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Brain networks for language

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Brain networks for language

Anatomy and functional roles of neural pathways supporting
language comprehension and repetition

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Abstract

The current thesis presents the anatomy and functional roles of fiber tracts involved in auditory language processing. It aimed at anatomically differentiating the course of the fiber tracts, as well as examining whether the fiber tracts can be differentiated functionally. Specifically addressed were the gray and white matter structures that underlie complex and simple syntactic processing, as well as word- and sentence-level semantic processing during both language comprehension and repetition, as well as phonological, phonetic and motor aspects of speech repetition.

The thesis first provides a literature review which introduces methods for accessing fiber tracts and discusses the precise course of different fiber tracts along with their proposed functional roles during auditory language processing. Second, the review is followed by two functional magnetic resonance (fMRI) experiments investigating the key brain regions of different linguistic functions during sentence comprehension and repetition. The resulting brain regions were then used in a tractography study to investigate the fiber tracts supporting the above mentioned linguistic functions in healthy adults. Finally, the functional roles of ventral and dorsal fiber tracts were studied in patients who demonstrated preoperatively lesioned, and postoperatively recovered fiber tracts.

The findings corroborate the existence of several anatomically differentiable ventral and dorsal fiber tracts. They furthermore suggest a functional differentiation into ventral fiber tracts supporting “simple” linguistic functions, and dorsal fiber tracts supporting “complex” linguistic functions, as well as working memory and speech repetition functions. Taken together, the present thesis can provide a detailed and comprehensive neurocognitive model of fiber tracts involved in auditory language processing that outruns the existing models and solves hitherto conflicting results.

Zusammenfassung

Die vorliegende Dissertation behandelt den anatomischen Verlauf und die Funktionen von Faserverbindungen, die zur Verarbeitung von Sprache im Gehirn beitragen. Ziel der Arbeit war es, die Faserverbindungen anatomisch voneinander abzugrenzen sowie zu untersuchen, ob sie auch funktionell voneinander abgrenzbar sind. Von besonderem Studieninteresse waren dabei diejenigen Faserverbindungen, die die Verarbeitung komplexer und einfacher syntaktischer Strukturen sowie die Verarbeitung von Wort- und Satzsemantik leisten, und zwar sowohl beim Sprachverstehen als auch beim Nachsprechen. Darüber hinaus wurden diejenigen Faserverbindungen untersucht, die bei phonologischen, phonetischen und motorischen Aspekten des Nachsprechens beteiligt sind.

In der vorliegenden Arbeit werden zunächst die Methoden dargestellt, die verwendet werden können, um den anatomischen Verlauf der Faserverbindungen sowie ihre möglichen Funktionen bei der auditorischen Sprachverarbeitung zu erforschen, sowie ein Überblick darüber gegeben, welche Erkenntnisse es bisher zu Anatomie und Funktion der Faserverbindungen gibt. Dem schließt sich die Darstellung zweier Experimente an, die mit funktioneller Magnetresonanztomographie diejenigen Gehirnregionen erforscht haben, welche beim Sprachverständnis und beim Nachsprechen besonders bedeutsam sind. Diese Regionen wurden in ein weiteres Experiment eingebracht, um mittels Traktographie herauszufinden, welche Faserbahnen im gesunden voll entwickelten Gehirn die oben genannten Sprachfunktionen ermöglichen. Abschließend werden die Erkenntnisse dargestellt, welche eine Studie über die bei der Sprachverarbeitung beteiligten Faserverbindungen erbracht hat, bei der Patienten mit Hirnödemen vor und nach erfolgter Therapie untersucht wurden.

Die Ergebnisse der vorliegenden Dissertation unterstreichen die Vermutung, dass etliche dorsale und ventrale Faserverbindungen anatomisch voneinander abgegrenzt werden können. Darüber hinaus legen sie den Schluss nahe, dass sich dorsale und ventrale Faserverbindungen auch funktionell voneinander unterscheiden lassen: Ventrale Pfade sind eher an "einfachen" linguistischen Funktionen beteiligt, während dorsale eher an "komplexen" linguistischen Funktionen sowie am Arbeitsgedächtnis und am Nachsprechen beteiligt sind. Die vorliegende Arbeit liefert abschließend ein detailliertes und umfassendes neurokognitives Modell, welches über bereits bestehende Modelle hinausgeht und bis dato widersprüchliche Ergebnisse miteinander in Einklang bringt.

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List of abbreviations

a	anterior
AF	arcuate fascicle
AG	angular gyrus
aIns	anterior insula
ATL	anterior temporal lobe
BA	Brodmann area
d	dorsal
DTI	diffusion tensor imaging
ECFS	extreme capsule fiber system
FA	fractional anisotropy
(f)MRI	(functional) magnetic resonance imaging
FOP	frontal operculum
IFG	inferior frontal gyrus
IFOF	inferior fronto-occipital fascicle
IFS	inferior frontal sulcus
ILF	inferior longitudinal fascicle
IPL	inferior parietal lobule
IPS	inferior parietal sulcus
ITG	inferior temporal gyrus
L, LH	left hemisphere
m	middle
MdLF	middle longitudinal fascicle
MFG	middle frontal gyrus
MR	magnetic resonance
MTG	middle temporal gyrus
p	posterior
PFC	prefrontal cortex
PMC	premotor cortex
R, RH	right hemisphere
ROI	region of interest
SFG	superior frontal gyrus
SLF I/II/III/IV/-tp	first/second/third/forth/temporoparietal component of superior longitudinal fascicle
SMA	supplementary motor area
SMG	supramarginal gyrus
SPL	superior parietal lobule
STG	superior temporal gyrus
STS	superior temporal sulcus
UF	uncinate fascicle
v	ventral

Chapter 1

Introduction

1.1 Research question

For over two decades, neuroscientists and linguists have investigated the cortical areas that enable humans to speak and to comprehend language (see, e. g., [Price, 2010](#), for a review). However, there is still much debate about the functions of various cortical areas, and a clear picture of how these areas are connected for information propagation has remained elusive. As a result, a number of studies have been conducted recently which investigate the anatomical connections between cortical areas, and their functional roles in language processing. However, this has still not resulted in a coherent picture ([Friederici, 2009a](#); [Friederici, 2011](#); [Weiller et al., 2011](#)). Therefore, the present thesis aims to determine which key brain regions and specific connections contribute to language processing, especially to syntactic and semantic processing during comprehension and repetition, as well as to sound and motor processes underlying speech repetition.

Key brain regions and connections of auditory language processing.

1.2 Background

We understand what somebody says to us because our brain enables us to store words which map onto concepts from the world, i. e., to collect phonological and semantic information. Additionally, our brain enables us to learn grammar rules, i. e., to collect syntactic information. During language comprehension, our brain retrieves and connects the stored information. In order to understand the input, it conducts a number of processes; of these, the semantic and syntactic processes are the subject of the present thesis, and are highlighted in [Chapter 3](#). Also in speech production our brain retrieves and connects the stored information, and conducts additional motor processes that

Processes during language comprehension and repetition.

lead to the production of the output. The semantic and syntactic, as well as sound and motor processes of overt speech repetition as one form of language production, i.e., saying exactly what was heard, are matter of the present thesis, and are highlighted in [Chapter 4](#).

Language is mainly processed frontally and temporally.

Many of the cortical areas that provide storage for and retrieval of linguistic information have been elucidated during recent decades. Most of these areas lie in the frontal and temporal lobes ([Vigneau et al., 2006](#); [Price, 2010](#)). However, the question remains how the information is propagated between these processing areas, thereby giving rise to one of the most prominent and important cognitive skills of humans: language.

Different information is processed via different processing streams.

It is assumed that different streams of processing are responsible for processing different kinds of information between cortical areas. It has been postulated that one stream runs from posterior brain regions dorsally in the direction of the frontal lobe, and one stream runs ventrally in the direction of the frontal lobe. This system was first described in the visual system ([Ungerleider & Mishkin, 1982](#)), then more recently in the auditory system ([Rauschecker & Scott, 2009](#)). With regard to the language domain, [Hickok and Poeppel \(2007\)](#) suggested that the dorsal stream is responsible for mapping auditory input to motor plans during speech repetition and production, and that the ventral stream is responsible for mapping auditory input to conceptual representations for the understanding of meaning during speech comprehension.

Anatomically, information is processed via fiber tracts.

Anatomically, the connections are realized as bundles of white matter, i.e., projections of nerve cells that proceed under the surface from one cortex area to another. The cellular projections bundle during their course, and form so-called *fiber tracts*. These fiber tracts enable areas of gray matter in the cortex to communicate with each other by transmitting information. Fiber tracts have been investigated and described for over a century (e.g., [Déjerine, 1901](#)). At present, dorsally and ventrally running fiber tracts are differentiated. Dorsal fiber tracts have been defined as running superior to the horizontal portion of the Sylvian fissure, and ventral fiber tracts have been defined as running inferior to the horizontal portion of the Sylvian fissure after passing through the subinsular white matter at the inferior level of the extreme and/or external capsule ([Anwander et al., 2007](#); [Umarova et al., 2010](#)). However, there is much debate about the precise course of the tracts: both the brain divisions they pass through and the terminating regions. This debate is addressed in detail in [Chapter 2](#).

Fiber tracts have functional roles.

Fiber tracts were long ago assumed to be involved in the transmission of information, for example, by neurologists who related fiber tract lesions to specific pathological behavior (e.g., [Lichtheim, 1885](#); [Wernicke, 1874](#)). The most prominent fiber tract for language processing has been the arcuate fascicle (AF) as it was thought to connect “the language centers”, i.e., Broca’s and Wernicke’s area.

Lesions to the arcuate fascicle were associated with a syndrome called “conduction aphasia” which was characterized by good language comprehension along with problems in speech repetition (e. g., [Geschwind, 1965](#), see also [Chapter 4](#)). This remarkable observation led to one of the most popular language models, the Wernicke-Geschwind model ([Geschwind, 1965](#); [Geschwind, 1970](#)), which describes how auditory and visual information is propagated via the arcuate fascicle for comprehension and production.

In recent years, new methods have evolved to elucidate the relationship between the functional processing streams and the associated anatomical fiber tracts for language.¹ Some studies have used electrocortico stimulation during neurosurgery (e. g., [Duffau, 2008](#)), whereas others noninvasively traced the diffusivity of white matter in the brain using diffusion tensor imaging (DTI) data. To perform this so-called *fiber tractography*, activations identified from functional magnetic resonance imaging (fMRI) can be used as the starting points for calculating the course of the fiber tracts. The resulting fiber tracts which are identified can then be related to the processes that underlie the fMRI activations. It is assumed that a fiber tract’s function is to enable these specific processes in the cortex by transmitting information between the connected cortical areas. Based on the connected areas, the tract’s functional role can thus be indirectly derived. Although the mapping is only indirect, combining fMRI with DTI data during fiber tractography is the best noninvasive method we have, so far, to map the functional architecture of the fiber tracts connecting brain areas.

Methods for relating fiber anatomy and function.

The application of these methods has led to further differentiations and enhancements of the Wernicke-Geschwind model (e. g., [Hickok & Poeppel, 2007](#); [Friederici, 2011](#); [Friederici, 2012b](#)). New methods and findings, however, may also lead to conflicting results about which fiber tracts support the propagation of which specific linguistic information: [Saur et al. \(2008\)](#) found a dorsal fiber tract which was involved in speech repetition and a ventral fiber tract which was involved in semantic processing, thereby providing evidence for the functional model of [Hickok and Poeppel \(2007\)](#); However, employing the fMRI based tractography method in an artificial grammar paradigm, [Friederici and colleagues \(2006a\)](#) found the dorsal fiber tract to be involved in processing complex syntactic structures, and the ventral fiber tract to be involved in processing simple syntactic structures. These divergent results concerning the functional roles of the dorsal and ventral fiber tracts could either originate from major differences between the studies in terms of stimulus material (i. e., word-level and sentence-level meaning, and syntactic structures in natural and artificial grammars) and task (i. e., repetition, listening, comprehension, and detection of syntactic violations), or they could result from the fact that both studies used different fMRI based start points for the tractography, and acted on the assumption that there is

The debate: conflicting findings.

¹See, for an overview on the methods used for investigating fiber tracts and for mapping fiber anatomy and function, [Section 2.1](#).

only one dorsal and one ventral fiber tract, thereby oversimplifying the brain.

The four pathway model.

To counteract this oversimplification of the brain, Friederici (2011) recently proposed a four pathway model of language processing in the left hemisphere, which assumes that the dorsal and the ventral fiber tract can be functionally segregated into several anatomical subcomponents. Friederici suggested that there are two fiber tracts running dorsally: One subserving the mapping of auditory input to motor plans during repetition (Saur et al., 2008), and another supporting higher linguistic processes during sentence comprehension, e.g., processing of complex syntax (Friederici et al., 2006a). Friederici also suggested two tracts running ventrally, one which supports initial local structure building processes during sentence processing (Friederici et al., 2006a), and a second tract which subserves semantic processing (Duffau et al., 2005). The assumptions of this model form the basis for the investigations of the present thesis.

1.3 Motivation and Hypotheses

Conflicting results and insufficiently understood fiber tracts.

From the few studies cited above it becomes clear that presently there is insufficient understanding of which fiber tracts specifically contribute to language processing, and which specific functions they subserve during language processing. The processing of complex versus simple syntactic structures, the repetition of sentences, as well as syntactic and semantic aspects during repetition are insufficiently understood at present. Moreover, there is disagreement about the precise course and the nomenclature of the fiber tracts. The present thesis, therefore, aims to provide an overview of which fiber tracts support transmission of which linguistic information during auditory language processing.

Hypotheses of the dissertation.

The present work hypothesizes that there is more than one dorsal fiber tract, as the controversy between Saur et al. (2008) and Friederici et al. (2006a), as well as developmental studies suggest: One dorsal tract was shown to be insufficiently pronounced in newborns and non-human primates as well as in the non-dominant hemisphere. Hence, this tract should be involved in a linguistic function that children and non-human primates are not able to perform, and which is lateralized to the dominant hemisphere (Catani et al., 2007; Lebel & Beaulieu, 2009), i.e., probably higher linguistic processing, for example, the processing of syntactically complex structures (Friederici et al., 2006a). This is in contrast to a second dorsal tract which was shown to be already pronounced in newborns as well as in non-human primates and which may, thus, be involved in a basic linguistic function that children and non-human primates are already able to perform, e.g., the mapping of auditory input to motor output. Also ventrally, the studies from Saur et al. (2008) and Friederici et al. (2006a), as well as

from the group around Duffau (Duffau et al., 2005; Maldonado et al., 2011) suggest that there is more than one fiber tract subserving language processing: one involved in the processing of simple syntactic structures, another involved in the processing of semantic information.

We thus formulated the following hypotheses:

- Processing of complex syntactic structure is performed in brain areas that connect to a **dorsal** fiber tract supporting transmission of this information: presumably the left posterior and middle superior temporal gyrus (STG) and inferior Brodmann area (BA) 44 of Broca's area connected via the arcuate fascicle or superior longitudinal fascicle (Friederici et al., 2006a; Anwander et al., 2007).
- Repetition of nonsense speech, i. e., motor and sound aspects of repetition, is performed in brain areas that connect to **another dorsal** fiber tract: presumably the left posterior superior temporal gyrus and BA 6/superior BA 44 via the arcuate fascicle or superior longitudinal fascicle (Saur et al., 2008).
- Processing of simple syntactic structure is performed in brain areas that connect to a **ventral** fiber tract supporting transmission of this information: presumably the left frontal operculum (FOP) and the anterior superior temporal gyrus connected to the uncinate fascicle (Friederici et al., 2006a; Anwander et al., 2007).
- Processing of semantic information is performed in brain areas that connect to **another ventral** fiber tract supporting transmission of this information: presumably the anterior superior temporal gyrus and BA 45 of Broca's area connected to the inferior fronto-occipital fascicle/extreme capsule fiber system (Friederici, 2011; Anwander et al., 2007; Saur et al., 2008).

1.4 Overview of the dissertation

Chapter 2 outlines the recent findings concerning the course of those fiber tracts involved in language processing, concerning their nomenclature, as well as their potential functional roles, after having provided an overview of the methods used for investigating fiber tracts and relating their anatomy to functional roles. The perspective of both psychologists and linguists will be taken in asking which fiber tracts support specific language functions, and the perspective of anatomists, in asking which language functions underlie specific fiber tracts. The chapter concludes with a neurocognitive model describing the most probable course, names and functional roles of those fiber tracts discussed as supporting auditory language processing.

Literature review.

Chapter 3 presents an fMRI experiment which searched for the key brain regions underlying auditory language comprehension, and Chapter 4 presents an fMRI experiment searching for the key brain re-

fMRI experiments.

gions underlying language repetition as compared to language comprehension.

Tractography study
on healthy subjects.

The resulting cortical regions of both experiments formed the basis for fiber tracking, presented in [Chapter 5](#). The key brain regions of syntactic and semantic processing during repetition and comprehension, as well as the key brain regions of phonological and motor aspects of speech repetition, were used to test the four-pathway-model proposed by Friederici (2011). The chapter concludes with a new neurocognitive model illustrating the assumed course and functional roles of fiber tracts involved in language comprehension and repetition.

Tractography study
on patients.

To identify which of these fiber tracts are essential for auditory language processing, a study with edema patients was performed which is presented in [Chapter 6](#). This study assessed both the integrity of fiber tracts as well as the behavioral performance on simple and complex syntactic processing during comprehension and repetition at two data points.

General discussion.

The general discussion in [Chapter 7](#) assesses to what extent the results of the different studies fall into place and draws conclusions from that. The key points are then illustrated in a concluding neurocognitive model.

Chapter 2

State of the art: Connections for language in the human brain

The white matter bundles that underlie comprehension and production of language have been investigated for a number of years. Several studies have examined which fiber bundles (or tracts) are involved in auditory language processing, and which kind of language information is transmitted by which fiber tract. However, there is much debate about exactly which fiber tracts are involved, their precise course in the brain, how they should be named, and which functions they fulfill. Therefore, the present chapter reviews the available language-related literature, and outlines a neurocognitive model of the pathways for language. Besides providing an overview of the current methods used for relating fiber anatomy to function, this chapter details the precise anatomy of the fiber tracts and their roles in phonological, semantic and syntactic processing, articulation, and repetition.

Based, with modifications, on:

Gierhan, S. M. E. (in press), "Connections for auditory language in the human brain.", Brain & Language.

Preface

Overview
of the chapter.

In the present chapter, first, the methods used for exploring fiber tracts and relating anatomy to function will be reviewed ([Section 2.1](#)). Second, the anatomy and nomenclature of the fiber tracts that are discussed as participating in language processing are expounded ([Section 2.2](#)). Finally, the language functions that have been attributed to the different fiber tracts will be stated ([Section 2.3](#)). The focus is on auditory language processing and its underlying left-hemispheric long-range association pathways, i.e., the structural connections between two lobes of the left hemisphere.

2.1 Methods for accessing language fiber tracts

Outline
of the section.

The following two sections outline the methods used for investigating the anatomy and functional roles of fiber tracts in the human brain. [Section 2.1.1](#) clarifies the methods applied in pure anatomical examinations. [Section 2.1.2](#) outlines the methods applied when relating the anatomy to the underlying function.

2.1.1 Exploring the anatomy

Dissection

Post mortem,
the brain can be
dissected.

In the exposed brain, dissection of the gray and white matter can be performed (e.g., [Martino et al., 2011](#)). This allows the course of the fiber bundles to be uncovered and studied in detail. However, with dissection it is rarely possible to study more than one fiber bundle simultaneously, because dissection is accompanied by discreation of the covering brain structure. Moreover, dissection methods can obviously only be applied post mortem.

Fiber tracking

Fiber tracking uses
diffusivity of
water molecules for
fiber reconstruction.

In the living brain, fiber bundles can be studied when using a specific diffusion weighted sequence in the magnetic resonance (MR) scanner, which measures the diffusivity of water molecules in the brain. Basser et al. (1994) showed that the principal diffusion direction of water in the brain is parallel to the fiber bundles. This local diffusion direction can be used by a fiber tractography algorithm to reconstruct the fiber bundles which exist in the brain (see Catani et al. (2002) for one of the first studies using fiber tractography, as well as Catani & Mesulam (2008)). Starting from one or more brain region(s) of interest (ROI), the principal diffusion direction parallel to the fiber direction is traced. If the

diffusion of the water molecules is highly parallel, the fibers are likely to be arranged in a bundle.

There are multiple methods for reconstructing the fiber tracts, e.g., deterministic and probabilistic calculations (for details see, e.g., [Mori, 2007](#)). In deterministic tractography, one single diffusion direction per voxel is interpolated and followed to reconstruct the tract; in probabilistic tractography, the probability of a diffusion direction per voxel is calculated and a likelihood map of a tract is reconstructed, which shows the probability that a particle traverses the voxels of the tract.

Deterministic vs. probabilistic tracking.

The amount of scientific insight that can be gained when studying the precise anatomy of the fiber tracts is affected by the extent to which the course of the fibers is constrained a priori by ROIs. Moreover, it makes a difference if only one starting region (so-called *seed region*) is used, or if target regions are also used. Other important considerations are, how big the ROIs are, and if the ROIs are terminating regions or bottleneck regions, i.e., an area the fibers of a tract have to pass through if they are constricted by surrounding brain structures. Based on the number of ROIs that researchers use, different tractography approaches have been distinguished:

Constraints and different approaches.

- **Single-ROI approach (also named: one-ROI approach):** One single seed ROI is chosen a priori and used for fiber tracking. The ROI can consist of one white matter voxel or a bigger volume of voxels. The ROI can be a terminating region or a bottleneck region of the intended tract. Thus, the course of the resulting fiber is restricted to only one region or even one voxel.
- **Double-ROI approach (two-ROI approach):** One seed ROI and one big target ROI (i.e., a whole lobe or gyrus) or two small ROIs (used as seed and target alternatively) are defined a priori and used for fiber tracking. Thus, the course of the resulting fiber tract is restricted to the fibers passing through both ROIs. The double-ROI approach is often used for partitioning of a fiber tract into subcomponents.
- **Multi-ROI approach (multiple-ROI approach):** Two or more ROIs are defined a priori and used for fiber tracking. One seed ROI together with multiple target ROIs, or multiple seed ROIs together with one target ROI ([Wakana et al., 2007](#)) are possible. Thus, the course of the resulting fiber tract is restricted to the fibers passing through all regions or explicitly not passing through some of the regions.

To determine the location of the ROIs for fiber tracking, functional imaging data (see the section “[Functional-based fiber tracking](#)” below), data from correlations between gray matter and behavioral performance (e.g., from voxel-based morphometry or cortical thickness analyses) or even a priori knowledge about the course of the fibers is consulted.

Different options for choosing ROIs.

2.1.2 Relating anatomy to function

Inference

Functional roles can be derived from comparisons between species or developmental stages.

One deductive method for investigating the functions of fiber tracts is to compare the fiber tracts or diffusivity parameters of different species (e. g., non-human primates vs. humans), or developmental stages (e. g., children vs. adults), against the background of what these groups are able to do. If a fiber tract is less pronounced in one group compared to another group, its function can be related to the behavioral ability that is less matured in the one group, compared to the other group. Some researchers additionally calculate correlations between structure and function, which makes this method more reliable.

Lesion mapping

Functional roles can be derived from mapping brain damage and clinical symptoms.

The functions that underlie different fiber tracts can also be studied by lesion mapping (as performed, for example, by [Dronkers et al., 2004](#); [Tyler et al., 2011](#)). To investigate language functions, lesion mapping is applied to patients that exhibit language deficits: patients with speech or language disorders, patients with different types of aphasia, or patients with semantic dementia or schizophrenia. In this method, the white and gray matter damage that causes the clinical symptoms is correlated with the behavioral performance in language tasks.

The damaged tract is reconstructed and correlated with clinical symptoms.

To reconstruct the damaged fiber tract, an image of the patient's brain is overlaid with fiber tracts from images of healthy participants' brains, or fiber tracking is directly applied to the patient's brain. The function of the damaged tract is then deduced from the ability that the patient lacks. To determine the quantitative relationship between clinical symptoms and the microstructural damage, the patient's behavioral performance is correlated with the diffusivity values (e. g., fractional anisotropy, mean diffusivity, axial/parallel/longitudinal diffusivity, radial diffusivity; see [Sundgren et al., 2004](#), for an overview of diffusivity values and their application to different diseases).

Functional-based fiber tracking

Functional roles can be inferred from imaging studies.

Possibly the simplest method for mapping function and anatomy of a tract is to infer their functional roles from neuroimaging studies (as performed, for example, by [Catani et al., 2005](#)). Neuroimaging investigates the functions of cortical areas. Based on the functions of interconnected cortical areas, the functional role of the tract that connects the areas is deduced.

A more reliable way to deduce the functional role of a tract is to perform fiber tracking directly on the data of preceding functional imaging studies (as performed, for example, by Friederici et al. (2006a), Kamada et al. (2007), Saur et al. (2008), as well as in the tractography study of the present dissertation, see Chapter 5). In this method, a fiber tract starting in a specific ROI is ascribed the functional role of transmitting the information that is processed in that ROI.

Imaging data can be utilized for fiber tracking.

One option for identifying the functionally informed seed region for fiber tracking is to use the white matter adjacent to fMRI activations. Ideally, the fMRI and diffusion data are derived from the same subjects so that a direct and precise individual mapping of function and anatomy is possible. However, some studies have also applied group averaged fMRI activations to individual brains, or used fMRI activations from other participants. Another possibility for locating functionally informed seed regions is to use those gray matter regions that show a strong correlation between damage and clinical symptoms in patients, e. g., regions revealed by lesion mapping.

Possibilities for identifying functionally informed seed regions.

When using functional-based fiber tracking, the relation between structure and function is only indirect, as is the case when using inference or lesion mapping. Moreover, the quality of the mapping strongly depends on the quality of the fMRI design used. Also, other cognitive functions or common, more general functions that might activate the cortical regions used as seed regions have to be considered as possible functional roles of the tract. However, a close relation between language fiber tracts and their cortical termination regions has been demonstrated. When combining stimulation of gray and white matter with fiber tractography, the terminations of the dorsal fiber tracts were shown to be essential for language (Ellmore et al., 2009). Taken together, functional-based fiber tracking is currently a valuable, precise, informative and noninvasive method for mapping functions onto fiber tracts.

