50%) Supramarginal gyrus (40%)	L L	259	-54	-31	40	8.08
Rolandic operculum/insula (100%)	L	24	-48	-1	4	5.87
Rolandic operculum/insula (100%)	R	34	48	5	4	6.27
Supplementary motor area (70%) Middle cingulate gyrus (50%)	L/R L/R	512	6	-4	52	10.00
Pre- and postcentral gyrus (82%) Supramarginal gyrus (5%) Inferior parietal lobule (4%)	R R R	645	36	-22	49	15.57
Thalamus (50%)	R	51	15	-22	4	6.51
Cerebellum (100%)	L	23	-18	-61	-23	5.74

L= left hemisphere; R=right hemisphere; MNI=Montreal Neurological Institute.

For spoken items, no significantly increased activation was found for meaningless compared to meaningful items (spoken-nonsense>spoken-sense). However, increased activation was seen for meaningful compared to meaningless items (spoken-sense>spoken-nonsense) in the left SMG and IPL, and bilaterally in the supplementary and cingulate motor area (Figure 2B; Table 2). Furthermore, there was increased right sided activation in the pre- and postcentral gyrus, presumably due to the button presses.

Table 2. Anatomical, cluster sizes (k, number of voxels), MNI coordinates and statistical T-values of areas of significant activation for the contrast spoken-sense>spoken-nonsense ($p_{FWE\ corrected}$<.05, k≥10). The percentages reflect the proportion of the activated cluster localized in each anatomical region.

Anatomical location	Side	Cluster size	MNI			T-value
			x	y	z	
Inferior parietal lobule (57%) Supramarginal gyrus (43%)	L L	63	-54	-31	40	6.82
Supplementary motor area (70%) Middle cingulate gyrus (30%)	L/R L/R	147	6	-7	52	7.77
Pre- and postcentral gyrus (94%)	R	395	42	-25	55	12.91

L= left hemisphere; R=right hemisphere; MNI=Montreal Neurological Institute

For melodically intoned items, no significantly increased activation was found for melodically intoned meaningless compared to meaningful items (melodic-nonsense>melodic-sense). For meaningful items compared to meaningless items (melodic-sense>melodic-nonsense) increased activation was seen left lateralized in the SMG and IPL. Left sided activation was observed in the posterior portion of the middle and superior temporal

gyrus (Sylvian parieto-temporal area) and in the middle and superior frontal gyrus (Figure 2C; Table 3). Right lateralized activation was seen in the insula, rolandic operculum, and pars opercularis of the inferior frontal gyrus (IFG). Increased bilateral activation was observed in the supplementary and cingulate motor area. Furthermore, increased right lateralized activation in the pre- and postcentral gyrus was seen, presumably due to the button presses.

Table 3. Anatomical, cluster sizes (k, number of voxels), MNI coordinates and statistical T-values of areas of significant activation for the contrast melodic-sense>melodic-nonsense ($p_{FWE\ corrected}$<.05, k≥10). The percentages reflect the proportion of the activated cluster localized in each anatomical region.

Anatomical location	Side	Cluster size	MNI			T-value
			x	y	z	
Inferior parietal lobule (50%) Supramarginal gyrus (40%)	L L	293	-51	-31	37	6.94
Inferior parietal lobule (20%) Angular gyrus (5%) Occipital middle gyrus (75%)	L L L	27	-30	-73	40	6.32
Superior and middle temporal gyrus (100%)	L	37	-57	-52	19	6.39
Superior and middle frontal gyrus (100%)	L	10	-21	20	58	5.91
Middle frontal gyrus (90%) Inferior frontal gyrus: pars triangularis (10%)	L L	28	-30	35	25	5.89
Insula (85%)	L	21	-36	11	4	5.70
Rolandic operculum/insula (97%)	L	24	-40	-1	7	5.75
Rolandic operculum/insula (66%) Inferior frontal gyrus: pars opercularis (10%)	R R	146	48	5	1	7.34
Supplementary motor area (37%) Middle cingulate gyrus (40%)	L/R L/R	900	6	-4	52	9.37
Pre- and postcentral gyrus (75%)	L	20	-54	2	22	5.58
Pre- and postcentral gyrus (77%) Supramarginal gyrus (7%) Inferior parietal lobule (4%)	R R R	669	36	-22	49	13.81
Thalamus (100%)	L	16	-12	-28	10	5.59
Thalamus (39%)	R	122	-3	-25	-2	7.01
Putamen (85%)	R	13	21	17	-11	5.35
Cerebellum (100%)	L	36	-21	-61	-23	5.95

L= left hemisphere; R=right hemisphere; MNI=Montreal Neurological Institute

Acoustic information: main effect and interactions

We found a main effect for the acoustic information factor ($F(1,72) = 26.31$ $p_{FWE\ corrected} < 0.05$). Post-hoc analysis revealed no increased activation for spoken compared with melodically intonated items (spoken>melodic). For the melodically intoned compared to spoken items (melodic>spoken), increased activation was seen bilaterally, but more pronounced in the left hemisphere, in the superior and middle temporal gyrus, Heschl's gyrus, supplementary motor area and in the ventral pre- and postcentral gyrus (at the level of the primary motor and somatosensory area of the face). In the posterior portion of the superior and middle temporal gyrus (Sylvian parieto-temporal area) activation was mainly left sided (Figure 2D; Table 4).

Table 4. Anatomical location, cluster sizes (k, number of voxels), MNI coordinates and statistical T-values of areas of significant activation for the contrast melodic>spoken ($p_{FWE\ corrected} < .05$, $k \geq 10$). The percentages reflect the proportion of the activated cluster localized in each anatomical region.

Anatomical location	Side	Cluster size	MNI			T-value
			x	y	z	
Superior and middle temporal gyrus (88%) Heschl's gyrus (12%)	L L	60	-51	-16	4	8.79
Superior and middle temporal gyrus (75%) Heschl's gyrus (4%)	L L	92	-51	-40	13	7.74
Superior temporal gyrus and pole (92%) Heschl's gyrus (7%)	R R	76	54	-10	1	7.16
Superior temporal gyrus (100%)	R	12	66	-26	7	5.63
Supplementary motor area (100%)	L/R	45	-3	-1	64	7.06
Pre- and postcentral gyrus (100%)	L	68	-51	-13	43	8.93
Pre- and postcentral gyrus (100%)	R	41	54	-4	43	7.72

L= left hemisphere; R=right hemisphere; MNI=Montreal Neurological Institute

For meaningless items, no increased activation was found for spoken versus melodically intoned items (spoken-non-sense>melodic-nonsense; melodic-non-sense>spoken-nonsense). Furthermore, for meaningful items, no increased activation was found for spoken compared with melodically intoned meaningful items (spoken-sense>melodic-sense). Only for melodically intoned compared to spoken meaningful items (melodic-sense>spoken-sense) increased activation was seen bilaterally in the superior and middle temporal gyrus, insula, supplementary and cingulate motor area, and in the ventral pre- and postcentral gyrus (at the level of the primary motor and somatosensory area of the face). Right lateralized activation was seen in the pars opercularis and triangularis of the IFG. Left sided activation was seen in the posterior portion of superior and middle temporal gyrus (Sylvian parieto-temporal area) (Figure 2E; Table 5).

Table 5. Anatomical, cluster sizes (k, number of voxels), MNI coordinates and statistical T-values of areas of significant activation for the contrast melodic-sense>spoken-sense ($p_{FWE\ corrected}$<.05, k≥10). The percentages reflect the proportion of the activated cluster localized in each anatomical region.

Anatomical location	Side	Cluster size	MNI			T-value
			x	y	z	
Superior and middle temporal gyrus (48%) Heschl's gyrus (5%) Pre- and postcentral gyrus (36%)	L L L	578	-51	-13	43	9.73
Superior and middle temporal gyrus (100%)	L	25	-51	-1	-11	6.44
Superior and middle temporal gyrus (90%) Heschl's gyrus (6%) Superior temporal pole (4%)	R R R	315	54	-10	-2	7.59
Angular gyrus (29%) Superior and middle occipital gyrus (71%)	R R	17	33	-64	34	5.62
Insula (57%)	L	19	-27	23	-2	6.13
Insula (48%)	R	25	30	23	-2	5.89
Inferior frontal gyrus pars opercularis (80%) Inferior frontal gyrus pars triangularis (20%)	L L	38	-45	14	19	6.38
Inferior frontal gyrus pars triangularis (25%) Inferior frontal gyrus pars opercularis (18%) Pre-and postcentral gyrus (46%)	R R R	271	54	-4	43	7.83
Supplementary motor area (51%) Superior medial frontal gyrus (30%) Middle cingulate gyrus (10%)	L/R L/R R	282	-6	2	61	7.60
Caudate nucleus (100%)	R	28	9	11	1	5.86

L= left hemisphere; R=right hemisphere; MNI=Montreal Neurological Institute

Discussion

Using a dedicated silent-gap acquisition, we found different patterns of activation for the auditory processing of melodically intoned language compared to normal spoken language. Compared to spoken language, melodic language recruited left sided brain regions in the left posterior portion of the superior and middle temporal gyrus (Sylvian parieto-temporal area), as well as the operculum and IFG with a right sided lateralization. Additionally there was activation along the superior temporal gyrus bilaterally. With regards to lexical-semantic processing, spoken and melodically intoned language showed similar left sided activation in the SMG and IPL.

Although our primary focus was to investigate auditory perception of spoken and melodically intoned language, we also investigated the informative content of the audi-

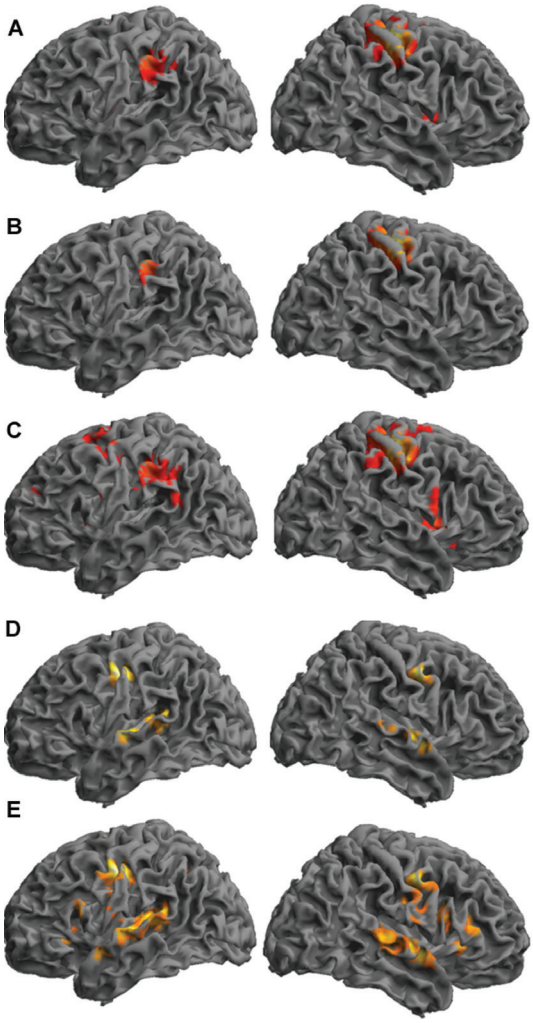

Figure 2. Three dimensional brain rendering with superposition of the activation maps displayed at PFWE corrected<0.05, k ≥ 10 for the following contrasts: (A) sense > nonsense stimuli, (B) spoken- sense > spoken-nonsense stimuli, (C) melodic-sense > melodic-nonsense, (D) melodic > spoken stimuli, (E) melodic-sense > spoken- sense stimuli.

tory stimuli. In the context of MIT this is important, because patients are trained with meaningful items, initially those that are frequently used in every day language and then progressing to less familiar utterances. The selected meaningful (real words) and meaningless (pseudowords) items only differed with respect to their accessibility to lexical access and meaning. For meaningful items both the word form and lexical-semantic content are successfully accessed, while such information is not available for meaningless items. We did not find any increased activation for meaningless compared to meaningful language. This finding is in line with the results of Binder et al[24] who also did not find differences when directly comparing brain activation patterns of participants passively listening to meaningless words (pseudowords and reversed words) with meaningful words. Furthermore, our results showed that irrespective of whether the items were normally spoken or melodically intoned, meaningful items showed greater activation in the SMG and IPL. This is in line with a review by Fiez[25] who suggested that long-term storage of conceptual and semantic knowledge is dependent on posterior regions. As expected, this activation was lateralized to the left hemisphere, which is dominant for speech processing[26, 27]. This finding is generally aligned with previous neuroimaging studies investigating lexical-semantic processing which, despite the use of various different tasks designs, reported activation for meaningful language in the inferior parietal areas around the temporo-parietal junction[28-31]. The activation emerging from such lexical decision tasks can principally be attributed to either lexical access or semantic processing. Contrary to what lesion language mod-

els propose, these two main processes are difficult to disentangle in the undamaged brain.

Overall melodically intoned stimuli compared to spoken stimuli showed bilateral, somewhat left lateralized activation, in the superior temporal gyrus and frontal/motor regions. Left sided activation was seen in the posterior portion of the superior and middle temporal gyrus, which was coined by Hickok and Poeppel[32] the Sylvian parieto-temporal (Spt) area. This Spt area is thought to be part of an auditory-motor integration system: a sensorimotor interface related to both speech comprehension and phonological aspects of speech production[33-35]. This area is thus activated for language production and guides speech perception. Nevertheless, Hickok et al[34] suggested that activation in the Spt area is not specifically dedicated to speech because it was found to be equally activated by both speech and non-speech stimuli. In fact, the Spt area was even found to respond better to music stimuli than to speech, indicating some degree of specificity for tonal stimuli within portions of this area. This degree of specificity for tonal stimuli is in line with our results showing increased activation for melodically intoned items, presumably due the tonal pattern of the melodic stimuli. So although this area is maybe not unique to speech signals as suggested by Hickok et al[34] it is sensitive to the tonal differences between normal speech and melodically intoned speech. What is interesting to note, however, is that we found pronounced activation in the Spt area specifically for the processing of *meaningful* melodically intoned items. Thus, it is not only the tonal pattern that triggers the activation in this area, but it is also the lexicality of the stimuli that plays an important role in activating this area.

The activation in the Spt area was accompanied by bilateral ventral motor activation at the level representing the face, and there was additional activation in the left IFG when lexical-semantic content was present. These findings can partially be interpreted in the context of the dorsal stream model proposed by Hickok and Poeppel[36] for auditory processing. The dorsal stream projects connections from the Spt area to the left frontal cortices, specifically to the dorsal portion of the premotor cortex and to the left IFG and ventral portion of the premotor cortex. The latter two are called the articulatory network[36]. This stream is thought to be involved in translating acoustic speech signals into articulatory representations in the frontal lobe. It is essential for speech production and guides speech perception before the next stage of speech comprehension. [36] Furthermore, the bilateral activation in the primary motor area at the level representing the face may be interpreted in the context of the pioneer motor theory of speech perception proposed by Liberman and Mattingly. [37] This theory suggests that co-articulation occurs in parallel to auditory processing to aid the auditory system in separating speech segments over longer intervals of time[38]. Taken together, our findings suggest that melodically intoned language perception recruits the articulatory system in the dorsal stream as well as motor priming areas more strongly than that of spoken language. This is an important finding in the context of MIT, since the first stages of this therapy focus on

intensively providing auditory input with prosodic features different from those used in normal speech. Such auditory input, simulated here with melodically intoned speech items, thus hypothetically serves to facilitate the activation of the articulatory system and priming of the motor areas for language production. Again, it seems that lexical-semantic content needs to be present for such processes to be optimally involved.

Furthermore, melodically intoned stimuli activated both temporal lobes rather symmetrically, as well as the right frontal lobe cortices, more than the normally spoken stimuli. This finding is in line with the study of Merril et al[16]. By using both a univariate and multivariate analysis the authors identified overlapping activation for song and spoken language in the superior temporal lobe bilaterally, but also suggested a differential role of the IFG and intraparietal sulcus in processing song and speech. Similar overlapping activation for speech and music stimuli in the superior temporal lobe bilaterally has been reported by Rogalsky et al[39]. In a review of fMRI studies investigating language processing, Price[40] highlighted that bilateral superior temporal lobe activation likely reflects differences in the acoustic complexity of the presented auditory stimuli. The present findings are therefore most likely a reflection of the different levels of auditory processing within the auditory cortex involved with melodically intoned language. We found that there was no increased activation along the superior temporal lobe during the auditory processing of spoken compared with melodically intoned stimuli, suggesting that the superior temporal lobe activation likely reflects the processing of different temporal information present in melodic intonation due to longer syllable duration[41]. This is a feature that aphasic patients following MIT may also get benefit from, because they also have a basic deficit processing the rapidly changing sequential information[42]. In addition, we see that the right frontal operculum and the pars opercularis of the IFG are more engaged in the processing of melodically intoned compared with spoken stimuli. The study of Merril et al[16] reported a similar role of the right IFG for pitch processing in song. Similar results were previously reported by Meyer et al[12], who investigated brain activation of the prosodic patterns of normal speech. This finding supports in part the hypothesis underlying MIT that musical elements of speech (melody and rhythm) engage right hemisphere frontal cortices. In melodically intoned language, which is a simplified version of singing, speech prosodic patterns are exaggerated by altering many acoustic features of normal spoken language[43]. The type of prosody we use in our melodically intoned stimuli is referred to as linguistic prosody, a type of prosody used in normal speech when stressing syllables, changing intonation while asking a question, and even when using intentioned melodies during mother-to-child speech. It is indeed the pars opercularis of the IFG, according to a recent meta-analysis of Belyk and Brown[44] that is more likely to become activate with linguistic prosody.

Some neuroimaging studies have aimed to differentiate the neural mechanisms of musical features of speech by either comparing spoken language with sung language or by using novel tones. To our knowledge, no previous neuroimaging study has investigated

the neural processing of melodically intoned meaningful language, an essential feature of MIT. While our findings strongly support the hypothesis that melodically intoned language is processed differently from spoken language, there are some issues that may need to be taken into account. Firstly, in order to keep participants engaged during the experiment, we decided to include a button press. The hand motor activation could easily be identified and could therefore simply be disregarded to not interfere with the further interpretation of the results of interest. Nevertheless, we need to consider the possibility that this button press upon meaningful words may have shifted attention toward meaningful items. Secondly, melodically intoned language is inherently slower than spoken language. The consequently longer exposure to melodically intoned stimuli may lead to unspecific increases in activation, which we accounted for by modeling the stimulus duration as a regressor of no interest. Thirdly, our stimuli set included both words and short phrases, so some confounding of lexical semantic and syntacting processing cannot be excluded with certainty. Finally, and crucially, although our eventual interest is aimed at understanding the effect of melody used in MIT for the treatment of aphasic patients, here we investigated the processing of melodic language in healthy participants. This is the first and necessary step in understanding the neurophysiological mechanisms underlying MIT, but our findings cannot be directly translated to aphasic patients. In our future work we will investigate melodic language processing, as well as the effect of MIT, in aphasic patients.

In conclusion, the present study demonstrates that the auditory processing of melodically intoned language activates a left lateralized motor-sensory network, which is much more engaged when lexical-semantic content is present, related to the articulatory system and motor priming. These systems are of great interest in the context of MIT. In line with the observations from lesion studies, Belin et al[43], that perilesional activation appears in aphasic patients after successful MIT, we can hypothesize that this therapy triggers not only activation in areas in the right hemisphere (as it was initially hypothesized by the developers of MIT) but may also activate perilesional areas in the left hemisphere. Naeser and Helm-Estabrooks[45], reported that patients with a lesion in Broca's area that extended to pre-motor area and lower motor sensory cortex area of the face are those that benefit the most of MIT therapy. When using the MIT technique, SLTs provide the aphasic patient with an auditory input of melodically intoned meaningful language. This activation might facilitate the production of the primed utterances, which enables the patient to train production of meaningful utterances. In addition, we found right hemispheric activation in the frontal operculum and IFG, which supports in part the hypothesis underlying MIT that musical elements of speech (melody) engage right hemisphere frontal cortices. The combination of melody and meaning in the auditory input may be a crucial aspect of MIT and that this technique improves language production by targeting language function as well as speech functions. Our current study provides a sound basis for the further investigation of melodic language processing in aphasic patients, and eventually the neurophysiological processes underlying MIT.

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Chapter 5

Differential Involvement of the Left Inferior Frontal Gyrus During Auditory Phonological and Semantic Processing in Older Healthy Adults

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Abstract

Background: Previous studies of phonological and semantic processing used language paradigms that were mainly focused on language production, and mostly included young participants. We examined the neural substrate of phonological and semantic auditory, i.e. receptive, processing in healthy older adults, which is more applicable to aphasia research. We specifically focus on the functional specialization within the left inferior frontal gyrus (IFG), given its proposed important role for compensation of language function in aphasia recovery.

Methods: Twenty-five healthy right-handed older adults performed an auditory phonological (rhyme decision) and semantic (semantic association) task during functional MRI. We performed whole-brain and region of interest (left IFG) analyses.

Results: Each linguistic process activated a different portion of the left IFG: phonological processing recruited the posterior dorsal part (BA44), while semantic processing recruited the anterior ventral part (BA47) of the IFG. Semantic compared to phonological processing also showed increased activation bilaterally in the middle temporal and middle frontal gyrus, in the left IFG pars orbitalis and inferior parietal lobule, and the right cerebellum.

Conclusion: These findings extend the previously described differentiation within the IFG for productive phonological and semantic processing to receptive processing of these linguistic processes in an older population. This allows for eventually furthering our insight into the neural mechanisms of cognitive-linguistic aphasia therapy and the – differential – role of the IFG in language recovery.

Introduction

Phonological and semantic processing are basic communicative functions with direct implications for word finding in spoken language[1,2]. Word finding disorders are frequently observed in patients with brain damage of various etiologies such as stroke, neurodegenerative disease and tumor[3-5]. A clarification of the underlying functional and neural mechanism is especially relevant for aphasic stroke patients. A word finding deficit (anomia) is one of the central and persistent problems in this patient group irrespective of their aphasia classification[6]. Cognitive-linguistic treatment methods that specifically target language at its impaired components, namely semantic and phonological processing, have shown to be effective for language recovery[7,8]. Especially at an early stage of aphasia after stroke, cognitive-linguistic treatment is thought to interact with the natural restoration of the neural circuits, specialized in the targeted functions[9,10]. However, the precise treatment-induced neural mechanisms are as yet relatively unknown[11-13] and can be further studied with functional imaging.

The neural substrates of normal phonological and semantic processing have been explored in functional neuroimaging studies with a variety of language paradigms, either evaluating these linguistics levels with an orthographic or auditory input route. Furthermore, some studies use phonological processing as a control condition to contrast semantic processing to directly[14]. The results have significantly improved our insight into the individual functional contribution of these language components. Insight into these processes is crucial for evaluating language recovery after aphasia. The current notion is that the left hemisphere language areas are crucial for successful therapy-induced recovery[12,13]. The specific left hemisphere key areas that are relevant for successful outcome with a specific therapy approach are not yet clearly identified, but the importance of the left inferior frontal gyrus (IFG) for compensation of language functions in aphasia has been highlighted in several studies [15-17]. Left IFG activation after language treatment has recently been reported to be significantly correlated with naming improvement[18], and with impairment-specific therapy[12]. Nevertheless, we do not know whether therapy focusing on semantic or phonological processing separately has differential effects on left IFG involvement in language recovery.

Despite efforts to refine methods and tasks, functional neuroimaging studies have not revealed consistent patterns of activation for phonological and semantic processing, possibly due to the diversity of the paradigms used to explore their neural roots. Both semantic and phonological processing require that both the input and output routes are intact, responsible respectively for the *perception* and the *production* of language. From studies using mainly verbal fluency, i.e. *productive*, language tasks two hypotheses regarding the functional organization of the left IFG in relation to phonological and semantic processing have arisen. One hypothesis suggests an anatomical differentiation for phonological and semantic operations within the left IFG[19-21]. The second hypothesis

proposes that both processes are encompassed within a more general "supramodal executive function" (i.e. for selecting task-relevant information among competing alternatives) of the left IFG [22,23]. In a meta-analysis, Costafreda et al.[24] reviewed both hypotheses and found that the results were most in accordance with the anatomical differentiation hypothesis: phonological fluency is represented in the dorsal portion of the IFG and semantic fluency in the ventral portion of the IFG. A subsequent study of Heim et al. [25] was partially in line with this meta-analysis. Phonological fluency activated the posterior portion of the left IFG more strongly than semantic fluency. Contrary to what was expected, however, semantic fluency did not elicit higher activation than phonological fluency in any part of left IFG.

Due to the fact that the vast majority of these studies have assessed these linguistic processes with speech production tasks – the language output route – the neural substrates of phonological and semantic processing via reception tasks, i.e. the language input route, is largely unexplored. Adequate phonological and semantic processing is dependent on intact in- and output routes. Furthermore, studies have been mostly focused on young participants, while insight into these processes is of particular interest in the older population, in which aphasia due to stroke is more frequent. During aging, our ability to understand and produce words changes, as shown by the few neuroimaging studies that investigated phonological and semantic processing in an older population[26-28].

In summary, from productive language studies in young healthy volunteers a functional differentiation for semantic and phonological processing within the left IFG can be suspected, which may have implications for language recovery and treatment options after aphasic stroke. Current findings however cannot be directly be extrapolated and applied to the study of neural plasticity after stroke. Firstly, because it is not known whether such functional differentiation is also present in older people, and secondly, because productive language tasks are highly demanding for aphasic patients. To study these linguistic processes in aphasic patients, a language task that taps into the input route, i.e. a perception task, is required instead.

In the present study, we used functional MRI with two receptive language paradigms in healthy older participants. The purpose of this study was to investigate the neurophysiological substrates of phonological and semantic language processing in healthy older adults, with a specific focus on the functional specialization of the left IFG.

Methods

Participants

Twenty-five right-handed volunteers (mean age 57 years, range: 43-70 years, standard deviation:8.3, 11 female) participated in this study. All participants were native Dutch speakers. Handedness was determined with the Edinburgh Handedness Inventory[29] indicating 100% right-handedness in all participants. None were under medical treatment or reported a history of neurological or psychiatric disorders. The study was approved by the institutional review board and all participants gave written informed consent prior to participation.

fMRI language paradigms

All participants performed an auditory phonological task (rhyme decision) and an auditory semantic task (semantic association decision). We preferred auditory over visual input to avoid the – difficult – conversion of orthographic information to phonological codes and overt articulation[30]. Stimuli in each task consisted of 36 pairs of disyllabic nouns, matched for word frequency within and across the tasks. All items were selected by a clinical linguist and were recorded with neutral prosody by a male speech and language therapist. Both tasks had the same control condition, in which either a tone (500Hz) or noise (Brownian noise) was presented. All recorded items had a duration of 3 s. The tasks were presented binaurally through an MR compatible headphone system (MR Confon, Magdeburg, Germany). Auditory stimuli were delivered using Presentation v13.0 software (Neurobehavioral Systems Inc. Albany, CA, US) installed on a desktop PC. External triggering by the MR system ensured synchronization of the stimulus paradigm with the imaging data acquisition and precise recording of task performance and response times through a fiber optic button response pad.

Each task was conducted in a block design consisting of 1 experimental condition and 1 control condition. Each task consisted of 12 alternating blocks of 21 s each. Each block in the experimental and control conditions started with a short instruction of 3 s duration. The blocks of the experimental condition consisted of 6 word pairs. Per block, half of the pairs rhymed in the phonological task, and half of the pairs were semantically associated in the semantic task. The order of these target stimuli was randomized in each experimental block. The control condition consisted of 3 tones and 3 noises, the order of which was also randomized within the blocks. Participants were required to press a response button upon hearing a word pair that rhymed or was semantically associated (in the phonological and semantic task respectively). In the control condition participants were required to press to the button upon hearing the noise. In order to minimize hand motor activation in the left hemisphere, even though this was expected to be accounted for in the control condition, we instructed the participants to press the

response button with the left hand. Participants were familiarized with the task prior to scanning inside the scanner. Different sample sets of items were used in the practice and fMRI sessions. Performance accuracy was calculated in the experimental conditions only, as the percentage of correctly identified and correctly rejected stimuli out of the total number of stimuli.

fMRI image analysis

Image acquisition and preprocessing

Scanning was performed on a 3.0T Discovery system (GE Healthcare, Milwaukee, IL, USA). An axial three-dimensional (3D) inversion recovery fast-spoiled gradient (FSPGR) T1-weighted image (echo time (TE)/ repetition time (TR)/inversion time (TI) 2.1/6.1/450 ms, flip angle 12 degrees, matrix 256 x 224, FOV 24.0x18.0 cm) with an effective slice thickness of 0.8 mm was acquired for anatomical registration purposes. Functional scans were acquired using a gradient echo-planar imaging pulse sequence (TE/TR 30/3500 ms, flip angle 90 degrees, matrix 96 x 96, FOV 24.0 - 26.0 cm) with a slice thickness of 3.0 mm (no gap). Total acquisition time was 5:12 min, which included 17:30 s of dummy scans that were discarded from further analysis.

Imaging data analysis was performed using SPM8 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, UK). Before spatial pre-processing, anatomical and functional images were manually aligned to the anterior commissure as reference plane. Subsequently all functional images were realigned to correct for the participant's motion during data acquisition.. Realignment graphs were inspected to check for excessive motion, none showing head displacement exceeding 3mm (voxel size). Realigned images were co-registered with the individual's high-resolution T1-weighed anatomical image[31]. The functional and anatomical images were normalized to the standard brain space defined by the Montreal Neurological Institute (MNI) using the "unified segmentation" [32] algorithm available within SPM8 . This resulted in resampled voxel sizes of 3x3x3 mm^3 for the functional and 1x1x1 mm^3 for the anatomical images. The normalized functional images were smoothed with a 3D Gaussian Full Width Half Maximum (FWHM) filter of 6x6x6 mm^3 to increase the signal-to-noise ratio, correct for inter-individual anatomical variation and to normalize the data [33].

Statistical analysis of fMRI data

All fMRI data were analyzed within the context of the General Linear Model (GLM), by modeling the experimental and the control conditions excluding the instructions provided at the beginning of each block. The blocks were convolved with the hemodynamic response function (HRF), corrected for temporal autocorrelation and filtered with

a high-pass filter of 128 s cut-off. Motion parameters were included in the model as regressors of no interest to reduce potential confounding effects of motion. First, the individual t-contrast images for the rhyme versus control (phonological processing) and the semantic association decision versus control (semantic processing) conditions were used to assess main effects of phonological and semantic processing respectively using one sample t-test group analyses. Second, the same t-contrasts were used to assess differences between phonological and semantic processing using a paired samples t-test. The following contrasts were created: phonological > semantic processing, and semantic > phonological processing. The threshold for significance to test for main effects was set at $p<0.05$ family wise error (FWE) corrected for multiple comparisons at peak level. For the direct comparison the threshold for significance was set at $p<0.05$ FWE corrected for multiple comparisons at cluster level.

To quantify the involvement of each portion of the left IFG in phonological and semantic processing, mean beta-values, representing activation estimates, were extracted from the pars orbitalis (POr), triangularis (PTr) and pars opercularis (POp) using Marsbar[34]. Within each region, these activation estimates were assessed for differences in phonological and semantic processing using a paired samples t-test with IBM SPSS Statistics (v20, IBM corporation, New York, USA) at a significance level of $\alpha = 0.05$.

Anatomical labeling of significantly activated clusters from the whole brain analyses was performed using the Automated Anatomical Labeling map[35] software extension to SPM8. Brodmann areas were identified with the Brodmann template implemented in MRIcron (http://www.mricro.com). Figures were created with MRIcron render function.

Results

Task performance

Participants performed well in both tasks with an average accuracy of 97% (SD:3.23) for the phonological condition and 98% (SD:1.79) for the semantic condition.

Main effects of phonological processing

With phonological processing (rhyme decision > control) activation was seen bilaterally in the superior temporal gyrus. Left sided activation was observed in the posterior portion of the inferior temporal gyrus, in the supplementary motor area (SMA) and in the posterior dorsal portion of the IFG (POp, PTr) extending to the premotor cortex. Right sided activation was observed in the cerebellum (Figure 1A;Table 1).

Table 1. Anatomical location, cluster sizes (k, number of voxels), MNI coordinates and statistical T-values of areas of significant activation for phonological processing ($p_{FWE\ corrected}$<.05 at peak level, k≥10).

Anatomical location	Side	BA	Cluster size	MNI			T-value
				x	y	z	
Superior temporal gyrus	L	22	322	-57	-19	1	15.07
Superior temporal gyrus	R	22	237	60	-4	-5	12.08
Inferior temporal gyrus	L	37	62	-42	-49	-17	9.67
Inferior frontal gyrus pars opercularis & Precentral gyrus	L	44 6	112	-51	11	28	9.69
Inferior frontal gyrus pars triangularis	L	45	10	-48	32	13	7.53
Supplementary motor area	L	6	15	-3	8	52	7.31
Cerebellum	R		29	21	-61	-29	8.82

L= left hemisphere; R=right hemisphere; BA=Brodmann area; MNI=Montreal Neurological Institute.

Main effects of semantic processing

With semantic processing (semantic association decision > control) activation was seen bilaterally in the superior temporal gyrus. Left sided activation was observed in the anterior ventral portion of the IFG (POr, PTr), in the dorsal part of the middle frontal gyrus and fusiform gyrus. Right-lateralized activation was observed in the insula extending to the IFG (POr) and in the cerebellum (Figure 1B; Table 2).

Table 2. Anatomical location, cluster sizes (k, number of voxels), MNI coordinates and statistical T-values of areas of significant activation for semantic processing ($p_{FWE\ corrected}$<.05 at peak level, k≥10).

Anatomical location	Side	BA	Cluster size	MNI			T-value
				x	y	z	
Superior temporal gyrus	L	22	287	-60	-7	-2	12.48
Superior temporal gyrus	R	22	332	60	-22	-5	11.95
Inferior temporal gyrus	L	37	24	-45	-61	-17	6.99
Inferior frontal gyrus pars orbitalis	L	47	45	-48	26	-5	10.84
Inferior frontal gyrus pars orbitalis	L	47	30	-48	44	-5	10.28
Inferior frontal gyrus pars triangularis	L	45	37	-42	11	25	8.18
Middle frontal gyrus	L	6	16	-42	2	52	8.28
Supplementary motor area	L	6	41	-6	14	52	10.01
Insula & Inferior frontal gyrus pars orbitalis	R	47	18	30	23	-5	8.94
Cerebellum	R		373	9	-76	-26	13.65

L= left hemisphere; R=right hemisphere; BA=Brodmann area; MNI=Montreal Neurological Institute.

Comparison of phonological and semantic processing

Left-lateralized increased activation was seen for semantic compared to phonological processing (semantic association decision > rhyme decision) in the middle and superior temporal gyrus, in the posterior portion of the inferior parietal lobule and in the anterior ventral portion of the IFG (POr) (Figure 1C; Table 3). Right-lateralized increased activation was seen in the cerebellum. There was no significantly increased activation for phonological compared to semantic processing (rhyme decision > semantic association decision).

Table 3. Anatomical location, cluster sizes (k, number of voxels), MNI coordinates and statistical T-values of areas of significant activation for semantic>phonological processing ($p_{FWE\ corrected}$<.05 at cluster level, k≥10).

Anatomical location	Side	BA	Cluster size	MNI			T-value
				x	y	z	
Middle temporal gyrus	L	21	95	-60	-43	-5	6.68
Middle temporal gyrus	R	21	61	45	-37	1	5.75
Inferior frontal gyrus pars orbitalis	L	47	76	-48	44	-5	6.01
Middle frontal gyrus	L	6	87	-39	5	52	4.85
Middle frontal gyrus	R	6	191	42	17	52	5.51
Inferior parietal lobule	L	7	129	-36	-73	46	5.81
Cerebellum	R		321	9	-76	-29	7.30

L= left hemisphere; R=right hemisphere; BA=Brodmann area; MNI=Montreal Neurological Institute.

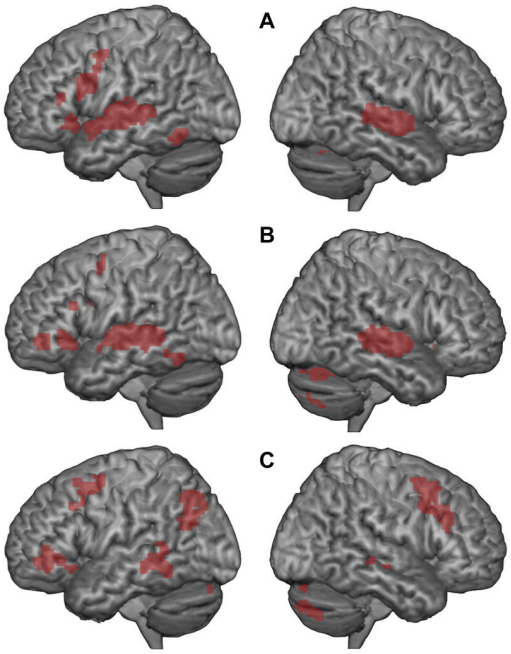

Figure 1. Three dimensional brain rendering with superposition of the activation maps displayed at p FWE corrected<0.05, k>10 for the following contrasts: A) phonological processing (rhyme decision > control), B) semantic processing (semantic association decision > control, C) semantic > phonological processing.

Quantitative involvement of the left IFG subportions

Mean beta values from the POr, PTr and POp for the main effect of phonological and semantic processing are shown in figure 2. These were significantly increased with semantic processing compared with phonological processing in the POr (t(25)=-2.64,p=0.014), but not in the PTr (t(25)= -1.99,p=0.058) and POp (t(25)=-0.36,p=0.720).

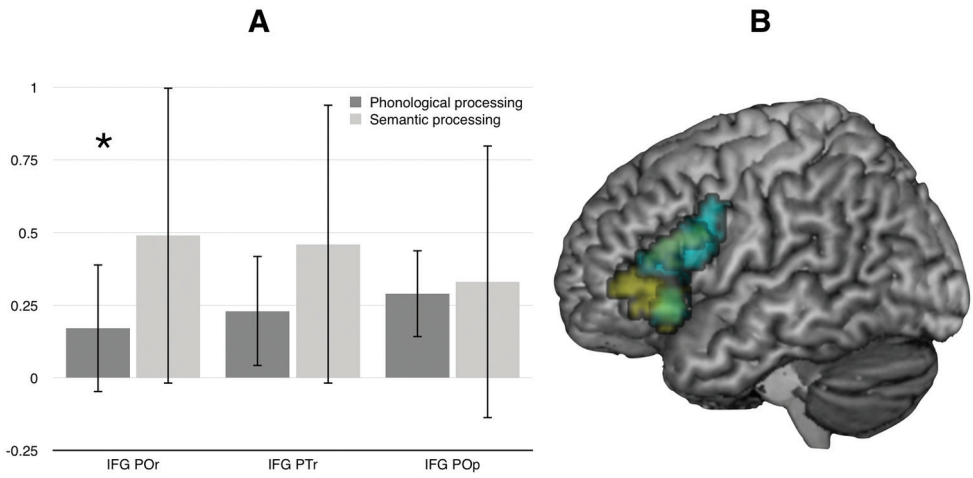

Figure 2. Left: Mean beta values from the POr, PTr and Pop of the left IFG for the main effect of phonological and semantic processing. * indicates a significant difference at p<0.05. Right: Three-dimensional brain rendering with superposition of the activation in the left IFG only for phonological processing in blue and semantic processing in yellow.