Functional-based fiber tracking is an indirect method.

Brain electrostimulation

The most direct method for determining the function of a fiber tract is to stimulate the fiber tract in awake participants and observe the impairments that the stimulation causes (e. g., Bello et al., 2008; Bizzi, 2009; Duffau et al., 1999). To derive the exact course of the fiber tract, the region that produced the impaired behavioral performance when stimulated is used as a seed region for functional-based fiber tracking.

Functional roles can be derived from stimulating tracts.

Brain electrostimulation allows direct mapping of anatomy and function. It can, however, only be conducted during neurosurgery, and is only applied to patients that already suffer from a neurological injury which makes them undergo surgery, e. g., brain tumors. Unfortunately, observations in the damaged brain narrow the explanatory power of the findings.

Limitations of brain electrostimulation.

2.2 Anatomy

Dorsal vs. ventral tracts.	The long-range fiber tracts most likely involved in language have been grouped into dorsal and ventral tracts: Dorsal tracts run superior to the horizontal portion of the Sylvian fissure, thereby connecting the frontal lobe with the parietal and temporal lobe; Ventral tracts run inferior to the horizontal portion of the Sylvian fissure, connecting the frontal lobe with the temporal and occipital lobe.
Dorsal vs. ventral processing streams.	The division into dorsal and ventral tracts is derived from vision research, where functional streams of processing have been differentiated dorsally and ventrally (Goodale & Milner, 1992; Ungerleider & Mishkin, 1982). Visual information has been postulated to be propagated differently, depending on the function that the information fulfills: ranging from early visual regions in the occipital lobe to higher visual regions in the parietal lobe or in the temporal lobe. Hence, a dorsal route or stream of processing (occipital to parietal) and a ventral stream of visual processing (occipital to temporal) could be differentiated. When this idea was adapted for the language system (Hickok & Poeppel, 2000; Rauschecker, 2011; Rauschecker & Scott, 2009), the dorsal and ventral streams of processing relating to vision were spatially shifted in an anterior direction from occipital-parietal and occipital-temporal streams to temporal-frontal streams, because the temporal and frontal lobes are the lobes that mainly realize language processing. In recent years, several research groups have sought after the functional processing streams' counterparts in the anatomy, i. e., white matter bundles that transmit linguistic information dorsally between the frontal, temporal, and parietal lobes; and ventrally between the frontal, temporal, and occipital lobes (e. g., Friederici et al., 2006a; Saur et al., 2008).
Direct vs. indirect tracts.	Direct, as well as indirect, tracts between the lobes have been suggested and discussed. Indirect tracts have a relay station in the cortical gray matter of the lobe that they pass through. For example, the frontal lobe projects to cortical regions in the parietal lobe and these parietal cortical regions then project further, to cortical regions in the temporal lobe. If both projections are regarded as realizing the same linguistic function, the projections are subsumed into one single, indirect fiber tract.
Direction of tracts.	Notably, the current methodology does not permit measurement of the direction of the information transmission. Thus, terms like "fronto-parietal" and "parieto-frontal" are used interchangeably. Likewise, whether a cortical region is a starting or a terminating region of a tract can only be inferred from the regions' functions.
Outline of the section.	In the following sections, the anatomy of the major white matter bundles that have been discussed as being involved in language processing are reviewed. Their naming was derived from the non-human primate literature and used heterogeneously. Therefore, the different

terms are outlined and clarified. Moreover, subcomponents will be reviewed that are discussed as being involved in some bundles, as well as the probable terminating regions of each tract.

The studies that are reviewed below were explorative in nature, with the goal of examining the course or terminations of the different long-range fiber tracts. Additionally, some studies with a double-ROI approach are reported, which means that the amount of scientific insight that could be gained into the course and terminations was restricted a priori. However, the reported double-ROI studies were, nonetheless, influential in terms of nomenclature or partitioning of cortical regions. The focus is on language-related studies that contributed to the understanding of fiber tracts involved in auditory language processing. However, the reported tracts are by no means exclusively involved in language processing, and probably also support other cognitive skills.

Characteristics of the reviewed studies.

2.2.1 Dorsal tracts

Dorsal language fiber tracts connect the frontal lobe to the temporal and the parietal lobe, passing through the white matter superior to the insular cortex. The most important dorsal tracts for language processing, discussed in the literature, appear to be the arcuate fascicle and the superior longitudinal fascicle.

Definition of “dorsal”.

Arcuate fascicle

In the 19th century, the arcuate fascicle (AF) was first characterized as a bundle that dorsally connects the classical language areas, Broca’s and Wernicke’s area, and described as being involved in language processing (see [Weiller et al., 2011](#)). Wernicke (1874) predicted, and Lichtheim (1885) observed, impaired language production, together with intact comprehension abilities, in patients whose AF was lesioned. This pattern was described as *conduction aphasia*. Conduction aphasia was explained by a disconnection of the language centers for production (Broca’s area) and perception (Wernicke’s area) and was ascribed to the lesioned AF ([Geschwind, 1965](#); [Lichtheim, 1885](#); [Wernicke, 1874](#)).

The arcuate fascicle was related to conduction aphasia.

In recent years, the introduction of diffusion imaging has made it possible to investigate this fiber bundle in the living human brain, and to determine the termination regions of the AF in more detail. For example, Friederici et al. (2006a) used a single ROI, from which they probabilistically traced fiber bundles in the individual brain. The seed was derived from a functional MRI study that was conducted on the same subjects. The authors observed a dorsal tract connecting posterior Broca’s area, i. e., BA 44, with the posterior and middle STG. Also, Saur et al. (2010) and Glasser & Rilling (2008) found BA 44 to be connected to the posterior STG (Figure 2.1 A).

The classic AF connects BA 44 and pSTG.

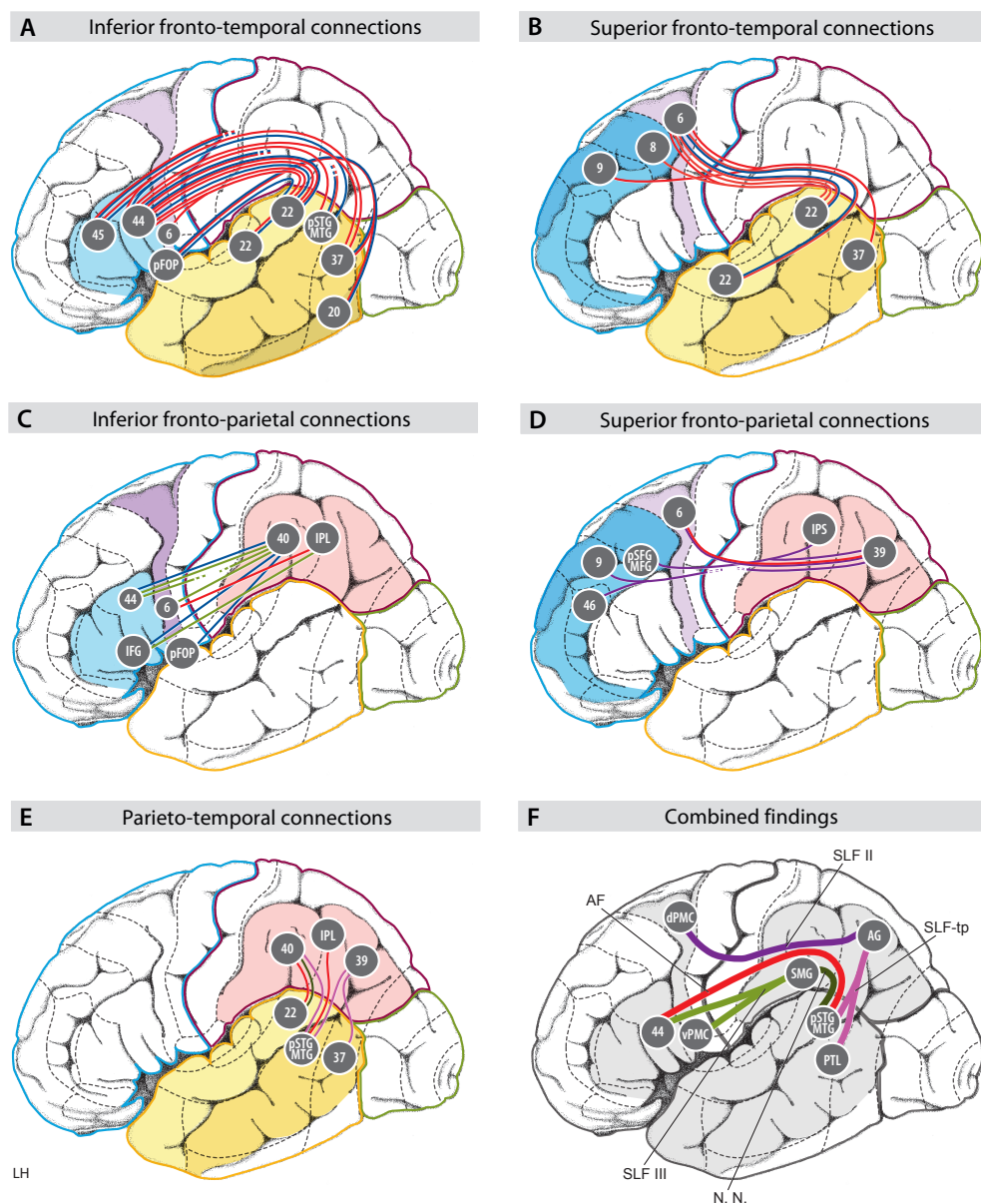


Figure 2.1: Schematic overview of the dorsal tracts reported in language-related fiber tracking studies (see Table B.1): A) Inferior fronto-temporal connections, B) Superior fronto-temporal connections, C) Inferior fronto-parietal connections, D) Superior fronto-parietal connections, E) Parieto-temporal connections. F) Construction and schematic illustration of the underlying patterns of A)–E) representing the most probable course of the fiber tracts. Each line in A)–E) represents a tract as found in one study. The names of the tracts, as given by the authors of the different studies, are color-coded: AF (red), SLF (blue), SLF III (light green), SLF II (purple), SLF-tp (pink). Unnamed tracts are printed in dark green. Double lines are drawn if a tract was named both AF and SLF, dashed lines if a study did not report the termination region. The size of the regions is arbitrary. Numbers indicate Brodmann areas. For abbreviations see page xv.

With regard to the frontal terminations, the dorsal frontal cortex has also been discussed (Figure 2.1 B). Saur et al. (2008, 2010), for example, showed the dorsal premotor cortex (PMC) to be connected with the STG. Using a double-ROI approach, Frey et al. (2008) identified a second fiber tract connecting BA 8 and dorsal BA 6 with the posterior STG, in addition to what they term as “the classic AF”, connecting BA 44 with the posterior STG. However, the authors admit the possibility that they traced the indirect running superior longitudinal fascicle (SLF; see below) rather than the actual AF, due to the limited resolution of the methodology, and huge inter-individual variability. Glasser & Rilling (2008) additionally delineated the posterior inferior frontal cortex (ventral BA 6) as a frontal termination region. With regard to the temporal terminations, these authors showed that BA 44 and ventral BA 6 are connected to the posterior middle temporal gyrus (MTG). Also, Martino et al. (2011) described the AF as being connected to the posterior MTG, in addition to the inferior temporal gyrus. As a frontal termination, the authors delineated the posterior frontal operculum, when comparing multi-ROI fiber tracking with cortex-sparing fiber dissection in the post mortem brain.

Frontal and temporal terminations.

The AF, especially its temporo-parietal portion (Liu et al., 2010; Thiebaut de Schotten et al., 2011), has been shown to be more pronounced in the left than in the right hemisphere, in both Western and Chinese populations (e.g., Catani et al., 2007; Lebel & Beaulieu, 2009; Powell et al., 2006; Qiu et al., 2011; Rodrigo et al., 2007; Vernooij et al., 2007). It has also been shown to be more prominent in humans than in chimpanzees and macaques (Rilling et al., 2008), and more matured in adults than in 7-year-old children (Brauer et al., 2011; Friederici et al., 2011). This corroborates the involvement of the AF in the human-specific ability, produced by the dominant hemisphere, to produce and understand language, especially higher-level processes that mature late during ontogeny, for example, dealing with syntactically complex structures.

Hemispheric and developmental differences.

Some authors have observed the AF to be an indirect tract with branches to the inferior parietal lobule (IPL; Catani et al., 2005), and specifically to the supramarginal gyrus (SMG; Parker et al., 2005; Powell et al., 2006). Powell and colleagues (2006), for example, did fiber tracking using a single-ROI approach on healthy participants who performed three language tasks during fMRI (verbal fluency, verb generation, reading comprehension). The fMRI activations determined the ROIs for tractography. The authors demonstrated a dorsal connection between Broca’s area and the posterior temporal lobe with connections to the SMG (in addition to a ventral connection, see Section 2.2.2). Using fiber tracking with a bottleneck ROI (lateral to the corona radiata), Catani et al. (2005) traced the AF and found that it connects the inferior frontal cortex (“Broca’s territory”, as they call it) and the posterior temporal cortex (“Wernicke’s territory”) directly. However, they also described a parallel fiber tract between the inferior frontal cortex and the IPL (“Geschwind’s territory”), as well as a fiber tract between the

The AF is a direct tract.

IPL and the posterior temporal cortex. The authors referred to these two last tracts as the indirect AF. However, the termination regions encompassed more than what is classically known to constitute Broca's and Wernicke's area. In fact, the anterior segment of the indirect pathway seemed to connect more the ventral PMC, more so than Broca's area, with the parietal cortex, and the posterior segment connected more to inferior areas in the posterior temporal lobe than the direct AF. Thus, Catani and colleagues possibly traced indirect fiber bundles that are different from the classical AF. It appears that these indirect tracts which go via the parietal lobe have been added to the SLF in subsequent studies (Figure 2.1 C).

Summary.

In sum, the AF connects Broca's and Wernicke's area directly; indirect segments via the parietal cortex have rather been attributed to the SLF. Specifically, the AF connects BA 44 with the posterior STG. Parts of the AF may also connect dorsal PMC or ventral BA 6 with posterior STG or MTG. Whether these components can be considered as belonging to the AF must, however, be questioned as these termination regions were more consistently shown to be involved in the SLF tracts (see next section). Moreover, recent investigations corroborate the anatomical differentiation of the AF connecting to BA 44, which is not present at birth and still not present at the age of seven (Brauer et al., 2011), and a different dorsal tract connecting to the PMC and the precentral gyrus, already present at birth (Friederici, 2012a; Perani et al., 2011).

Superior longitudinal fascicle

Definition of the different SLF parts in monkeys.

The superior longitudinal fascicle (SLF) and the arcuate fascicle were first regarded as one single bundle running under the frontal and the parietal gray matter in a dorsal course. Investigations of the white matter of monkeys however, distinguished the AF and three different SLF bundles (Petrides & Pandya, 1984; Schmahmann & Pandya, 2006). The AF has been assigned to the fiber bundle that connects the frontal cortex to the temporal cortex directly, without sending out branches to the parietal cortex; whereas the fibers connecting the frontal cortex with the gray matter of the parietal lobe have been assigned to the SLF. The SLF has been further delineated into three different fronto-parietal bundles, SLF I, II, and III, separated by their cortical areas of origin. The SLF I has been described as running medially, connecting superior portions of the frontal and the parietal lobe. As these regions do not strongly participate in language processing (see Vigneau et al., 2006), the SLF I is not assigned language functions, and will not be considered in the rest of this thesis. The SLF II has been described as traveling from the dorsal premotor and the prefrontal cortex to the caudal IPL, and the SLF III has been described as traveling from the ventral premotor and the prefrontal cortex to the rostral IPL in the monkey (Petrides & Pandya, 1984; Schmahmann et al., 2007).

This classification into AF, SLFI, II and III has been adapted to the human brain. In humans, the same stem portions of the four dorsal fiber bundles have been identified (Frey et al., 2008; Makris et al., 2005; Thiebaut de Schotten et al., 2012). Moreover, a fifth dorsal long-range fiber tract has been delineated, connecting the posterior temporal cortex with the gray matter of the inferior parietal cortex (Figure 2.1 E). As mentioned in the previous section, this temporo-parietal tract was first described as an additional component of the AF (Catani et al., 2005; Makris et al., 2005). However, with the adaptation of the monkey nomenclature to the human brain, the temporo-parietal tract has been henceforth named the SLF, or more precisely, the SLF-tp (Galantucci et al., 2011), whereas the name AF has been reserved for the direct connection between the frontal and the temporal gyrus. The SLF-tp differs from the posterior part of the direct AF in that it does not arch in an anterior direction around the posterior end of the Sylvian fissure, but runs in a posterior direction to the angular gyrus (AG), where it terminates in the gray matter (Galantucci et al., 2011). The SLF-tp has also been discussed as belonging to the ventral running middle longitudinal fascicle (MdLF) or the inferior longitudinal fascicle (ILF Frey et al., 2008; Makris & Pandya, 2009). The SLF-tp actually seems to consist of two temporo-parietal components, one connecting SMG with posterior STG (Parker et al., 2005), and a second connecting AG with posterior MTG (Martino et al., 2011). However, because this assumption relies on only a few studies, it is also possible that the two components belong to one single fiber tract. There is clearly a need for more research investigating the temporo-parietal connections involved in language processing.

In humans, there are (at least) five dorsal tracts.

Several studies have tried to delineate the precise anatomical terminations of the different components of the SLF. With regard to the parietal terminations, SLF II has been identified as connecting the AG with the frontal cortex, and SLF III has been identified as connecting the SMG with the frontal cortex (Galantucci et al., 2011). With regard to the frontal terminations, SLF II has been identified as connecting dorsal frontal regions (Figure 2.1 D), especially the dorsal BA 6, but also BA 8, 9, and 46, with the parietal cortex (Croxson et al., 2005; Frey et al., 2008; Makris et al., 2005; Saur et al., 2008; Saur et al., 2010; Thiebaut de Schotten et al., 2012). SLF III has been identified as connecting posterior ventral frontal regions (Figure 2.1 C), especially the ventral BA 6 and 44, with the parietal cortex (Croxson et al., 2005; Hua et al., 2009; Makris et al., 2005).

Parietal and frontal terminations.

The connectivity profiles of the inferior frontal terminating regions have been subject to separate investigations. Posterior regions, i.e., premotor and motor cortex, have been shown to have exclusively dorsal connections to the parietal and temporal cortex. In particular, the ventral premotor cortex (BA 6) has often been delineated as the terminating region of the inferior fronto-parietal connection (Catani et al., 2005; Hua et al., 2009; Makris et al., 2005). Bernal & Altman (2010) went one step further. Using a bottleneck-approach, they claimed that the dorsal tracts are connected, nearly exclusively, to the dorsal and ven-

Connections of the inferior frontal cortex.

tral precentral gyrus (premotor and motor cortex). However, in 41.6 % of their subjects, some fibers also reached Broca's area. Concerning the inferior frontal gyrus (IFG), some authors have proposed a clear differentiation of BA 44 being connected to temporal regions dorsally, and BA 45 being connected to temporal regions ventrally (Frey et al., 2008; Griffiths et al., 2012; Kaplan et al., 2010). Anwander et al. (2007) also observed dorsal connections starting in BA 45. The authors seeded in the different voxels of the IFG. Based on the different connectivity profiles of the seed voxels, the IFG was parceled into subparts, each showing a similar connectivity pattern. The IFG appeared to have three different parts, connecting to the posterior regions: BA 44, only connected dorsally; BA 45, mainly connected ventrally, but also, to a lesser extent, dorsally; and the frontal operculum, only connected ventrally. One study also showed BA 47 to be connected dorsally to the posterior regions when comparing human with non-human fiber tracts using a multiple-ROI approach (Thiebaut de Schotten et al., 2012). Others, however, found BA 47 to be connected ventrally to the posterior regions (Saur et al., 2008; Saur et al., 2010).

Summary.

In sum, besides the AF which directly connects the frontal with the temporal cortex, three SLF fiber bundles have been delineated as being involved in language processing: the SLF II, the SLF III and the SLF-tp. The SLF II connects the dorsolateral prefrontal and the premotor cortex (especially dorsal BA 6) with the AG, the SLF III connects the ventrolateral frontal cortex (mainly ventral BA 6 and BA 44, but also partly BA 45) with the SMG. The SLF-tp connects the IPL with the posterior temporal cortex, thereby being distinct from the posterior portion of the AF. Two different parts of the SLF-tp have been discussed, one connecting SMG with posterior STG (perhaps as supplement of the SLF III), and another connecting AG with posterior MTG (as supplement of the SLF II). However, more research is clearly needed, especially with regard to the SLF-tp.

2.2.2 Ventral tracts

Definition of "ventral", and the extreme capsule problem.

The ventral fiber tracts for language processing connect the frontal lobe to the temporal and occipital lobes, passing through the bottleneck of the anterior ventral extreme and/or external capsule. Although these capsules have long ago been distinguished by neuroanatomists, the current resolution of the DTI methodology does not permit differentiation of which capsule is actually passed through by the ventral long-range fiber tracts. Monkey studies, however, imply that it is the extreme capsule because its fibers are oriented in an anterior-posterior direction, contrary to the fibers of the external capsule (Petrides & Pandya, 2009; Schmahmann et al., 2007).

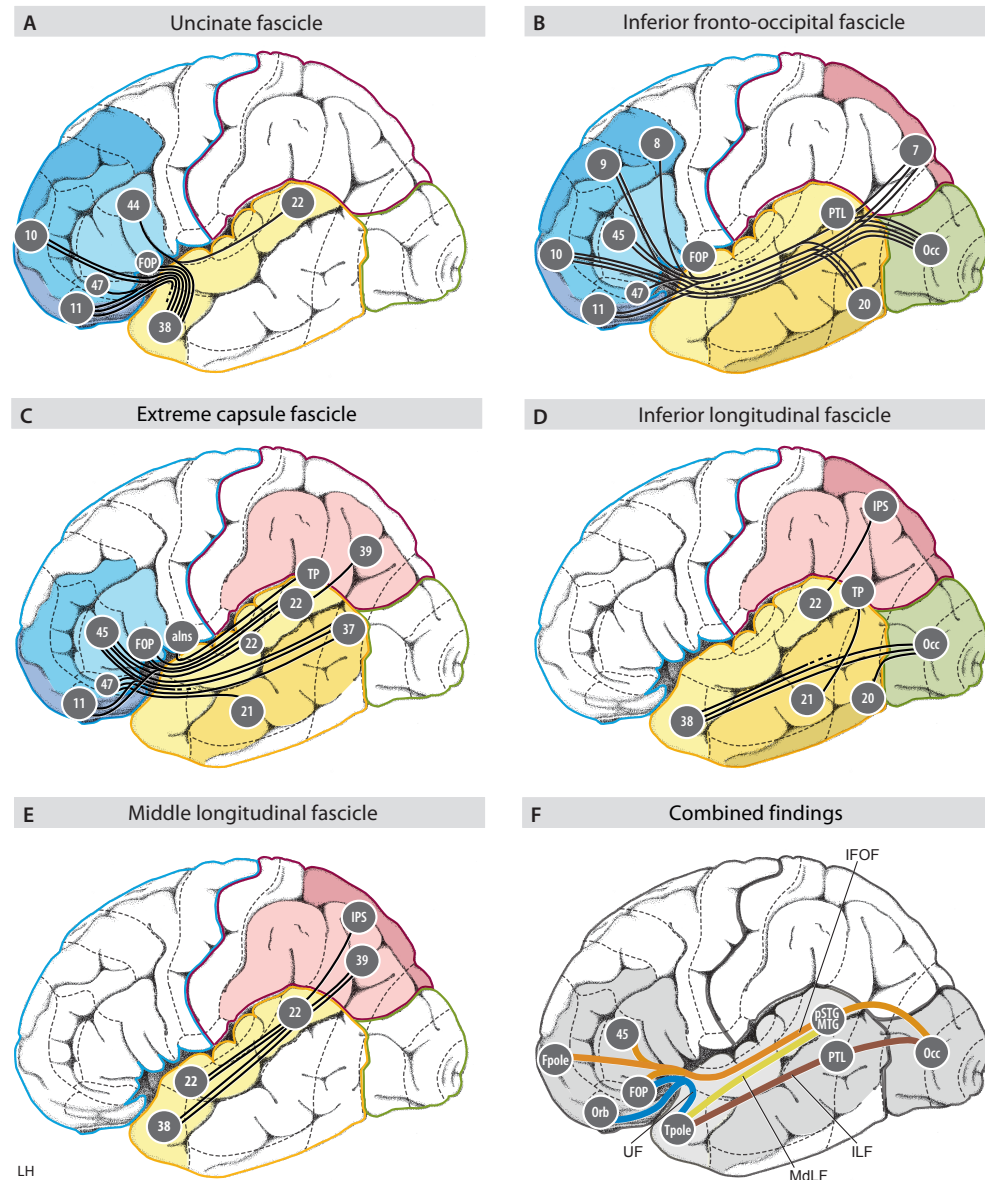


Figure 2.2: Schematic overview of the ventral tracts reported in language-related fiber tracking studies (see Table B.2). Each panel illustrates the course of the fiber tracts that were named by the authors of the different studies A) Uncinate fascicle, B) Inferior fronto-occipital fascicle, C) Extreme capsule fascicle, extreme capsule, external capsule or extreme capsule fiber system, D) Inferior longitudinal fascicle, and E) Middle longitudinal fascicle. F) Construction and schematic illustration of the underlying patterns of A)–E) representing the most probable course of the fiber tracts. Each line in A)–E) represents a tract as found in one study. Dashed lines are drawn if a study did not report the termination region. The size of the termination regions is arbitrary. Numbers indicate Brodmann areas. Fpole = frontal pole; Occ = occipital cortex; Orb = orbitofrontal cortex; PTL = posterior temporal lobe; TP = temporoparietal border region; Tpole = temporal pole. For other abbreviations see page xv.