Discussion

In this study we investigated auditory phonological and semantic processing in older healthy adults to elucidate whether these linguistic processes recruit different portions of the left IFG. We found that both language tasks elicited overlapping activation in PTr of the left IFG. In addition, activation for phonological processing extended to the posterior dorsal portion of the left IFG (POp), while semantic processing extended to the anterior ventral portion (POr). A direct comparison between the two language tasks indicated that semantic association activated the left POr stronger than rhyme decision.

These findings indicate that the left IFG is differentially engaged in an older population on a receptive level. This corresponds to studies investigating phonological and semantic processing on a productive and receptive level in a younger population, as demonstrated in the meta-analysis by Costafreda et al. [24] and the study of Booth et al. [36]respectively. There are some studies that failed to demonstrate such differentiation within the IFG, such as the aforementioned study of Heim et al. [25], and the study by Johnson

et al.[28]. Heim et al. [25] used a within-subjects experiment with a productive fluency task and found that semantic fluency did not elicit higher activation than the phonological fluency task in any part of left IFG. The study of Johnson et al. [28] evaluated auditory phonological and semantic processing in both younger and older adults. They found that both groups activated the left IFG for the semantic task but not for the phonological task. A possible reason why they did not find differential activation may be related to differences in task design: Instead of comparing phonological and semantic processing to a baseline condition, as done in the present study, they implemented a phonological task (matching auditorily presented neologistic word pairs) as a control condition for their semantic tasks.

We found that semantic auditory processing most prominently engages the anterior portion of the IFG, in particular the POr (BA 47). Several studies, using a variety of imaging methods and paradigm designs, have consistently demonstrated the involvement of this region in healthy younger adults in semantic decision-making [37-39] and retrieval [40,41]. This portion of the left IFG is thought to play a specific semantic role [42], in processing the semantic relationships between words or phrases and retrieving semantic information[19]. For phonological processing, on the other hand, we observed more involvement towards the posterior portion of the IFG (BA 44), which has been suggested to play a role in phonological encoding[14, 43,44]. A transcranial magnetic stimulation (TMS) study of the properties of the left IFG found that stimulation of the posterior portion of the left IFG interfered with phonological working memory[45]. A more recent TMS study of Gough et al.[44] tested the spatial dissociation of phonological and semantic processing in the left IFG and found that stimulation of the anterior portion of the IFG increased response latencies when the participant focused on word meaning (synonym judgments), but not when they focused on the sound patterns of words (homophone judgments). The reverse was seen when the posterior part of the left IFG was stimulated.

The functional representation in distinct regions of the IFG can be partially interpreted in the context of the ventral and dorsal stream model proposed by Hickok and Poeppel [46]. Each stream is thought to serve a different language function: the ventral pathway subserves semantic processing, while the dorsal pathway supports processing such as auditory-to-motor mapping mainly required in phonological processing. Anatomically, the ventral pathway connects anterior portions of IFG, that we found to be activated during semantic processing (BA 45/47), to the temporal cortex [47]. As explained above, this portion of the left IFG supports semantic processes, and in particular controlled processes at the word-level such as semantic judgment or categorization [39,48] and lexical-semantic access [49]. From a functional point of view, there is less agreement regarding the dorsal stream[46]. This stream connects an articulatory network (comprising the posterior portion of the IFG, premotor cortex and insula) to a sensorimotor interface (comprising a region between the superior temporal gyrus and the inferior parietal lobe). The functional role of this stream has been mainly explored with word repetition[50,51],

and lesions along the dorsal stream cause speech repetition deficits[47]. We found similar regions along the dorsal stream to be activated for receptive phonological processing, namely the posterior portion of the left IFG (BA 44) extending to the premotor cortex (BA 6) (both regions being part of the articulatory network) and the superior temporal gyrus. Both the receptive rhyme decision and the productive word repetition tasks require phonological decoding by accessing the phonological store. We propose that our findings contribute to the understanding of the functional role of the dorsal stream of sound-to-motor mapping, given the observed involvement of the articulatory network not only in productive but also in receptive phonological processing.

Both phonological and semantic processing involved several regions in the brain in addition to the IFG, including the superior temporal cortex, the SMA and the cerebellum in line with previous studies[36]. The two linguistic processes also activated some of these brain regions differentially, with semantic processing involving the middle temporal cortex, the inferior parietal lobule and the middle frontal gyrus as well as the cerebellum more than phonological processing. This finding is in line with previous studies comparing semantics and phonology [19,52].

Bilateral activation of the temporal cortex during rhyme decision and semantic association has previously been reported and is thought to be due to recognizing speech sounds[53]. The differential activation for semantic processing in the middle temporal gyrus is in line with the ventral stream model of word-to-meaning mapping, with the middle temporal gyrus being involved in lexical-semantic processes[54,55]. This is further supported by the TMS study of Whitney et al., 2011[56] in healthy participants: stimulation of the posterior portion of the middle temporal gyrus and ventral portion of the IFG (i.e. POr) selectively disrupted executively demanding semantic judgment.

The premotor cortex and SMA are motor areas both involved in speech.[57, 58] Even when receptive tasks are used, i.e. no speech is produced, these areas are generally activated presumably due to preparation of speech or to inner speech.[46, 59] Activation of the premotor cortex was seen as a main effect of phonological but not of semantic processing. As mentioned above, the premotor cortex is considered part of the articulatory network, involved in sound-to-word mapping according to the dorsal stream model. A recent TMS study of Krieger-Redwood et al., 2013 [58] also supports the role of the premotor cortex during phonological processing. Their study demonstrated that this region plays an important role in phonological judgments of auditory speech stimuli (i.e. mapping sound to speech) but is not necessarily involved in semantic processing (i.e. mapping speech to meaning).

In contrast to studies of language production we did not observe activation in the inferior parietal lobule during phonological, but only during semantic processing.[14, 53] As suggested by the review study of Burton 2001, activation in this region is seen in tasks

that require short-term storage of phonological information. However, activation of this area is likely to be observed in tasks that require an output such as rhyme production.[60] The fact that we did not observe activation in this region during receptive rhyme decision suggests that it is not involved in the input route of phonological processing.

The role of the cerebellum in language processing is not yet well-understood but is receiving increasing attention.[61] In our study, its involvement was more pronounced for semantic than for phonological processing. This finding is in line with the suggestion from Roskies et al., (2001) [62] that the right cerebellar hemisphere may be functionally related to the left inferior frontal cortex for semantic processing.

Our findings of differential involvement of the subportions of the IFG as well as other brain regions are not only in line with those from language production studies, but also with those in healthy younger participants. This is not necessarily a given, since there are some reports of differences in language processing between younger and older adults. [63,26] Using a visual word rhyme judgment task, Geva et al., (2012) [63] found that older adults had increased activation in the PTr of the *right* IFG, even though their task performance was similar to that of younger adults. In our study, we did not find any right frontal activation for phonological processing, while the pattern of activation we found was very similar to previous studies using an auditory rhyme decision task in younger participants.[36] We only observed right-hemispheric IFG (POp), as well as insular, activation during semantic processing. This is in line with findings from Meinzer et al., (2009) [26] who compared younger and older adults for a phonemic and semantic fluency task, and found additional right inferior and middle frontal activation in older adults during the semantic task only. This difference in activation was found to be negatively correlated with performance. Moreover, younger adults recruited different sub-portions of the left IFG for both fluency tasks, while the older participants failed to show this distinction. Right-hemispheric frontal activation was also observed by Johnson et al., 2001 [28] during their auditory semantic decision task in younger healthy participants. This suggests that such frontal activation may not necessarily be associated with aging, but rather with task performance.

Some methodological issues should be discussed. A strength of our study is that it evaluated auditory phonological and semantic processing in healthy older adults, a population that is not commonly studied for normal language processing. A potential drawback of our study is that we used real words instead of non-words in the rhyme decision task, which means that lexico-semantic access cannot be excluded. We considered the use of non-words, but decided against it thinking that this would hamper the implementation of this task for the assessment of language in aphasic patients, since performing rhyming tasks with non-words is harder than it is with real words. Furthermore, our eventual aim is to understand the neural mechanism underlying auditory phonological and semantic processing in the context of language treatment in apha-

sic patients. We investigated these linguistic levels in healthy participants rather than patients. This is the first and necessary step in understanding the neurophysiological mechanisms underlying language recovery after aphasic stroke, but our findings cannot be directly translated to aphasic patients. In future studies, we plan to investigate these two specific linguistic levels, as well as the effect of treatment, in aphasic patients.

In conclusion, the present study revealed an antero-posterior functional gradient in the left IFG for semantic auditory processing, and the reverse for phonological auditory processing, in healthy older adults. These findings support the proposed dorsal and ventral stream model of language, which thus far has been primarily based on productive language studies. Our findings furthermore indicated that phonological and semantic processing can be evaluated using a relatively simple receptive task. This type of task is expected to be suitable for aphasic patients with different degrees of aphasia severity. In future patient studies we aim to further our insight into the neural mechanisms of cognitive-linguistic aphasia therapy and the role of the IFG in language recovery.

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Chapter 6

The Relationship Between Hemispheric Lateralization of Auditory Language Processing and Severity of Post-Stroke Aphasia Assessed with Functional MR Imaging

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Paper in preparation

Abstract

Background and Purpose: Neuroimaging studies of aphasia debate the role of the left and right hemispheres in language recovery. A widely held interpretation is that left hemisphere activation after stroke reflects a better language recovery. According to this view, the persistent shift of language function to the right hemisphere impedes post-stroke aphasia recovery. The purpose of our study was to assess with fMRI the relationship between language lateralization and language recovery, both at the level of language production and comprehension, in chronic aphasia patients.

Methods: Thirty-six chronic aphasia patients with left hemispheric stroke participated. All patients underwent extensive language function evaluation and fMRI at 3T during the performance of an auditory passive listening task. Language lateralization indices (LI) were determined using a threshold independent method, and correlated with language test performance.

Results: There was no difference in LI between mildly and severely aphasic patients. Language lateralization was not correlated with aphasia severity. Lesion volume, however, was significantly greater in severely than in mildly aphasic patients, and was found to be an independent predictor of language comprehension performance.

Conclusion: Our findings challenge the widely held hypothesis that language recovery is related with language lateralization: independent of aphasia severity, whether at the level of production or comprehension, language was more commonly left than right lateralized in the chronic phase after stroke.

Introduction

Aphasia, an impairment of language production and/or comprehension, is a frequent consequence of left-hemispheric stroke. After focal brain damage, language network reorganization is thought to enable language recovery[1]. In the last few years, functional neuroimaging has increasingly been used to investigate how language activation changes after aphasic left-hemispheric stroke. However, the mechanism underlying natural restoration of language function after aphasic stroke remains poorly understood.

Neuroimaging studies in aphasia have focused either on spontaneous recovery[2], or on brain plasticity in response to treatment, mostly at the chronic stage after stroke. Both lines of investigation have primarily focused on whether patients compensate for their functional loss by increasing the level of language-related brain activation in the left or the right hemisphere. Saur et al.[2] used repeated functional magnetic resonance imaging (fMRI) examinations with parallel language testing to examine the reorganization in the language network from the acute to the chronic stage in 14 aphasic patients after stroke. They suggested that reorganization during language recovery proceeds in three phases. In the initial few days after stroke, activation in the remaining left-hemispheric language areas was reduced. In the second phase around 12 days after stroke, there was an upregulation of the entire language network followed by strong bilateral activation with a peak in the right hemisphere. This shift was correlated with early improvement. Later, in the chronic phase, activation shifted to a normal left lateralized pattern, with comparatively higher activation in left perilesional regions. Persisting right hemispheric activation in the chronic stage appeared to correlate with absence of recovery. Most recent neuroimaging studies investigating brain plasticity in response to treatment of aphasia [3-6] have suggested that recovery of language is a simple reversal of normal left hemisphere lateralization (i.e., transferring language functions as a whole to the right hemisphere), or exclusive recruitment of left perilesional and other language areas, or a combination of the two. Left hemispheric activation after therapy seemed to correlate with language improvement, suggesting that right-hemispheric activation prior to aphasia therapy indicates the patients' potential for further language improvement.[3]

Considering the findings from these studies, a widely held interpretation of left hemisphere activation after stroke is that it reflects a better language recovery. According to this view, the persistent shift of language function to right hemisphere impedes post-stroke aphasia recovery.[7] The recruitment of the right hemisphere may be maladaptive and reflect inefficient language processing rather than being beneficial to recovery.[8] These assumptions should however be interpreted with care since there are some critical issues regarding neuroimaging studies evaluating language in aphasia.[9-12] Among these are studies which evaluate only small groups of patients, including patients with not only lesions in the left hemisphere, and implement language paradigms that may not be suitable for severely aphasic patients.

The purpose of our study was to assess the relationship between language lateralization and language recovery, both at the level of language production and comprehension, in the chronic phase after stroke.

Methods

Patients

Patients were recruited from our database of stroke patients, the local rehabilitation clinic, aphasia therapy centers, the national aphasia association ('Afasie Vereniging Nederland') and private speech and language therapist (SLT) practices. During a period of 3 years (June 2010-June 2013), around 300 candidates were screened for eligibility for inclusion. Inclusion criteria were i) aphasia after left hemispheric stroke; ii) time post-onset more than 1 year and less than 10 years; iii) age < 75 years; iv) Dutch as native language; v) testable with ScreeLing (Screening of aphasia and its linguistic deficits) [13]; vi) aphasia ascertained with a score <5 on the Goodglass and Kaplan's Aphasia Severity Rating Scale (ASRS)[14] and/or a score <29 on the shortened version of the Token Test [15]; vii) right handed as assessed with the Edinburgh Handedness Inventory[16]. Exclusion criteria were i) subarachnoid hemorrhage or subdural hematoma upon presentation as assessed by the treating Neurologist; ii) cortical lesions in the right hemisphere visible on the baseline MRI scan (lacunar infarcts were acceptable); iii) severe dysarthria; iv) bilingualism; v) left handed or ambidexter; vi) premorbid dementia; vii) illiteracy; vii) severe developmental dyslexia; viii) severe hearing deficit; ix) severe perceptual visual disorder; x) recent psychiatric history; xi) contraindication for MRI. The study was approved by the institutional review board and all patients gave written informed consent prior to participation.

Behavioral evaluation

An extensive aphasia test battery was administered before the fMRI session. For the present study we used 2 standardized tests commonly used clinically to measure language production and language comprehension in aphasic patients: a semi-standardized interview for spontaneous speech (production) and the shortened version of the Token Test (comprehension). Severity of spontaneous speech impairment was scored on the ASRS, an ordinal scale ranging from 0, very severe aphasia with no usable speech or auditory comprehension, to 5, minimally discernable speech handicaps. We classified patients with scores 0-2 as severely aphasic, and those with scores 3-5 as mildly aphasic.

fMRI language paradigm

All participants performed an auditory passive listening task, which consisted of 6 short stories (experimental condition) that they needed to listen to attentively during scanning. Participants were familiarized with the task prior to scanning. The topics of the short stories were real daily life events. To keep the patients alert, each story had an increasing level of difficulty, concerning the word frequency, the word imageability and the complexity of the syntactic structures. Each story was followed by the same story in reverse speech as a control condition. At the start of each story and its reverse, a 3 s instruction announced the start of each condition. All recorded stories and their reverse versions had a duration of 30 s. After the scan session task performance was assessed with a short multiple (4) choice questionnaire of simple questions regarding the content of the stories. Task performance was rated by calculating the percentage of correct answers out of all responses.

The task was presented binaurally through an MR compatible headphone system (MR Confon, Magdeburg, Germany), using Presentation v13.0 software (Neurobehavioral Systems Inc. Albany, CA, US) installed on a desktop PC. External triggering by the MR system ensured synchronization of the stimulus paradigm with the imaging data acquisition.

Image acquisition and preprocessing

Scanning was performed on a 3.0T Discovery system (GE Healthcare, Milwaukee, IL, USA). An axial three-dimensional (3D) inversion recovery fast-spoiled gradient (FSPGR) T1-weighted image (echo time (TE)/ repetition time (TR)/inversion time (TI) 2.1/6.1/450 ms, flip angle 12 degrees, matrix 256 x 224, FOV 24x18 cm) with an effective slice thickness of 0.8 mm was acquired for anatomical registration purposes. A 2D T2 weighted fluid attenuated inversion recovery (T2-FLAIR) was acquired for lesion delineation (TE/ TR/TE 120/8000/2250 ms, matrix 256 x 256, FOV 24 cm, slice thickness 5 mm). Functional scans were acquired using a gradient-echo echo planar imaging pulse sequence (TE/TR 30/3000 ms, flip angle 90 degrees, matrix 96 x 96, FOV 24 -26 cm) with a slice thickness of 3.0 mm (no gap). Total acquisition time was 6:51 min, which included 15 s of dummy scans that were discarded from further analysis.

Imaging data analysis was performed using SPM8 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, UK). Anatomical and functional images were first manually aligned to the anterior commissure as reference plane. Then all functional images were realigned to correct for the participant's motion during data acquisition, and co-registered with the individual's high-resolution T1-weighted anatomical image.[17] The segmentation parameters of the T1-weighted anatomical image were used to spatially normalize this and the functional images to standard MNI space

using the unified segmentation.[10,18,19] Normalization resulted in resampled voxel sizes of 3x3x3 mm^3 for the functional and 1x1x1 mm^3 for the anatomical images. The normalized functional images were smoothed with a 3D Gaussian Full Width Half Maximum (FWHM) filter of 6x6x6 mm^3 to increase the signal-to-noise ratio, correct for inter-individual anatomical variation and to normalize the data.[20]

The stroke-related lesion was delineated manually on the T2-FLAIR images using MRIcron (http://www.mricro.com), defined as lost tissue only. An experienced neuroradiologist (MS) reviewed all lesion delineations and reported the anatomical localization of the lesion.

Statistical analysis and interpretation of fMRI data

All fMRI data were analyzed within the context of the General Linear Model (GLM), by modeling in a blocked design the experimental and the control conditions excluding the instructions. The blocks were convolved with the hemodynamic response function (HRF), corrected for temporal autocorrelation and filtered with a high-pass filter of 128 s cut-off. Motion parameters were included in the model as regressors of no interest to reduce potential confounding effects of motion. First, the individual t-contrast images for the experimental versus control condition were generated for all participants to assess the main effect of auditory comprehension. Then, individual lateralization indices (LI) were determined. The number of activated voxels within each cerebral hemisphere was calculated using a threshold independent method. [21,22] The LI was defined as: (LH-RH)/(LH+RH), where LH and RH are the number of activated voxels in the left and right hemisphere respectively. Participants' activation was classified as left lateralized for LI values between 0.1 and 1.0, right lateralized for LI values between -0.1 and -1.0, or symmetrical for LI values between or equal to -0.1 and 0.1. [21]

Statistical analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences version 20 (SPSS, IBM Corporation, New York, USA). Differences in age, time post-stroke, lesion volume, and task performance between the mildly and severely aphasic patients were examined using independent samples t-tests. Gender differences between the two groups were examined using a Chi-squared test.

To test for the difference in LI on the level of language production, LIs between the mildly and severely aphasic patient groups were compared with an independent samples t-test. To investigate whether LI was associated with severity of language comprehension a linear regression analysis was performed with performance on the Token Test as the

dependent variable, and with lesion volume as a potential confounding factor. We used a significance level of $\alpha = 0.05$ for all analyses.

Results

Patients

Of about 300 potential candidates, 39 aphasic patients met the inclusion criteria and were included in the study and underwent MRI and behavioral testing. Patient characteristics are shown in Table 1. Post hoc, 3 patients were excluded from the analyses: 2 due to a right hemispheric cortical lesion and 1 due to low data quality. From the remaining 36 patients, 5 patients had a hemorrhagic stroke, and 3 patients had suffered a second stroke. In these patients, time post-onset was calculated from the first stroke.