Uncinate fascicle

The UF connects
ATL with frontal lobe.

The uncinate fascicle (UF; [Figure 2.2 A](#)) has been described as a white matter bundle running in a hook-shape through the bottleneck of the extreme capsule, thereby connecting the anterior temporal lobe with the inferior frontal cortex ([Déjerine, 1901](#)). It has been delineated in several studies investigating the fiber tracts underlying language processing. As a termination region in the temporal lobe, the studies have consistently depicted the anterior temporal lobe ([Anwander et al., 2007](#); [Friederici et al., 2006a](#)), especially superior ([Hua et al., 2009](#); [Martino et al., 2011](#); [Thiebaut de Schotten et al., 2012](#)) and middle regions ([Martino et al., 2011](#)). As termination regions in the frontal lobe, a variety of regions have been discussed: the frontal pole ([Hua et al., 2009](#); [Thiebaut de Schotten et al., 2012](#)), the pars orbitalis of the IFG ([Thiebaut de Schotten et al., 2012](#)), the medial orbitofrontal cortex ([Croxson et al., 2005](#); [Martino et al., 2011](#)) the lateral orbitofrontal cortex ([Croxson et al., 2005](#); [Martino et al., 2011](#); [Thiebaut de Schotten et al., 2012](#)), the anterior frontal operculum ([Anwander et al., 2007](#); [Friederici et al., 2006a](#)), and even BA 44 of Broca's area ([Parker et al., 2005](#)). The subinsular portions of the UF have been shown to be more pronounced in the left than in the right hemisphere ([Rodrigo et al., 2007](#)).

Inferior fronto-occipital fascicle

Course and
frontal terminations
of the IFOF.

A second ventral fiber bundle which connects the frontal and the temporal lobe, through the bottleneck of the extreme capsule, is the inferior fronto-occipital fascicle (IFOF; also abbreviated in the literature as IFO, IOFF, IOF; [Figure 2.2 B](#)). The IFOF has been described as running more superior through the bottleneck of the extreme capsule than the UF ([Thiebaut de Schotten et al., 2012](#)). As frontal termination regions, the anterior inferior frontal cortex, specifically BA 45, 47 and the frontal operculum ([Anwander et al., 2007](#); [Hua et al., 2009](#); [Sarubbo et al., 2011](#)), the lateral and medial orbitofrontal cortex and the frontal pole ([Hua et al., 2009](#); [Sarubbo et al., 2011](#); [Thiebaut de Schotten et al., 2012](#)), as well as the dorsolateral prefrontal cortex ([Sarubbo et al., 2011](#); [Thiebaut de Schotten et al., 2012](#)) have been discussed. [Sarubbo and colleagues \(2011\)](#) distinguish a superficial component that terminates in the IFG (pars orbitalis and triangularis), from a deep component that terminates in more anterior and superior rostral areas.

Posterior
terminations.

The occipital cortex has been revealed as a possible posterior termination region ([Hua et al., 2009](#); [Martino et al., 2011](#); [Powell et al., 2006](#); [Sarubbo et al., 2011](#); [Thiebaut de Schotten et al., 2012](#)), but so have connections to the posterior STG and MTG ([Powell et al., 2006](#); [Sarubbo et al., 2011](#)), as well as the temporo-basal area and the superior parietal lobule ([Martino et al., 2011](#); [Sarubbo et al., 2011](#)). The IFOF has been shown to be more matured in humans than in non-human primates ([Thiebaut de Schotten et al., 2012](#)), suggesting a human-specific function to the IFOF, e.g., language.

Extreme capsule

The long-range fiber tract that ventrally connects the frontal to the posterior temporal cortex in humans has been named the IFOF, the extreme capsule (EmC; [Figure 2.2C](#)) and the extreme capsule fiber system (ECFS) likewise. In monkey studies, the EmC has been delineated as a separate fiber bundle, i. e., the extreme capsule fascicle, and described as connecting the ventrolateral prefrontal cortex, the caudal orbitofrontal cortex, as well as BA 45, to the middle STG and the superior temporal sulcus (STS; [Schmahmann & Pandya, 2006](#)). In humans, the EmC/ECFS tract has been described as connecting BA 45 ([Croxson et al., 2005](#); [Frey et al., 2008](#); [Makris & Pandya, 2009](#)), the frontal operculum ([Makris & Pandya, 2009](#); [Saur et al., 2008](#); [Saur et al., 2010](#)) and the lateral orbitofrontal cortex ([Croxson et al., 2005](#); [Makris & Pandya, 2009](#)) via the middle STG/STS ([Frey et al., 2008](#); [Makris & Pandya, 2009](#)) with the posterior MTG and STG ([Saur et al., 2008](#); [Saur et al., 2010](#)) and the border region to the parietal cortex ([Wong et al., 2011](#)). Also, connections from the anterior insula ([Wong et al., 2011](#)), and pars orbitalis ([Saur et al., 2010](#)), as well as connections to the anterior STG ([Saur et al., 2008](#)) and MTG ([Saur et al., 2010](#)) have been suggested.

The EmC tract connects inferior frontal with posterior temporal cortex.

Interestingly, in the language-related studies, no study delineated both the IFOF and an extreme capsule fascicle. Rather, the fiber tract that has been denoted the EmC or the ECFS resembles, in big parts, the tract that has been denoted the IFOF. When compared to the IFOF, the frontal termination regions of the EmC tract and the IFOF appear to be similar. The posterior termination regions, however, differ in that the EmC tract reaches the posterior temporal and the parietal lobe, whereas the IFOF has been described as reaching the occipital cortex by the majority of studies.

EmC vs. IFOF.

It is thus possible that there is an additional long-range fiber tract, the extreme capsule fascicle, connecting the inferior frontal lobe via anterior parts of the extreme capsule with the posterior temporal regions. However, because big parts of this fiber tract are similar to the IFOF, the differences between the two tracts are perhaps only ostensible. Actually, the double-ROI approaches that have been often used for tracking of the EmC tract with ROIs in the posterior temporal and frontal cortex ([Frey et al., 2008](#); [Saur et al., 2008](#); [Saur et al., 2010](#)) prevent the finding of occipital connections. Thus, the findings of the EmC tract in humans might actually be findings of the IFOF. [Schmahmann et al. \(2007\)](#), on the contrary, suggested that the findings of the IFOF might actually be findings of the EmC and/or UF conflated with the ILF, because the EmC tract, but not the IFOF, could be delineated in monkeys using an autoradiographic isotope technique. However, in humans, the IFOF, but not an EmC tract, was delineated long ago by [Déjerine](#) using post mortem dissections (see [Déjerine, 1901](#); [Sarubbo et al., 2011](#)).

EmC and IFOF seem to be the same.

The choice of
"IFOF" over "EmC".

Taken together, the EmC tract and the IFOF might be one and the same tract as no study—to our knowledge—has ever delineated both in one brain. Whether this tract should be named the EmC tract or the IFOF depends on the perspective. For the remainder of this thesis, the term "IFOF" will be used as, in humans, the EmC captures all the white matter between the insular cortex and the claustrum (in its whole length and height), and hence encompasses many more fibers and not only the long-range fibers of an anterior-posterior directionality. These have been shown to only be situated in anterior parts of the EmC (Sarubbo et al., 2011). Note, however, that the IFOF, contrary to what the name implies, may encompass fibers that do not reach the occipital cortex.

Inferior longitudinal fascicle

The ILF connects
anterior temporal
with occipital cortex.

The inferior longitudinal fascicle (ILF; Figure 2.2 D) has been found to connect the ventral part of the temporal lobe with the occipital and parietal cortex in monkeys (Schmahmann & Pandya, 2006; Thiebaut de Schotten et al., 2012). In the language-related literature in humans, a lateral component of the tract has been described to connect the temporal pole with the occipital cortex (Galantucci et al., 2011; Hua et al., 2009; Martino et al., 2011). A medial component of the ILF has been delineated as connecting anterior fusiform gyrus with occipital cortex (Martino et al., 2011). Frey and colleagues (2008) also described the connection between posterior STG/STS and inferior parietal sulcus (IPS) as belonging to the ILF or MdLF. Unfortunately, no other explorative examinations related to auditory language processing have explicitly investigated the ILF.

Middle longitudinal fascicle

The MdLF connects
anterior with
posterior temporal
cortex.

The middle longitudinal fascicle (MdLF; Figure 2.2 E) connects anterior with posterior temporal regions. Saur et al. (2008, 2010) stated that the MdLF connects anterior with posterior STG, thereby collecting fibers from the anterior and posterior MTG. These connected regions were derived from an fMRI study and a priori determined as seeds for tracking. Using a bottleneck single-ROI approach, Makris & Pandya (2009), as well as Makris et al. (2009) described the MdLF as connecting the temporal pole and middle STG/STS with the AG, running mainly in the white matter of the STG, lateral to the IFOF and superior to the ILF but medial to the temporal portions of the dorsal fiber tracts. There are, however, no other studies delineating the tract to be involved in auditory language processing.

2.2.3 Summary

One direct
dorsal tract.

Dorsally (Figure 2.1 F), there is one direct pathway involved in auditory language processing which connects the frontal lobe with the temporal

lobe, and two indirect pathways with participation of the parietal gray matter.

- I. The **direct dorsal tract** connects BA 44 (posterior Broca's area) with the posterior STG and is named the arcuate fascicle (AF) in the majority of the studies. Some studies also describe the posterior MTG as a temporal termination, and some do not differentiate between the STG and the MTG. Only a negligible amount of studies support BA 45 or ventral BA 6 as frontal terminations.

The indirect pathways are remarkably distinguishable in both the frontal, and the parietal regions they connect. A superior pathway connects superior frontal regions, via the AG, with the temporal cortex, whereas an inferior pathway connects inferior frontal regions, via the SMG, with the temporal cortex.

Two indirect dorsal tracts.

- II. The **superior indirect tract** connects the dorsolateral frontal cortex (mainly dorsal BA 6), via the AG, with the posterior temporal cortex. The tract's fronto-parietal part corresponds to a tract named the superior longitudinal fascicle II (SLF II), whereas its parieto-temporal part was previously described as the SLF-tp. The termination region in the temporal lobe is the posterior STG and/or the posterior MTG, depending on the study. A few studies have delineated a direct tract between the dorsal premotor cortex and the posterior temporal lobe. However, as the current methodology has limited resolution, and there is much inter-individual variability, it is possible that this direct tract encompasses the parietal cortex, and hence corresponds instead to the superior indirect tract described here.
- III. The **inferior indirect tract** connects the posterior inferior frontal lobe, via the SMG, with the posterior temporal cortex. The tract's fronto-parietal part corresponds to the SLF III which runs laterally to the AF. There is no consistent nomenclature for the tract's parieto-temporal part. BA 6 and BA 44 have mainly been suggested as frontal terminations, but also partly BA 45. In the temporal lobe, the tract probably ends in the superior posterior temporal cortex.

Ventrally (Figure 2.2 F), there are two main pathways (based on the number of times they have been delineated) involved in auditory language processing which connect the frontal to the temporal lobe, traveling through the bottleneck of the extreme capsule.

Two main ventral tracts.

- I. The **uncinate fascicle (UF)** connects, hook-shaped, the inferior frontal and the prefrontal cortex with the anterior temporal cortex. Fibers connecting the medial and the lateral orbitofrontal cortex and the anterior frontal operculum with the superior portion of the anterior temporal lobe were especially shown in language-related fiber tracking studies.

- II. The **inferior fronto-occipital fascicle (IFOF)** connects the inferior frontal cortex with the posterior temporal and the occipital cortex, running superiorly to the UF through the bottleneck of the extreme capsule. Especially, anterior Broca's area (BA 45) and the deep anterior frontal operculum, as well as the frontal pole were connected with the posterior temporal and the occipital cortex in language studies. The course of the IFOF resembles the course of what some authors called the extreme capsule tract.

Two additional ventral tracts.

There are two additional ventral pathways connecting anterior temporal cortex with posterior areas in the temporal and occipital lobe which have been delineated less frequently in the fiber tracking studies related to auditory language processing. However, these pathways have been shown to be involved in visual language processing, and may be also involved in auditory language processing via short-range connections, possibly playing a dispensable role.

- III. The **inferior longitudinal fascicle (ILF)** connects the temporal pole with the posterior temporal and the occipital cortex. It runs mainly in the white matter of the MTG.
- IV. The **middle longitudinal fascicle (MdLF)** connects the temporal pole with the posterior superior temporal cortex. It runs mainly in the white matter of the STG, lateral to the IFOF and superior to the ILF but medial to the temporal portions of the dorsal fiber tracts.

2.3 Function

Definition of functional roles.

In the following sections, the studies will be reviewed that have tried to relate linguistic functions to the different fiber tracts, using the methods described above. Because fiber tracts are white matter bundles, they have the capacity to transmit specific kind of information. In transmitting information, they give rise to a cognitive ability, given the interplay with activation in the gray matter regions they connect. The specific ability they afford, together with the connected cortical areas, is called the functional role of the fiber tract, e. g., retrieval of word meanings, analysis of word order, storage of syntactic structures, and so forth. The functional roles that will be considered separately in the following sections along with the fiber tracts that are discussed to support these functional roles are phonological processing, articulation, speech repetition, semantic processing, and syntactic processing.

2.3.1 Phonological processing

Phonology is associated with SLF-tp.

Rolheiser, Stamatakis, & Tyler (2011) showed that phonological processing during both comprehension and production tasks relies on the dorsal fiber tracts exclusively (they subsume it as "AF/SLF"). The au-

thors correlated the performance of post-stroke patients in language comprehension and production tasks with white matter damage of the AF/SLF and a ventral pathway. More specifically, it has been suggested that phonological processing is a function of the temporoparietal part of the AF/SLF system, because electrostimulation of the temporal white matter underlying the posterior superior temporal cortex elicited phonological impairments (Duffau et al., 2002; Duffau et al., 2009). Also, Parker and colleagues (2005) attributed a function in syllable discrimination and identification during speech perception to the temporoparietal pathway. However, that was based on functional activations from different participants. Mapping white matter damage to phonological errors in spontaneous speech and naming, Galantucci and colleagues (2011) distinguished the temporoparietal part of the direct AF from the temporoparietal SLF, which is the pathway connecting the AG with the posterior temporal cortex (SLF-tp). They showed that only the SLF-tp, and not the temporoparietal portion of the AF, was significantly more damaged in patients with the logopenic variant of primary progressive aphasia than in healthy controls. Because these patients show phonological deficits, the authors again attributed the SLF-tp with a function in phonological processing. Thus, it can be concluded that the SLF-tp may be a crucial white matter pathway for phonological processing.

2.3.2 Articulation

Dronkers (1996) and colleagues (Dronkers et al., 1993; Ogar et al., 2006) formerly showed that articulatory planning deficits are best explained by damage to the superior precentral gyrus of the insular cortex, in combination with damage to a dorsal tract. This was confirmed by Bates et al. (2003) using voxel-based lesion symptom mapping who localized the white matter damage that was most associated with production deficits in the parietal parts of the AF/SLF. Also Davtian et al. (2008) associated the SLF with speech production, because they caused speech arrest when dissecting the border of a tumor contacting the SLF. Moreover, in patients with the non-fluent variant of primary progressive aphasia, the AF, the SLF III, the SLF II and the SLF-tp were demonstrated to be the affected tracts by showing lower diffusivity (i.e., white matter damage) compared with healthy controls (Galantucci et al., 2011; Wilson et al., 2010). These patients showed, among other language disabilities, motor speech deficits. Those articulation deficits were hence supposed to result from the white matter damage of at least one of the damaged components. Using electrostimulation, Duffau and colleagues (Duffau, 2008; Maldonado et al., 2011) delineated that stimulation of the SLF III induced dysarthria or complete anarthria, supporting this pathway as having a role in articulation, and verbal working memory for articulation, specifically through its connection to ventral BA 6, not Broca's area (Knight, 2011). Stimulation of a more posterior and deeper white matter portion under the SMG, corresponding to the direct fronto-temporal AF, did not induce articu-

Articulation is associated with SLF III.

lation deficits. Thus, it is likely that it is the SLF III which is a crucial white matter tract for articulation. Whether the SLF II and the SLF-tp are also recruited during articulation, remains subject to future studies.

2.3.3 Speech repetition

Repetition was associated with AF.

Historically, speech repetition has been associated with the AF: In patients with conduction aphasia, impaired repetition was shown to accompany a lesion in the AF and other white matter structures that connect Broca's and Wernicke's area, while in patients with transcortical aphasia, intact repetition ability was accompanied by an intact AF (Geschwind, 1965). However, empirical reports challenged the view that the AF supports speech repetition. For example, two patients with lesions of the AF showed an intact repetition ability, but impairments of verbal fluency and comprehension when it came to complex ideational material (Selnes et al., 2002; Shuren et al., 1995). Moreover, it was shown that cortical lesions per se can produce conduction aphasic syndromes without the AF being directly lesioned (Anderson et al., 1999).

Repetition is still associated with AF.

Berthier et al. (2012) cite three possible reasons to explain these controversial findings. Firstly, the studies may have investigated different white matter structures, because the AF shows a large inter-individual variability, both intra- and inter-hemispheric. Similarly, the studies may have investigated different segments of the AF, because the dorsal tract is more than one single fiber bundle as it also encompasses SLF components. Lastly, the studies may have investigated those patients that were able to use other white matter tracts for repetition, e. g., the right AF or the ventral pathways. Berthier et al. (2012) therefore adhered to the view that the AF or some of the SLF components are crucial fiber tracts for repetition. This hypothesis has been corroborated by findings in glioma patients who show repetition deficits if the AF is lesioned (Bizzi et al., 2012). The authors additionally demonstrated that damage of only the cortical areas in the prefrontal cortex is not sufficient for repetition deficits.

Repetition is also associated with SLF-tp, SLF III and SLF II.

Investigating the different components in detail, the following picture emerges: Galantucci et al. (2011) observed that in patients with the logopenic variant of primary progressive aphasia, the most damaged tract was the SLF-tp. The SLF-tp is hence suggested to have a role in repetition, because the patients showed deficits in sentence repetition. Also, correlating damage of white matter tracts with behavioral measures in aphasic patients, Breier et al. (2008) reported that both a temporo-parietal and a horizontal part of the dorsal white matter bundles contribute to repetition—independent of the cortical areas they connect. Unfortunately, the authors do not provide detailed anatomical descriptions. More specifically, Fridriksson and colleagues (2010) showed the white matter underlying the SMG to be associated with speech repetition, when correlating diffusion data of stroke

patients with their ability to repeat. This finding supports the inferior indirect dorsal tract, and specifically the SLFIII, as playing a role in repetition. Using functional-based fiber tracking, Saur and colleagues (2008), however, showed that repetition of meaningless words is associated with the superior dorsal tract, which connects the temporal cortex to the dorsal PMC (which they delineated as a direct tract, contrary to the discussion above).

Taken together, these results suggest that both the SLF-tp, which connects the posterior temporal cortex with the AG, as well as the SLFIII, which connects SMG with posterior inferior frontal cortex, can be attributed a functional role in repetition. Hence, both the tract involved in phonological processing (SLF-tp), as well as the tract involved in articulation (SLFIII), appear to be involved in repetition. This perfectly adds up as both abilities are necessary for a proper repetition. The connection to the dorsal PMC (directly from the posterior temporal area or mediated by the AG and SLFII) is an additional candidate for facilitating repetition. This connection could be specifically relevant for speech motor planning and control during repetition, as these are well-known functions of the dorsal PMC.

At least
the SLF-tp and SLF III
support repetition.

2.3.4 Semantic processing

Pathways passing through the anterior temporal lobe, but not dorsal pathways support semantic processing, as shown by a study that compared the mean diffusivity of fiber tracts (i.e., the integrity, respective damage of the fiber tracts) between patients with semantic dementia and healthy controls (Agosta et al., 2010). The anterior temporal tracts of the semantic dementia patients were damaged, which probably led to the observed severe difficulties in semantic comprehension and production tasks, like comprehension of single words, naming, reading, and generating of semantic associations, while syntactic, phonology and fluency was relatively spared.

Pathways through
the ATL support
semantic processing.

Both the UF and the IFOF are long-range fiber tracts that pass through the anterior temporal lobe to the frontal lobe. Wilson et al. (2011) related both tracts to deficits in word-level semantic processing, but could not differentiate between them because damage to the tracts was correlated. Papagno et al. (2011) suggested that the most relevant function that the UF is involved in is naming famous people, but not semantic processing. This is because the surgical removal of the UF resulted in impaired retrieval of word forms for proper names, compared to unimpaired retrieval in patients whose UF was not removed.

UF is possibly
involved in other
cognitive skills.

Stimulation of the IFOF, on the other hand, elicited semantic impairments (De Witt Hamer et al., 2011; Duffau et al., 2005; Duffau et al., 2009; Mandonnet et al., 2007), whereas stimulation of the UF (Duffau et al., 2009) or the ILF (Mandonnet et al., 2007) or the MdLF

IFOF is crucial for
semantic processing.

	<p>(De Witt Hamer et al., 2011) or stimulation of the tracts within the white matter under the SMG (Maldonado et al., 2011) did not. The authors concluded that the IFOF is crucial for language semantic processing, whereas the ILF, the UF and the MdLF are dispensable, meaning that their semantic functions can be compensated by the IFOF.</p>
Evidence for IFOF supporting semantic processing.	<p>Also, several other studies have shown the IFOF to be the most important tract for semantic processing. Kubicki and colleagues (2011) revealed that white matter abnormalities in the IFOF in schizophrenic patients predicted semantic deficits. More specifically, Galantucci and colleagues (2011) delineated that it is the anterior and middle portions of the IFOF that are most relevant parts for semantic processing. Abnormalities of these portions in primary progressive aphasia patients predicted the quality of single-word comprehension and retrieval. Also, the maintenance of the word meanings in working memory, and the integration into the overall sentence meaning is probably supported by the IFOF, as suggested by a study using the MTG and BA 47 as ROIs for fiber tracking (Turken & Dronkers, 2011). These ROIs were the cortical areas in which high-level language comprehension deficits and lesions of aphasic patients correlated most. The regions appeared to be connected via the IFOF. A component of the AF which connects the MTG dorsally with the frontal lobe has been suggested to play a role in the integration of word meanings with other linguistic and cognitive properties (Turken & Dronkers, 2011).</p>
IFOF supports semantic processing also during production.	<p>Moreover, not only is semantic processing supported by the IFOF during comprehension, but also during production tasks. Rolheiser and colleagues (2011) showed in a study with post-stroke patients that the pathway connecting BA 45 with posterior MTG correlates with performance in semantic comprehension and production tasks (i. e., a property knowledge task and picture naming task). Dorsal pathways showed no correlation with semantic processing at all.</p>
IFOF is crucial for lexical semantic processing.	<p>In sum, the IFOF, especially anterior and middle portions, appears to be the most relevant tract supporting semantic processes, during both comprehension and production, and especially on the word-level. The contribution of other ventral fiber tracts to semantic processing seems to be dispensable. No dorsal fiber tracts have been shown to be involved.</p>

2.3.5 Syntactic processing

Inferior frontal white matter supports syntax.	<p>To investigate which fiber tracts support transmission of syntactic information, Flöel et al. (2009) examined the integrity of white matter around Broca's area and of the fiber tracts that start in the area. They found that the white matter integrity highly correlated with the ability to learn an artificial grammar. This finding suggests that the pathways around Broca's area transmit syntactic information. Unfortunately, the authors did not delineate BA 44 from BA 45, nor did they give a</p>
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description of the observed pathways. From the figure they provided, however, it can be inferred that both dorsal and ventral fiber tracts correlated with grammar learning success.

This observation is in line with the findings of Rolheiser and colleagues (2011), who correlated the performance of post-stroke patients in language comprehension and production tasks with the white matter damage of the “AF/SLF” and of a ventral pathway connecting BA 45 and posterior MTG. The authors showed that both the dorsal and the ventral pathway participated in syntax comprehension and production. Another study from the same group confirmed this finding with respect to the processing of syntactic ambiguities (Papoutsis et al., 2011). Also, Griffiths and colleagues (2012) recently showed the same ventral pathway to be involved in syntactic processing, and specified the dorsal pathway as connecting BA 44 and posterior MTG when they did tractography based on brain regions involved in syntactic processing (from an fMRI study in a different group of healthy participants). Moreover, the authors found that the disruption of one or both of these tracts in post-stroke patients led to syntactic deficits, whilst the patients showed fewer or no semantic deficits. This observation corroborates the assumption that both a dorsal and a ventral tract, which anatomically correspond to the AF and the IFOF, probably participate in syntactic processing. However, it cannot be ruled out that it is the affected cortical regions and not the white matter that correlated with syntactic processing deficits in these studies.

Dorsal and ventral tracts support syntax.

Friederici et al. (2006a) raised the question of whether the dorsal and ventral tracts support different syntactic functions. Using a functional-based fiber tracking single-ROI approach with seed regions informed by fMRI activations of the same subjects, the authors observed that a dorsal fiber tract, directly connecting BA 44 and posterior temporal cortex, was crucial for processing of complex syntax, and ventral pathways were crucial for processing local structures in a simple syntax. Contrary to the results from the Tyler lab reported above (Griffiths et al., 2012; Papoutsis et al., 2011; Rolheiser et al., 2011), which restricted their ventral pathway a priori to fibers connecting BA 45 with posterior MTG, Friederici and colleagues (2006a) described the ventral pathway for simple syntactic processing as connecting the deep frontal operculum with the superior temporal cortex. The frontal operculum was connected both to the anterior STG via the U-shaped UF and to the posterior temporal regions via the IFOF. The frontal operculum served as a seed region because it was the most activated area in a violation detection task on a simple artificial grammar. Thus, the functional conclusion of the dorsal pathway being involved in processing syntactically complex structures, and the ventral pathway being involved in processing syntactically simple structures is based on the special case of violation detection in artificial grammar. No other study until now could actually delineate ventral pathways as being involved in processing syntactically simple structures. This

Complex syntax is supported by AF, simple syntax by ventral tracts.

sparse evidence is possibly due to the difficulty of segregating brain correlates of simple syntactic processing in fMRI paradigms.

The ventral tracts are probably dispensable.

Interestingly, Wilson et al. (2011) showed that comprehension and production of syntactic structures is only supported by a dorsal fiber tract (which they delineated as connecting inferior frontal cortex with posterior temporal lobe), whereas it is not supported by ventral tracts, like the UF or the IFOF. The authors used a bottleneck single-ROI approach for fiber tracking, and correlated the resulting tracts with behavioral measures from patients with primary progressive aphasia. They assessed comprehension and production by using syntactic structures that also encompassed complex syntactic ones, like passive or embedded constructions. Thus, from this study there is no clear conclusion about the fiber tracts specifically involved in the processing of simple syntactic structures. However, patients with lesions restricted to the ventral pathways have been shown to perform fairly well at syntactic processing (Wilson et al., 2012), suggesting that the ventral pathways are at least dispensable when it comes to syntactic processing. The dorsal pathway, on the contrary, has been suggested to participate in complex syntactic processing, perhaps as a reflection of the identification of long-distance syntactic relations and sequence analysis (Weiller et al., 2011).

Syntax is supported by the AF, and perhaps also by ventral tracts.

Taken together, there is evidence that syntactic processing is supported by a dorsal fiber tract, especially when it comes to the processing of complex syntactic structures. This dorsal tract corresponds to the AF, which directly connects BA 44 and the posterior temporal cortex. A ventral pathway, including the frontal operculum, may be involved in processing of simple syntactic structures, although it was suggested to be dispensable. Whether it is the IFOF, the UF, or both, is unresolved at present. Especially the specific contribution of the ventral fiber tract to syntactic processing needs further research.

2.3.6 Summary

Phonology is supported by SLF-tp.

The inspection of the literature shows that phonological processing is supported by a pathway connecting the posterior temporal cortex with the angular gyrus, which is called SLF-tp. This tract seems to be different from the temporoparietal portion of the arcuate fascicle which directly connects the temporal cortex with the frontal cortex, thereby coursing through the white matter of the parietal lobe without sending branches to the cortex of the parietal lobe.

Articulation is supported by SLF III.

The most relevant fiber tract for articulation was shown to be the SLF III, a component of the superior longitudinal fascicle that connects the posterior inferior-frontal cortex, including ventral premotor cortex, with the supramarginal gyrus. We currently lack enough fine-grained investigations to make precise conclusions about the frontal terminations. It is possible that only the ventral premotor cortex, and not the

posterior IFG, is the cortical site that is connected to the parietal cortex, because the posterior IFG was also shown to be directly connected to the posterior temporal lobe via the AF.

Performing repetition is supported by tracts that are also involved in phonological processing (SLF-tp) and articulation (SLF III), as well as by a tract connecting the posterior superior temporal cortex with the superior frontal lobe. This direct connection between the temporal cortex and the superior frontal lobe is, however, questionable. There is evidence that the posterior temporal cortex is only connected to the angular gyrus via the SLF-tp, and from the angular gyrus to the superior frontal gyrus via the SLF II. Nonetheless, the phonological aspects of repetition are supported by the SLF-tp, and the articulatory aspects by the SLF III, which are in turn controlled by the dorsal premotor cortex via the SLF II or a direct connection.

Repetition is supported by SLF-tp, SLF III, and SLF II.

Semantic processing seems to rely most on anterior and middle portions of the IFOF, connecting the temporal lobe with the inferior frontal language areas. The tract is not only relevant for the processing of single word meanings for comprehension, but also for production. It is also suggested that the IFOF supports the integration of the word meanings into the sentence. However, confirming this requires more empirical evidence.

Semantics is supported by IFOF.

Syntactic structures have been shown to be processed by both dorsal and possibly also ventral fiber tracts, depending on the complexity of the structures. It has been shown that complex syntactic structures, for example sentences with a non-canonical word order or hierarchical grammar, are transmitted via the AF connecting BA 44 with the posterior temporal cortex, whereas simple syntactic structures, for example local phrase structures, were suggested to be transmitted via a ventral pathway, i. e., the IFOF and/or the UF. This ventral pathway may be dispensable.

Syntax is supported by AF, UF and/or IFOF.

The remaining tracts that were additionally delineated in language-related studies, i. e., the ILF and the MdLF, have not been unequivocally allocated to a linguistic function. It seems that they may be of minor importance during auditory language processing, are involved via short-range connections, have been investigated less, or have been wrongly delineated as separate tracts and actually merge functionally into other tracts.

ILF and MdLF seem less important for auditory language processing.

In sum, phonological processing and articulation are supported by dorsal fiber tracts only. Phonological processing recruits a temporoparietal connection (SLF-tp) and articulation recruits a parieto-frontal connection (SLF III). Speech repetition is also exclusively supported dorsally by recruitment of the fiber tracts for phonological processing and articulation, in addition to a connection to the dorsal premotor cortex (SLF II). Semantic processing, at least of single words, is supported by a ventral tract (IFOF) only. Syntactic processing needs both the

Summary.

dorsal (AF) and the ventral (IFOF or UF) fiber tracts, depending on the complexity of the syntactic structures. These conclusions need further empirical support.

2.4 Conclusion and Outlook

Neurocognitive model.

The present review provides a new neurocognitive model which is illustrated in Figure 2.3. It appears that mainly three different dorsal (direct, inferior indirect, superior indirect), and two different ventral (UF, IFOF) long-range fiber tracts are involved in auditory language processing.

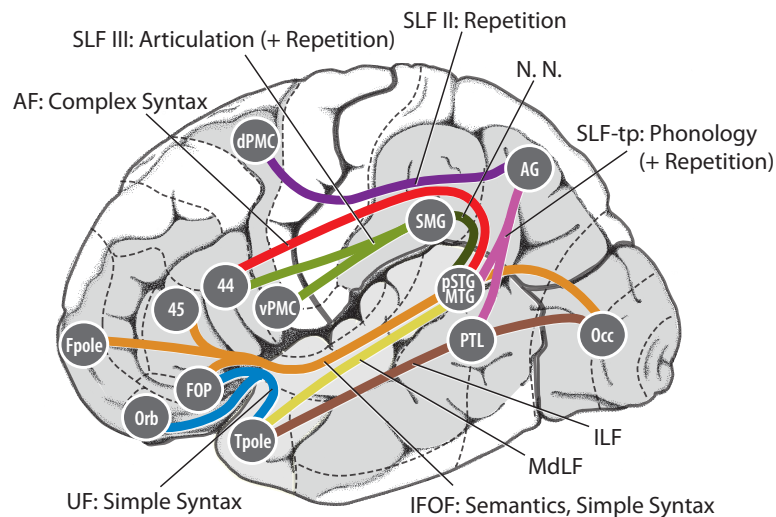


Figure 2.3: Neurocognitive model which illustrates the most probable course of the left-hemispheric fiber tracts involved in language processing along with their names and most probable functional roles—as revealed by the present review. Numbers indicate Brodmann areas. Fpole = frontal pole; Occ = occipital cortex; Orb = orbitofrontal cortex; PTL = posterior temporal lobe; Tpole = temporal pole. For other abbreviations see page xv.

Anatomy and function of dorsal tracts.

Dorsally, the AF directly connects BA 44 with the posterior STG and seems to be involved in processing complex syntax. An additional (inferior) indirect dorsal tract consists of connections from the posterior inferior frontal cortex to the SMG (via the SLF III) and from the SMG to the posterior temporal cortex (unnamed connection). The SLF III is reported to be involved in articulation and repetition. A superior indirect tract consists of connections from the dorsolateral frontal cortex to the angular gyrus (via the SLF II), and from the angular gyrus to the posterior temporal lobe (via the SLF-tp). The SLF-tp is reported

to be involved in phonological processing. In addition to the SLF III, repetition is also supported by this superior indirect tract, which is also discussed as being a direct tract without the involvement of parietal cortical areas.

Ventrally, the UF connects the inferior frontal and the prefrontal cortex, through the bottleneck of the extreme capsule, with the anterior temporal lobe, and is discussed as being involved in the processing of local syntactic structures, e. g., in simple sentences. The IFOF connects the inferior frontal cortex, through the bottleneck of the extreme capsule, with the posterior temporal and the occipital cortex, and seems to be involved in lexico-semantic processing, i. e., processing of single word meanings. A functional role in the processing of simple syntax is also discussed, although the ventral tracts may be dispensable in syntactic processing. The IFOF appears to be similar to the fibers that have been previously denoted to be part of the extreme capsule fiber tract by some authors.

Anatomy and function of main ventral tracts.

Additionally, there are two ventral fiber tracts that are not connected to the frontal lobe which are less frequently reported as being involved in auditory language processing. The ILF connects the temporal pole with the posterior and occipital cortex. The MdLF connects the temporal pole with the posterior superior temporal cortex. Their functions in auditory language processing may be dispensable.

Anatomy and function of additional ventral tracts.

More studies are clearly needed to support the mapping of function and anatomy for language processing. For some linguistic processes, only a handful of studies have been conducted to date. Moreover, different aspects of the processes have to be delineated and studied specifically. For example, phonological processing for production should be distinguished from reception and non-language sound processing. Also, linguistic subprocesses, for example syllable discrimination and phonetic processing, word category, verb argument structure, and morpho-syntactic processing, should be investigated in detail.

Limitations and required extensions.

The neurocognitive model of fiber tracts underlying auditory language processing that is derived here needs further support by empirical studies. For instance, the integration of functional and effective connectivity findings can provide information about which connections are actually used, which specific functions the connections fulfill, and in which direction the information is propagated. For example, a recent study using Directed Partial Correlation Analysis and Dynamic Causal Modeling, showed that the connection between the IFG and the posterior superior temporal cortex is modulated by complex syntactic structures (Den Ouden et al., 2012). This finding supports the AF as being involved in processing complex syntactic structures. Moreover, the integration of short-range fiber tracts and tracts that cross the hemispheres, as well as the integration of right-hemispheric fiber tracts and linguistic functions, would strengthen the model. For example,

Future perspectives.

the encoding of prosody is a typical right-hemispheric function which should not be neglected when deliberating on language processing. Also, temporal information from neurophysiological data should be included in the model to allow for conclusions about the directionality of the information flow. This was, for example, the attempt of a recent language comprehension model by Friederici (2012b).

Other cognitive
domains
should be included.

After all, it is well known that also other cognitions like memory and attention, play a role in comprehending and producing language. Thus, our understanding of language processing and the human brain will only be successful and comprehensive if we also incorporate the fiber tract knowledge from other cognitive domains.

Chapter 3

fMRI study: Key brain regions for sentence comprehension

Several different studies have focused their spotlight on the brain regions underlying discrete aspects of language comprehension, but were often limited in their ability to take a holistic perspective. The present within-subjects study investigated different kinds of syntactic and semantic processes simultaneously and compared the underlying brain regions directly. Healthy adults listened to meaningful and meaningless sentences with a complex or basic syntactic structure, and word lists in the magnetic resonance scanner. We found that the left frontal operculum activates during simple syntactic operations. Syntactically complex sentences, however, induced increased activation in the left posterior inferior frontal sulcus, probably as a correlate of enhanced syntactic working memory demands. The left anterior middle temporal gyrus manifested as the key region for word-level semantic processes, and the left posterior superior temporal sulcus was revealed to be the key region for encoding the overall sentence meaning, e. g., when integrating syntax and word semantics. Thus, our direct comparison within-subjects corroborates the theory that the key brain regions underlying different syntactic and semantic processes during language comprehension are locally separated in the human brain.

Preface

Overview
of the chapter.

The present chapter presents an fMRI study that aimed to identify the key brain regions involved in different linguistic processes during language comprehension. The identification of these brain regions will represent the starting point for the identification of connections between the regions (presented in [Chapter 5](#)). These connections are thought to support language comprehension through connecting the key regions of language comprehension.

3.1 Introduction

Syntactic processes
during sentence
comprehension.

Consider *what happens when you hear or read sentences*, e. g., the present one. In order to understand the sentence, a number of different processes take place in the brain ([Friederici & Kotz, 2003](#); [Friederici, 2012b](#); [Friederici & Weissenborn, 2007](#)). These processes can be described using a schematic diagram ([Figure 3.1](#)). As a first and basic step for processing syntax ([Figure 3.1 A](#)), the brain encodes the word categories, e. g., verb and noun, and then builds local phrases on the basis of the word category information, like the verb phrase “*read sentences*” in the above example. Second, the brain encodes morphological information, e. g., plural markers, like the “*s*” of “*sentences*” in the above example, or the verb’s inflection. Furthermore, the argument structure of the verb is built, and it is checked in terms of whether the arguments fulfill the verb’s so-called selectional restrictions. For instance, in the example above, “*read*” can take one argument, which has to be a direct object and which has to be something that can be read; namely “*sentences*”. All these syntactic processes—at the phrase-level and sentence-level—are assumed to be “simple syntactic” computations, necessarily taking place whenever a sentence is processed ([Figure 3.1 A2](#)). If the brain has to process a sentence with an unusual, i. e., non-canonical, word order, like an object-first sentence in which the object is placed before the subject, additional cognitive processes take place (for an overview, see [Grodzinsky & Santi, 2008](#)). We refer to these additional syntactic computations, which are necessary for understanding complex syntactic structures, as “complex syntactic” computations ([Figure 3.1 A1](#)). In the case of object-first sentences, the necessary complex syntactic computation is reordering of phrasal arguments in the syntactic hierarchy.

Semantic processes
during sentence
comprehension.

For processing semantics ([Figure 3.1 B](#)), first the meanings of the single words in a sentence have to be accessed, retrieved, and encoded; a process summarized as “word-level semantics” or “lexical-semantic processing” ([Figure 3.1 B3](#)). Second, semantic relations between the words in a sentence are established, and the words’ thematic roles are assigned in close collaboration with the above described syntactic processes. For the final understanding of a sentence, the hitherto acquired semantic and syntactic knowledge is integrated to an overall sentence meaning

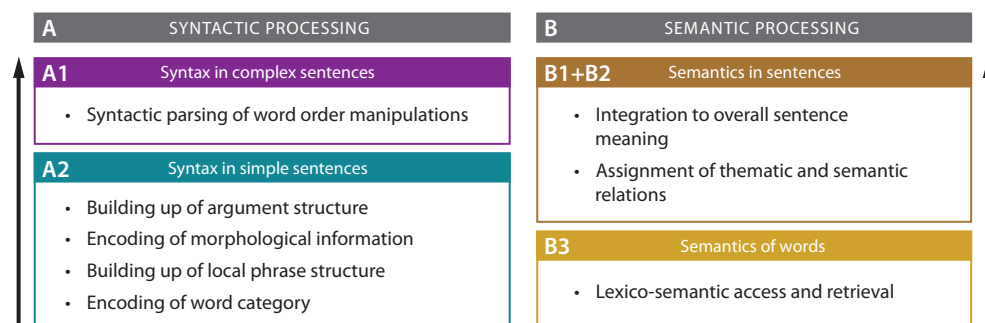


Figure 3.1: Schematic of syntactic (A) and semantic (B) processing stages which are assumed to underlie auditory sentence comprehension (visualization of the sentence comprehension model by Friederici & Weissenborn (2007); see also Friederici & Kotz (2003), Friederici (2012b)). During the processes B1 and B2, syntax and semantics interact. The arrows represent the postulated order of processing within the syntactic and semantic domain, but not across them. Syntactic and semantic processes run roughly in parallel, however, there is a debate (that is not subject to the present study) as to which subprocesses are prior to others. Thus, the schematic does not represent temporal correspondence of syntactic and semantic processes.

(Figure 3.1 B1+B2), which we call “sentence-level semantics” for simplicity, but which also encompass interaction with syntax.

The aim of the present fMRI study was to investigate which brain areas underlie the syntactic, as well as the word-level and sentence-level semantic processes that go on during understanding of simple and complex sentences. We chose the novel approach of exploring the key neural regions of all these processes within the same subjects which permits a valid comparison of the results.¹

Study aim.

Previous studies investigating both syntax and semantics in sentence comprehension, using various experimental manipulations, showed that a range of temporal and frontal regions are involved. For example, detection of syntactic violations activated the frontal operculum and the STG (Brauer & Friederici, 2007), especially the anterior STG (Friederici & Kotz, 2003; Rüschmeyer et al., 2005). These areas were also activated when the processing of correct syntactic structures was investigated by contrasting correct sentences with syntax-free lists of words (Friederici et al., 2000; Vandenberghe et al., 2002). In particular, the authors of the aforementioned studies explored the neural correlates of word category encoding (rather than those of phrase structure building) as they used word lists that allowed for the construction of minimal phrases between two words. Specifically exploring the neural correlates of phrase structure building, the anterior temporal lobe was nevertheless activated, when contrasting sentences with word lists that were constructed to not contain grammatical phrases (Stowe et al., 1999).

Known correlates of simple syntactic processes.

¹The resulting key regions served in a subsequent study as starting points to investigate the fiber tracts supporting sentence comprehension (as will be reported in Chapter 5).

Correlates of complex syntactic processes.

Only a few studies have investigated semantic processes together with complex syntactic processes, e. g., by using conjoined active sentences versus object relative sentences (Newman et al., 2003; Newman et al., 2010), or by manipulating the word order (Bornkessel et al., 2005). These studies demonstrated BA 44, in particular, to be critically involved in processing syntactic complexity (Newman et al., 2003; Newman et al., 2010; Bornkessel et al., 2005).

Correlates of word-level semantic processes.

The neural correlates of lexico-semantic processes during sentence comprehension have been investigated by either inserting pseudowords (Friederici et al., 2000; Humphries et al., 2006), varying the congruency or semantic relatedness (Humphries et al., 2006; Newman et al., 2010; Dapretto & Bookheimer, 1999), varying the verb class (Bornkessel et al., 2005), or using repetition suppression (Devauchelle et al., 2009). These studies found the anterior IFG, i. e., BA 45 and BA 47, to be involved in processing the semantic aspects of a sentence (Dapretto & Bookheimer, 1999; Newman et al., 2003; Newman et al., 2010; Rüschemeyer et al., 2005). In the temporal cortex, the STG (mostly bilateral) and MTG have been shown to be involved in lexico-semantic processing (Devauchelle et al., 2009; Friederici et al., 2003), especially the more posterior parts (Brauer & Friederici, 2007; Vandenberghe et al., 2002), and also the anterior temporal pole (Vandenberghe et al., 2002).

Correlates of sentence-level semantic processes.

Only a few studies have investigated sentence-level semantic processes, generally by reporting regions that only activated for semantic manipulations only when a syntactic structure is available, or regions involved in both semantic and syntactic processing. Two areas were mainly demonstrated: the anterior temporal cortex and the posterior temporal cortex/angular gyrus. On the one hand, using both semantically congruent, incongruent or invalid (inserting pseudowords), sentences and word lists as stimuli, Humphries et al. (2006) showed parts of the left anterior middle temporal cortex to be involved in building a basic constituent structure by using syntactic information and probably semantic context information. Rogalsky and Hickok (2009) also demonstrated the anterior STS/MTG, to respond nearly equally to semantic and syntactic features. Additionally, an interaction of semantic and syntactic manipulations in the anterior temporal pole was shown by Vandenberghe et al. (2002). On the other hand, Humphries et al. (2006) revealed the left angular gyrus to be primarily engaged in combining semantic pieces and integrating them with syntactic information to form an overall sentence meaning. A region in the temporal cortex, i. e., the posterior STS, was interpreted as mapping semantic features to syntactic argument hierarchies, because it reacted to both syntactic and semantic manipulations (Bornkessel et al., 2005).

Methods of the present study.

With the present study, we were able to investigate the neural correlates of simple and complex syntactic, as well as word-level and sentence-level semantic processes, in the same subjects, thus allowing a direct comparison of the underlying brain areas. We did so by using a within-

		SEMANTICS	
		Meaningful (real words)	Meaningless (pseudowords)
SYNTAX	Complex syntax (Object-first sentences)	Dann ruft den _{ACC} Fahrer der _{NOM} Baron. Then summons the _{ACC} driver the _{NOM} baron.	Ponn schlott den _{ACC} Gurrloht der _{NOM} Schneize. Ponn schlott the _{ACC} gurrlloht the _{NOM} schneize.
	Simple syntax (Subject-first sentences)	Dann ruft der _{NOM} Baron den _{ACC} Fahrer. Then summons the _{NOM} baron the _{ACC} driver.	Ponn schlott der _{NOM} Schneize den _{ACC} Gurrloht. Ponn schlott the _{NOM} schneize the _{ACC} gurrlloht.
	Missing syntax (Word lists)	dann Sport hin Baron sehr Fahrer then sport toward baron very driver	ponn Kieh laff Schneize mill Gurrloht ponn kieh laff schneize mill gurrlloht

Figure 3.2: Examples of the stimuli used in the experiments (with literal English translations). The syntactic and semantic contrasts performed are indicated with arrows. Color-coding is according to Figure 3.1. ACC=accusative; NOM=nominative.

subjects fMRI design, with the factors syntax (3 levels: complex, simple, missing syntax) and semantics (2 levels: meaningful, meaningless). We thereby provide comparisons in one study that are more valid than comparisons made across different studies.

We varied the factor syntax in the present study by using object-first sentences as complex sentences with a non-canonical structure, subject-first sentences as simple sentences with a canonical syntactic structure, and lists of words as stimuli without any syntax (sample stimuli are given in Figure 3.2). Subjects listened to the stimuli and were requested to answer a probe every now and then. During stimulus presentation, they did not know if a probe would follow or not.

Studying syntax.

Contrasting simple sentences with syntax-free word lists, on the one hand, allowed us to study cognitive processes that underlie the processing of simple syntax. These cognitive processes are assumed to be equivalent to the simple syntactic processes we introduced above (Figure 3.1 A2). Moreover, we assumed these simple syntactic processes to underlie the comprehension of every kind of sentence, i. e., to be independent of the canonicity of a structure. Thus, they should be identifiable for both canonical and non-canonical syntactic structures. We tested this hypothesis by performing a conjunction analysis that analyzed the overlap between simple sentences contrasted against word lists, and complex sentences contrasted against word lists.

Studying simple syntax.

In the literature, two brain regions are mainly discussed as neural correlates of phrase structure building (see Friederici, 2009b; Friederici & Kotz, 2003): the inferior frontal cortex and the anterior temporal lobe. Within the inferior frontal cortex, the deep frontal operculum has been especially shown to be involved in phrase structure building processes

Simple syntax should activate frontal operculum and ant. STG/STS.

(Friederici et al., 2000; Friederici et al., 2003; Stowe et al., 1999; Friederici et al., 2006a)—a region that covers the cortex between the anterior insula and the crown of the IFG and was shown to be different in its receptorarchitecture (Amunts et al., 2010) and connectivity profile (Anwander et al., 2007) from the adjacent BA 44 and 45 of Broca’s region. Notably, the function of the frontal operculum is not entirely clear, as activation in this area is often not separable from the adjacent anterior insula: Because of their close spatial relationship, frontal operculum and anterior insula are hard to differentiate (Rogalsky & Hickok, 2011), and thus they are often mapped undifferentiated or reported as a conjoined activation (e.g., Stowe et al., 1999). As a result, there are a number of alternative interpretations of the function of the frontal operculum/anterior insula, for example, monitoring during repetition (Saur et al., 2008), and general evaluation of linguistic structures (Grewe et al., 2005). Within the anterior temporal lobe, the anterior STG and STS especially were shown to be activated in studies comparing sentences with word lists (Friederici et al., 2000; Vandenberghe et al., 2002; Stowe et al., 1999), or investigating detection of syntactic violations (Friederici et al., 2003), thereby pointing to the anterior STG/STS as having a function in sentence comprehension. Supporting this assumption, the region was suggested to support basic morpho-syntactic aspects of sentence comprehension (Dronkers et al., 2004). Moreover, a recent meta-analysis detected the anterior STS to be involved in phrase structure building: It reacts specifically to phrases, as opposed to the middle STG which specifically reacts to phonemes, and the anterior STG which specifically reacts to words (DeWitt & Rauschecker, 2012). Taken together, we hypothesized that activations of the left frontal operculum and anterior STG/STS would be correlates of simple syntactic processes.

Studying
complex syntax.

Contrasting complex with simple syntactic sentences, on the other hand, allowed us to study complex syntactic computations (Figure 3.1 A1). In line with previous research, we assumed that, when hearing syntactically complex sentences, the brain has to carry out more demanding syntactic processes than when hearing syntactically simple sentences or hearing word lists, i.e., reordering of phrasal arguments in the hierarchy.

Complex syntax
should activate
Broca’s area and
post. temporal
cortex.

Complex syntactic processes during sentence comprehension were previously demonstrated to require left Broca’s region, encompassing both BA 44 and 45. This was shown in neuroimaging studies manipulating word order (Röder et al., 2002; Bornkessel et al., 2005; Bornkessel-Schlesewsky et al., 2009; Grewe et al., 2005; Kinno et al., 2008), using embedding (Friederici et al., 2009; Makuuchi et al., 2009), or using syntactic movement (Stromswold et al., 1996; Cooke et al., 2002; Ben-Shachar et al., 2003; Ben-Shachar et al., 2004; Caplan et al., 2008; Lee & Newman, 2010; Newman et al., 2010; Santi & Grodzinsky, 2010; Meltzer et al., 2009)². Most of these studies also showed activation in either the

²See Rogalsky et al. (2011) for a different interpretation of the BA 44 activation in syntactic complexity paradigms.

posterior STG/STS or the MTG. We thus hypothesized that complex syntactic stimuli would activate left Broca's area and the posterior temporal cortex.

In the present study, we varied the factor semantics by replacing all content words with pseudowords which were derived from the original content words. The resulting stimuli had the same phonological and phonotactic properties, as well as the same syntactic structures as the original "meaningful" stimuli but were "meaningless" in that they bear no content.

Studying semantics.