We classified 16 patients with scores of 0-2 on the ASRS as mildly aphasic, and 20 patients with scores of 3-5 as severely aphasic. All patients were in the chronic phase after stroke (M= 37 months, range = 12 - 82), which was not different between the mildly and severely aphasic patients (t(34)=.041, n.s.). All patients answered the multiple choice questionnaire after the MRI session (M=69% correct, range=17%-100%).

There was no difference in age (t(34)= -.623, n.s.), task performance (t(34)= 1.623, n.s.) or gender (χ^2 (2, n=36) = .823, n.s.) between mildly (M = 54 years, range = 28–75, 8 male) and severely aphasic patients (M = 57 years, range = 30-74, 13 male).

Table 1. Patient characteristics

ID	G	Age (years)	MPO	Stroke type	ASRS score / classification•	Lesion Volume	Cortical lesion localization
C01	M	61	46	I	1 / Severe	66.32	Frontal-insular
C02	M	71	41	I	3 / Mild	0.91	None (white matter only)
C03	F	74	40	I	1/ Severe	51.09	Frontal-parietal-temporal-insular
C04	F	75	44	I	5/ Mild	21.83	Insular
C05	M	46	22	I	1 / Severe	96.56	Frontal-parietal-temporal-insular
C06	M	51	17	I	3 / Mild	25.30	Frontal-insular
C07	F	30	33	I	1 / Severe	162.17	Frontal-parietal-temporal-insular
C08	M	56	23	I	4 / Mild	83.81	Posterior temporal-insular-parietal
C10	M	66	36	I	3 / Mild	85.72	Insular-parietal-temporal
C11	M	50	17	I	0 / Severe	209.35	Frontal-parietal-temporal-insular

C12	M	48	20	H	2 / Severe	24.13	None
C13	F	47	16	I	4 / Mild	27.91	Frontal-parietal-temporal-insular
C14	F	48	12	I	1 / Severe	103.38	Frontal-parietal-temporal-insular
C15	M	65	40	H	2 / Severe	64.06	Frontal-insular-parietal
C16	M	52	14	H	3 / Mild	28.45	Parietal
C17	M	61	36	I	1 / Severe	84.27	Frontal-parietal-temporal-insular
C18	F	63	21	I	4 / Mild	25.04	Insular-parietal-temporal
C19	F	58	18*	I	2 / Severe	42.81	Frontal-insular
C20	M	60	13*	I	3 / Mild	46.17	Frontal-parietal-temporal-insular
C21	F	28	28	I	4 / Mild	35.53	Insular-parietal-temporal
C22	F	52	53	I	3 / Mild	51.99	Insular-parietal
C23	M	57	16	I	2 / Severe	103.14	Frontal-parietal-temporal-insular
C24	F	65	59	I	1 / Severe	86.98	Frontal-parietal-temporal-insular
C26	M	63	59*	H	2 / Severe	36.22	Temporal-insular
C27	F	34	65	I	4 / Mild	25.24	Frontal-insular
C28	M	63	36	I	3 / Mild	14.50	Temporal-insular
C29	F	61	64	I	0 / Severe	111.67	Frontal-parietal-temporal-insular
C30	F	40	59	H	3 / Mild	114.78	Frontal-parietal-temporal-insular
C31	M	59	63	I	2 / Severe	48.67	Insular-parietal-temporal
C32	M	47	26	I	0 / Severe	295.90	Frontal-parietal-temporal-insular
C33	M	53	12	I	1 / Severe	187.90	Frontal-parietal-temporal-insular
C34	M	67	38	I	1 / Severe	41.13	Frontal-insular
C35	M	70	43	I	0 / Severe	306.40	Frontal-parietal-temporal-insular
C37	M	60	50	I	3 / Mild	33.10	Frontal-insular
C38	F	51	82	I	3 / Mild	91.30	Frontal-parietal-temporal-insular
C39	F	51	78	I	0 / Severe	158.15	Frontal-parietal-temporal-insular

ID= Identification number of the patient in the study, G=gender, F=female, M=Male, H= hemorrhagic, I=Ischemic, MPO=months post onset, *= patients who suffered a second stroke, ASRS= Aphasia Severity Rating Scale, •=classification based on the scores of the ASRS

Language lateralization, lesion volume and aphasia severity

The majority (n=17) of patients with lateralized language activation were left lateralized. Only 5 patients showed right lateralized activation (Figure 1, Table 2). There was no difference in LI between mildly (M = .12, range = -.21–0.49) and severely (M = .06, range =-.21–.39) aphasic patients (t(34)= .998, n.s.). At the level of production, based on the ASRS scores, severely aphasic patients had larger lesions (M = 114 ml, range = 24–306) than mildly aphasic patients (M = 45 ml, range = 0.9–115) (t(34)= -3.184, p<.05).

There was no association between LI and performance on the Token Test, corrected for lesion volume (β LI = .176, t(33/35) = 1.204, n.s.). Lesion volume, however, was an independent predictor of performance on the Token test (β Lesion volume = -.560, t(33/35) = -3.480, p<0.05) demonstrating that the larger the lesion the lower the performance on the Token Test (Figure 2).

Table 2. Scores on the behavioral tests and language lateralization index during the passive listening task

ID	Token Test	ASRS score / classification•	LI	LI classification
C01	15.5	1 / Severe	0.07	Symmetrical
C02	15	3 / Mild	0.08	Symmetrical
C03	1.5	1/ Severe	0.11	Left lateralized
C04	27.5	5/ Mild	0.01	Symmetrical
C05	0	1 / Severe	0.11	Left lateralized
C06	27.5	3 / Mild	0.11	Left lateralized
C07	5	1 / Severe	-0.01	Symmetrical
C08	21.5	4 / Mild	0.49	Left lateralized
C10	6	3 / Mild	0.00	Symmetrical
C11	2.5	0 / Severe	-0.02	Symmetrical
C12	11	2 / Severe	0.04	Symmetrical
C13	34	4 / Mild	0.24	Left lateralized
C14	16	1 / Severe	-0.21	Right lateralized
C15	17	2 / Severe	-0.03	Symmetrical
C16	16	3 / Mild	0.33	Left lateralized
C17	24.5	1 / Severe	0.18	Left lateralized
C18	30	4 / Mild	0.08	Symmetrical
C19	8.5	2 / Severe	0.09	Symmetrical
C20	25	3 / Mild	-0.04	Symmetrical
C21	31.5	4 / Mild	-0.13	Right lateralized
C22	30.5	3 / Mild	0.18	Left lateralized
C23	9.5	2 / Severe	0.18	Left lateralized

C24	8	1 / Severe	-0.11	Right lateralized
C26	6.5	2 / Severe	0.11	Left lateralized
C27	28.5	4 / Mild	0.29	Left lateralized
C28	26	3 / Mild	0.16	Left lateralized
C29	6	0 / Severe	-0.12	Right lateralized
C30	18	3 / Mild	-0.21	Right lateralized
C31	4.5	2 / Severe	0.20	Left lateralized
C32	8.5	0 / Severe	0.39	Left lateralized
C33	5	1 / Severe	-0.03	Symmetrical
C34	19.5	1 / Severe	0.16	Left lateralized
C35	7.5	0 / Severe	0.21	Left lateralized
C37	28.5	3 / Mild	0.17	Left lateralized
C38	29	3 / Mild	0.08	Symmetrical
C39	1	0 / Severe	-0.07	Symmetrical

ID= Identification number of the patient in the study, ASRS= Aphasia Severity Rating Scale, •=classification based on the scores of the ASRS, LI= Lateralization Index

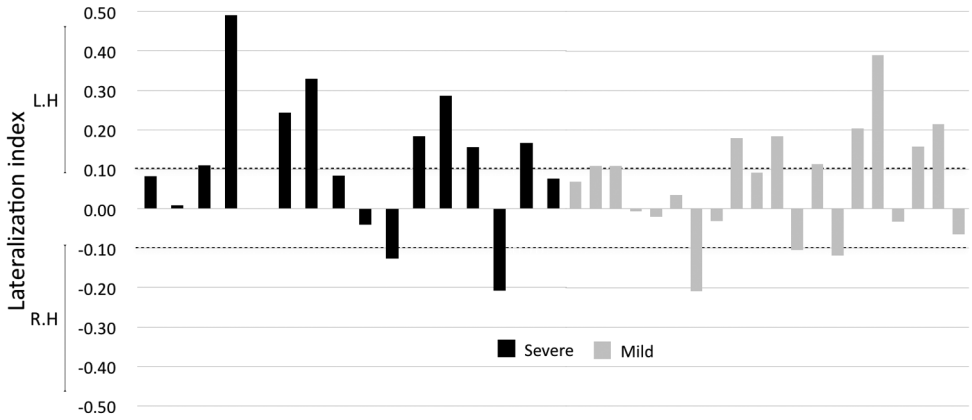

Figure 1. Lateralization index in severely and mildly aphasic patients. Patient's activation was classified as left lateralized for LI values between 0.1 and 1.0, right lateralized for LI values between -0.1 and -1.0, or symmetrical for LI values between or equal to -0.1 and 0.1. L.H=Left Hemisphere, R.H=Right Hemisphere.

Discussion

The purpose of this study was to investigate the relationship between language lateralization and language recovery both on the level of production (ASRS scale) and on the level of comprehension (Token Test) at the chronic phase after stroke, to assess the widely held hypothesis that good recovery is related to left lateralized language processing, while right-sided lateralization is associated with poor recovery. Using a simple

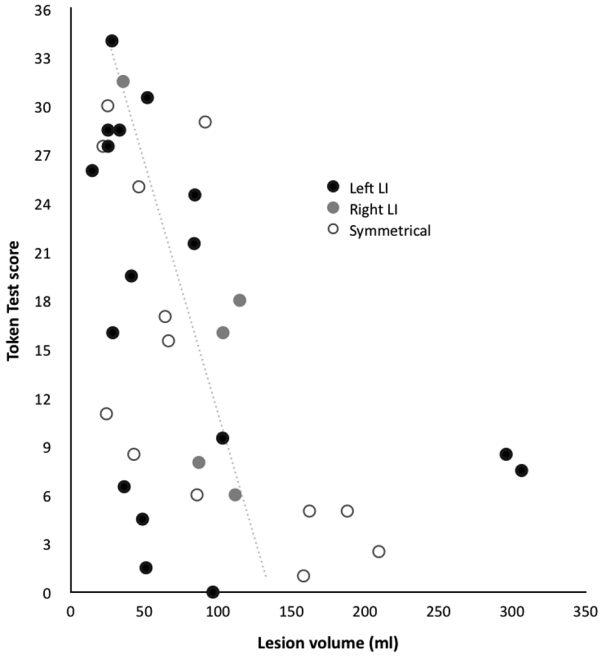

Figure 2. Scatterplot describing the relationship between performance on the Token Test and the lesion volume. The language representation is indicated (see legend) for left-lateralized (Left LI), right-lateralized (Right LI) and symmetrical activation in each of the participants.

passive listening task, which could be performed even by severely aphasic patients, in a large group of chronically aphasic patients, we found that language lateralization was not correlated with aphasia severity. Lesion volume, however, was significantly greater in severely than in mildly aphasic patients, and was found to be an independent predictor of language comprehension performance.

Previous neuroimaging studies that investigated aphasia recovery (either on spontaneous recovery or in response to treatment) have shown inconsistent patterns of activation in the left and right hemisphere after stroke. The only functional neuroimaging study that longitudinally examined language recovery [2] suggested that left hemisphere activation in the chronic phase correlated with improved language function. Right hemisphere structures do play a beneficial role in the early stages of recovery from aphasia, but ultimately it is the left hemisphere that sustains effective language function. Additionally, other studies have also reported that the recruitment of the right hemisphere homologous language areas can be considered as being maladaptive, reflecting inefficient language processing rather than being beneficial to recovery.[8] In fact, it is postulated that a persistence of right hemisphere involvement inhibits the left hemisphere from resuming its role in language processing, and thereby limiting language recovery.[7] Furthermore, it can be expected that lesion size has a confounding effect: smaller lesions may be related to less severe aphasia, but also to larger remaining language areas or perilesional areas in the left hemisphere. Conversely, more extensive lesions are likely associated with more severe aphasia, but also would result in less re-

maining functioning tissue in the left hemisphere. This would lead to the recruitment of undamaged right-hemispheric areas of the language processing network.[3] Although only assessed cross-sectionally, our results not only challenge the assumption that left hemisphere is correlated with better language recovery, but also indicate that lesion size was an independent predictor of language recovery.

We found that language was left lateralized in the majority of patients with lateralized language function, irrespective of their aphasia severity. Additionally, we observed that activation was commonly symmetrical in both the mildly and severely aphasic patients. Our findings are in line with those from Zahn et al.,2004 [23] who investigated patients with severe global aphasia. They also reported no correlation between the side of language activation and the comprehension ability of the patients. Patients showed bilateral activation for different language tasks (phonetic, lexical and semantic tasks) mainly in the left extrasylvian temporal and right posterior parietal regions. Many neuroimaging studies of language processing with healthy volunteers have reported right hemisphere activation as well as extrasylvian recruitment across language domains and different language processing conditions.[24-29] Observed increases in right hemisphere activation after stroke may therefore not reflect a true quantitative increase but rather, the emergence of activity made necessary by the functional deficit of the language-dominant hemisphere.[8]

There are several, mostly methodological, explanations for the fact that our findings do not support the notion that good recovery is associated with left lateralized activation. Most previous studies on language recovery investigated small groups of patients with similar deficits. Our patient group is not only larger in comparison with these studies but also rather heterogeneous with regards to their language deficits. Inherent to our research question, we included patients who had variable degrees of aphasia, which included both impairments of language production and language comprehension. We classified aphasia severity based on the spontaneous speech analysis, a measurement for the communication deficit, which indirectly measures comprehension deficits. Given the variety of language impairments, we analyzed language activation during a passive listening task, which could even be performed by severely aphasic patients. Passively listening to sentences or stories is a task commonly used in fMRI research to investigate auditory comprehension, especially in patient populations. Given that several linguistic processes occur simultaneously when listening to a spoken story (phonology, semantic and syntax processing), a language network involving all such processes can be identified. Therefore it has been a widely used paradigm for obtaining an overall activation measure of language comprehension processing in the brain. While this task has the advantage of being useful for all degrees of aphasia severity, it is not focused on a specific language deficit. A second main difference with many previous neuroimaging studies investigating language recovery, is that we calculated language LI with a threshold-independent method. LI calculation is a method that has been often applied

in neuroimaging studies to determine functional hemispheric language lateralization presurgically in patient populations with epilepsy and tumor.[21] However, with the more commonly used threshold based methods, thresholding of activation is a problem because a failure of detection of activation in a number of patients at predefined SPM thresholds is often observed.[30] This method is thus prone to significant within-patient variability which could render its results unreliable.[21] Suarez et al., 2009 demonstrated that the threshold-independent method is more robust than the threshold-dependent method since it generates distinct LIs that are more concordant with gold standard clinical findings such those provided with the electrocortical stimulation and intracarotid amytal test (known as the Wada test). A final reason that may explain why our results do not support the hypothesis that good recovery is related to left lateralized language processing, is that we considered the lesion volume in our analysis, a factor that has only rarely been taken into account in the published neuroimaging studies investigating aphasia recovery.[11,31] Even though we demonstrated that lesion size was not a confounding, but rather an independent predictor of recovery, it is conceivable that a certain confounding effect was neglected in previous studies.

It does not seem surprising that lesion size predicts aphasia severity. Several studies have addressed lesion size to investigate patterns of aphasia severity and recovery. [32-36] However, patients vary with regards to lesion characteristics and the language deficits with which they present.[8] In our study, we included patients with a wide range of scores on the the ASRS and the Token test. When considering the scores on language comprehension, we confirm previous findings by Kertsez et al., 1979 [32], that the larger the lesion, the poorer the score is at the level of language comprehension. When assessing our patient group at the level of spontaneous speech, we also observed that the lesion volume was significantly different in mildly and severely aphasic patients. Schofield et al., 2012 [24] investigated 21 patients with severe and moderate speech comprehension impairments, who also had a range of impairment severity on tests of speech production, reading and writing. They found that both patient groups did not differ in terms of lesion volume, contrary to our findings. It is possible that this discrepancy is due to differences in methodology of lesion delineation. They used an automated method for lesion detection, which might detect not only lost tissue but also gliotic (damaged but not lost) tissue. Assuming that gliotic tissue may still be functional, they may have overestimated the size of the lezion. They did find that compared to the moderately impaired patients, patients with severe impairment had sustained significantly more damage to left posterior insula, Heschl's gyrus and planun temporale. These results suggest that to account for behavioral differences in patients, it is necessary to take lesion site as well as lesion volume into account.

Although the passive listening task a suitable task to evaluate patients with different degrees of aphasia severity, a disadvantage is that task performance cannot be monitored. Therefore, no certainty is obtained that the task has been "performed" and there

is the risk that patients lose attention and that other cognitive processes interfere and activate brain regions that also are involved in speech comprehension. We attempted to at least partially assess task performance with the post-scan questionnaire. Additionally, patients vary greatly with respect to the aspects of language that are disrupted following stroke. For instance some show lexical- semantic impairments, some syntax-based deficits, and others show central phonemic problems. These different impairments might also induce different patterns of language activity, which in turn may lead to a less clearly lateralized pattern as might be expected from a task evaluating a specific linguistic level.

We specifically focused on patients at the chronic stage after stroke, a period in which language activation should be stabilized, independent of the degree of aphasia severity. We especially considered this factor because several studies have shown a shift in activation from the right to the left hemisphere in the acute phase after stroke. A limitation of our study, however, is that it is cross-sectional. Further limitations are that patients in our study may have received different types of language therapy that might have influenced their recovery process. Furthermore, our study investigated language activation within the left and right hemisphere as a whole, whereas focusing on regions of interest could have increased the chance to detect perilesional and plastic, i.e.outside the language network, activation. This approach may have attenuated true lateralized language activation. Finally, as mentioned above, although a passive listening task is suitable for different aphasia severities because of the claim on general linguistic processing, other more specific language tasks could perhaps invoked a clearer lateralized pattern.

Taken together, our findings challenge the widely held hypothesis that language recovery is related with language lateralization: independent of aphasia severity, whether at the level of production or comprehension, language was more commonly left than right lateralized. The question remains, however, whether therapy induced language recovery has an effect on language lateralization, which we currently investigate in a randomized controlled trial.

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Chapter 7

Language Lateralization after Melodic Intonation Therapy: an fMRI Study of Treatment Related Plasticity in Chronic and Sub-Acute Aphasia

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Abstract

Background: There is an ongoing debate whether the effect of Melodic Intonation Therapy (MIT) in patients with severe non-fluent aphasia depends on recruitment of RH structures for language functioning or on re-recruitment of LH language structures. So far, neuroimaging studies have produced conflicting evidence.

Objective: To investigate whether intensive MIT induces a shift in language lateralization in sub-acute (< 3 months post-onset (po)) and chronic (> 1 year po) stroke patients with aphasia.

Methods: In a multiple case study with pre-post-design 5 sub-acute and 4 chronic stroke patients received intensive MIT (6 weeks, 30 sessions). Pre- and post-treatment they underwent fMRI scanning with a passive listening task to determine language lateralization indices (LI).

Results: After MIT, no consistent shift of language activation was found to either the LH or the RH. Sub-acute patients were predominantly right lateralized and tended to become more right lateralized, whereas chronic patients showed a reverse pattern.

Conclusion: The contrasting activation patterns in sub-acute and chronic MIT patients before as well as after treatment, suggest that MIT-induced reorganization of language occurs in interaction with a dynamic recovery process after stroke. Time post onset should be addressed systematically in studies of treatment-induced language recovery.

Introduction

Since the 1970s, when the Boston Group developed Melodic Intonation Therapy (MIT) for patients with severe aphasia[1], this technique has been successfully applied in English[2-4], as well as in many other languages, including German[5], French[6], Dutch[7], Romanian[8], Persian[9] and Japanese.[10] The MIT concept was based on the intriguing observation that singing has a facilitatory effect on language production in many patients with severe non-fluent aphasia. In 1989 MIT was published as a well-structured treatment program to promote language production.[11] MIT uses melodic patterns of 3 or 4 tones to emphasize the natural intonation, thus facilitating verbal production. The speech and language therapist (SLT) and the patient produce melodically intoned target utterances in unison, while tapping the rhythm with their left hand. In several steps, they work towards the independent production of spoken utterances. In 1994 MIT was recommended to treat aphasia by the American Academy of Neurology, based on class III evidence.[12] Since that time the evidence in support of MIT effectiveness has accumulated.[7,13,14]

The brain correlates of MIT-induced recovery are still unclear.[13] Originally, the effects of MIT were interpreted in line with the Right Hemisphere (RH) hypothesis of language recovery, which assumes that the undamaged RH is capable of taking over the language functions of the damaged structures in the left hemisphere (LH). [1,2,15,16] Activating the RH's music functions was thought to promote recruitment of RH structures for language processing. In support of this view, Naeser and colleagues found that poor MIT responders had bilateral lesions, while good responders had unilateral LH lesions in Broca's area and/or subcortical structures, not affecting Wernicke's area or the temporal isthmus. They concluded that an intact RH is needed for MIT to be successful.[17]Later neuroimaging studies yielded conflicting evidence, however. In a PET study, patients who responded well to MIT showed less rather than more RH activation, suggesting that the RH does not play a crucial role in MIT induced language recovery. In fact, the authors suggest that RH activation may even reflect maladaptation[6], as RH overactivation inhibits activation of spared structures in the LH. Recent studies yielded similar results.[18] In further support of an important role of the LH, we found that in healthy speakers, melodically intoned language not only activates RH structures, but also a left lateralized motor sensory network, related to the articulatory system.[19] On the other hand, Schlaug and colleagues reported functional as well as structural RH changes after MIT. In an fMRI study of two patients with chronic Broca's aphasia they showed increased language activation of the RH after MIT.[3] In further case studies MIT was shown to lead to structural changes in the RH arcuate fasciculus.[4,20,21]

At different points in time, different recovery mechanisms are at work[22] and treatment-induced reorganizational processes in the language network may therefore be different at different points in time. In the sub-acute stage, behavioral therapy probably interacts with natural recovery processes[23], whereas learned non-use may play a role in

the chronic stage. In two randomized controlled studies we found that the behavioral outcome of MIT depends on time post onset. MIT started within 3 months post stroke yielded larger benefits, as compared to MIT started at 3.5-5 months post stroke[7] or in the chronic phase (> 1 year post onset).[24]

In this paper we present a multiple case study using fMRI to investigate the reorganization of language in response to MIT. Elaborating on our earlier finding that auditory presentation of melodically intoned language activates a left lateralized motor sensory language network in healthy speakers[19], we assume that LH activation is crucially related to the facilitatory as well as the therapeutic effect of MIT in patients with non-fluent aphasia. We hypothesize that that the positive effects of intensive MIT result from re-recruitment of LH structures, rather than recruitment of RH language homologues.

To investigate the impact of timing on MIT related language reorganization, we included patients who either had sub-acute aphasia (< 3 months post stroke) or chronic aphasia (> 1 year post stroke).

Methods

Design

We performed a multiple case fMRI study with a pre-post design. In a convenience sample of 4 chronic and 5 sub-acute stroke patients with aphasia, lateralization of activation in response to spoken language was established before and after a MIT intervention of 6 weeks. In addition, we report lesion information and language data for each participant.

The medical ethics committee of Erasmus MC University Medical Center approved the study. Patients were included after giving informed consent.

Participants

Between January 2010 and August 2011 a convenience sample of four chronic and five sub-acute stroke patients were included. All except one were participants of our randomized controlled trials (Dutch trial register NTR1961)[7,24] who were allocated to the experimental condition. Treatment was provided following the protocol of these randomized MIT effect studies. The patient who did not participate in the MIT trial (Table 1; A1) started treatment at 2 weeks post stroke, i.e. earlier than the other sub-acute patients. In her case, MIT was given following the same treatment protocol as used in both trials.

All patients had severe aphasia and were referred to the researchers as candidates for MIT[25], meeting the following criteria:

- Aphasia after LH stroke
- Non-fluent (< 50 words/minute)
- Articulation deficits
- Repetition severely affected
- Moderate to good auditory comprehension
- Right handed
- No severe hearing deficit or psychiatric history relevant for language and communication
- No intensive MIT prior to the start of the study
- Written informed consent prior to participation in the study
- No contra-indication for MRI scanning
- Intervention and language assessments

MIT was given during 6 weeks with a minimum intensity of 5 hours per week. SLTs were trained to follow the original American manual.[7,11] They used a set of utterances of increasing complexity, starting with a few formulaic phrases such as "good morning", but moving on to unfamiliar and longer utterances, such as "a one hour delay" or "what a wonderful cook you are". At least 50% of the therapy time was committed to this set; in addition, the SLT and the patient composed a set of personally relevant utterances, such as utterances related to their jobs, hobbies or family.

Language assessments pre- and post treatment included the Aachen Aphasia Test (AAT, Dutch version) [26] and the Amsterdam Nijmegen Everyday Language Test (ANELT). [27,28] In addition, pre-treatment auditory comprehension of words was tested with the Psycholinguistic Assessments of Linguistic Processing in Aphasia (PALPA, Dutch version) [29]

Handedness was scored using the Edinburgh Handedness Inventory (EHI) [30]

FMRI task, acquisition and analysis

All patients underwent fMRI scanning twice: [1] immediately prior to the start of a 6 weeks period of MIT and [2] immediately after completion of this treatment. They performed an auditory passive listening task, consisting of 6 30-second stories (experimental condition). Although MIT aims to improve language production, we did not use an overt production task for this fMRI study. Passive listening is a robust global language task, which can be performed by patients with a severe form of aphasia. For the population of MIT candidates, overt production tasks are very challenging and may lead to imaging difficulties related to head motion, distortion, and susceptibility artefacts. Patients were familiarized with the task prior to scanning. Each story was followed by

the same story in reverse speech as a control condition. A 3 s instruction announced the start of each condition. The task was presented binaurally through the scanner's headphone system, using Presentation v13.0 software (Neurobehavioral Systems Inc. Albany, CA, US) installed on a desktop PC. External triggering by the MR system ensured synchronization of the stimulus paradigm with the imaging data acquisition.

Scanning was performed on a 3T MR system (HD platform, GE Healthcare, Milwaukee, WI, US) using an 8-channel head coil for reception of the signal. For anatomical reference, a high-resolution 3 dimensional (3D) Inversion Recovery (IR) Fast Spoiled Gradient Echo (FSPGR) T1 weighed sequence was acquired, with the following pulse sequence parameters: repetition time (TR)/echo time (TE)/inversion time (TI) 10.5/2.1/300 ms; flip angle 18°; effective voxel size 0.6x0.7x0.7 mm; acquisition time 4:40 min. A T2 fluid attenuation inversion recovery (FLAIR) sequence was used for lesion delineation (TR/TE/TI 8002/123/2000 ms; flip angle 90°; reconstructed voxel size 0.8x0.8x2.5 mm^3).

For functional imaging, a single shot T2*-weighted gradient echo echo-planar imaging (EPI) sequence sensitive to blood oxygenation level dependent (BOLD) contrast was used (TE/TR 30/3000 ms; flip angle 75°; voxel size 3.4x2.3x3.5 mm^3; 39 slices with full brain coverage). Total duration was 6:51 min, which included 15 s of dummy scans that were discarded from further analysis.

Imaging analysis was performed using SPM8 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, UK). Images were manually reoriented to the anterior commissure and subsequently all T2*-weighed functional images were realigned and then co-registered with the T1-weighed anatomical image.[31] The functional and anatomical images were normalized to the standard brain space defined by the Montreal Neurological Institute (MNI) as provided within SPM8, using unified segmentation[32,33], resulting in resampled voxel sizes of 3x3x3 mm^3 for the functional and 1x1x1 mm^3 for the anatomical images. The normalized functional images were smoothed with a 3D Gaussian Full Width Half Maximum (FWHM) filter of 6x6x6 mm^3.[34]

All fMRI data were analyzed using the General Linear Model (GLM), by modeling in a blocked design the experimental and the control conditions excluding the instructions. The blocks were convolved with the hemodynamic response function (HRF), corrected for temporal autocorrelation and filtered with a high-pass filter of 128 s cut-off. Motion parameters were included in the model as regressors of no interest to reduce potential confounding effects of motion. First, the individual t-contrast images for the experimental versus control condition were generated for all patients to assess the main effect of auditory comprehension. Then, the number of activated voxels within each cerebral hemisphere was determined using a threshold independent method.[35,36] Individual lateralization indices (LI) were determined, defined as: (vLH-vRH)/(vLH+vRH), where vLH and vRH are the number of activated voxels in the left and right hemisphere respective-

ly. Patients' activation was classified as left lateralized for LI values between 0.1 and 1.0, right lateralized for LI values between -0.1 and -1.0, or symmetrical for LI values between or equal to -0.1 and 0.1.[36]

Lesion information was obtained at the first fMRI session. The stroke-related lesions were delineated manually on the T2-FLAIR images using MRIcron (http://www.mricro.com), defined as lost tissue only. An experienced neuroradiologist (MS) reported the anatomical localization of the lesion.

Results

Demographic data, baseline characteristics and improvement of language production are presented in Table 1 for the sub-acute patients and in Table 2 for the chronic patients. This multiple case study does not allow for testing for statistical significance of group differences. Informal assessment shows no substantial differences between both groups in average age (sub-acute 51.2y; chronic 54.0y) AAT language comprehension (sub-acute 43.8; chronic 44.8) or PALPA semantic comprehension (sub-acute 36.8; chronic 38.5). Language production scores showed larger differences. Scores were lower in sub-acute patients for Spontaneous Speech (median sub-acute 0.8; chronic 1.5) as well as for the ANELT (sub-acute 17.6; chronic 24.75).

One chronic patient (Table 2; C2) was referred to the trial as right-handed, but his EHI score indicated that he was ambidextrous.

Table 1. Participants with sub-acute aphasia (n=5); baseline characteristics and improvement of language production

Baseline characteristics	A1	A2	A3	A4	A5
Age (years)	25	61	59	55	56
M/F	F	M	M	F	F
Education (years)	12	15	15	13	8
Handedness; EHI	Right; 1.0	Right; 1.0	Right; 0.9	Right; 1.0	Right; 1.0
Time post stroke (months)	0.5	2	3	2	2
Hemiparesis - Arm - Leg	 R-paralysis R-paresis	 R-paralysis unknown	 R-paralysis R-paresis	 R-paresis R-paresis	 Intact Intact
Language Production Spontaneous Speech, AAT (0-5) ANELT-A (10-50)	 1 25	 0 10	 2 29	 1 10	 0 14

Auditory comprehension					
Words & Sentences (AAT; 0-60)	45	45	40	50	39
Words (semantics, PALPA; 0-40)	35	36	40	38	35
Improvement of language production					
Δ Spontaneous Speech	2*	1	1	0	2*
Δ ANTAT-A *Group average vd Meulen et al[4] = 6.6*	7**	0	14*	11*	17*
Δ AAT-repetition *Group average vd Meulen et al[4] = 28.5*	50*	36*	10*	29*	81*
Δ AAT-naming *Group average vd Meulen et al[4] = 20.5*	49*	10	32*	6	33*

EHI Edinburgh Handedness Inventory; Amb: ambidexter; ASRS Aphasia Severity Rating Scale; ANELT Amsterdam Nijmegen Everyday Language Test; AAT Aachen Aphasia Test; PALPA Psycholinguistic Assessments of Linguistic Processing in Aphasia; R=right-sided. Δ: post-MIT score - pre-MIT score. *Significant improvement according to test manual. ** Approaches significance according to test manual

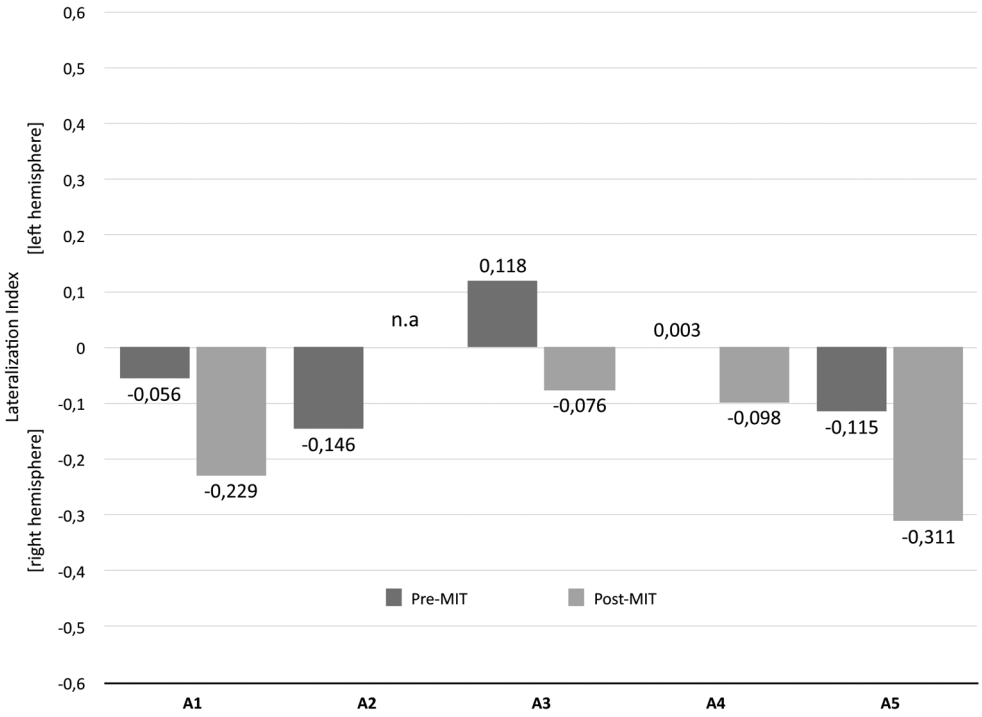

Figure 1. Lateralization index in participants with post-acute stroke (n=5). Patient's activation was classified as left lateralized for LI values between 0.1 and 1.0, right lateralized for LI values between -0.1 and -1.0, or symmetrical for LI values between or equal to -0.1 and 0.1, n.a= no activation.

Table 2. Participants with chronic aphasia (n=4); baseline characteristics and improvement of language production

Baseline characteristics	C1	C2	C3	C4
Age (years)	64	66	21	65
M/F	M	M	F	M
Education (years)	10	8	17	13
Handedness; EHI	Right; 1.0	Amb; 0.5	Right; 1.0	Right; 1.0
Time post stroke (months)	40	17	18	37
Hemiparesis - Arm - Leg	 R-paralysis R-paresis	 Intact Intact	 R-paralysis R-paresis	 R-paresis R-paresis
Language Production				
Spontaneous Speech, AAT (0-5)	1	1	2	2
ANELT-A (10-50)	27	20	23	29
Auditory comprehension				
Words & Sentences (AAT; 0-60)	53	39	48	39
Words (semantics, PALPA; 0-40)	39	37	38	40
Improvement of language production				
Δ Spontaneous Speech	0	0	0	0
Δ ANTAT-A *Group average vd Meulen et al[4] = 0.4*	2	2	8*	1
Δ AAT-repetition *Group average vd Meulen et al[4] = 6.1*	10	21*	26*	18*
Δ AAT-naming *Group average vd Meulen et al[4] = 3.1*	9	13	-	-6

EHI Edinburgh Handedness Inventory; Amb: ambidexter; ASRS Aphasia Severity Rating Scale; ANELT Amsterdam Nijmegen Everyday Language Test; AAT Aachen Aphasia Test; PALPA Psycholinguistic Assessments of Linguistic Processing in Aphasia; R=right-sided. Δ: post-MIT score - pre-MIT score. *Significant improvement according to test manual. ** Approaches significance according to test manual

Patients with sub-acute aphasia

As compared to the experimental group in our randomized trial7, language improvement was above average in the sub-acute patients, indicating that the patients were above-average responders to MIT. Substantial improvement of repetition was present in all cases, generalizing to spontaneous speech in 2 patients, to verbal communication in 4 patients and to naming in 3 patients. (Table 1) This pattern of improvement is in line with the results found in the sub-acute group.[7]

Lesion information for the sub-acute patients is listed in Table 3. All patients had left hemispheric lesions of the MCA vascular territory, which included the left superior temporal, insular and striatocapsular regions in all patients. Lesion volumes were around 30-55 ml, with one outlier, A4, whose lesion was considerably larger (141 ml). The inferior frontal gyrus was affected in 3 patients, while in none of the patients the supplementary motor area (SMA) was involved.

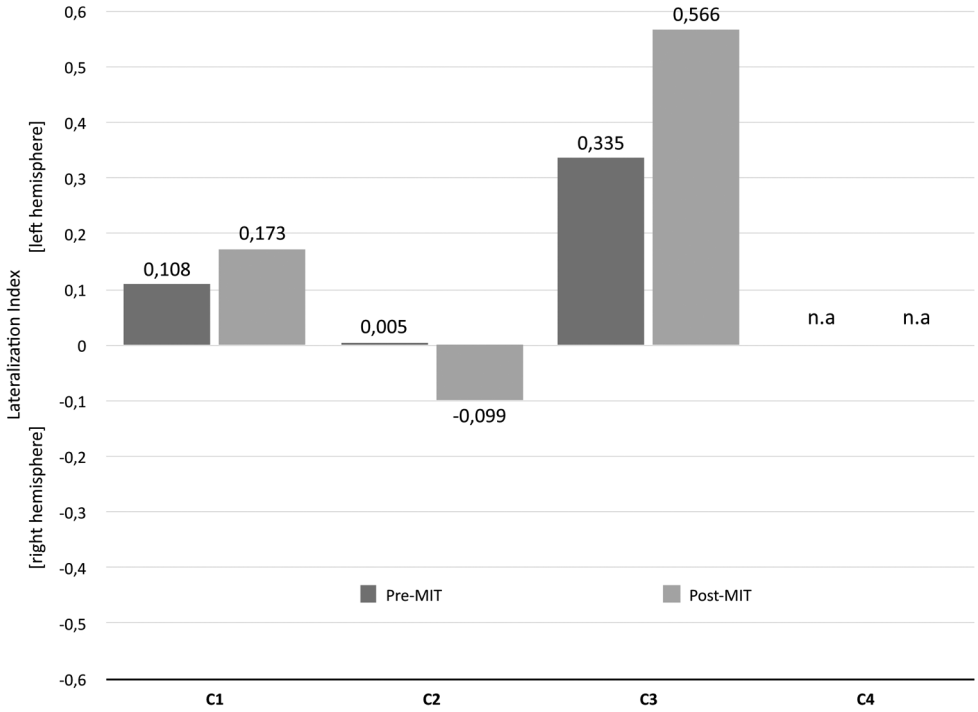

Figure 2. Lateralization index in participants with chronic stroke (n=4). Patient's activation was classified as left lateralized for LI values between 0.1 and 1.0, right lateralized for LI values between -0.1 and -1.0, or symmetrical for LI values between or equal to -0.1 and 0.1, n.a= no activation.

LIs obtained for each patient immediately before and after the 6 week MIT period are shown in figure 1. Before MIT, 1 sub-acute patient showed left-lateralized activation, while activation was symmetrical in 2 and right-lateralized in a further 2 patients. After treatment, all patients except one (A2) showed a rightward shift of activation.