Contrasting meaningful with meaningless word lists allowed us to investigate word-level semantic processes, i.e., the processing of word meanings (Figure 3.1 B3). Imaging studies have shown that word meanings are encoded in the entire MTG, the anterior temporal lobe, midline structures and the pars orbitalis (BA 47) of the IFG (Binder et al., 2009; Humphries et al., 2007; Price, 2010; Specht et al., 2008; Patterson et al., 2007; Noppeney et al., 2007).

Word-level semantics should activate temporal cortex and IFG.

Contrasting meaningful with meaningless sentences allowed us to investigate the cognitive processes that are specific to the processing of meaning in a sentential environment (Figure 3.1 B1+B2). The neural correlates of these cognitive processes lack empirical evidence because they cannot easily be differentiated from word-level semantic processes. Nevertheless, the posterior temporal and adjacent inferior parietal areas have been proposed to at least play some role in encoding the overall sentence meaning (Lau et al., 2008; Binder et al., 2009; Humphries et al., 2007). One possible role could be the integration of word-level semantic and syntactic information into an overall sentence meaning (Friederici, 2004; Grodzinsky & Friederici, 2006; Lau et al., 2008). This hypothesis is based on the fact that there is activation of posterior STS only when syntactic structures are processed in a natural meaningful environment, in contrast to an artificial environment (Opitz & Friederici, 2004; Friederici et al., 2006a; Bahlmann et al., 2008; Friederici et al., 2009). Moreover, this hypothesis is based on the finding that the posterior STG/STS is activated when semantically violated structures cannot be integrated into the prior structure (Friederici et al., 2003; Schlesewsky & Bornkessel, 2004), and when complex syntactic structures in natural language (which carries semantic information) are processed (Friederici et al., 2009; Bornkessel et al., 2005), but not when such structures are processed in artificial grammar, which is free of semantic information (Friederici et al., 2006a). However, Pallier et al. (2011) proposed the anterior STS, in addition to temporo-parietal junction, as the cortical regions that bind syntactic roles to lexico-semantic representations, which themselves are provided by posterior STS and IFG. Taking these findings together, we assumed that the middle temporal lobe and BA 47 are activated during word-level semantic processes and the posterior STS is activated during sentence-level operations, possibly as a correlate of syntactic-semantic integration.

Sentence-level operations should activate posterior STS.

Summary.

In summary, the goal of the present study was to investigate and directly compare the key brain areas of the left hemisphere that are involved in simple syntactic processing of natural sentences, as compared to complex syntactic processing, word-level, and sentence-level semantic processing, within the same subjects. We did so by manipulating syntax (complex, simple, missing) and semantics (meaningful, meaningless) in an fMRI design. We hypothesized that simple syntactic processes would activate left frontal operculum and the anterior STG/STS, complex syntactic stimuli would activate left Broca's area and the posterior temporal cortex, word-level semantic processes would activate the middle temporal lobe and BA 47, and sentence-level processes would activate the posterior STS, possibly as a correlate of syntactic-semantic integration.

3.2 Methods

3.2.1 Participants

20 healthy subjects participated.

20 healthy, right-handed subjects (12 male), aged 22.9–33.9 years (mean age = 27.1 years, standard deviation (SD) = 3.34 years) participated in the study. Participants were native German speakers, were free from neurological or psychiatric disorders and had no auditory, motor or memory deficits. Their reading span was above 2.5 words (mean: 3.5 words, range: 2.5–4.5 words; measured by a German version of the Daneman and Carpenter reading span test; [Daneman & Carpenter, 1980](#)) Subjects' forward digit span was above 6.0 digits (average: 7.1 digits), and their backward digit span was above 4.0 digits (average: 5.6 digits). Before participating in the study, subjects were informed about the procedure and potential risks and gave their written consent. The study was approved by the Research Ethics Committees of the University of Leipzig.

3.2.2 Experimental design and materials

3 x 2 design.

German complex and simple syntactic sentences, and syntax-free word lists made up of real words or pseudowords served as stimuli. These experiment had a 3 x 2 design with syntax (complex/simple/missing) and semantics (meaningful/meaningless) as factors, leading to six different kinds of stimuli: sentences with object-first position (complex syntax), sentences with subject-first position (simple syntax), as well as syntax-free word lists (missing syntax), all both with and without lexical meanings (see [Figure 3.2](#)).

Check of syntactic complexity.

We checked the syntactic complexity of the stimulus material in a behavioral pretest. Subjects rated our sentences significantly more

acceptable if the subject preceded the object, consistent with the linear precedence rules (Uszkoreit, 1986). This confirms the notion that our subject-first sentences are more canonical than our object-first sentences (see e.g., Bornkessel et al., 2005; Fiebach et al., 2005; Friederici et al., 2006a; Röder et al., 2002; Wilson et al., 2010).

For constructing stimuli without meaning, we used pseudowords with the same phonological properties as real words but with no lexical meaning. For constructing pseudowords, the syllables of the real word stimuli were randomly mixed, thereby preserving the original stress pattern while creating unknown and meaningless syllable combinations that sounded like real words. Phonotactic legality was assured by controlling the new syllable transitions with the CELEX lexical database (Baayen et al., 1993). Semantic associations were avoided by checking that changing one phoneme of the pseudoword did not result in a real word. Moreover, a semantic association pretest eliminated the most associable pseudowords.

Construction of pseudowords.

Each real word sentence consisted of two bisyllabic animated masculine nouns, stressed either on the first or second syllable, with a mean written word frequency between 12.0 and 12.1 (within a range of 8–16; <http://wortschatz.uni-leipzig.de/>), and one inflected monosyllabic transitive verb with a mean frequency of 11.4 (within a range of 8–16). Within one stimulus, words were arranged such that there was no dominant noun, i.e., both nouns could theoretically be the subject and object of the verb. The sentence structure was constant across conditions: adverb (“dann”: *then*) - inflected verb - determiner (“der”/“den”: *the*) - noun - determiner (“den”/“der”: *the*) - noun. Jabberwocky sentences had the same structure: pseudo-adverb (“ponn”) - inflected pseudo-verb - determiner (“der”/“den”: *the*) - pseudo-noun - determiner (“den”/“der”: *the*) - pseudo-noun.

Structure of sentences.

Word lists consisted of the same nouns used in the sentences. To exclude syntactic processes when hearing word lists, all function words, as well as all verbs, were eliminated. Because verbs are always inflected in German and German is a language with free word order, the inclusion of verbs at any position of the list could have lead to unintended syntactic and sentence-level semantic processes. Instead, articles were replaced by adverbs (“hin”: *toward*; “sehr”: *very*), and verbs were replaced by monosyllabic nouns. These nouns had the similar mean written frequency (11.1) within the same range as the verbs of the sentence stimuli. Moreover, the adverbs were chosen so that they could not serve as prefixes for the words that followed. These nouns were inanimate and masculine. Nouns that were aurally the same as adjectives (e.g., “Arm”: *arm/poor*), inflected verbs (e.g., “Bau”: *building/build*) or any other linguistic structure, as well as nouns that could form such a word by exchanging the nucleus, were excluded during stimulus creation. Thus, the word lists were of the form: adverb (“dann”: *then*) - monosyllabic noun - adverb (“hin”: *toward*) - noun - adverb (“sehr”: *very*) - noun. Pseudoword lists had the same structure:

Structure of word lists.

pseudo-adverb (“ponn”) - monosyllabic pseudo-noun - pseudo-adverb (“laff”) - pseudo-noun - pseudo-adverb (“mill”) - pseudo-noun. Word lists had the same length (8 syllables), prosody, sequence of mono- and bisyllabic words (1 - 1 - 1 - 2 - 1 - 2 syllables), and amount of variable words between stimuli within one condition (3 words) as the sentence stimuli.

Further characteristics.

In a pretest, all stimuli were rated for their ability to be pronounced and repeated, for use in the repetition experiment (Chapter 4). 30 stimuli were chosen out of 45 per condition. Thereby, word frequency and comparability of the conditions were controlled. Stimuli were spoken with natural emphasis and prosody by a young female voice, recorded with AlgoRec TerraTec Edition and edited with Gold Wave (version 5.63). The task request was spoken by a young male.

3.2.3 Procedure

Experimental set-up.

Subjects took part in two fMRI sessions, one week apart. In each session, they did both a comprehension and a repetition experiment (see Chapter 4), one after the other. The starting experiment was counterbalanced across participants and sessions. Moreover, diffusion tensor imaging data was collected after the experiments or in a separate session (see Chapter 5). Before scanning, participants were trained on four training stimuli per condition, per experiment.

Task.

In the comprehension experiment, subjects listened carefully, eyes closed, to the stimuli. After 20 trials per run (i. e., 17 % of all trials) subjects answered a probe by pressing one of two buttons, which were counterbalanced across subjects. Probes were announced by a male voice. Probes were either questions (“Ruft der Baron den Fahrer?”: *Summons the baron the driver?*) or comparisons (“dann Sport hin Prüfer sehr Fahrer”: *then sport toward examiner very driver*; see Figure 3.2 for the main stimuli). Because we held the word order of the probe constant and did not switch to verb-final word order through application of the perfect tense, the task was the same for sentences and word lists, i. e., comparison of stimulus and probe. The only difference between the conditions was the intrinsic difference between sentences and word lists: for sentence conditions, syntactic analysis had to be additionally carried out to understand who does what to whom. In both the sentences and the word lists, half of the probes matched the preceding stimulus, the other half were structurally or lexically manipulated. In half of the structurally manipulated probes, the articles or adverbs were interchanged, in the other half, the nouns were interchanged. In one third of the lexically manipulated probes, the verb or monosyllabic noun was exchanged, in another third, the first bisyllabic noun was exchanged, in the last third, the second bisyllabic noun was exchanged. The newly inserted words were derived from other lexically manipulated probes. The same task was applied to real word and pseudoword conditions. If a probe had to be answered,

was announced by a male voice after the stimulus (duration: 1100 ms), thus, subjects did not know during stimulus presentation if a probe would follow the stimulus or not. The same task was applied to the pseudoword conditions.

180 stimuli were binaurally presented, which equals 30 stimuli per condition. Stimuli had a mean duration of 2.69 s (range: 2300–3120 ms). Each trial was jittered, with a mean jitter duration of 1 s (range: 510–1520 ms), and consisted of the stimulus followed by a period of silence of 5 s. A trial lasted on average 9 s. Trials were presented in mini blocks that contained only one condition each and had a length of five items. There was a rest period of 6 s after each mini block. The comprehension experiment had a mean length of 23.5 min per session.

Trial design
and timing.

3.2.4 Data acquisition

The study was performed on a whole-body 3 Tesla Trio scanner (Siemens Healthcare, Erlangen, Germany). Each participant's head was fixed in the coil with stabilization cushions to reduce head motion. For sound presentation, a specific digital audio presentation system (MR confon, Magdeburg, Germany; www.mr-confon.de) was used.

3 Tesla MR scanner
was used.

Structural data was acquired using a T1-weighted 3D MP-RAGE sequence with selective water excitation and linear phase encoding (inversion time = 650 ms; repetition time = 1300 ms; repetition time of the gradient-echo kernel (snapshot FLASH) = 10 ms; echo time = 3.93 ms; flip angle = 10°; bandwidth = 130 Hz/pixel (i.e., 67 kHz total); image matrix = 256 × 240 pixel²; field of view = 256 × 240 mm²; slab thickness = 192 mm; 128 partitions; 95 % slice resolution; sagittal orientation; spatial resolution = 1 × 1 × 1.5 mm³; two acquisitions). To avoid aliasing, oversampling was performed in the read direction (head-foot). Magnetization preparation consisted of a non-selective inversion pulse.

Structural data
acquisition.

Functional data was acquired from 30 axial slices (thickness = 4 mm; no gap) by using a gradient-echo planar imaging (EPI) with an echo time of 30 ms, flip angle of 90°, repetition time of 2 s, and an acquisition bandwidth of 100 kHz. The matrix acquired was 64 × 64 pixel² with a field of view of 192 × 192 mm². The resulting voxel size was 3 × 3 × 4 mm³. The functional run of the comprehension experiment had on average 734 volumes.

Functional data
acquisition.

3.2.5 Behavioral data analysis

Behavioral data was analyzed using IBM SPSS Statistics (version 19). Button presses were recorded using Presentation software (Neurobehavioral Systems, Inc.; <http://www.neurobs.com/>).

3.2.6 Functional imaging data analysis

Preprocessing steps. Using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/>), functional images were adjusted to slice-acquisition timing, and realignment for motion-correction was performed. Following this, the images were co-registered, segmented into gray and white matter, and normalized on the MNI template (Montreal Neurological Institute). After normalization, the data was resliced retaining the original voxel size. Finally, spatial smoothing using a Gaussian filter with 12 mm full width at half maximum was carried out. In the general linear model, each trial was modeled separately, with the onset of the stimulus being the onset of the event. The probes were modeled as an additional regressor. The events were convolved with the canonical hemodynamic response function included in SPM8.

Group analyses and thresholds applied. After estimation of the first-level model, single-subject contrast images for each condition against zero were entered into group-level random effects analyses, and statistical parametric maps visualized significantly active brain voxels in the second-level contrasts. We performed flexible-factorial analyses of variance (ANOVAs) for the main and differential effects. The semantic main effect (real words > pseudowords), and the parametric contrast of syntax (complex > simple > missing syntax) were thresholded at $p < .05$, FWE-corrected, the differential effects and the conjunction analysis were thresholded at $p < .001$ (uncorrected). To protect against false-positive results, we used a cluster extent of 16 original voxels which is equivalent to 22 resampled voxels, both of which define a volume of 594 mm^3 to correct for multiple comparisons at $p < .05$ assuming an individual voxel type I error of $p = .001$ (Slotnick et al., 2003).

3.3 Results

3.3.1 Behavioral results

Above chance level results in all conditions. Subjects responded significantly above a 50 % chance level in all conditions (69–85 % correct responses; $p < .001$, two-tailed; binomial test). Only 3.16 % of the probe questions were not answered at all.

Word lists were answered more correctly and quicker than sentences. The behavioral data was analyzed using a 3×2 factorial, repeated-measures ANOVA with syntax (complex, simple, missing) and semantics (meaningful, meaningless) as within-subjects factors. The ANOVA revealed a main effect of syntax ($F_{2,38} = 4.956$, $p = .012$) with word lists being answered more correctly than sentences. We observed no main effect of semantics ($F_{1,19} = .010$, $p = .922$), and no significant interaction ($F_{2,38} = 1.369$, $p = .267$). Mean response times did differ significantly be-

tween the conditions in the factor syntax: Button presses for word lists were faster than for sentences ($F_{2,38} = 3.470$, $p = .041$). We observed no main effect of semantics ($F_{1,19} = 1.720$, $p = .205$), and no interaction between the two factors ($F_{2,38} = .020$, $p = .867$).

In addition, we analyzed the response behavior to different probe types: not manipulated probes (50 % of all probes), structurally manipulated probes (approx. 25 %) and lexically manipulated probes (approx. 25 %). We observed that the subjects had a harder time responding to meaningless conditions than to meaningful conditions: In meaningless conditions, structurally manipulated probes were answered below chance level (mean correct answers: 40.38 %; $p > .05$, two-tailed; binomial test). This was not the case for meaningful conditions (mean correct answers: 66.07 %; $p < .05$, two-tailed; binomial test). However, it should be noted that the data basis of these calculations is sparse: Each subject only answered a total of 29 probes. Nonetheless, to be on the safe side, we will report the fMRI contrasts of syntactic processing for meaningful stimulus material only. Lexically manipulated probes and probes that were not manipulated were answered correctly significantly above chance level in all conditions (mean correct answers across meaningless conditions: 85.57 %, across meaningful conditions: 93.85 %; $p < .005$, two-tailed; binomial test).

Meaningless
structurally
manipulated probes
were answered
below chance level.

3.3.2 fMRI results

In the baseline contrasts (one-sample t-tests; [Figure 3.3](#)), all conditions evoked an activation in auditory areas, i. e., bilateral Heschl's gyri, the entire STG, and the anterior STS.

Auditory cortex
activation.

In order to examine syntactic processing, a nonlinear parametric T-contrast that accounts for the different amount of syntactic complexity in the conditions was calculated (complex syntax [2] > simple syntax [1] > missing syntax [-3]; [Figure 3.4 A](#); [Table B.3](#)). We observed left-hemispheric activations in the posterior inferior frontal sulcus (IFS), in a cluster encompassing the frontal operculum and parts of BA 45, activation in the posterior STS, as well as bilateral activations in a border region of the precuneus/inferior parietal sulcus.

Syntax:
pIFS, FOP, pSTS.

We calculated the main effect of semantic processing by contrasting meaningful stimuli against meaningless stimuli, collapsed across syntactic conditions ([Figure 3.4 B](#); [Table B.3](#)). Five left-hemispheric clusters showed a main effect of semantic processing, three in the frontal lobe: pars orbitalis (BA 47), a medial part of pars opercularis (BA 48; 13.9 % of activation cluster in BA 44, 1.1 % in BA 45; following Eickhoff et al. (2007)), and the posterior inferior frontal sulcus, and two in the temporal lobe: the anterior MTG/STS, and the posterior MTG/STS.

Semantics:
BA 47, BA 48, pIFS,
aMTG/STS,
pMTG/STS.

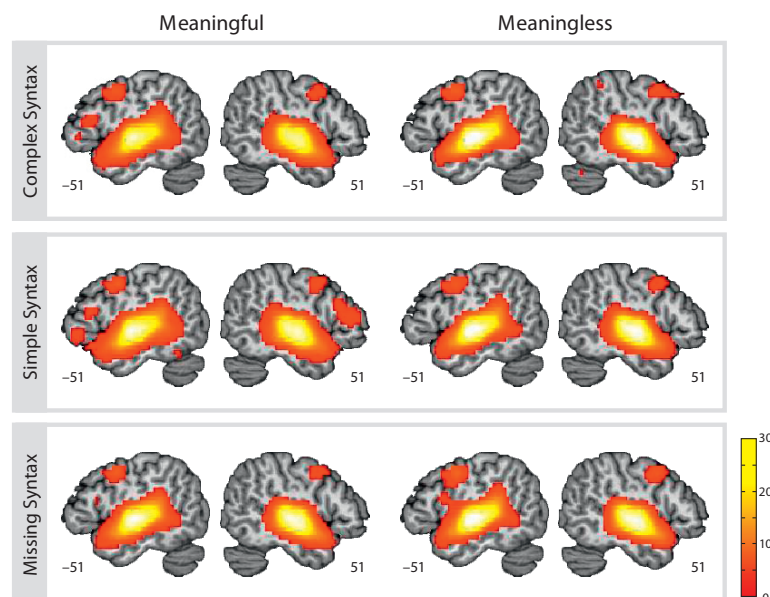


Figure 3.3: Baseline contrasts. Activation maps are laid over a rendered standard brain. Numbers indicate the layers (in MNI coordinates). Scale visualizes significance of activations in z-scores.

Sub-contrasts.

We performed several sub-contrasts to test our specific hypotheses about the areas involved in processing complex and simple syntax, and word-level and sentence-level semantics (see [Figure 3.4](#)).

Simple syntax:
FOP, BA 45, IFS,
alns, pSTS.

To determine the brain areas involved in simple syntactic processes we subtracted activations in response to word lists from activations in response to simple natural sentences ([Figure 3.4 A2](#), [Table B.4](#)), and revealed activation of a right frontal cluster encompassing the right anterior insula, a left frontal cluster encompassing the frontal operculum, BA 45, anterior insula and IFS, activation of the left posterior STS, and the right posterior STG, as well as activation of medial and subcortical structures.

Basic syntax:
FOP, 45, pIFS.

We were specifically interested in those processes that underlie the processing of each sentence, independent of the canonicity of its syntactic structure. These were determined by looking for the overlap between activations in response to simple syntactic processing (word lists subtracted from simple natural sentences) and activations in response to complex syntactic processing (word lists subtracted from complex natural sentences). This conjunction analysis revealed left-hemispheric activations in a cluster encompassing the frontal operculum and BA 45, in the posterior IFS, and the inferior parietal sulcus, as well as activations

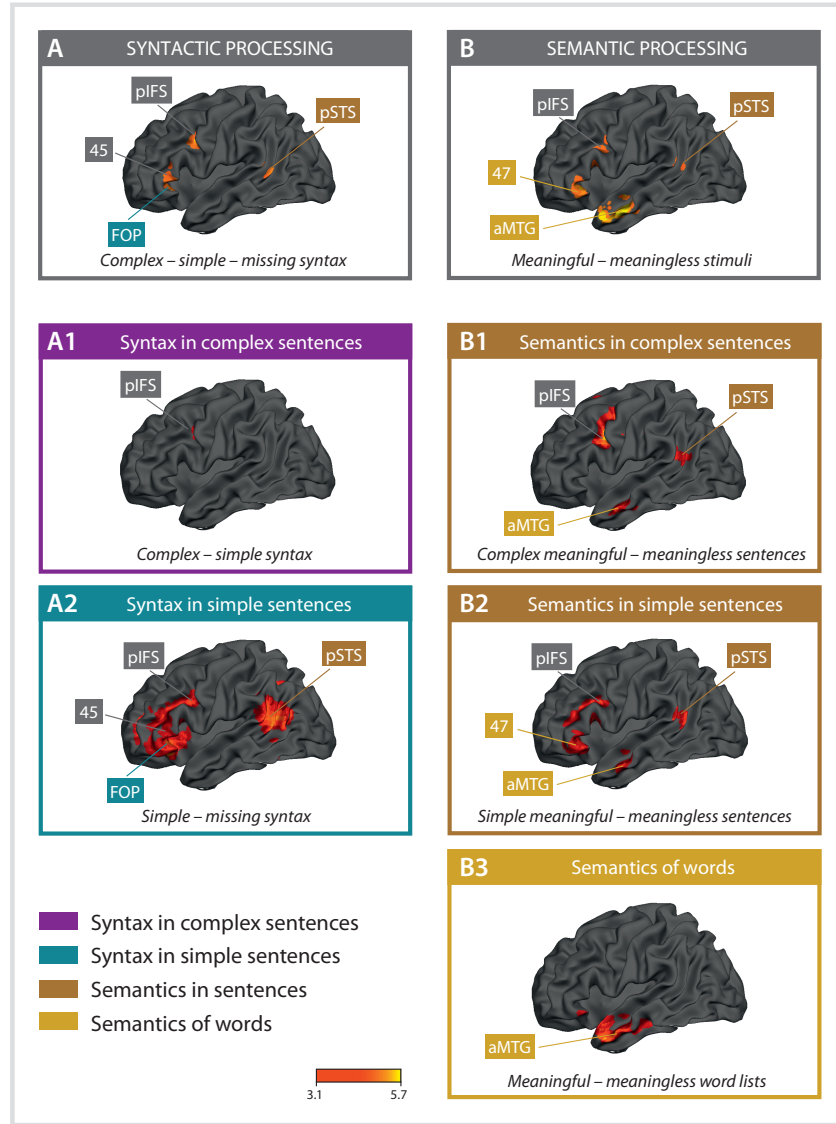


Figure 3.4: Specific contrasts of syntax and semantics: (A) Parametric effect of syntactic processing; (A1) complex syntactic processing; (A2) simple syntactic processing. (B) Semantic main effect; (B2) processing of meaningful versus meaningless simple sentences; (B3) processing of meaningful versus meaningless word lists. Note that the semantic contrasts of sentence material (B1+B2) also include syntactic operations, as visualized in Figure 3.1. Left-hemispheric activation maps are laid over a rendered standard brain. Key brain regions are named. They are color-coded according to our interpretations and comparable to Figure 3.4. The scale visualizes significance of activations in t -values. The main effects (A, B) are thresholded $p < .05$, FWE-corrected, the differential contrasts (A1–A2, B1–B3) are thresholded at $p < .001$, $k \geq 16$, uncorrected. For abbreviations see page xv.

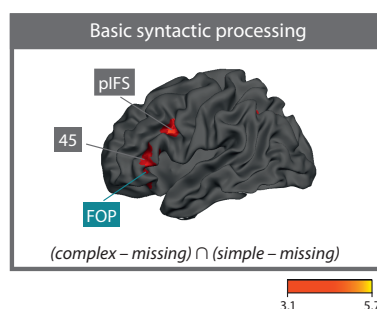


Figure 3.5: Conjunction of complex vs. missing, and simple vs. missing meaningful sentences, thresholded at $p < .001$, $k \geq 16$, uncorrected. Left-hemispheric activation maps are laid on a rendered standard brain. Key brain regions are named and color-coded according to our interpretations (see Figure 3.1). Scale visualizes significance of activations in t-values. For abbreviations see page xv.

in bilateral precuneus, the right posterior IFS, and the right anterior insula (Figure 3.5, Table B.4).

Complex syntax:
pIFS.

Brain areas involved in complex syntactic processes were determined by subtracting activations in response to simple natural sentences from activations in response to complex natural sentences (Figure 3.4 A1, Table B.4). We revealed activation in the left posterior IFS.

Sentence-level
semantics:
pSTS, aMTG, pIFS.

Brain areas involved in sentence-level semantic processes were determined by subtracting activations in response to pseudoword sentences from activations in response to real word sentences. In doing this, we revealed activation of the left posterior STS, the anterior MTG, bilateral posterior IFS, and medial structures for complex sentences (Figure 3.4 B1, Table B.5). We revealed activation of the same structures for simple sentences, but in addition, we found the left BA 47 and anterior and middle parts of the IFS activated (Figure 3.4 B2, Table B.5).

Word-level
semantics:
aMTG.

In contrast, brain areas involved in word-level semantic processes were determined by subtracting activations in response to pseudoword lists from activations in response to real word lists (Figure 3.4 B3, Table B.5). This subtraction revealed activation of the left anterior MTG.

3.4 Discussion

Goal and
summary of results.

The goal of the present fMRI study was to examine, within the same subjects, which neural regions of the dominant hemisphere are involved in simple syntactic processes, as compared to complex syntactic, as well as in word-level and sentence-level semantic processes. We

demonstrated that these different aspects of language processing are realized by different neural networks. First, the left frontal operculum was involved in syntactic processes during both complex and simple sentence comprehension; second, we revealed the left anterior MTG to be a key region for word-level semantic processing, and third, the left posterior STS emerged as a common computational region for semantics and syntax.