Patients with chronic aphasia

Like the sub-acute patients, the chronic fMRI patients were above average responders to MIT, showing above average improvement of language production, as compared to the chronic patients in the trial (Table 2).[24] Recovery was more restricted than in the sub-acute patients. Again, this pattern is in line with the trial results.[24] Repetition improved substantially after MIT, but there were no functional benefits in verbal communication or naming. Only one participant showed a significant improvement of 8 points on the ANELT (C3). Three out of four showed significant improvement on the -untrained- AAT repetition task.

Table 3 summarizes the lesion information. All patients had left hemispheric lesions of the middle cerebral artery (MCA) vascular territory. C4's lesion was relatively small, compared to the larger lesions in C1, C2 and C3 (74-88 ml). Language areas that were involved

Table 3. Participants with sub-acute stroke (n=5). Lesion location and lesion size

	A1	A2	A3	A4	A5
Inferior Frontal Gyrus	-	-	+	+	+
Insula	+	+	+	+	+
Superior Temporal Gyrus	+	+	+	+	+
Middle Temporal Gyrus	-	-	-	+	-
Angular/Supramarginal Gyrus	+	-	+	+	+
Supplementary Motor Area	-	-	-	-	-
Striato-capsular	+	+	+	+	+
Cortical language region Summary	Insular-Temporoparietal	Insular-Temporal	Frontal-insular-temporoparietal	Frontal-insular-temporoparietal	Frontal-insular-temporoparietal
Lesion Volume (MRIcron (ml))	n.a.[1)]	32.40	55.51	141.16	50.57

+ Affected; - Unaffected; [1)] No tissue loss yet

included the left inferior frontal gyrus in 2 patients, the left posterior parietotemporal region in 3 patients, and the striatocapsular region in 3 patients. The left SMA was unaffected in all patients with an exclusively left-hemispheric stroke. One patient however (C1) had a lesion of the left SMA, but no other left-sided language areas, in addition to an extensive right-hemispheric stroke, unknown at the aphasia center referring him for the MIT study. He had a right-sided hemiparesis and the SLT assumed he had a unilateral LH lesion. C1 was no exception in that he showed above average improvement of language production.

Two patients (C1 and C3) were left-lateralized, both pre- and post treatment (Figure 2). After treatment, this left-lateralization became more pronounced in both patients. Notably, C3, who was most strongly left-lateralized before treatment and considerably more so after treatment, also showed the largest language recovery. For C4, no activation was observed during the passive listening task at either session. One patient, C2, showed no lateralization prior to treatment (LI= 0.05). It might be argued that the pattern seen in C2 (LI-pre – LI post = - 0.149) could be interpreted as a shift of activation to the RH after MIT. However, the RH lateralization post MIT LI is marginal, just

Table 4. Participants with chronic stroke (n=4). Lesion location and lesion size

	C1	C2	C3	C4
Inferior Frontal Gyrus	left: - right: -	+	+	-
Insula	left: - right: +	+	+	+
Superior Temporal Gyrus	left: - right: +	-	+	+
Middle Temporal Gyrus	left: - right: +	-	-	-
Angular/Supramarginal Gyrus	left: - right: +	+	+	+
Supplementary Motor Area	left: + right: -	-	-	-
Striato-capsular	left: - right: +	+	+	+
Cortical language region Summary	left SMA; right insular- temporoparietal	frontal-insular-parietal	frontal-insular-temporoparietal	insular-temporoparietal
Lesion Volume (MRIcron (ml))	87.94	74.04	77	27.40

+ Affected; - Unaffected; C1: bilateral lesion. C2-4:unilateral lesion (left)

approaching the criterion for right lateralization (LI<-0.1).

Discussion

In this fMRI study, we did not find a consistent shift of language activation after MIT to either the LH or the RH. The results therefore do not support our hypothesis that MIT-induced language improvement is crucially related to reactivation of LH structures, nor are they in support of the notion that MIT promotes RH recruitment for language processing. Before as well as after MIT, sub-acute and chronic patients differed in their activation patterns obtained during the passive listening task. The chronic patients were predominantly left-lateralized, with increased left-lateralization post-treatment in 2 out of 4 patients. The sub-acute patients showed a reverse pattern. Only 1 of 5 sub-acute patients was left lateralized pre-treatment, whereas language activation tended to shift rightwards in all but one. Overall, in line with the earlier trial results, the sub-acute patients of this fMRI study benefited more from MIT than the chronic patients. It might be argued, in support of the concept of increased RH involvement after MIT, that better responders show increased RH activation. However, the finding that there was no correlation between language improvement and activation shift does not support this interpretation. The chronic patient with the most favorable response to MIT showed a significant shift of activation to the LH.

An alternative interpretation may be that time post onset, rather than type of treatment, was decisive for the observed lateralization of language activation, in line with the concept of a dynamic reorganization pattern over time. In a recovery study with 14 participants, Saur et al[37] concluded that there are at least 3 phases in the process of language reorganization: [1] a phase of strongly reduced activation in the LH language areas in the first days, [2] an up-regulation of activity with recruitment of RH homologue language areas after 2 weeks, and [3] a normalization of activation, with re-activation of LH areas at about 1 year post stroke. At 2 weeks post stroke, RH activation was correlated with language recovery, whereas patients with persistent RH activation at 1 year post stroke showed less recovery.[37,38] Because of the long interval between the second (2 weeks post stroke) and the third scans (1 year post stroke), the study does not provide information about the exact timing of this reactivation of the LH, but a recent study reported that intensive treatment within the first 2 weeks may promote an early re-shift to the LH.[39]

Our findings in the sub-acute MIT patients might fit into such a dynamic process of language recovery. They have a severe aphasia and are still strongly right-lateralized at 2-3 months post onset. Possibly, in case of a favorable recovery process, they may show a re-shift to the LH later in their first year post onset. If this were the case, MIT would delay rather than promote a re-shift to the LH as the application of MIT results in a rightward shift of language activation. The chronic patients on the other hand, do not fit into the dynamic recovery pattern proposed by Saur et al.[37] As suitable MIT candidates, they all had severe chronic aphasia with restricted recovery over one or more years, but none were right-lateralized. In fact, 2 out of 4 were left lateralized pre-treatment, thus showing the normalization of activation that Saur and colleagues found in chronic patients with favorable recovery. After MIT, these two chronic patients showed a further shift of activation towards the left hemisphere after treatment and this tendency was strongest in the patient with the most favorable recovery.

Our cross-sectional data cannot rule out the possibility that the sub-acute and chronic MIT candidates differed systematically in other variables related to time post onset. One possibility is that the different activation patterns in sub-acute and chronic MIT patients are related to differences in aphasia severity and lesion size. A comparison of severity is difficult in our groups. Comprehension scores were comparable in both groups, although with a slight advantage for sub-acute patients. Chronic patients had higher production scores. Three out of 4 chronic MIT candidates had larger LH lesions than the sub-acute group and initially they may have been more severely affected. It has been argued that in patients with extensive lesions language recovery is limited and will necessarily depend on RH recruitment, as hardly any LH structures potentially relevant for language are intact.[20,40] However, based on lesion size the expected lateralization pattern would be opposite to our findings, i.e. a stronger tendency for lateralization towards the RH in chronic patients and towards the LH in sub-acute patients.

Although MIT is aimed at language production, we chose to use a passive listening task. This ensured robust language activation with a task which MIT candidates would be able to perform with a required level of performance of 60-90%.[41] An overt production task would have been more closely related to the focus of MIT, i.e. improved language production. However, to select a relevant language production task was considered impossible, because in this group of patients overt production is expected to be very restricted pre-MIT and considerably higher post-MIT. We are aware however, that the patterns found here might be different when using other fMRI language tasks more directly related to the focus of treatment.[42]

MIT, as provided in its original form, implies a multimodal approach. Like in many other studies we concentrate on melodic intonation as the crucial element for the therapeutic success of MIT. However, the positive treatment effects have also been attributed to other components, such as stimulation of rhythm[43], motor activation as a result of hand-tapping3 or a positive impact of music on mood. Whereas the musical components could be expected to promote right-hemisphere involvement, the rhythm component as well as the hand tapping may be expected to promote LH involvement. It is very likely, that these components are not mutually exclusive, and each element potentially contributes to the overall effect[44] and may thus have an impact on language lateralization.

This study has several limitations. Like in other studies on MIT-induced language reorganization, the number of patients is small and, in spite of the robust passive listening task, a lack of activation was observed in some patients. This hampers the interpretation of the results because many factors may interact to produce the individual fMRI patterns. Also, this study lacks control data, as we did not investigate patients with aphasia not receiving MIT. Such data are crucial to establish the variation of activation patterns over time. This is of special interest in sub-acute patients in whom spontaneous recovery may also still be at play.

To the best of our knowledge, this is the first study of treatment-related language reorganization to suggest that time post onset may play an important role in treatment-induced language reorganization after stroke. Intensive MIT over 6 weeks does not promote a uniform pattern of either left or right language lateralization in patients with severe non-fluent aphasia. In spite of considerable individual variation across subjects, the reorganization patterns observed in sub-acute and chronic patients showed opposite directions. In future studies of treatment-induced language reorganization in aphasia, the factor time post onset should therefore be addressed systematically.

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Chapter 8

General Discussion

In this thesis, I have used functional MRI to study the neural substrates of language processing in both healthy participants and in patients with a focus on understanding aphasia recovery, either spontaneously or after language therapy. In this chapter I will outline the main findings from the studies described in this thesis, together with the clinical implications and suggestions for future research.

I. Functional anatomical models of language

Current neuroimaging studies investigating language recovery in aphasic patients are aimed at unraveling the neural changes that accompany spontaneous and treatment based recovery of specific language functions. For the interpretation of neural changes due to specific language therapy in these patients, it is necessary to understand the normal organization of language. I investigated three language functions in healthy participants that are commonly targeted during language therapy for aphasic patients: melodically intoned language, and phonological and semantic language processing.

Melodically intoned language is a key feature used in Melodic Intonation Therapy (MIT) [1], a language therapy that aims to facilitate language production in non fluent aphasic patients by using musical elements of speech: exaggerated intonational sentence patterns. This therapy is thought to elicit speech by the activation of the musical functions: rhythm, stress and intonation, stored in the right hemisphere.[2] Phonological and semantic processing are two basic linguistic components targeted in Cognitive Linguistic Therapy [3-5] to treat word findings deficits, a central and persistent problem in aphasic patients.

I interpreted the results of these three language functions in healthy participants in light of the dual (dorsal and ventral) stream model for auditory language processing proposed by Hickok and Poeppel[6-8]. The dorsal stream supports processing such as auditory-to-motor mapping mainly required in phonological processing, and the ventral stream subserves semantic processing.[9] I specifically focused on two regions which are part of these streams: the Sylvian parieto-temporal area (Spt area) and the inferior frontal gyrus (IFG).

Additionally, I investigated the role of the cerebellum in language processing. The function of the cerebellum is not limited to the control of motor function as has been thought for a long time in the past. With the increasing number of fMRI studies investigating language functions, cerebellar activation has also been observed under some specific language task conditions.[10-12] Although its precise connection with language processing in the cerebrum is not clear, its function in language processing is receiving increasing attention.[13]

a) Motor-sensory network during language processing

A crucial element of MIT is the melodically intoned auditory input: the patient listens to the therapist singing a target utterance. I investigated the differential perceptual processing of spoken and melodically intoned language using both meaningful and meaningless words. I found different patterns of activation for the auditory processing of melodically intoned language compared to normally spoken language. Compared to spoken language, melodic language recruited brain regions in the left posterior portion of the superior and middle temporal gyrus (Spt area). This Spt area is thought to be part of the auditory-motor integration system: a sensorimotor interface related to both speech comprehension and phonological aspects of speech production. [14-16]

The activation in the Spt area was accompanied by bilateral motor activation at the level representing the face, and there was additional activation in the left IFG when lexical-semantic content was present (thus, while listening to meaningful melodically intoned items). These findings can partially be interpreted in the context of Hickok and Poeppel's dorsal stream model for auditory processing. [8] The dorsal stream projects connections from the Spt area to the left frontal cortices, specifically to the dorsal portion of the premotor cortex and to the left IFG and ventral portion of the premotor cortex. The latter two are called the articulatory network. [8] This stream is thought to be involved in translating acoustic speech signals into articulatory representations in the frontal lobe. It is essential for speech production and guides speech perception before the next stage of speech comprehension. [8] Furthermore, the bilateral activation in the primary motor area at the level representing the face may be interpreted in the context of the pioneer motor theory of speech perception proposed by Liberman and Mattingly in 1985 [17]. This theory suggests that co-articulation occurs in parallel to auditory processing to aid the auditory system in separating speech segments over longer intervals of time.[18] This is an important finding in the context of MIT, since the first stages of this therapy focus on intensively providing auditory input with prosodic features different from those used in normal speech. Such auditory input, simulated here with melodically intoned speech items, thus hypothetically serves to facilitate the activation of the articulatory system and priming of the motor areas for language production.

b) Role of the left IFG in phonological and semantic processing

Phonological and semantic processing are basic linguistic components with direct implications for word finding in spoken language.[19,20] A word finding deficit (anomia) is one of the central and persistent problems in aphasic patients irrespective of overall aphasia severity.[21] I investigated auditory phonological and semantic processing to elucidate whether these linguistic processes recruit different portions of the left IFG, given its proposed important role for the recovery of language function in aphasia.[1,222] I had a particular interest in investigating these linguistic processes in the older population,

which is the age group in which aphasia due to stroke is more frequent. I found that auditory phonological and semantic processing elicited overlapping activation in the pars triangularis (BA 47) of the left IFG. In addition, activation for phonological processing extended to the posterior dorsal portion of the left IFG (BA 44), while semantic processing extended to the anterior ventral portion (BA 45). A direct comparison between the two linguistic levels indicated that semantic processing activated the left pars orbitalis of the left IFG stronger than phonological processing. The functional representation in distinct regions of the IFG can again be partially interpreted in the context of Hickok and Poeppel's model. [2,8] As mentioned above, each stream is thought to serve a different language function: the ventral pathway subserves semantic processing, while the dorsal pathway supports processing such as auditory-to-motor mapping mainly required in phonological processing. Anatomically, the ventral pathway connects anterior portions of IFG, that I found to be activated during semantic processing (BA 45/47), to the temporal cortex.[3-5,9] As explained above, this portion of the left IFG supports semantic processes, and in particular controlled processes at the word-level such as semantic judgment or categorization [6-8,23,24] and lexical-semantic access [9,25]. I found regions along the dorsal stream to be activated for receptive phonological processing, namely the posterior portion of the left IFG (BA 44) extending to the premotor cortex (BA 6) (both regions being part of the articulatory network) and the superior temporal gyrus. I propose that these findings contribute to the understanding of the functional role of the dorsal stream of sound-to-motor mapping, given the observed involvement of the articulatory network not only in productive but also in receptive phonological processing.

c) Cerebro-cerebellar language lateralization

So far neuroimaging studies of language processing have mainly focused on cerebral brain regions for language processing. Both lesion and functional neuroimaging studies, however, suggest that not only the cerebrum is involved in language processing, but that the cerebellum also contributes to various cognitive language components and aspects of language production[10-13,26] and language comprehension[13,27]. Some further studies have provided evidence for a so-called crossed cerebro-cerebellar language lateralization pattern in healthy persons, both with typical, left-sided and with atypical, right-sided language lateralization.[11,14-16,28] This pattern however has mainly been explored in right handed participants.

By using a covert verb generation task, I analyzed the cerebral and cerebellar language activation in healthy participants individually to allow the observation of crossed cerebro-cerebellar activation in left and right-handers with typical and atypical language representation. I found a significant dependency between language lateralization in the cerebrum and in the cerebellum, in line with previous studies describing the crossed cerebro-cerebellar language lateralization pattern. The more strongly language was

lateralized towards a cerebral hemisphere, the more strongly it was lateralized to the contralateral cerebellar hemisphere, irrespective of whether cerebral language representation was typical or atypical. Only in a minority of healthy participants I did not observe this crossed cerebro-cerebellar language lateralization pattern. In these cases either cerebral or cerebellar activation was found to be symmetrical. However, none of the healthy participants showed symmetrical language lateralization in both the cerebrum and the cerebellum. This leads me to think that there might be other factors at play that determine language lateralization apart from handedness, such as the type of language processing that is targeted and task performance. To the best of our knowledge, our study is the first to confirm crossed cerebro-cerebellar activation in a large group of left handed healthy participants with a high prevalence of atypical language representation.

In conclusion, in the studies on healthy volunteers I found that auditory processing of both melodically intoned meaningful language and phonological information activates regions involved in the dorsal stream, which requires activation of the articulatory motor network. This frontal activation seems to be very localized, as it does not comprise the complete IFG but only its most posterior portion, extending to the motor regions responsible for motor-oral functions. Furthermore I could confirm previous observations that subportions of the IFG have distinct roles in processing of phonological and semantic information. In a direct comparison between semantic and phonological processing I observed that activation during semantic processing did not extend to regions involved in articulatory-motor network but specifically activated the *anterior* portion of the IFG.

Additionally I established that language activation in the cerebellum is contralateral to cerebral activation. This pattern of activation seems to be consistent in right and left handed participants irrespective of whether they had typical or atypical cerebral activation.

II. Language processing in patients with a brain tumor

Functional MRI is a feasible diagnostic neuroimaging tool for determining hemispheric language dominance in brain tumor patients preoperatively. [8,29] Nevertheless, activation patterns must be interpreted with great care when the tumor is in or near the presumed language areas, where tumor tissue or mass effect can lead to false negative fMRI results.[8,30] Determining language dominance is additionally challenging in left-handed brain tumor patients. Left-handers are known to have less well defined language lateralization patterns, with more atypical right-sided language lateralization compared to right-handers.[8,31-33]

I focused on the crossed cerebro-cerebellar language activation described above in healthy participants. I hypothesized that cerebellar activation might be an additional indicator to evaluate language dominance since it is generally undisturbed by the tumor localized in the presumed supratentorial language areas. By implementing a verb generation task, I assessed the crossed cerebro-cerebellar activation in left and right handed tumor patients. In line with previous studies investigating crossed language activation pattern, I also found a significant dependency between language lateralization in the cerebrum and in the cerebellum in brain tumor patients.

When cerebellar activation is found to be lateralized, we can as a rule of thumb assume that there is contralateral cerebral language dominance. This crossed cerebro-cerebellar pattern of activation could be included as a diagnostic tool in future guidelines of clinical fMRI examinations, by implementing a language task that it is known to involve the cerebellum such as the verb generation task. This crossed pattern is particularly useful in left-handed brain tumor patients, in whom language representation is commonly atypical, resulting in diagnostic uncertainty especially when there is potential interference of the tumor with language activation.

In patients showing symmetrical cerebellar activation other examinations such as the Wada test and electrocortical stimulation may still be required to determine language dominance in both patients with typical and as well as in patients with atypical language representation.

III. Language recovery in aphasic patients

I investigated the relationship between language lateralization and language recovery (either spontaneously or after language therapy) to assess the widely held hypothesis that good recovery is related to left lateralized language processing, and right-sided lateralization with poor recovery. Using a simple passive listening task, which could be performed even by severely aphasic patients, I explored language lateralization in mild and severe chronic aphasia patients and in severe sub-acute and chronic aphasia patients following intensive MIT.

Comparing patterns of language lateralization in a large group of mild and severe aphasia patients, I found that language lateralization was not correlated with aphasia severity. Most of both the mild and severe aphasia patients showed left sided language lateralization. Lesion volume, however, was significantly greater in severely than in mildly aphasic patients, and was found to be an independent predictor of language comprehension performance as measured with the Token Test, a test used in general to measure the presence and the severity of aphasia in stroke patients.

I also investigated the shift of language lateralization in sub-acute and chronic aphasic patients after intensive MIT, and found that time post onset may play an important role in treatment-induced language reorganization after stroke. In spite of considerable individual variation across subjects, the reorganization patterns after therapy observed in sub-acute and chronic patients showed opposite directions. Sub-acute patients showed right lateralized language activation pre and post treatment while chronic patients showed left lateralized language activation that remained left lateralized after treatment. Intensive MIT over 6 weeks did not promote a uniform pattern of either left or right language lateralization in patients with severe non-fluent aphasia in the sub-acute and chronic stage.

Taken together, these findings challenge the widely held hypothesis that language recovery is related with language lateralization. The pattern of language lateralization seems to be related with the time post onset and not with the aphasia severity or therapy effects. In both studies I found that irrespective of aphasia severity, language was more commonly left than right lateralized in chronic aphasia patients. Patients with sub-acute aphasia, however, showed a right lateralized language activation, which did not shift to the left dominant hemisphere with language therapy. Furthermore, lesion size was an independent predictor of language recovery. It is expected that lesion size has a confounding effect on language activation: smaller lesions may be related to less severe aphasia, but also to larger remaining language areas or perilesional areas in the left hemisphere. Conversely, more extensive lesions are likely associated with more severe aphasia, but also would result in less remaining functioning tissue in the left hemisphere. This would lead to the recruitment of undamaged right-hemispheric areas of the language processing network. [17,34] Independent of the lesion size, both severe and mild patients showed either left or right lateralized language activation.

I investigated the language activation in the aphasic patients described above using a passive listening task, a simple task that could be performed by all patients irrespective of their aphasia severity. Different patterns of language activation can be expected when applying tasks targeting specific linguistic levels. As I described in the study on healthy participants, we could observe specific patterns of activations triggered by the language functions trained during two types of language treatments, MIT and CLT. Linguistic function targeted in these treatments activates different brain regions, which might explain why some patients benefit more from one type of language therapy depending on the functioning of those brain regions. The pattern of language recovery might then not only depend on the language deficit of the patient but also on the ability of damaged or non damaged language areas to be activated during these specific language treatments.

IV. Methodological aspects

The studies presented in this thesis show that fMRI provides exciting new opportunities to explore language processing in clinical populations, especially to increase our understanding of the neural substrates and neural changes that support spontaneous and therapy related language recovery in patients with aphasia. However, there are some experimental issues that arise in research of language functions in a clinical population. Across the studies presented in this thesis, two common aspects need to be considered, the language tasks used and the method to evaluate language lateralization.

We used two tasks, the verb generation (in tumor patients) and a passive listening task (in aphasic patients). The verb generation task is a preferred task to localize language areas in tumor patients [12, 18, 35-37] and has been properly validated with electrocortical stimulation [19, 20, 38]. Although the brain tumor patients recruited in our study were not severely aphasic, this task may still be too difficult to perform by patients with severe aphasia. The passive listening task is a simple task suitable for use in even severely aphasic patients [21, 39] and it has been widely used in fMRI studies to obtain an overall activation measure of language comprehension. This task, however, might not be specific to assess language recovery following language therapy since it might not reflect the linguistic processing targeted during treatment. As addressed more in detail below, in our Functional Imaging of Aphasia Therapy study (FIAT-study) I designed two fMRI tasks evaluating linguistic levels targeted during CLT (rhyme decision and semantic association task), which can be implemented in aphasic patients with different degrees of aphasia severity while recording task performance. Furthermore, although both tasks used here are easy to be implemented to evaluate language functions in patients, there is a lack of behavioral monitoring. As described in chapter 2, there are decisions to be made when designing an fMRI experiment and building an fMRI paradigm, especially when investigating language processing in patients, namely regarding task design, stimulus modality and response mode (monitoring). In the case of the verb generation task, we preferred patients to perform this task covertly to avoid motor artifacts due to articulation. Covert paradigms have been shown to reliably elicit activation in language related brain areas.[40] The disadvantage of covert paradigms is that task performance cannot be monitored, thus it is difficult to be certain whether the patients could perform the task, and therefore language activation may not be reliable. In the study evaluating language dominance in tumor patients an experienced neuroradiologist visually inspected the pattern of activation in each patient ensuring that language activation was present; in healthy participants we selected language region of interest (ROI) to ensure that we were obtaining brain activation due to the task. For the passive listening task implemented in the studies with aphasic patients, we checked patient's performance with a multiple choice questionnaire after the scan session.

The second common aspect across the studies presented in this thesis is the method we used to evaluate language lateralization. There are several factors that need to be

considered when evaluating language lateralization, such as the type of language processing that is targeted (overall language function or a specific linguist process), volume of brain tissue included in the analysis (whole brain or ROI), and the algorithms and thresholds used in the image analysis (threshold dependent or not).[41] In the studies described in this thesis, I used a threshold independent method to calculate language lateralization which generates lateralization indices that are more in agreement with clinical findings and is less prone to within-subject variability than a threshold dependent calculation.[42]

Patient inclusion is one of the most discussed limitations in neuroimaging studies in aphasia. In our study, we recruited only a small number of patients for the evaluation of the treatment effect of MIT. These patients (severe non-fluent patients) had a similar degree of aphasia severity at different phases after stroke (sub-acute and chronic stage) which allowed us to study the effect of MIT during the dynamic process of language recovery. Another limitation of this study, like that in many other fMRI studies investigating language treatment effects, was the lack of control data. This is a drawback with regards to the external validity of the treatment assessment. Nonetheless, to recruit patients to participate in a randomized controlled trial is not an easy task. Patients often hesitate to participate if they may be randomized to a control arm without therapy, especially in the acute phase of stroke, a period in which they are eager to practice in order to improve their language deficits. In the study described in chapter 6, we were able to recruit 39 aphasic patients, a large number of patients for a task-related fMRI study of language recovery. To avoid the interference of the dynamic effects during language recovery, we assessed language activation at the chronic stage after stroke, in a group of patients with different degrees of aphasia severity.

Furthermore, I investigated specific language tasks targeted on language treatment in healthy participants and not – yet – in patients. The findings of these studies cannot be directly translated to aphasic patients, but they offer some advantages: first, the validity of the language task can be verified instead of simply assuming that such a task will elicit activity in a given number of regions; second, it allows the comparison of activation pattern changes in aphasic individuals to assess whether changes occur within or outside of the "normal" language network. [43] Finally, aphasia due to stroke is more frequent in older population. In one of our studies investigating the neural mechanism of MIT, however we recruited younger participants. We addressed this issue in a later study investigating the neural mechanism underlying CLT, in which we recruited older participants.

V. Future perspectives

For the assessment of language dominance in tumor patients we explored the crossed cerebro-cerebellar pattern as an additional diagnostic tool. The mechanism underlying this pattern remains to be elucidated. Connectome analyses could be used to investigate white matter pathways that may be responsible for these findings. In addition it would be interesting to see whether this crossed pattern of language activation remains when other language tasks are used.

The pioneer longitudinal study of Saur et al[44] has shown that activation patterns change over time as a function of natural recovery. Up to date, there is no evidence yet to suggest that aphasia treatment influences the progressive dynamics of brain reorganization during the different phases of recovery.[45] As discussed in chapter 8, the effects of treatment on language recovery in acute and chronic aphasic stroke cannot be assumed to be the same. Some methodological aspects should be considered in future neuroimaging in aphasia treatment studies. Longitudinal studies are necessary to investigate the neuronal reorganizational processes in response to different forms of language therapy provided at different times post-onset [43]. Repeated assessments in the same individual are required to assess the effects of aphasia treatment on both the behavioral level and with regards to functional brain plasticity, and the extent to which improvements are retained in the long term. As described above, in order to evaluate the real impact of treatment, a control group of patients without treatment is necessary.[46] Another consideration is the fMRI task used to evaluate the effects of treatment. As discussed above, passive listening is a global language task that might be not specific enough to the language deficits in our aphasic population. As explored in our studies in healthy participants, it is necessary to incorporate fMRI tasks that relate directly to the linguistic level targeted during language treatment. In this way we can interpret activation changes as a function of treatment.[46] Finally, next to task related fMRI, other MR techniques such Diffusion Tensor Imaging (DTI) and Arterial Spin Labeling (ASL) may be used to examine how structural damage or compromised cerebral perfusion influences language activation. Combining these techniques holds a considerable potential to provide a more comprehensive understanding of brain activity during language processing.

In our FIAT study, I will further explore functional and structural changes during language recovery in patients following intensive CLT using fMRI, ASL and DTI. Aphasic patients in the acute and chronic stage were randomized to follow intensive CLT or no therapy during 4 weeks. Before, after and 3 months after randomization, activation patterns during phonological and semantic tasks were measured using a rhyme decision and semantic association fMRI task. Additionally, overall language activation was evaluated with a passive listening task and an overt naming task. Next to the patient group, aged matched healthy participants were scanned twice, at an interval of 4 weeks. Shortly, I will compare the activity in language-related brain regions between aphasic patients receiving CLT treatment, in order to observe different strategies of reorganiza-

tion as an effect of language treatment. I expect to give further insight into the mechanisms underlying language improvement related to therapy and how a specific type of treatment is associated with a specific brain activation pattern.

The potential role of fMRI in the assessment of language processing in clinical research can hardly be overestimated. Our results demonstrate how fMRI can be used to visualize how the language system is reorganized in brain damaged patients. Specifically for aphasia research it allows to show how specific language therapies can enhance language reorganization in connection with changes in behavioral testing and therefore optimize language recovery. The current knowledge from neuroimaging studies in aphasia treatment is not yet ready to be implemented in standard clinical practice. Our results, however, suggest that fMRI may help to predict rehabilitation outcome, and provide guidance regarding the optimal treatment for patients with specific patterns of brain activity during relevant tasks. The FIAT study will hopefully aid in further unraveling this process.

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Chapter 9

Summary Samenvatting

Summary

Aphasia is a language disorder in patients with brain damage of various etiologies such as stroke, trauma, neurodegenerative disease and tumor.[1-3] All language modalities are disturbed: speaking, comprehension of spoken and written language, and writing. A clarification of the underlying functional and neural mechanism of language functions is becoming increasingly relevant for patient care and clinical research. In this thesis I explored with functional magnetic resonance imaging (fMRI) language lateralization in brain tumor patients and language recovery in aphasic patients. In addition, I investigated in healthy participants specific language functions that are targeted in **Melodic Intonation Therapy** (MIT)[4] and **Cognitive Linguistic Therapy** (CLT)[5-7], two frequently used treatment methods.

In **chapter 2**, I provided a brief introduction into the basics of language fMRI and task design for current applications of this technique in both clinical and research practice. I also summarized how different language levels have been explored with a variety of language tasks that have improved the neuroanatomical models of language processing. One of the models that has lately been explored and translated to aphasia research is the model proposed by Hickok and Poeppel [8-10]. The authors propose a dual stream (dorsal, ventral) model for auditory language processing. The dorsal stream projects connections dorso-posteriorly from inferior parietal and posterior frontal lobe regions and is involved in auditory-motor integration by mapping acoustic speech sounds to articulatory representations. An example of a task targeting this stream is repetition of speech. [9,10] The ventral stream projects ventro-laterally to the middle and inferior temporal cortices and serves as a sound-to-meaning interface by mapping sound-based representations of speech to widely distributed conceptual representations. Hence, this stream supports the perception and recognition of meaningful speech.[9, 10]

Both lesion and functional neuroimaging studies suggest that not only the cerebrum is involved in language processing, the cerebellum also contributes to various cognitive language components and aspects of language production [11,12] and language comprehension[13]. Some further studies have provided evidence for a so-called crossed cerebro-cerebellar language lateralization pattern in healthy persons, both with typical, left-sided and with atypical, right-sided language lateralization.[14, 15] **Chapter 3** explores this cerebro-cerebellar language lateralization pattern in healthy participants and in brain tumors patients with a focus on atypical language representation. Twenty healthy participants (13 left handed and 7 right handed) and 38 patients (19 left handed) with a brain tumor underwent fMRI with a covert verb generation task. Language activation in the cerebrum and in the cerebellum was separately classified as left-sided, right-sided or symmetrical. Crossed cerebro-cerebellar language activation was present in both healthy participants and patients, irrespective of handedness, or typical or atypical language representation. Thus next to evaluating language lateralization in the cerebrum,

language lateralization in the cerebellum can be considered as an additional diagnostic feature to determine language dominance in brain tumor patients. This is particularly useful in cases of uncertainty, such as the interference of the brain tumor with cerebral language activation on fMRI, and atypical language representation.

Current efforts of neuroimaging studies investigating language recovery in aphasic patients are aiming to understand the neural changes that support treatment based recovery of targeted language functions. For the interpretation of neural changes due to specific language therapy in these patients, understanding the normal language organization is a required step. I investigated language functions in healthy participants which are targeted during MIT and CLT (semantics and phonology),frequently used treatment methods in aphasia.

Melodically intoned language is a key feature used in MIT, a well-known language therapy that aims to facilitate language production in non fluent aphasic patients by using musical elements of speech. The concept of this therapy was based on the observation that singing has a facilitatory effect on language production in severe non fluent aphasia patients. It is unclear whether singing an utterance or listening to an utterance with exaggerated intonational pattern triggers language production. In **chapter 4** I studied the differential auditory processing of spoken and melodically intoned language. Nineteen right-handed healthy volunteers performed an auditory lexical decision task in an event related design consisting of spoken and melodically intoned meaningful and meaningless items. Irrespective of whether the items were normally spoken or melodically intoned, meaningful items showed greater activation in the supramarginal gyrus and inferior parietal lobule, predominantly in the left hemisphere. Melodically intoned language activated both temporal lobes rather symmetrically, as well as the right frontal lobe cortices, indicating that these regions are engaged in the acoustic complexity of melodically intoned stimuli. Compared to spoken language, melodically intoned language activated sensory motor regions and articulatory language networks in the left hemisphere, but only when meaningful language was used. Our results suggest that the facilitatory effect of MIT may – in part – depend on an auditory input which combines melody and meaning. As such, they provide a sound basis for the further investigation of melodic language processing in aphasic patients, and eventually the neurophysiological processes underlying MIT.

Phonological and semantic processing are two main linguistic levels targeted in CLT to treat word finding deficits, a central and persistent problem in aphasic patients. **Chapter 5** focuses on the neural substrate of phonological and semantic auditory, i.e. receptive, processing in healthy older adults. Results in this age group are more applicable to aphasia research. I specifically focused on the functional specialization within the left inferior frontal gyrus (IFG), given its proposed important role for the recovery of language functions in aphasia. Twenty-five healthy right-handed older adults performed an au-

ditory phonological (rhyme decision) and semantic (semantic association) task during functional MRI. I performed whole-brain and region of interest (left IFG) analyses. Each linguistic process activated a different portion of the left IFG: phonological processing recruited the posterior dorsal part (BA44), while semantic processing recruited the anterior ventral part (BA47) of the IFG. Semantic compared to phonological processing also showed increased activation bilaterally in the middle temporal and middle frontal gyrus, in the left pars orbitalis of the IFG and inferior parietal lobule, and the right cerebellum. These findings extend the previously described differentiation within the IFG for productive phonological and semantic processing to receptive processing of these linguistic processes in an older population. This allows for eventually furthering our insight into the neural mechanisms of cognitive-linguistic aphasia therapy and the – differential – role of the IFG in language recovery.

Furthermore I investigated the relationship between language lateralization and language recovery (both spontaneously and after language therapy) to assess the widely held hypothesis that good recovery is related to left lateralized language activation, while right-sided lateralization is associated with poor recovery.[16] In **Chapter 6** I explored the relationship between language lateralization and language recovery, both at the level of language production and comprehension, in 36 patients with mild and severe chronic aphasia after left hemispheric stroke. All patients underwent language function evaluation and fMRI during the performance of an auditory passive listening task. Language lateralization indices (LI) were determined using a threshold independent method, and correlated with language test performance. There was no difference in LI between mildly and severely aphasic patients. Language lateralization was not correlated with aphasia severity. Lesion volume, however, was significantly greater in severely than in mildly aphasic patients, and was found to be an independent predictor of language comprehension performance. Our findings challenge the widely held hypothesis that language recovery is related with language lateralization: independent of aphasia severity, whether at the level of production or comprehension, language was more commonly left than right lateralized.

In **chapter 7** I investigated whether intensive MIT induces a shift in language lateralization in sub-acute and chronic non-fluent aphasic patients. We found no consistent shift of language activation to either the left or the right hemisphere. Sub-acute patients were predominantly right lateralized and tended to become more right lateralized, whereas chronic patients showed a reverse pattern. Intensive MIT over 6 weeks did not promote a uniform pattern of either left or right language lateralization in patients with severe non-fluent aphasia in the sub-acute and chronic stage. Time post onset may play an important role in treatment-induced language reorganization after stroke in spite of considerable individual variation across subjects.

My results demonstrate the utility of implementing fMRI to investigate how the language system is reorganized in brain damaged patients. Specifically for aphasia research fMRI allows to show how specific language treatment methods have the potential to enhance language reorganization and therefore optimize language recovery. Some methodological aspect should be considered in future neuroimaging in aphasia treatment studies. Longitudinal studies are necessary to investigate the neuronal reorganizational processes in response to different forms of language therapy provided at different times post-onset. Repeated assessments in the same individual are required to assess the effects of aphasia treatment on both the behavioral level and at the level of functional brain plasticity, and the extent to which improvements are retained in the long term. Furthermore a control group of patients without treatment is necessary. Another consideration is the fMRI task used to evaluate the effects of treatment. Passive listening is a global language task not specific enough to measure differential effects of treatment methods. As explored in my studies in healthy participants, it is necessary to incorporate fMRI tasks that relate directly to the linguistic level targeted during language treatment, in this way we can interpret activation changes as a function of treatment.[17] Finally, next to task related fMRI, other MR techniques such diffusion tensor imaging and arterial spin labeling may be used to examine how structural damage or compromised cerebral perfusion respectively influence language activation. Combining these techniques holds a considerable potential to provide a more comprehensive understanding of brain activity during language processing.

Samenvatting

Afasie is een taalstoornis tengevolge van hersenletsel bij verschillende etiologieën zoals een beroerte, een trauma, een neurodegeneratieve ziekte of een tumor[1-3]. Bij een afasie zijn alle taalmodaliteiten gestoord: spontane taal, het begrijpen van gesproken taal, lezen en schrijven. Een verduidelijking van het onderliggende functionele en neurale mechanisme van taalfuncties is in toenemende mate relevant voor de patiëntenzorg en voor het klinische onderzoek. In dit proefschrift onderzoek ik de lateralisatie van taal bij patiënten met een hersentumor en het taalherstel van afatische patiënten. Bij gezonde proefpersonen evalueer ik de specifieke taalfuncties die aangesproken worden bij de Melodische Intonatie Therapie (MIT)[4] en bij Cognitieve Linguistische Therapie[5-7], twee frequent gehanteerde therapiemethoden.

In **hoofdstuk 2** geef ik een introductie waarin ik de fundamentele aspecten van fMRI-onderzoek in relatie tot taal bespreek, alsmede het mogelijke onderzoeksdesign voor toepassing van deze techniek in de klinische setting en in meer fundamenteel onderzoek. Ik beschrijf hoe de verschillende taalniveaus onderzocht kunnen worden met een verscheidenheid aan taaltaken die de neuro-anatomische modellen van taalverwerking gunstig beïnvloed hebben. Een van de modellen die recent zijn onderzocht en toegepast bij afasie, is dat van Hickok en Poeppel [8-10]. De auteurs stellen een tweesporig (dorsaal en ventraal) model voor voor de auditieve taalverwerking. De dorsale route projecteert dorso-posterior verbindingen vanaf inferopariëtale en posterofrontale gebieden en is betrokken bij de auditieve motorische integratie door het omzetten van akoestische spraakklanken in articulatorische representaties. Een voorbeeld van een taak die via deze route verloopt is het nazeggen[9-10]. De ventrale route projecteert ventro-lateraal naar de middelste en inferiore temporale hersengebieden en functioneert als een 'klank-naar-betekenis' interface via het omzetten van op klank gebaseerde taalrepresentaties naar breed gedistribueerde conceptuele representaties. Deze route ondersteunt de perceptie en de herkenning van betekenisvolle taal [9-10].