3.4.1 Key regions of syntactic processes

The neural network which is recruited for syntactic processes during comprehension of simple sentences comprises the left frontal operculum as its key region. Interestingly, the frontal operculum is active independent of the canonicity of the sentence structure (as revealed by the conjunction analysis), and is not activated during semantic contrasts. Thus, the left frontal operculum seems to be the key region for those syntactic processes that are required during the processing of both complex and simple syntactic material. This is in line with studies that showed increased activation of the left frontal operculum when processing sentences with pseudowords (Friederici et al., 2000), sentences with local phrase structure violations (Friederici et al., 2003; Brauer & Friederici, 2007), or local structure violations in artificial grammar sequences (Friederici et al., 2006a). The frontal operculum—together with its adjacent anterior insula—is, however, also discussed as having a role in word production (Bohland & Guenther, 2006; Price et al., 2003; Saur et al., 2008), or a more general role in the evaluation of linguistic structures (Grewe et al., 2005; Ferstl et al., 2008). The present study suggests the left frontal operculum plays a strong role in analyzing local phrase structures. The more general perspective of evaluating linguistic structures should, as a consequence, be confined: The role of the left frontal operculum in language processing seems to be to evaluate the local substructures of linguistic structures.

FOP is key region for processing local structure.

We also found activation in the posterior STS when comparing simple sentences to word lists. We interpret this posterior STS activation as being a common computational area for syntactic and semantic processing because it is also seen to be activated in the sentence-level semantic contrast (see discussion below). Activation of the posterior STS revealed in the simple syntactic contrast was not found in the conjunction analysis. Thus, the region seems to only contribute to syntactic operations once the entire sentence structure is well processed—which was obviously not the case for our complex syntactic material. When listening to complex sentences, it appears that subjects performed simple syntactic operations, mediated by the frontal operculum, and activated their syntactic working memory, mediated by the posterior IFS, but did not come to an understanding of the overall sentence structure, which is indicated by a lack of activations in the complex syntactic contrast and only fair behavioral performance in the complex sentence condition. The present data suggest that the posterior STS

pSTS mediates understanding of overall sentence structure.

mediates the understanding of the overall sentence structure (probably for encoding of the overall sentence meaning, see below), and thus does not appear in the conjunction analysis.

pIFS supports syntax through fulfilling a more general cognitive function.

The neural network normally recruited for complex syntactic processes, as compared to simple syntactic processes, was not detected in the present study. This is probably due to the fact that performance with complex syntactic structures was very poor, which led to low activation. When contrasting complex with simple syntactic material, we found only the left posterior IFS to be activated. This area was also activated in all other contrasts involving sentence material. We therefore assume that the posterior IFS is not a specific syntactic area, but supports a more general function that is, nevertheless, dedicated to syntax, e.g., syntactic working memory. Indeed, the posterior IFS was shown to be a more general area that is recruited when comprehensive material has to be processed for maintaining sentences in memory (Makuuchi et al., 2009; Henson, 2001), or for controlling decisions under conditions of enhanced uncertainty (Huettel et al., 2005). Thus, through fulfilling one of these functions, it is probable that the area contributes to complex syntactic processing as part of a larger network (Friederici et al., 2011).

3.4.2 Key regions of semantic processes

aMTG encodes word meaning.

For semantic processing, we observed networks that are different from the syntactic networks. Word-level semantic processes mainly required the anterior MTG. This region was previously discussed as encoding word meanings when real words were contrasted with pseudowords during lexical decision making (Davis & Gaskell, 2009), repetition (Peters et al., 2009), and production (Menenti et al., 2011), as well as when selective attention to semantic anomalies was contrasted with resting baseline in fMRI (Rogalsky & Hickok, 2009). Furthermore, the anterior MTG was confirmed as part of the semantic network in a recent sophisticated meta-analysis (Binder et al., 2009). In the present study, the anterior MTG activation in all semantic contrasts is thus interpreted as reflecting word-level semantic processes.

aMTG supports semantics, whereas aSTS/STG may support syntax.

The anterior temporal lobe was related to semantic processes as a result of lesion studies and studies with semantic dementia patients: Damage of anterior MTG and inferior temporal gyrus resulted in severe domain-general conceptual-semantic deficits, affecting both the understanding and production of verbal material (Noppeney et al., 2007; Patterson et al., 2007). However, the anterior temporal lobe, in particular the more superior regions in the STS or STG, has also been discussed as having a role in sentence-level combinatorial semantic processes (Humphries et al., 2006; Vandenberghe et al., 2002; Price, 2010) and syntactic processes (Stowe et al., 1998; Humphries et al., 2005), even in the absence of semantic information (Friederici et al., 2000; Humphries et al., 2006). This points towards a possible functional

differentiation of the anterior MTG/inferior temporal gyrus and the anterior STG/STS, with the more inferior regions being involved in encoding of word meanings, and the more superior regions being involved in sentence-level operations, including semantic and syntactic combinatorics. In the present study, anterior temporal correlates for word-level and sentence-level semantic processes were only found in the MTG. The anterior MTG activation could thus be a reflection of lexico-semantic processes during word list and sentence processing. Since we found no superior temporal activations for our sentence-level semantic contrasts, the anterior STS/STG may hold primarily responsible for combinations of syntactic elements.

As discussed in the [Introduction](#), this syntactic function of the anterior superior temporal lobe is in line with findings from studies contrasting sentences with word lists or addressing phrase structure building processes. In the syntactic contrasts of the present study, however, frontal operculum activation, rather than anterior temporal activation, was revealed as a correlate of simple syntactic processes. This raises the possibility that these two regions play different roles during simple syntactic processing. The anterior temporal lobe, on the one hand, may support a function that is subtracted away in the respective contrasts, i.e., a function needed for the processing of both our sentence and word list stimuli, such as a “(specialized) form of memory encoding, which is necessary for the maintenance of lexical order and identity or content” (Stowe et al., 1999, pp.794–795). The frontal operculum, on the other hand, seems to be responsible for the more linguistic functions during simple syntactic processing.

aSTS/STG and FOP may play different roles in simple syntactic processing.

During sentence comprehension (when contrasting meaningful with meaningless sentences), the left posterior STS was required for both simple and complex sentences (in addition to the anterior MTG and the posterior IFS, to which we ascribed a function in syntactic working memory, see discussion above). This region demonstrated no activation when syntax was missing. From this we conclude that the posterior STS supports operations that involve syntax. In particular, the region was activated whenever both syntax and semantics were present, i.e., during processing of sentence meaning (contrasting meaningful with meaningless sentences) and during processing of meaningful sentences (contrasting simple sentences with word lists). This suggests that the posterior STS supports operations that involve both syntax and semantics, e.g., the integration of these two kinds of linguistic information. Notably, this has been suggested to be the case during natural language processing, but not in an artificial grammar situation (Friederici et al., 2006b; Bahlmann et al., 2008; Opitz & Friederici, 2004), or when the sentence meaning or structure is violated (Friederici et al., 2003). Our finding is supported by a study showing posterior STS activation when verb-argument relations that rely on both syntax and meaning are to be processed (Bornkessel et al., 2005).

pSTS supports integration of syntax and semantics.

3.5 Summary and Conclusion

Key regions are separable: FOP for simple syntax, aMTG for word meanings, pSTS for integration.

In sum, the present study demonstrates, in a direct comparison within the same subjects, that the key brain regions for simple syntactic processes, and word-level and sentence-level semantic processes are separable. The present study corroborates the left frontal operculum as a correlate of local structure analysis, the left anterior MTG as an encoding area for word meanings, and the left posterior STS as a common computational area for syntax and semantic in natural languages, e. g., for the integration of syntax and semantics.

Chapter 4

fMRI study: Key brain regions for sentence repetition

Although sentence repetition is widely used as a diagnostic tool for assessing brain development and integrity, its underlying brain regions have been poorly investigated in the past. We therefore asked healthy human participants in the MR scanner to overtly repeat complex and simple syntactic sentences, as well as word lists, all containing either real words or semantic-free pseudowords. We compared our data with the neural correlates of sentence comprehension to examine whether comprehension and production of sentences share neural resources. Our results indicate that syntax- and semantic-free repetition relies on brain areas that are involved in sequencing, phonology and articulation. Processing complex syntax during repetition involves left Broca's area and the posterior superior temporal sulcus (STS), and processing simple syntax involves left anterior STS. Processing of word meanings relies on the left middle temporal gyrus. Moreover, a region in the posterior STS/AG emerged as a common computational region for syntax and semantics during repetition, probably indicating that it serves a function in syntactic-semantic integration. These regions have been similarly reported for syntactic and semantic processes during comprehension. Therefore, our study supports the view that the neural basis of syntactic and semantic processing steps is independent of the input and output modalities.

Preface

Overview
of the chapter.

The present chapter presents an fMRI study that was conducted to investigate the key brain regions underlying language repetition, and to compare these regions with the key brain regions for language comprehension. The results of the present study will represent—in addition to the results from our fMRI study on language comprehension ([Chapter 3](#))—another starting point for the identification of connections involved in auditory language processing (presented in [Chapter 5](#)).

4.1 Introduction

Conduction aphasia
is associated with
impaired repetition.

Many decades ago, neurologists noted that lesions to the white matter pathway connecting the “sensory language area”, i. e., Wernicke’s area, and the “motor language area”, i. e., Broca’s area, elicited a so-called *disconnection syndrome* ([Wernicke, 1874](#); [Geschwind, 1965](#)). This specific syndrome was referred to as conduction aphasia, and is characterized by deficits in integrating sensory and motor representations leading to severe repetition impairments along with fluent but phonemically erroneous speech output and relatively preserved language comprehension (e. g., [Wernicke, 1874](#); [Buchsbaum et al., 2011](#)).

Lack of empirical
evidence for the
neural correlates of
sentence repetition.

Because of the relatively preserved comprehension abilities of conduction aphasic patients, speech repetition joined language comprehension as a diagnostic tool to assess language development (e. g., [Gathercole et al., 1994](#)) and brain integrity (see e. g., the repetition subtests of the Aachen Aphasia Test or Western Aphasia Battery). However, despite the frequent use of repetition as a task, the neural correlates underlying repetition have been inadequately investigated up to now. Especially the neural correlates of semantic and syntactic processing during sentence repetition and their (dis)agreement with the correlates of sentence comprehension lack empirical evidence. Therefore, we designed a study with the aim of specifying which brain regions are involved in pure repetition, i. e., repetition that is free from syntax and semantics, and which brain regions are involved in semantic and syntactic processes during sentence repetition. We were specifically interested in how these brain regions relate to the brain regions which underlie semantic and syntactic processes during sentence comprehension.¹

Repetition as
a composite
cognitive behavior.

Repeating sentences aloud is an action that encompasses both speech perception and speech production. Thus, to successfully fulfill the task of repetition, both analysis of the input, as well as articulation of the output are required. In-between these two aspects, the brain completes several de- and encoding processes that may also comprise semantic and syntactic steps (see [Friederici & Levelt, 1988](#); [Indefrey & Levelt,](#)

¹The resulting key regions served in a subsequent study as starting points to investigate the fiber tracts supporting language processing (as will be reported in [Chapter 5](#)).

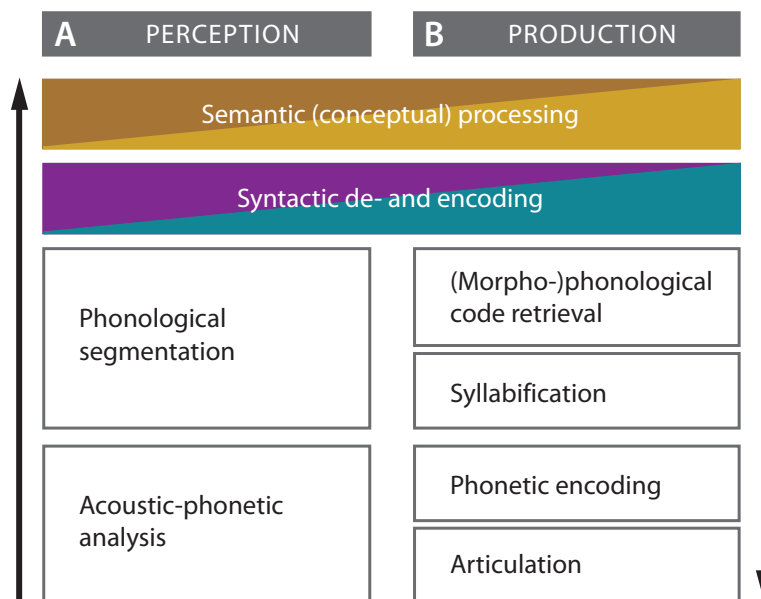


Figure 4.1: Processing stages during sentence repetition: A) perception stages, B) production stages. The perceptual syntactic and semantic stages are itemized in Figure 3.1 and color-coded accordingly. Based on Friederici & Levelt (1988), and Indefrey & Levelt (2004).

2004; Morton, 1980)². These cognitive processes underlying repetition have been discussed for a long time, producing en route, for example, the so-called *Logogen Model* (Morton, 1969; Morton, 1980)³. In this model, and still today, the following questions are of specific interest: How are words and the meanings of words represented in the brain, which processes take place during repetition to access these representations, and how is perception connected to production? Extending these questions to the repetition of sentences, we add: How are syntactic representations processed?

In the context of the present study, we tackle the neural correlates of these various cognitive processes underlying repetition, and specifically address the relation between perceptive and productive processes. We illustrate the processes in Figure 4.1, and describe them as follows: First, when a sentence is heard, the brain analyzes the input acoustically, i. e., it makes a phonetic spectro-temporal analysis. This analysis is followed by a phonological decoding process in which the input is phonologically segmented into phonological units. Following this, the sentence is syntactically and semantically processed, i. e., grammatical properties and lexical concepts are accessed and used. During the syntactic stage, basic syntactic processes are carried out, e. g., phrase

The various cognitive processes underlying repetition.

²Also, repetition via a non-lexical route that spares semantic and syntactic steps is possible (see below).

³See also, for an overview, Coltheart et al. (2001).

structure building processes. In the case of syntactically non-canonical input, additional syntactic processes have to take place, e. g., reordering of elements. During the semantic stage, both the individual word meanings, as well as the overall sentence meaning, are processed (for details about syntactic and semantic processing steps see [Friederici & Weissenborn, 2007](#), as well as [Section 3.1](#) and [Figure 3.1](#)). Once the input is phonetically, phonologically, syntactically and semantically encoded, the system prepares the output. For response production, the brain carries out a (morpho-)phonological encoding step, in which the phonology of the words' morphemes is accessed. Following this, these phonological units are clustered into syllables, a process which is called *syllabification*. Syllabification is context-dependent in the sense that the phonological units are clustered depending on the phonology of the surroundings. Subsequently, phonetic encoding takes place, encompassing articulatory planning of the output and motor control, which is then followed by the final articulation.

Incremental processing.

These processes are widely accepted to take place in an incremental manner ([Indefrey & Levelt, 2004](#); [Marslen-Wilson, 1975](#); [Marslen-Wilson & Welsh, 1978](#)). This means that the brain may be already preparing the articulation of the sentence's beginning while, at the same time, still acoustically analyzing later parts of the sentence.

Potential overlap between perception and production.

The representations, described above, that are accessed during repetition (i. e., phonological codes, lexical entries, grammar, concepts, ...) have been discussed as being shared between the perception and the production system (see [Friederici & Levelt, 1988](#)). The processes, on the contrary, are thought to require specific neural resources, at least during the acoustic-phonetic and phonological stages. However, the processes during the semantic-conceptual stage, and probably also during the syntactic stage, are thought to be shared between the perception and production system (see [Indefrey & Levelt, 2004](#)).

Non-lexical repetition route.

It is possible to repeat speech without doing syntactic and semantic analyzes, i. e., via a so-called *non-lexical repetition route* ([Baron et al., 2008](#); [Dell et al., 2007](#); [Hanley et al., 2004](#); [Morton, 1980](#)). However, in the case of sentence repetition, it is probable that syntactic and semantic processing steps take place. Not only is comprehension automatically triggered when perceiving language ([Hinojosa et al., 2004](#)), it is also easier to repeat a sentence if the overall meaning was also decoded: Access to and encoding of semantic representations have been shown to influence the quality of word list repetition (see [Dell et al., 2007](#)). Moreover, the presence of syntactic structure has also been shown to ameliorate repetition (in contrast to the absence of syntactic structure during word list repetition; [Martin & Saffran, 1990](#); [Miller & Selfridge, 1950](#))—an effect that is known as the “sentence superiority effect” in the memory literature ([Baddeley et al., 2009](#); [Cattell, 1886](#)). Thus, during successful and quick repetition of sentences, word meanings as well as syntactic features are accessed and encoded.

There are several studies with patients suffering from various diseases which investigate the brain regions involved in sentence repetition. Some of these studies also report control group data. For example, in epilepsy patients, Lehericy et al. (2000) demonstrated a reliable activation of a temporo-parietal area, encompassing the STG and the inferior parietal lobule, during sentence repetition (compared to a rest condition). Moreover, in some patients, the inferior and middle frontal gyrus, the supplementary motor area (SMA) and the cingulate areas were also activated. In healthy controls, Lehericy et al. (2002) reported very similar regions to be involved in sentence repetition, with additional activation of the bilateral STS, and the inferior temporal gyrus. The results have been replicated in both epilepsy patients and control subjects (Thivard et al., 2005), confining the activation to the bilateral STG and the MTG, extending to the parietal cortex, as well as to the dorsolateral and the ventrolateral frontal cortex. Moreover, another study used sentence repetition as a tool to discover differences between action and object observations in healthy subjects (Tremblay & Small, 2010). The authors reported similar activations (contrasting sentence repetition in healthy adults against a resting baseline), including activation of the dorsal and ventral PMC, the primary motor area, the pars triangularis and opercularis of the IFG, as well as the superior parietal lobule and the inferior parietal sulcus. Unfortunately, to our knowledge, no study to date has investigated the brain regions underlying semantic and syntactic processes during sentence repetition.

Brain regions
underlying
sentence repetition.

Taken together, existing research indicates that the cortical areas underlying sentence repetition (and to a lesser extent also word repetition) are not entirely clear, particularly when it comes to specific sub-processes. Our study therefore aimed to investigate both the cortical areas underlying pure repetition, i. e., repetition of speech that is free from syntactic structure and semantic content, and the areas underlying simple syntactic processes as opposed to complex syntactic processes, as well as word-level semantic processes as opposed to sentence-level processes during repetition. Moreover, we compared our results to the key brain regions of language comprehension to investigate if the syntactic and semantic systems are task-independent.

Study aim.

We asked healthy human adults to overtly repeat sequences of words in the MR scanner. We used the same stimulus material as for the fMRI comprehension study, presented in Chapter 3: Sequences of words were manipulated with respect to structure (containing different kinds of syntax or no syntax) and content (containing meaningful or meaningless words). Thus, subjects had to repeat complex sentences (i. e., object-first sentences), simple sentences (i. e., subject-first sentences), and word lists, all containing content words (semantic information); moreover, subjects had to repeat the semantic-free counter parts, namely complex jabberwocky sentences, simple jabberwocky sentences, and pseudoword lists (see Figure 3.2).

Methods of the
present study.

Contrasts performed. We studied

- a) **pure repetition** by contrasting repetition of pseudoword lists with repetition of matched real word lists (subtracting away activations in response to semantic information of words),
- b) processing of **simple syntax** during repetition by contrasting simple sentences with word lists (subtracting away activations in response to any syntactic processes),
- c) processing of **complex syntax** during repetition by contrasting complex sentences with simple sentences (subtracting away activations in response to simple syntactic processes),
- d) **word-level semantic processing** by contrasting word lists with pseudoword lists (subtracting away activations in response to phonological aspects), and
- e) **sentence-level semantic processing** by contrasting sentences with jabberwocky sentences (subtracting away activations in response to syntactic and phonological aspects).

The results were then compared to the key brain regions underlying syntactic and semantic processes during sentence comprehension (as revealed in [Chapter 3](#) and in previous studies).

Hypotheses.

As correlates of pure repetition (i. e., repetition of speech that is free from syntax and semantics), we hypothesized that there would be activation of areas known to support speech production, i. e., the motor and premotor cortex, the cerebellum, and the insula ([Lehéricy et al., 2002](#); [Thivard et al., 2005](#); [Tremblay & Small, 2010](#)), as well as areas known to support phonological processing, i. e., the posterior inferior frontal cortex, the posterior temporal cortex and the SMG (e. g., [Bookheimer, 2002](#); [Buchsbaum et al., 2005](#); [Burton et al., 2005](#); [Heim, 2005](#); [Vigneau et al., 2006](#); [Friederici, 2006](#)). The neural correlates of syntactic and semantic processing during sentence repetition have not yet been investigated. If, as is discussed above, it is the case that syntactic and semantic processing relies, during comprehension and production, on the same neural resources, the neural correlates of syntactic and semantic processing during sentence repetition should activate the same regions as we found or as have been reported for sentence comprehension: BA 44 and the posterior STG/STS (e. g., [Friederici et al., 2009](#); [Grewe et al., 2005](#); [Röder et al., 2002](#)) should be activated for syntactic complexity during sentence repetition, and the frontal operculum and the anterior STG/STS should be activated for simple syntactic processing during sentence repetition, as has been shown for sentence comprehension (e. g., [Stowe et al., 1999](#); [Friederici et al., 2000](#); [Friederici et al., 2003](#); [Vandenberghe et al., 2002](#)). The bilateral frontal and the temporal areas should activate during word-level semantic processing, especially the anterior IFG and Wernicke's area, as has been reported for word comprehension (e. g., [Binder et al., 2009](#); [Bookheimer, 2002](#); [Vigneau et al., 2006](#)). The anterior and posterior superior temporal/parietal areas should activate during sentence-level semantic processing, as has been shown for sentence comprehension ([Humphries et al., 2006](#); [Lau et al., 2008](#); [Vandenberghe et al., 2002](#)).

4.2 Methods

The present study was conducted equivalent to the comprehension experiment presented in [Chapter 3](#). In the following sections, only repetition-related changes of the methods or additions are therefore outlined.

Similar methods as in comprehension study.

4.2.1 Participants, design, material, data acquisition

Participants, study design, material, procedure, as well as data acquisition and analysis parameters were equivalent to the comprehension experiment (see [Section 3.2](#)).

4.2.2 Procedure

Subjects listened, eyes closed, to the stimuli and repeated them overtly (i. e., with vocalization) immediately after hearing. A repetition trial consisted of the stimulus followed by the overt repetition response of the subjects. The repetition experiment had a length of 22.2 min per session. The functional run of the repetition experiment had 672 volumes.

Task and trial design.

4.2.3 Behavioral data analysis

Oral answers were recorded using a specific digital audio presentation system (MR confon; <http://www.mr-confon.de/>) and the software OptiMRI (version 2.2), and inspected manually. A stimulus did not count as correctly repeated when the subject made any kind of pronunciation mistake.

Measure applied.

4.2.4 Functional imaging data analysis

In the general linear model, stimulus offset was modeled as response onset. To remove effects of accuracy on pseudoword repetition we inserted the subject- and condition-specific accuracy values as a regressor in the general linear model. We performed flexible-factorial analyses of variance (ANOVAs) for the main and differential effects. All contrasts—the semantic main effect (real words > pseudowords), and the parametric contrast of syntax (complex > simple > missing syntax), as well as the differential effects—were thresholded at $p < .05$, FWE-corrected.

General linear model and thresholds used.

4.3 Results

4.3.1 Movement results

Participants' heads were stable.

We analyzed the stability of the subjects' heads throughout the experiment to capture possible head movements that may have been caused by overt speaking. Stability was acquired as the mean of the signal intensity standard deviation of the time series (given as a percentage). Mean stability was not significantly different between the repetition experiment presented here and a perception experiment (see [Chapter 3](#)) which was performed during the same sessions ($p = 0.32$, two-tailed t -test). Moreover, no single subject had to be excluded because the magnitude of all movements lay within the standard deviation. For repetition, the mean stability value was 1.99 (SD = 0.17, range: 1.73–2.38) in the first session, and 1.99 (SD = 0.13, range: 1.79–2.26) in the second session. For perception, the mean stability value was 1.97 (SD = 0.12, range: 1.79–2.22) in the first session, and 1.97 (SD = 0.12, range: 1.74–2.22) in the second session.

4.3.2 Behavioral results

Meaningful conditions were repeated more accurately than meaningless conditions.

Subjects repeated 99.5% of all stimuli. The quality of the repetition responses was, however, dependent on the conditions: The repeated-measurements analysis of variance (ANOVA) yielded a main effect of semantics ($F_{1,19} = 83.637$, $p < .001$), a main effect of syntax ($F_{2,38} = 14.598$, $p < .001$), and an interaction between both factors ($F_{2,38} = 10.849$, $p < .001$). This means that meaningless conditions were repeated significantly worse than their corresponding meaningful conditions; word lists were repeated significantly worse than simple syntactic stimuli in meaningful conditions ($F_{1,19} = 12.740$, $p = .002$) and meaningless conditions ($F_{1,19} = 26.145$, $p < .001$); moreover, word lists were also repeated significantly worse than complex stimuli if presented in a meaningless environment ($F_{1,19} = 12.803$, $p = .002$). The repetition quality of complex syntactic stimuli did not differ significantly from the repetition quality of simple syntactic stimuli, both in meaningful conditions ($F_{1,19} = 3.397$, $p = .081$) and meaningless conditions ($F_{1,19} = 1.516$, $p = .233$).

4.3.3 fMRI results

Auditory and motor activations.

In one-sample t -tests (against zero), each of the repetition conditions showed activation in bilateral auditory and motor areas of the temporal and frontal cortex, as well as in the cerebellum and subcortical structures ([Figure 4.2](#)).

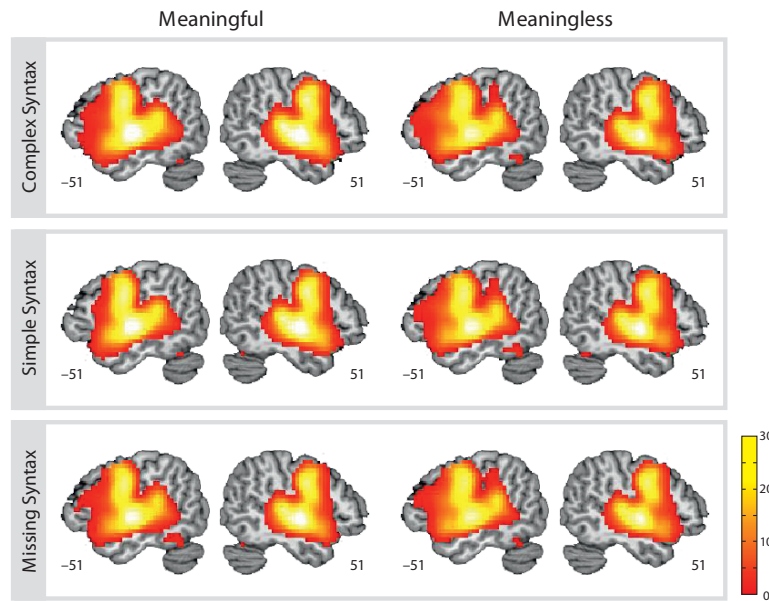


Figure 4.2: Baseline contrasts. Activation maps are laid over a rendered standard brain. Numbers indicate the layers (in MNI coordinates). Scale visualizes significance of activations in z-scores.

We observed that the following areas activated for pure repetition (i. e., repetition of speech which is free from syntax and semantics), when subtracting the activations in response to meaningful words lists from those in response to meaningless word lists (Figure 4.3, Table B.6): the left anterior insula, the dorsal PMC, the ventral PMC (probability for BA 44: 50 %; following Eickhoff et al. (2007)), the SMG, the intraparietal sulcus, and the right cerebellum, as well as the bilateral SMA, the cingulate gyrus, and subcortical structures (i. e., parts of thalamus and the basal ganglia).

Pure repetition:
aIns, dPMC, vPMC,
SMG, IPS, SMA.

To examine the overall effect of syntax, a nonlinear parametric T-contrast was calculated (complex syntax[2] > simple syntax[1] > missing syntax[-3]; Figure 4.4 A, Table B.7), accounting for the different amount of syntactic complexity in the conditions. This contrast revealed activation of the left anterior MTG/STS, as well as a bilateral cluster of activation in the posterior STS and AG, activation in the left parahippocampal gyrus and posterior insula.

Syntax:
aMTG/STS,
pSTS/AG.

In subsequent analyses, we contrasted activations in response to simple sentences with those in response to word lists to investigate the correlates of simple syntactic processes. This contrast revealed patterns of activation in the left anterior MTG/STS, the posterior insula, and the AG/posterior STS (Figure 4.4 A2, Table B.8).

Simple syntax:
aMTG/STS,
pSTS/AG.

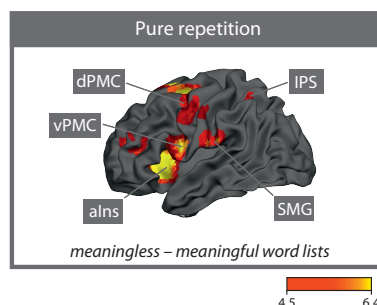


Figure 4.3: Pure repetition contrast (meaningless vs. meaningful word lists), i. e., free from syntax and semantics, thresholded at $p < .05$, FWE-corrected. Left-hemispheric activation map is laid over a rendered standard brain. Key brain regions are named. Scale visualizes significance of activations in t-values. For abbreviations see page xv.

Complex syntax:
BA 44/45, STS.

Also, we contrasted activations in response to complex sentences with those in response to simple sentences to investigate the correlates of complex syntactic processing. Activations were observed in the left IFG (BA 44/45) and the left STS (Figure 4.4 A1, Table B.8).

Semantics:
pSTS/AG, aMTG,
mMTG.

The main effect of semantic processing (meaningful > meaningless stimuli; Figure 4.4 B, Table B.7), revealed only left-hemispheric activations: a cluster of activation in the left AG and posterior STS, activation in the left anterior MTG, the posterior cingulate gyrus, and the dorsomedial prefrontal cortex, as well as in the middle MTG.

Sentence-level
semantics:
pSTS/AG, aMTG.

We then investigated the correlates of semantic processing separately for the word level and different sentence levels. To analyze semantic processing at the level of sentences, we contrasted, on the one hand, activations in response to meaningful with those in response to meaningless simple sentences. We obtained clusters of activation in the left AG and posterior STS, as well as in the anterior MTG, and in midline structures (dorsomedial prefrontal cortex, precuneus; Figure 4.4 B2, Table B.9). On the other hand, we contrasted activations in response to meaningful with those in response to meaningless complex sentences, and obtained similar activated regions as we did for simple sentences, but found additional clusters of activation in the left posterior MTG, as well as in the right AG and the anterior MTG (Figure 4.4 B1, Table B.9).

Word-level
semantics: MTG.

Furthermore, to analyze semantic processing at the word level, we contrasted activations in response to meaningful words lists with those in response to meaningless word lists and obtained clusters of activation in large parts of the anterior, middle and posterior MTG (Figure 4.4 B3, Table B.9).

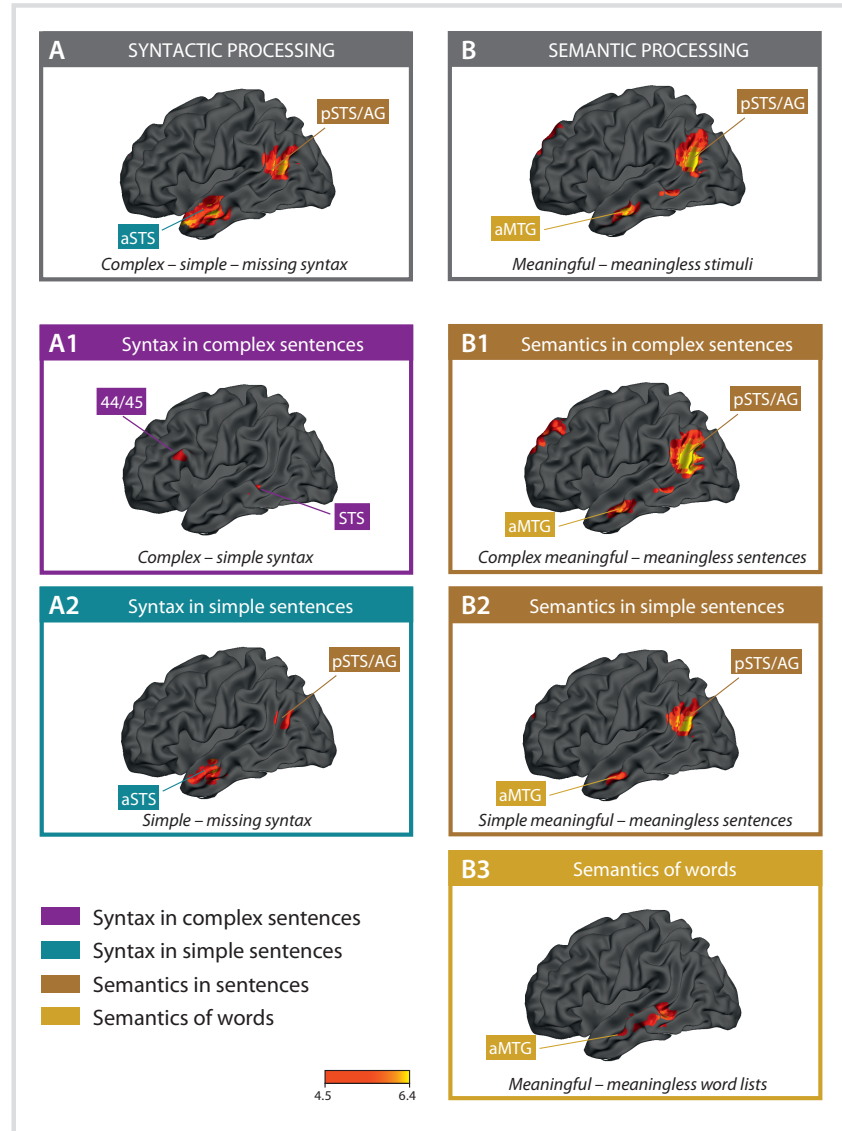


Figure 4.4: Specific contrasts of syntax and semantics: (A) Parametric effect of syntactic processing; (A1) complex syntactic processing; (A2) simple syntactic processing. (B) Semantic main effect; (B1) processing of meaningful versus meaningless complex sentences; (B2) processing of meaningful versus meaningless simple sentences; (B3) processing of meaningful versus meaningless word lists. Note that the semantic contrasts of sentence material (B1+B2) also include syntactic operations. Left-hemispheric activation maps are laid over a rendered standard brain. Key brain regions are named and color-coded. Scale visualizes significance of activations in t-values. All effects are thresholded $p < .05$, FWE-corrected. For abbreviations see page xv.

4.4 Discussion

Goal and
summary of results.

The present study aimed to investigate the key brain regions underlying word and sentence repetition, as compared to word and sentence comprehension. We were particularly interested in syntax- and semantic-free (i. e., pure) repetition on the one hand, and syntactic and semantic processes during repetition on the other hand—specifically complex and simple syntactic processes, as well as word-level and sentence-level semantic processes. We found that a range of motor related brain regions are involved in pure repetition, as well as the left SMG, the ventral and dorsal PMC, and the bilateral intraparietal sulcus. The processing of simple syntactic structures during repetition activated the left anterior STS/MTG and the posterior STS/AG, while the processing of complex syntactic structures during repetition activated left Broca's area and a region in the left (posterior) STS. Access and retrieval of word semantics relied on the left MTG, whereas a region in the left posterior STS/AG specifically activated when not only semantics, but also syntax was available. Many of these syntactic and semantic areas have also been reported and were also found to be activated during language comprehension (cf. [Chapter 3](#)). Therefore, the present data suggests that syntactic and semantic information and/or processes are represented independent of the input and output modalities.

4.4.1 Key regions of pure repetition

Pure repetition
comprises
phonological,
phonetic and
motor aspects.

Repetition that is free from syntactic and semantic features is called “pure repetition” because it only comprises phonological, phonetic and motor aspects of repetition. Pure repetition can be measured using meaningless words, i. e., pseudowords. Compared to normal word repetition, repetition of pseudowords probably also enhances phonological, phonetic and motor demands, because pseudowords are unfamiliar and unknown.

Speech production
areas activate during
pure repetition.

As correlates of pure repetition, we revealed among others activations in the SMA and cerebellum, activations of the left anterior insula, portions of the basal ganglia and the thalamus. These regions are known to be involved in speech production and articulation (e. g., [Eickhoff et al., 2009](#); [Riecker et al., 2008](#)). The anterior insula and the cerebellum have thereby been proposed to be specifically involved in the process of phonetic encoding, i. e., articulatory planning and motor control ([Indefrey & Levelt, 2004](#)). In particular, the anterior insula has been discussed as having a role in articulatory planning ([Dronkers, 1996](#); [Price, 2010](#); [Wise et al., 1999](#)), by supplying temporal resolution and encoding of sound modulations ([Bamiou et al., 2006](#)), whereas the cerebellum has been discussed as having a role in motor control by subserving online sequencing of syllables before and during overt speech production ([Ackermann, 2008](#)). In the present study, the left SMG, the ventral

and dorsal PMC and the intraparietal sulcus were also activated during pure repetition. These activations are discussed in detail below.

The SMG supports phonological aspects of speech, as has been consistently reported in previous studies (see [Sliwinska et al., 2012](#), for a summary of studies). In the present study, we delineated the SMG's anterior inferior portion during pure repetition. This portion strongly corresponds to a region whose breakdown is the best predictor of impaired speech repetition, as was shown by [Fridriksson et al. \(2009\)](#). Regarding the function of this region during repetition in more detail, the SMG, and sometimes the more superior or posterior portions specifically, have been discussed as supporting attention to phonetic and segmental information for syllable discrimination during perception ([Blumstein, 2009](#); [Moser et al., 2009a](#)) and articulation ([Parker et al., 2005](#)). Moreover, the proposal that the SMG has a role during the syllabification stage of repetition was supported by the finding of [Bohland and Guenther \(2006\)](#), who showed the bilateral superior and the inferior parietal cortex areas correlate with increased syllable sequence complexity during overt production. Thus, there is strong evidence that the anterior inferior portion of the SMG, found in the present study, plays a role during speech repetition. Its specific role tends to be syllabification, however confirmation of this requires additional experimental research which specifically investigates sub-portions of the SMG.

SMG supports syllabification.

[Bohland and Guenther \(2006\)](#) also found that parts of the left ventral PMC and the left pars opercularis of the IFG correlated with the complexity of a syllable sequence during speech production. Within their IFG region lies the left lateralized ventral PMC/BA 44 activation cluster found in the present study. Our activation cluster is also consistent with an IFG activation found by [Warburton et al. \(1996\)](#) when contrasting pseudoword repetition with a resting baseline, and a ventral PMC/BA 44 activation found by [Moser et al. \(2009b\)](#) when contrasting pseudoword with word repetition. As was the case for the SMG, the ventral PMC/BA 44 has been proposed to subserve syllabification ([Indefrey & Levelt, 2004](#)), reflecting the more sophisticated syllable sequencing mechanisms during the production of pseudowords, as compared to real words. Also, the dorsal PMC has been discussed as subserving sequencing because it houses working memory for temporal order ([Wager & Smith, 2003](#)). Actually, the sequencing mechanisms provided by the ventral and dorsal PMC have been suggested to be domain general ([Schubotz & von Cramon, 2003](#)). In particular, the authors propose that the ventral PMC/BA 44 not only processes syllables but also other sequentially structured information, for example morpho-syntactic information of a sentence (see also [Opitz & Friederici, 2004](#)). The ventral PMC/BA 44 uses mainly surface features of a sentence, whereas the dorsal PMC uses spatial features of the sentence for language perception, especially if a motor output should be produced, and to make action plans for language production ([Schubotz & von Cramon, 2003](#)). The dorsal PMC has furthermore

vPMC supports sequencing,
dPMC supports response selection.

been discussed as subserving response selection based on the sensory input (Badre, 2008; Koechlin et al., 2003). Taken together, our ventral PMC/BA 44 activation in the pure repetition contrast seems to reflect a sequential analysis of the input for perception and production, and the dorsal PMC seems to be responsible for a temporo-spatial analysis of the input for motor planning and response selection. In particular, the ventral PMC/BA 44 activation is likely to reflect syntax-free sequencing, because the contrast was free from syntax and semantics. More superior parts of this region seem to be involved in syllabification, and more inferior parts in articulatory sequencing (Papoutsis et al., 2009). The dorsal PMC activation, on the other hand, presumably reflects motor preparation and response selection for repetition.

IPS retains the phonological input in mind.

In addition, the left anterior intraparietal sulcus was activated in the pure repetition contrast of the present study. This region has been suggested to constitute parts of a domain-general fronto-parietal executive system, supporting attention and working memory, for example (Ravizza et al., 2004; Ravizza et al., 2011). Concerning attention, the intraparietal sulcus has been shown to activate whenever top-down attention to memories is needed (Fox et al., 2006; Posner & Petersen, 1990), i.e., when internally represented goal-directed responses have to be accessed (Cabeza et al., 2008). During repetition, the intraparietal sulcus thus achieves access to represented articulatory patterns and top-down attention to the correct articulation. Those attentional processes are understandably enhanced if syllables have to be articulated in an unfamiliar configuration (as is the case during pseudoword repetition), which in turn leads to an enhanced activation of the intraparietal sulcus. Concerning working memory, the intraparietal sulcus activates whenever content has to be retained in working memory; probably through binding of sensory features to representations (Mecklinger & Opitz, 2003). During repetition, the intraparietal sulcus hence achieves retention of the input phonology in memory until the output has to be produced. Thus, our bilateral activation of the parietal cortex (intraparietal sulcus), observed during repetition of meaningless stimuli, probably reflects attempts of the executive system to accomplish good repetition performance, i.e., attention and working memory.

Temporal cortex is involved in syntactic and semantic aspects of repetition.

Our pure repetition activations are consistent with the activations previously found for sentence repetition (Lehéricy et al., 2002; Thivard et al., 2005; Tremblay & Small, 2010). There are, however, two main differences. First, we did not find any temporal activation, whereas previous repetition studies did. As an explanation, we suggest that the temporal cortex codes for semantic and syntactic aspects of sentence repetition more than for phonological, phonetic and articulatory aspects, because we found temporal regions activated in our syntactic and semantic contrasts (see below). The previous repetition studies that report temporal activation, however, did not make a differentiation between the various repetition processing stages and so could not rule out syntactic and semantic processes. They are thus also

likely to incorporate correlates of syntactic and semantic processes in their findings, which may explain their report of temporal cortex activation. Second, we did not observe a significant activation in the temporo-parietal junction, a region suggested to play a key role in auditory-motor integration (Hickok & Poeppel, 2007). However, auditory-motor integration is needed for all kinds of repetition. Thus, it is probably subtracted away in our differential contrast.

4.4.2 Key regions of syntactic and semantic processes during repetition as compared to comprehension

We were specifically interested to see whether brain regions known to support syntactic and semantic aspects of sentence comprehension also support syntactic and semantic aspects of sentence repetition. We predicted a large overlap of activation in response to repetition and comprehension, both for semantic and syntactic aspects of processing. This hypothesis was based on the assumption that syntax and semantics are central systems that are represented in a modality free manner, and that work independent of input or output constraints (Friederici & Levelt, 1988). Our prediction was supported by the present data.

Syntax and semantics should be represented independent from modalities.

During repetition of syntactically simple sentences, we observed activation of the left anterior STS/MTG, as well as activation of the posterior STS/AG (which will be discussed below, along with the semantic contrasts). The anterior STS has previously been shown to be a correlate of simple syntactic processing during language comprehension, namely as a correlate of phrase structure building processes (De Witt Hamer et al., 2011; Friederici et al., 2003; Dronkers et al., 2004). Thus, this aspect of simple syntactic processing during sentence repetition appears to recruit the same neural structure as simple syntactic processing during sentence comprehension. We furthermore hypothesized that the frontal operculum would be revealed as a correlate of simple syntactic processing, because it was shown in our comprehension study (Chapter 3) and in the literature to participate in phrase structure building processes during language comprehension (Friederici et al., 2006a; Friederici et al., 2000; Friederici et al., 2003; Stowe et al., 1999). However, the frontal operculum was not activated during repetition in any of the contrasts in the present study. One may therefore assume that the frontal operculum only codes for phrase structure building during comprehension paradigms, and not at all during sentence repetition paradigms. This is contrary to the proposition of Saur et al. (2008) who assigned a monitoring function to the frontal operculum during repetition. In the present study, we rather found the adjacent anterior insula to be involved in repetition, but only in phonological or (presumably) articulatory aspects, and not in syntactic or semantic aspects of repetition.

aSTS/MTG supports phrase structure building independent from modality.

BA 44/45 and STS support complex syntax independent from modality.

During repetition of syntactically complex sentences, we observed activation of the two core regions that were previously reported to code the processing of syntactic complexity during sentence comprehension: Broca's area (BA 44) and the posterior STS (Bornkessel et al., 2005; Friederici et al., 2009; Grewe et al., 2005; Röder et al., 2002). The only difference between our results and these previous findings is that our inferior-frontal activation lies in a slightly more anterior region, on the border to BA 45. This border position is, however, consistent with recent findings of studies that contrasted passive or scrambled sentences with active or non-scrambled sentences in English (Santi & Grodzinsky, 2010), in Japanese (Hirotani et al., 2011; Kinno et al., 2008), and in German (Makuuchi et al., 2012). We, therefore, assume our inferior-frontal activation to be a correlate of syntactic complexity, particularly during sentence repetition, rather than a correlate of another cognitive process. Overall, the regions that are required for processing of syntax during sentence repetition, especially during repetition of non-canonical sentences, largely overlap with the regions that were shown in the literature to be required for syntactic processing during language comprehension. This supports the syntactic system's central, modality-independent status that we and others proclaim.

The entire MTG supports word-level semantics during repetition.

When investigating word-level semantic processes, we exclusively found activation of the left MTG, encompassing anterior, middle and posterior portions. The MTG, is known to be involved in semantic processing, during both language comprehension and production (e.g., Binder et al., 2009; Heim, 2005; Indefrey & Levelt, 2004; Lau et al., 2008; Price, 2010). During repetition of speech, word-level semantic processes were previously proposed to be located in the whole MTG when contrasting repetition of real words with pseudowords (Peters et al., 2009), as well as in the middle and posterior MTG when contrasting real word repetition with saying the word "crime" to reversed words (Price et al., 1996), or when contrasting picture naming with reading of visually and orthographically controlled pseudowords (Acheson et al., 2011). Moreover, a posterior temporal/angular region was also previously assigned to lexico-semantic processes during repetition when contrasting real word repetition with pseudoword repetition (Castro-Caldas et al., 1998; McCrory et al., 2000). Thus, there is evidence in the literature that all parts of the MTG contribute to lexico-semantic processing during speech repetition, and the findings of our study are consistent with this. This finding is different from sentence comprehension, where we only found anterior aspects of the MTG to be involved in word-level semantic processing (cf. Chapter 3), educing the idea that middle and posterior aspects of the MTG are specific for semantic processes during production. Which specific semantic process is subserved by the MTG during repetition (e.g., lexical access or selection), and whether this process is language-specific or part of a domain-general cognitive function (see Price, 2010) is not yet entirely clear and remains subject to future investigations.

When sentences were repeated, we observed additional activation in a region covering the left posterior STS and the AG. This region was reported in our comprehension study and other comprehension studies as a region subserving integration of syntax and semantics (e.g., [Friederici, 2004](#); [Grodzinsky & Friederici, 2006](#); [Lau et al., 2008](#)). The present study suggests that integrating syntax and semantics can also be a function of the posterior STS during sentence repetition: We saw this region activate during sentence repetition if, and only if, both syntax and semantics were available, i.e., in contrasts that measured repetition of meaningful sentences. Thus, it is likely that the posterior STS/AG region subserves a computation that is common for syntax and semantics, e.g., the integration of both. An alternative interpretation of the function of the posterior STS/AG region in sentence repetition is that it supports lexico-semantic processing, as reviewed above. However, in the present study, the contrast measuring lexico-semantic processing showed no activation in the region. This makes the lexico-semantic interpretation of the posterior STS/AG activation rather unlikely.

pSTS integrates syntax and semantics independent from modality.

Taken together, our differential contrasts show that semantic and syntactic processes during repetition and comprehension rely on very similar brain regions. Thus, semantic and syntactic stages of the perception and production systems seem to share neural resources as was proposed and argued previously, at least on the conceptual level ([Friederici & Levelt, 1988](#); [Indefrey & Levelt, 2004](#); [Price, 2010](#)). Our finding is consistent with a recent study demonstrating shared cortical areas for sentence comprehension and production using fMRI adaptation ([Menenti et al., 2011](#)).

Syntax and semantics have a central, modality-independent status.

Our study is restricted to language repetition and did not investigate language production. Thus, we cannot draw conclusions about the conceptual processes during sentence production and their relation to sentence comprehension. Moreover, those neural correlates of repetition that we showed to be similar to comprehension correlates may only reflect the comprehension side of repetition. The production side of repetition may then be reflected in additional neural correlates, other than these. However, this pattern is, though conceivable, rather improbable as we did not reveal additional areas of activation in our repetition experiment that were not activated in our comprehension experiment, or that were not reported in the context of comprehension previously.

Limitations of the present study.

4.5 Summary and Conclusion

In sum, our study provides—for the first time—an insight into the key brain regions underlying different cognitive processes during sentence repetition. Pure repetition, i.e., speech repetition that is free from syntax and semantics, was shown to rely on classical areas associated with

Syntactic and semantic key regions are shared by repetition and comprehension.

phonology and articulation, as well as the left supramarginal gyrus (probably as a correlate of syllabification), the dorsal and ventral premotor cortex (as correlates of sequencing operations), and the intraparietal sulcus (as a correlate of executive operations). Syntactic and semantic processes mostly rely on the same left-hemispheric areas as syntactic and semantic processes during sentence comprehension: Broca's area and the posterior STS activated during processing of complex syntax, the anterior STS during processing of simple syntax, and the MTG during word-level semantic processing, as well as a region in the posterior STS/AG during a computation that is common for syntax and semantics, e. g., syntactic-semantic integration. The data support the notion of syntax being associated with a central neural system recruited during comprehension, as well as during repetition. The same holds true for semantics. Future studies are needed to differentiate whether it is the processes or the representations that share neural resources between language comprehension and repetition.

Chapter 5

Tractography study: Fiber tracts for sentence comprehension and repetition

It is widely debated which specific fiber tracts subserve specific language functions and what their anatomy is. We combined functional magnetic resonance and diffusion tensor imaging using a within-subjects design, to track the fiber bundles involved in repetition, syntactic, and semantic processes. We identified two separable dorsal fiber tracts and their functional roles: one tract connecting dorsal premotor cortex with posterior middle temporal gyrus branching to the parietal lobe; another tract connecting posterior Broca's area with posterior superior temporal gyrus. The former corresponds, at least in its fronto-parietal part, to the superior longitudinal fascicle and is involved in pure repetition; the latter corresponds to the arcuate fascicle and is involved in the processing of syntactic complexity. Processing simple syntactic structures and word-level semantics is supported by ventral fiber tracts. With these data we provide a new neurocognitive model of the fiber tracts involved in language processing that solves hitherto conflicting results.

Preface

Overview
of the chapter.

In the present chapter, the four pathway model by Friederici (2011) as introduced in the [Introduction](#) section, was investigated experimentally. For this purpose, the key regions delineated in the fMRI studies ([Chapter 3](#) and [Chapter 4](#)) were used as starting points for fiber tracking. The chapter closes with a new neurocognitive model visualizing the key brain regions and fiber tracts found to be involved in language processing.