Eerder lesie- en functioneel neuroimaging onderzoek suggereert dat niet alleen het cerebrum betrokken is bij de taalverwerking, maar ook het cerebellum. Beide zijn betrokken bij verschillende cognitieve taalcomponenten en aspecten van taalproductie[11-12] en taalbegrip[13]. Enkele andere studies hebben aanwijzingen gevonden voor een zogenaamd gekruist cerebro-cerebellair taal lateralisatie patroon bij gezonde proefpersonen, zowel in het kader van een typische linkszijdige als een atypische rechtszijdige lateralisatie van de taal. In **Hoofdstuk 3** wordt dit cerebro-cerebellaire taal lateralisatie patroon bij gezonde proefpersonen en bij patiënten met een hersentumor onderzocht, met het accent op een atypische taalrepresentatie. Twintig gezonde proefpersonen (13 linkshandigen en 7 rechtshandigen) en 38 patiënten (19 linkshandigen) met een hersentumor voerden tijdens fMRI een taak uit waarbij gevraagd werd om stilzwijgend werkwoorden te genereren bij een gegeven zelfstandig naamwoord. De taalactivatie in

het cerebrum en in het cerebellum werd apart van elkaar geklassificeerd als linkszijdig, rechtszijdig of symmetrisch. Zowel bij gezonde proefpersonen als bij patiënten werd een gekruiste cerebro-cerebellaire taalactivatie gevonden, onafhankelijk van handigheid of typische of atypische taal lateralisatie. Bijgevolg kan naast het evalueren van de taal lateralisatie in het cerebrum, taal lateralisatie in het cerebellum worden beschouwd als een bijkomend diagnosticum. Dit is vooral relevant bij onzekerheid vanwege interferentie van de tumor met de cerebrale taalactivatie bij fMRI-onderzoek, of vanwege een atypische taalrepresentatie.

Een actueel doel van neuroimaging studies die het taalherstel van afatische patiënten onderzoeken, is het verkrijgen van inzicht in de neurale veranderingen die het herstel van taalfuncties door behandeling ondersteunen. Om deze neurale veranderingen vanwege specifieke taaltherapie bij afatische patiënten te begrijpen is onderzoek naar de taalverwerking van gezonde proefpersonen vereist. Ik onderzocht de taalfuncties (semantiek en fonologie) bij gezonde proefpersonen die tijdens MIT en CLT, frequent gehanteerde therapiemethoden bij afasie, centraal staan.

Melodisch geïntoneerde taal is een essentieel aspect van de MIT, een bekende therapie waarbij de taalproductie van niet-vloeiende afasiepatiënten gefaciliteerd wordt door het benadrukken van de muzikale aspecten van de taal. Het concept van deze therapie is gebaseerd op de observatie dat zingen een faciliterend effect heeft op de taalproductie van deze patiënten met een ernstige niet-vloeiende afasie. Het is niet duidelijk of het zingen van een zin, of juist het luisteren naar een zin met een overdreven intonatiepatroon de taalproductie in gang zet.

In **hoofdstuk 4** onderzocht ik de differentiële auditieve verwerking van gesproken en melodisch geïntoneerde taal. Negentien rechtshandige vrijwilligers voerden een lexicale decisietaak taak uit in een event-related design, dat bestond uit gesproken en melodisch geïntoneerde betekenisvolle en betekenisloze items. Onafhankelijk van het feit of de items normaal uitgesproken of melodisch geïntoneerd werden, veroorzaakten betekenisvolle items een sterkere activatie in de supramarginale gyrus en in het inferiore pariëtale gebied, voornamelijk in de linker hemisfeer. De melodisch geïntoneerde taal activeerde zowel vrij symmetrisch de beide temporale kwabben als rechtszijdig de frontale kwab, hetgeen betekent dat deze gebieden betrokken zijn bij de complex akoestische verwerking van de melodisch geïntoneerde stimuli. Vergeleken met de gesproken taal activeerde de melodisch geïntoneerde taal alleen als betekenisvolle taal gebruikt werd de sensorimotorische gebieden en de articulatorische taal netwerken in de linker hemisfeer. Onze resultaten suggereren dat het faciliterende effect van de MIT gedeeltelijk afhankelijk is van de auditieve input waarbij melodie en betekenis gecombineerd zijn. Dit is een goed uitgangspunt voor verder onderzoek naar de verwerking van melodisch geïntoneerde taal van afatische patienten, en naar de neurofysiologische processen die aan de MIT ten grondslag liggen.

De fonologische en semantische taalverwerking zijn twee belangrijke taalniveaus die een rol spelen bij de woordvinding. Een woordvindingsstoornis is een centraal en persistent probleem van afatische patiënten, die hiervoor behandeld worden met CLT. **Hoofdstuk 5** is gericht op het neurale substraat van de auditieve, i.e. receptieve, fonologische en semantische verwerking van gezonde oudere volwassenen. De resultaten in deze leeftijdsgroep zijn toepasbaar in het afasie-onderzoek. Ik richtte mij specifiek op de functionele specialisatie van de linker gyrus frontalis inferior (IFG), vanwege haar prominente rol bij het herstel van de taalfuncties bij afasie. Vijfentwintig gezonde rechtshandige oudere volwassenen voerden een auditieve fonologische (rijm decisie) en een semantische (semantische associatie) taak uit tijdens fMRI. Ik voerde een analyse uit van zowel het hele brein als selectief van de linker IFG. Elk linguïstisch proces activeerde een ander gedeelte van de linker IFG: de fonologische verwerking was gerelateerd met activatie in het posteriore dorsale deel (BA44), en de semantische verwerking was gerelateerd met het anterieure ventrale deel (BA47) van de IFG. In vergelijking met de fonologische verwerking liet de semantische verwerking ook een sterkere bilaterale activatie zien in de middelste gyrus temporalis en frontais, het pars orbitalis van de linker IFG, de inferiore pariëtale kwab, en in het rechter cerebellum. Deze bevindingen omtrent de receptieve verwerking van deze linguïstische processen in de oudere populatie zijn een aanvulling op de eerder beschreven differentiatie binnen de IFG voor de productieve fonologische en semantische verwerking. Dit kan ons inzicht in het neurale mechanisme van CLT en in de differentiële rol van de IFG in het taalherstel versterken.

Verder onderzocht ik de relatie tussen taallateralisatie en taalherstel (zowel spontaan als na taaltherapie) om de algemeen aangehouden hypothese te toetsen dat een goed herstel gerelateerd is aan een linkszijdige taalactivatie, en een slecht herstel aan een rechtszijdige taalactivatie [16]. In **Hoofdstuk 6** onderzocht ik de relatie tussen taallateralisatie en taalherstel, zowel op het gebied van de taalproductie als de taalperceptie bij 36 patiënten met een lichte en een ernstige chronische afasie tengevolge van een beroerte in de linker hemisfeer. Alle patiënten kregen voerden een auditieve passieve luistertaak uit tijdens fMRI. De taallateralisatie index (LI) werd bepaald met behulp van een threshold-onafhankelijke methode, en gecorreleerd met de resultaten van een taaltest. Er was geen verschil in LI tussen patiënten met een lichte en een ernstige afasie. De lateralisatie van de taal was niet gecorreleerd met de ernst van de afasie. De omvang van de lesie was echter significant groter bij patiënten met een ernstige afasie dan bij patiënten met een lichte afasie, en deze variabele bleek een onafhankelijke predictor te zijn van de mate waarin het taalbegrip gestoord was. Deze bevindingen zetten vraagtekens bij de algemeen aanvaarde hypothese dat het taalherstel gerelateerd is met taal lateralisatie; onafhankelijk van de ernst van de afasie, hetzij op het gebied van productie of begrip, was taal meer links dan rechts gelateraliseerd.

In **Hoofdstuk 7** onderzocht ik of een intensief toegepaste MIT een verschuiving teweeg zou brengen in de lateralisatie van taal bij sub-acute en chronische niet-vloeiende afa-

siepatiënten. We vonden geen consistente verschuiving van taalactivatie naar hetzij de linker of de rechter hemisfeer. Sub-acute patiënten waren voornamelijk rechts gelateraliseerd en vertoonden de neiging naar een sterkere lateralisatie naar rechts, terwijl chronische patiënten het omgekeerde patroon lieten zien. Een intensieve MIT van 6 weken bij patiënten met een ernstige niet-vloeiende afasie in de subacute en chronische fase veroorzaakte geen uniform patroon van hetzij een lateralisatie naar rechts of naar links. De tijd na het ontstaan van de beroerte speelt mogelijk een belangrijke rol bij de reorganisatie van taal na behandeling, ondanks de aanzienlijke individuele variatie bij de proefpersonen.

Mijn resultaten tonen de mogelijkheden en het belang van fMRI aan bij het onderzoek naar de reorganisatie van het taalsysteem van patiënten met een hersenbeschadiging. Speciaal voor het afasie-onderzoek kan fMRI aantonen welk potentieel specifieke behandelmethoden hebben om de reorganisatie van taal te verbeteren en bijgevolg het taalherstel te bevorderen. Bij toekomstig onderzoek moet rekening worden gehouden met een aantal methodologische aspecten. Longitudinale studies zijn noodzakelijk om de neuronale reorganisatieprocessen te onderzoeken, gekoppeld aan verschillende vormen van taaltherapie in verschillende stadia na het ontstaan van de afasie. Herhaalde metingen bij dezelfde proefpersoon zijn vereist om de effecten van afasietherapie op gedragsniveau en op het niveau van de functionele plasticiteit van de hersenen vast te stellen, alsmede de mate waarin verbeteringen op de lange duur beklijven. Eveneens is een controlegroep van patiënten zonder behandeling noodzakelijk. Een ander discussiepunt is de fMRI-taak die gebruikt wordt om de effecten van een behandeling te meten. Een passieve luistertaak is een globale taaltaak die niet specifiek genoeg is om differentiële effecten van therapiemethoden te onderzoeken. Zoals aangetoond in mijn onderzoek bij gezonde proefpersonen, is het noodzakelijk om fMRI-taken toe te passen die direct gerelateerd zijn met het linguïstische niveau waar de behandeling op gericht is. Alleen op deze wijze kunnen we een verandering in activatie interpreteren als een gevolg van de behandeling[17]. Tenslotte, naast een taakgerelateerde fMRI, kunnen andere MR technieken zoals diffusie tensor imaging en arterial spin labeling toegepast worden om te onderzoeken hoe structurele schade of een stoornis in de cerebrale doorbloeding de activatie van taal kunnen beïnvloeden. Het combineren van deze technieken is veelbelovend om een gedegen inzicht te krijgen in de activiteit van de hersenen tijdens het verwerken van taal.

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Epiloque

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List of Publications

Méndez Orellana CP, Visch-Brink EG, Vernooij M, Kalloe S, Satoer D, Vincent A, van der Lugt A, Smits M. Crossed cerebro cerebellar language lateralization: an additional diagnostic feature for assessing atypical language representation in presurgical functional MR imaging. AJNR Am J Neuroradiol. 2015;36(3):518-24. doi: 10.3174/ajnr.A4147.

Méndez Orellana CP, Visch-Brink EG, Weterings A, Steketee RME, Koudstaal PJ, van der Lugt A, Smits M. Differential involvement of the left inferior frontal gyrus during auditory phonological and semantic processing in older healthy adults. Brain and Language, submitted.

Steketee RME, Bron EE, Meijboom R, Houston GC, Klein S, Mutsaerts HJMM, **Méndez Orellana CP**, de Jong FJ, van Swieten JC, van der Lugt A, Smits M. Early-stage differentiation between presenile Alzheimer's disease and frontotemporal dementia using arterial spin labeling MRI. European Radiology, in press.

Bron EE, Smits M, van der Flier WM, Vrenken H, Barkhof F, Scheltens P, Papma JM, Steketee RM, **Méndez Orellana CP**, Meijboom R, Pinto M, Meireles JR, Garrett C, Bastos-Leite AJ, Abdulkadir A, Ronneberger O, Amoroso N, Bellotti R, Cárdenas-Peña D, Álvarez-Meza AM, Dolph CV, Iftekharuddin KM, Eskildsen SF, Coupé P, Fonov VS, Franke K, Gaser C, Ledig C, Guerrero R, Tong T, Gray KR, Moradi E, Tohka J, Routier A, Durrleman S, Sarica A, Di Fatta G, Sensi F, Chincarini A, Smith GM, Stoyanov ZV, Sørensen L, Nielsen M, Tangaro S, Inglese P, Wachinger C, Reuter M, van Swieten JC, Niessen WJ, Klein S; Alzheimer's Disease Neuroimaging Initiative. Neuroimage. 2015;111:562-79. doi: 10.1016/j.neuroimage.2015.01.048.

Méndez Orellana CP, van de Sandt-Koenderman ME, Saliasi E, van der Meulen I, Klip S, van der Lugt A, Smits M.Insight into the neurophysiological processes of melodically intoned language with functional MRI.Brain Behav. 2014;4(5):615-25. doi: 10.1002/brb3.245.

Wolthuis N, **Méndez Orellana CP**, Nouwens F, Jonkers R, Visch-Brink EG, Bastiaanse R. Stabiliteit spontane taal bij chronische milde afasie. Stem-, spraak- en taalpathologie 2014;19:103-120

Méndez Orellana CP, Visch EG, Smits M. *Functional imaging of language processing: basic principles and acquired insights*. Published in Dutch in: Het (voor)beeldig brein. Robert E, Visch-Brink E, Beeckman A (eds). Antwerp-Apeldoorn Garant publishers 2013. ISBN 978-90-441-3026-3.

Méndez Orellana CP, Visch-Brink EG, De Jong-Hagelstein M, Koudstaal PJ, van der Lugt A, Smits M. Decreased relative contribution to language processing of the right hemisphere after language therapy assessed with fMRI in chronic aphasia patients. Procedia - Social and Behavioral Sciences, 61, 20–21. doi:10.1016/j.sbspro.2012.10.060

Hermes D, Vansteensel MJ, Albers AM, Bleichner MG, Benedictus MR, **Méndez Orellana CP**, Aarnoutse EJ, Ramsey NF. fMRI based localization of motor imagery areas for implantable BCIs. J Neural Engineering 2011; 8 (2): 025007. doi: 10.1088/1741-2560/8/2/025007

PhD Portfolio

Name:	Drs.C.P Méndez Orellana
Erasmus MC Departments:	Radiology and Neurology
Research School:	COEUR

1. PhD training	**Year**	**Workload ECTS**
General courses		
Cardiovascular Medicine, Rotterdam	2009	1,5
Statistics (NIHES) Introduction to Data Analysis	2010	1,0
Scientific Writing in English for Publication - writing to be read	2010	2
PhD day -2x	2010, 2011	0,2
The basic introduction course on SPSS	2012	0,8
Biomedical English Writing and Communication	2012	4
Research Integrity	2012	0,1
Consultation center for Patient Oriented Research (CPO)	2014	0,3
Specific courses		
ESMRMB School of MRI - Clinical fMRI: Theory and Practice (Thessaloniki, GR)	2009	1,5
ESMRMB Hands - On MRI course on fMRI & DTI (Rotterdam, NL)	2009	1,5
Statistical Parametric Mapping for fMRI (Wellcome Trust Centre for Neuroimaging, UCL, London, UK)	2010	1,5
ESMRMB Lectures on MR course on fMRI: From Neurophysiology to Cognitive Neuroscience (Maastricht, NL)	2010	1,5
International Summer School on Cognitive Neuroscience (UCL Institute of Cognitive Neuroscience, London, UK)	2011	1,5
ESMRMB Lectures on MR course on Resting State fMRI - Analysis and Interpretation (Magdeburg, DE)	2012	1,5
Neuroradiology and Funtional Neuroanatomy (UCL Institute of Neurology, London, UK)	2012	1,5
FreeSurfer Tutorial and Workshop (VU University Medical Center Department Radiology, Amsterdam, NL)	2012	1,5
Training School of Aphasia Researchers (COST Action IS1208, Ħ'ABard, MT)	2014	1,5

Seminars and workshops

Simposium Functional Neuroimaging: New clinical applications (Neurosurgery Center Tilburg,NL)		0,5
Workshop Endnote & Literature search (Erasmus MC, NL)	2010	0,2
The imaging workshop for MDs (Erasmus MC, NL)	2010	0,25
Aphasia clinics: complexity aphasia therapy (Erasmus MC, NL)	2012	0,1
Aphasia Clinics: primary progressive aphasia (Erasmus MC, NL)	2011	0,1
COST Meeting: Collaboration of Aphasia Trialist (Nice, FR)	2014	1,0
COST Meeting: Working Group Effectiveness of Interventions (Rotterdam, NL)	2014	1,0

Presentations

Functional MRI Meetings (Department of Radiology, Erasmus MC)	2010 - 2012	0,3
Radiology Research Lunch (Department of Radiology, Erasmus MC)	2013	0,1
Aphasia Lab - meeting (Prof.dr. Lambon Ralph) (Department of Neurology, Erasmus MC)	2011	0,1
Functional Imaging in Aphasia Treatment (Information day Rotterdam Aphasia Therapy Study, Erasmus MC)	2013	0,1
Functional Imaging in Aphasia Treatment (Aphasia Center Rotterdam, Utrecht, Den Haag - Delft)	2010 - 2013	0,3

(Inter)national conferences

28th Annual Scientific Meeting of ESMRMB (Leipzig, DE). Oral presentation	2011	1,5
18th Annual Meeting of the Organization for Human Brain Mapping (Beijing, CN). Poster presentation	2012	1,3
13th International Science of Aphasia (Groningen, NL). Oral presentation	2012	1,5
50th Annual Meeting Academy of Aphasia (San Francisco, US). Oral presentation	2012	1,5
European Congress of Radiology (Vienna, AT). Poster presentation	2012, 2013	2,6
Aphasia conference (Zeist, NL). Oral presentation	2013	0,7
Aphasia: Junior researchers days (Groningen, NL). Oral presentation	2013	1,5

TEACHING ACTIVITIES

Lecturing

Aphasia research (Universidad Austral, Chile)		0,5

Supervising Master's theses

Supervision research projects 4th year medical students	2012	0,6
Clinical Neuropsychology: 3 master students	2011 - 2013	3
Speech and Language Pathology: 1 master student	2009	0,6

Other

Organization of the sixth edition of EMLAR Experimental Methods in Language Acquisition Research	2010	3
MRI safety course level 2	2010	0,3
	total	**46,05**

About the Author

Carolina Patricia Méndez Orellana was born in Santiago, Chile, on 24 January 1984. She completed secondary school at the "Colegio Pedro de Valdivia de Providencia" (2002) and studied Speech and Language Therapy at Universidad Mayor, Santiago. Right after graduating in December 2006, she was awarded an Excellent Scholarship to follow the prestige Master of Cognitive Neuroscience at the University of Utrecht. She moved to the Netherlands in September 2007. She carried out her major research project on controlling Brain Computer Interface by motor imagery supervised by Dr. Hermes and Prof. dr. N.F Ramsey at the Brain Center Rudolf Magnus, Division of Neuroscience, Department of Neurology and Neurosurgery, University Medical Center Utrecht.

In 2009 she moved to Rotterdam to carry out her minor research project at Erasmus MC on improving fMRI language paradigms for the Rotterdam Aphasia Therapy Study (RATS-3) together with her supervisors Dr. Visch-Brink and Dr. Marion Smits. She obtained her Master´s degree in Cognitive Neuroscience in 2009 and started her PhD coordinating the Functional Imaging in Aphasia Treatment study at the department of Neurology and Radiology, of which some results are described in this thesis.

In January 2015, Carolina moved to Chile together with her husband Herre and their baby Benjamin. Carolina is currently working as assistant professor (junior researcher) at the Speech and Language department, Faculty of Medicine, at the Pontificia Universidad Católica de Chile.

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