5.1 Introduction

Methods of
the present study.

The present tractography study aimed at providing a comprehensive view on the different functional roles and the anatomy of the fiber tracts involved in language processing that can consolidate the contradictory findings of Friederici et al. (2006a) and Saur et al. (2008) (see [Chapter 1](#)). To achieve this goal, we performed fiber tracking from functional-based starting points, so-called *seed regions*, which demonstrated involvement in the following linguistic functions in our comprehension ([Chapter 3](#)) and repetition ([Chapter 4](#)) studies: phonological and motor aspects of repetition, as well as syntactic processing of differing complexity, word-level and sentence-level semantic processing. We aimed at using those regions as seed regions that were overlapping between comprehension and repetition to make claims about task-independent fiber tracts. For that purpose, conjunction analyses between the comprehension and repetition experiment were performed. The main activation peaks of the fMRI group analyses, projected onto the nearest individual white matter region, served as starting points for the probabilistic tractography. To differentiate the fiber tracts, we used a general linear model that statistically evaluated the tractography results between fiber tracts across subjects.

Hypotheses.

Following the model proposed by Friederici (2011), we hypothesized that one dorsal fiber tract connecting the dorsal premotor cortex and the posterior STG would be involved in pure repetition, i.e., repetition that is free from syntax and meaning. A second dorsal tract connecting posterior Broca's area (that is BA 44) and the posterior STG should be involved in complex syntactic processes. Moreover, we hypothesized that one ventral tract, connecting the frontal operculum and the anterior STG, would be involved in simple syntactic processes. A second ventral tract connecting anterior Broca's area (BA 45) and the STG should be involved in word-level semantic processes.

Summary.

Taken together, the components of this study are intended to reconcile hitherto conflicting results concerning the anatomy and functional roles of language fiber tracts, and afford a better understanding of the anatomy and function of the human brain.

5.2 Methods

5.2.1 Functional imaging data analysis

To investigate the common regions for comprehension and repetition, we performed conjunction analyses in addition to the analyses already performed in the context of the comprehension and repetition experiments (Chapter 3, Chapter 4). We conducted a full factorial ANOVA for the conjunction analyses. In the current chapter, the reported effects from the conjunction analyses were thresholded at $p < .01$, $k \geq 11$, uncorrected, the reported effects from the comprehension and repetition experiments were thresholded at $p < .05$, FWE-corrected.

Conjunction analyses were performed.

5.2.2 DTI data acquisition

Diffusion-weighted data was acquired with a 32-channel phased-array head coil from 88 axial slices using a twice-refocused spin echo echo-planar-imaging sequence (Reese et al., 2003) (echo time = 100 ms, repetition time = 12 s, image matrix = 128×128 pixel², field of view = 220×220 mm², resolution = $1.72 \times 1.72 \times 1.7$ mm³). Additionally, fat saturation was employed together with 6/8 partial Fourier imaging and generalized auto-calibrating partially parallel acquisitions (acceleration factor = 2; Griswold et al. (2002)). Diffusion weighting was isotropically distributed along 60 diffusion-encoding gradient directions with a b-value of 1,000 s/mm². Seven datasets with no diffusion weighting (b0) were also acquired initially and interleaved after each block of 10 diffusion-weighted images as anatomical reference for off-line motion correction. Cardiac gating was not employed, in order to limit the acquisition time. The diffusion MRI sequence lasted 16 min.

Acquisition parameters.

5.2.3 DTI data analysis

For skull-stripping, T1-weighted structural scans were used. Following that, the brain images were co-registered into Talairach space (Talairach & Tournoux, 1988). The seven acquired images without diffusion weighting served to estimate motion correction parameters using rigid-body transformations (Jenkinson et al., 2002), implemented in FSL (University of Oxford, UK; <http://www.fmrib.ox.ac.uk/fsl>). Motion correction parameters were interpolated for all 67 volumes and combined with a global registration to the T1 anatomy. The gradient direction for each volume was corrected using the rotation parameters. The registered images were interpolated to the new reference frame with an isotropic voxel resolution of 1 mm. Finally, for each voxel, a diffusion tensor (Basser & Pierpaoli, 1996) was fitted to the data.

Analysis parameters.

5.2.4 Selection of seeds

Seeds were selected based on relevance for language.

We performed probabilistic fiber tracking from seed points that we derived from the peaks of the main fMRI activation clusters. We chose those clusters as clusters for seeds that we delineated in our discussion, based on prior studies on language processing, as being most relevant for language processing (see [Chapter 3](#) and [Chapter 4](#)). This led to six seed points: dorsal premotor cortex, IFG, frontal operculum, anterior STS, posterior STS, and anterior MTG. We did not trace from general motor related areas (e. g., anterior insula, supplementary motor area, cerebellum, precentral gyrus) or areas known to subserve domain-general cognitive skills (e. g., inferior frontal sulcus, dorsomedial prefrontal cortex). For the remaining clusters, we set a cut-of of 25 voxels to be considered as clusters for seeds, which led to two additional seed points, one in the ventral premotor cortex and one in the supramarginal gyrus. Our seed points are all placed in the left hemisphere, as we did not observe additional different language-relevant activations in the right hemisphere.

5.2.5 White matter tractography

Definition of white matter seeds.

As seeds for probabilistic fiber tracking, we used the individual white matter voxels that were closest to the main peaks of the fMRI group analyses: First, we chose the peaks of the main clusters of the fMRI group contrasts as reported above. Second, to project these group coordinates onto the individual structural scans, the inverse registration coefficients of both the linear and nonlinear registration of the subjects' structural scans to the standard MNI template were applied to the coordinates using FSL. We manually checked carefully that the projected seeds did not jump a sulcus and did not come to lie in an adjacent structure. If this was the case, the seed point was slightly adjusted to cover the region of interest. Third, to ensure that the coordinates used for the probabilistic tracking were effectively placed in the white matter, a white matter skeleton for each individual was produced within FSL using TBSS ([Smith et al., 2006](#)) by thresholding the fractional anisotropy (FA) maps of the subjects using an FA value of 0.25. Last, for each individual and coordinate, the voxel on the white matter skeleton with the smallest distance to the original coordinate was defined as a seed.

Tractography algorithm.

We applied probabilistic fiber tracking in the individual space using an established in-house algorithm (vdconnect; [Anwander et al., 2007](#)). This algorithm computes a trajectory originating from a seed by performing a series of random walks through the surrounding voxels, thereby obtaining a probabilistic map of the structural connectivity of the seed voxel. The random walks are constrained by the orientation of the diffusion tensor in the specific voxel and its neighboring voxels. The algorithm performs Monte Carlo simulations in order to repeat the procedure a fixed amount of times. The degree of connectivity strength

between voxels was calculated on the basis of the number of times the random walk terminates in a specific voxel. The resulting connectivity maps represented how probable it is for each voxel to be connected to the seed region. For comparisons between and across subjects, the resulting connectivity maps per seed region for each subject were normalized into standard space using the nonlinear registration warps already estimated.

We were specifically interested in differentiating the various tracts that are reliable across subjects. We did so by analyzing which voxel predominantly belongs to which tract across subjects. In order to compare how much (the white matter of) a voxel is involved in the different tracts or, in other words, to compare how much the different connectivity maps contribute to the connectivity of a voxel—reliably across subjects—we inserted the (unsmoothed) connectivity maps into a general linear model (Argyelan et al., 2009). We performed a full factorial design using SPM8, and report the resulting T-maps thresholded at $p < .01$, FWE-corrected. Additionally, we classically plotted the amount of subjects showing a tract per voxel for analyzing which faculty of a tract is consistent across subjects and which tract faculties are inter-individual highly variable (Figure 5.3; see also Figure 5.4 for individual tracts).

Statistical group analysis.

5.3 Results

5.3.1 fMRI results

The neural networks underlying, on the one hand, pure repetition, and, on the other hand, complex syntactic processing, simple syntactic processing, as well as sentence-level and word-level semantic processing, were the focus of the current thesis. We, therefore, calculated specific contrasts, as reported in Chapter 3 and Chapter 4. Moreover, as we aimed to make task-independent claims about the fiber tracts supporting linguistic functions (except for pure repetition), we additionally calculated the overlap between the repetition and comprehension experiment performing conjunction analyses (see Figure 5.1, and Table B.10).

We performed conjunction analyses.

For simple syntactic processing, the left posterior STS/angular gyrus was commonly activated during repetition and comprehension. The conjunction analyses revealed no overlapping area for complex syntactic processing. For word-level semantic processing, the left anterior MTG was commonly activated during repetition and comprehension, for sentence-level semantic processing the left posterior STS, as well as the anterior MTG and STS.

Results of the conjunction analyses.

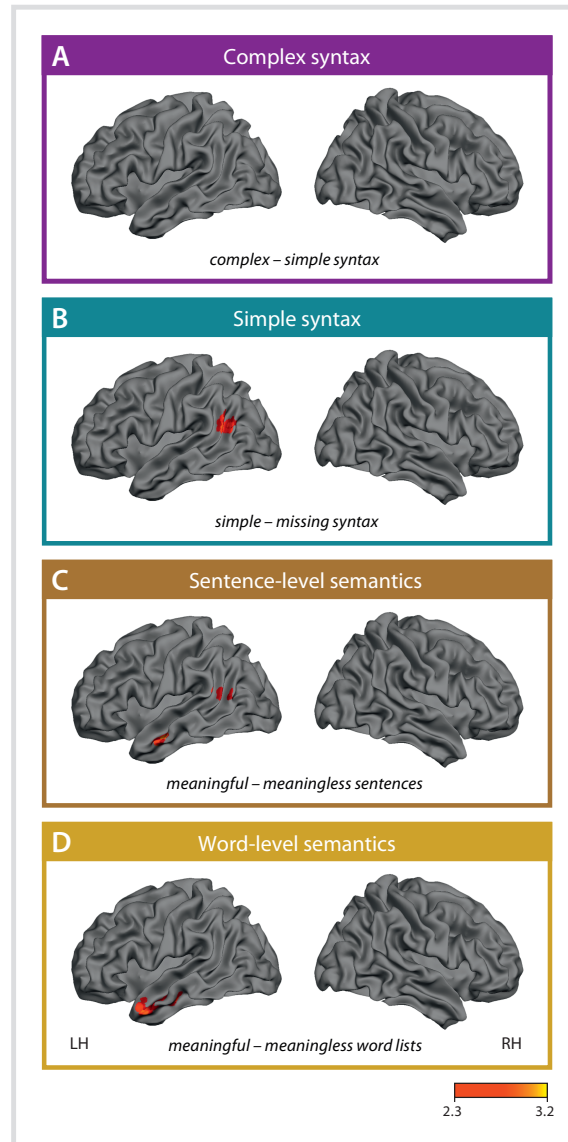


Figure 5.1: Results of the conjunction analyses of the repetition and comprehension study. For comprehension, only meaningful stimulus material was included. Scale visualizes significance of activations in t-values. All contrasts are thresholded $p < .01$, $k \geq 11$, uncorrected.

5.3.2 Tractography results

As seeds for probabilistic tractography, we used the task-independent fMRI activations, which we delineated as being most relevant for language processing (for a detailed description of the selection of our seed regions, see Section 5.2.4): from the conjunction analyses reported above (Section 5.3.1), as well as from the pure repetition contrast reported in Chapter 4. For the syntactic contrasts, we had to derive our seeds from the experiment-based analyses (see Chapter 3 and Chapter 4) because the conjunction analyses showed no significant syntax-specific results. The reason for that could be that the two tasks, repetition and comprehension, may require partly different syntactic processes, as discussed in Section 4.4.2.

Contrasts underlying the seeds.

Hence, we derived the following key activations as seeds from the fMRI analyses: the left dorsal premotor cortex (group maximum in MNI coordinates: -39, -4, 50), as well as the left ventral premotor cortex (-51, 5, 14) and the supramarginal gyrus (-60, -22, 22) as activated during pure repetition (Figure 5.2 A); Broca's area (-54, 20, 22) as activated during complex syntactic processing (Figure 5.2 B), the left frontal operculum (-33, 29, -6) and the left anterior STS (-45, 11, -26) as activated during simple syntactic processing (Figure 5.2 C), the left posterior STS (nbreakdash-63, -55, 18) as activated during sentence-level semantic processing (Figure 5.2 D), and the left anterior MTG (-51, 8, -26) as activated during word-level semantic processing (Figure 5.2 E).

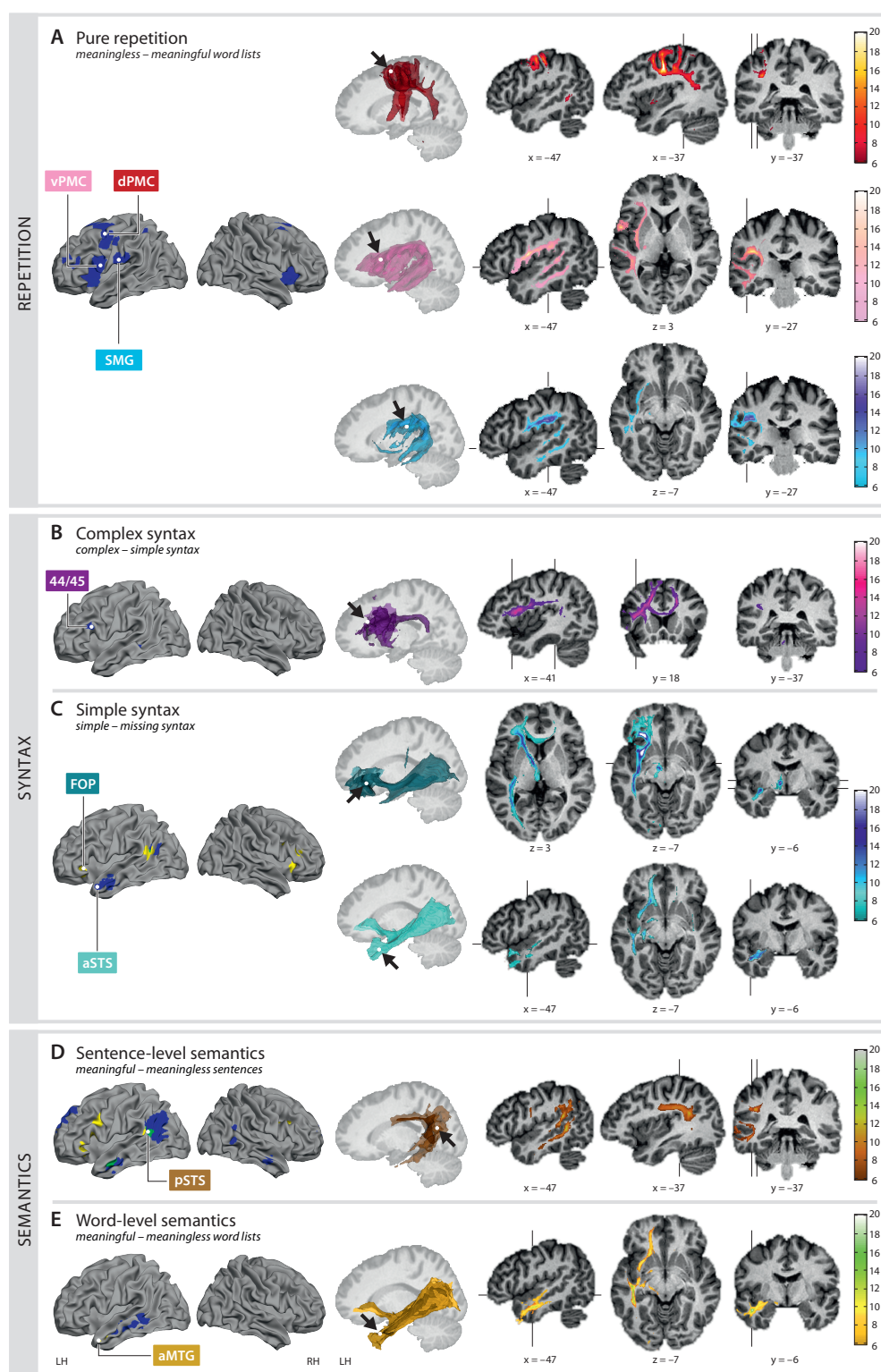
Seeds chosen:
dPMC, vPMC, SMG;
BA 44/45; FOP,
aSTS; pSTS; aMTG.

Using these seeds and analyzing the resulting tractography maps statistically to compare the different tracts, we obtained the following results (Figure 5.2 displays a schematic view of the observed fiber tracts; some individual tracts are visualized in Figure 5.4; an interactive 3D figure is available on <http://openscience.cbs.mpg.de/bihler>): Dorsally, we found two distinct fiber tracts, one running to the posterior MTG when seeding in the dorsal premotor cortex (functional contrast: pure repetition), and another running directly to the posterior STG when seeding in BA 44/45 (functional contrast: complex syntax). Tracking from the ventral premotor cortex and supramarginal gyrus seeds (functional contrast: pure repetition) revealed that both regions are connected to the temporal cortex. When seeding in the posterior STS (functional contrast: sentence-level semantics), we obtained a tract that runs within the arcuate fascicle in the direction of the frontal lobe and branches out into the angular gyrus. It connects the middle portions of the STG and the MTG and the precentral gyrus, without reaching the IFG.

Resulting dorsal tracts.

Ventrally, fibers from seeds in the frontal operculum and the anterior STS (functional contrasts: simple syntax), as well as from the anterior MTG (functional contrast: word-level semantics) pass through the extreme and/or external capsule. These ventral fibers follow the white matter along the temporal lobe (inferior fronto-occipital fascicle and inferior longitudinal fascicle) to the posterior temporal cortex and

Resulting ventral tracts.



the occipital cortex. Connections running via the uncinate fascicle to the temporal pole, as well as to the orbitofrontal cortex and the frontal pole are apparent in all ventral tractograms, but differently pronounced. Using our group analysis method, which allows us to compare tractograms directly by making a statistical analysis contrasting the three tractograms ($p < .001$, $k \geq 16$, uncorrected), we revealed that, compared to the other two seed points, the anterior MTG is most strongly connected to anterior parts of the MTG, whereas the anterior STS is most strongly connected to anterior parts of the STG and involves the uncinate fascicle most. The frontal operculum has more frontal connections, as well as more connections to the posterior temporal cortex through the white matter of the superior temporal lobe, whereas the anterior MTG and STS have more inferior connections to the posterior temporal cortex through the white matter of the middle temporal lobe. It appears that the inferior longitudinal fascicle is the fiber tract mostly involved in the connections of the anterior MTG and STS, whereas the frontal operculum, on the contrary, connects more via the inferior fronto-occipital fascicle.

Detailed fiber tract descriptions

In the following sections, we describe the detailed course of the fiber tracts as revealed in the group analyses.

Detailed descriptions
of the obtained
tractograms.

Seed left dorsal premotor cortex (activation cluster in pure repetition): The fibers passing through the dorsal premotor cortex connect the region locally with middle frontal gyrus, as well as pre- and postcentral gyrus. They additionally form two major tracts: One tract connects the region dorsally with posterior MTG, thereby sending out branches to the inferior parietal lobule. The other tract connects the region via the corticospinal tract with the brain stem. Additionally, there are connections to the middle insular cortex.

Seed left ventral premotor cortex (activation cluster in pure repetition): The fibers passing through the ventral premotor cortex connect the frontal cortex with the temporal cortex through posterior parts of the extreme and/or external capsule, thereby traveling along ample parts of the insular cortex. Additionally, some fibers run within the arcuate fascicle, and branch out into the supramarginal gyrus. Frontal portions

Figure 5.2 (preceding page): **Column 1 and 2:** fMRI results of the contrasts of interest overlaid on a rendered standard brain. Repetition activations appear in blue, comprehension activations in yellow, overlap is shown in green. The regions used as seed points for fiber tractography are indicated and outlined as white dots. **Column 3:** Statistically significant group-level results of the probabilistic fiber tracking. Arrows point at the seed regions used for fiber tracking which are outlined as white dots. For the overlap between tracts we refer to an interactive 3D online figure (<http://openscience.cbs.mpg.de/bihler>). **Last columns:** Representative slices (given in MNI coordinates and indicated as lines behind the other slices) demonstrating the fiber tracking results. Connectivity strength is given in t-values and represented as color gradient. For abbreviations see page xv.

reach pars triangularis, temporal portions reach middle STG and middle MTG.

Seed left supramarginal gyrus (activation cluster in pure repetition): The fibers passing through the supramarginal gyrus connect the region locally through the posterior external capsule with the insular cortex. They additionally form two major tracts: One tract connects supramarginal gyrus via the SLF III with ventral premotor cortex, the other

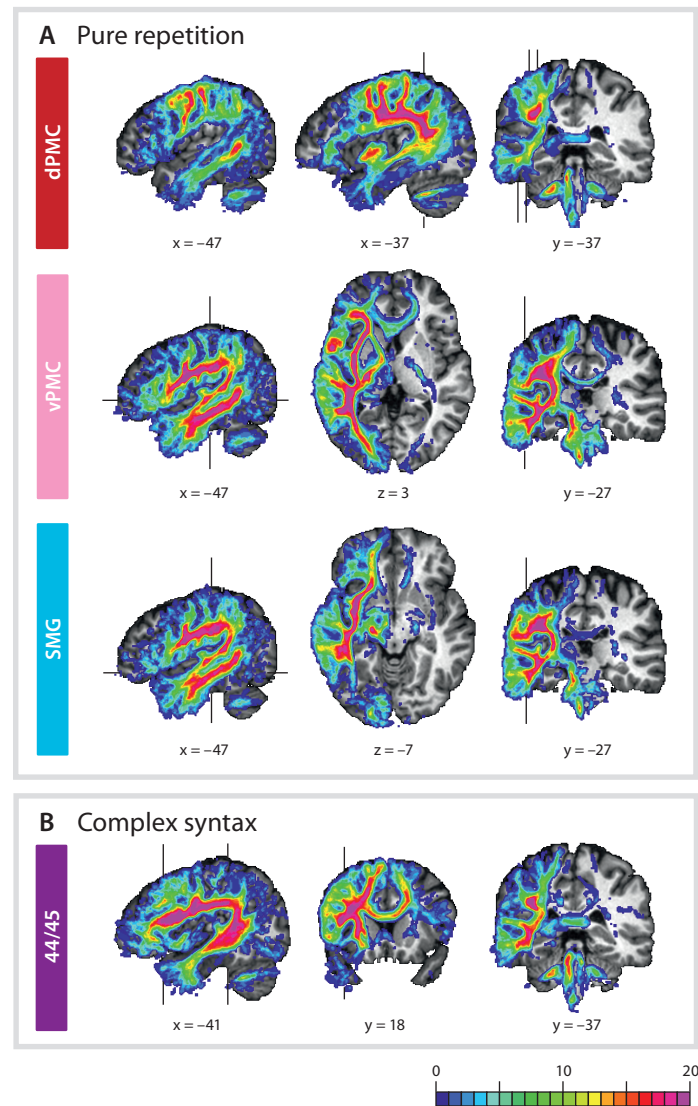
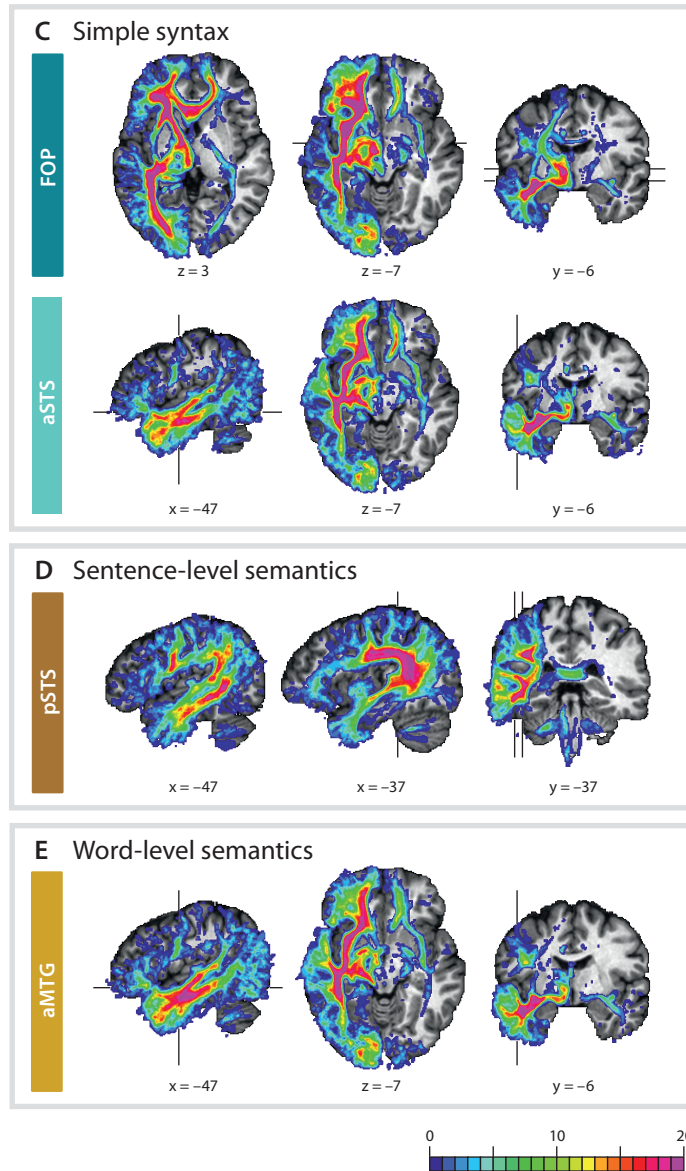


Figure 5.3: For caption and continuation see next page.



Continuation of Figure 5.3. Voxel-wise individual fiber tractograms of all subjects overlaid as density maps on representative slices (given in MNI coordinates and indicated as lines behind the other slices). Tractograms start from the investigated seed regions, projected on the individual brains. Colors indicate number of subjects demonstrating an above threshold connectivity strength in that specific voxel (see Section 5.2.5). See Figure 5.2 for position of seed regions and subadjacent functional contrasts. For abbreviations see page xv.

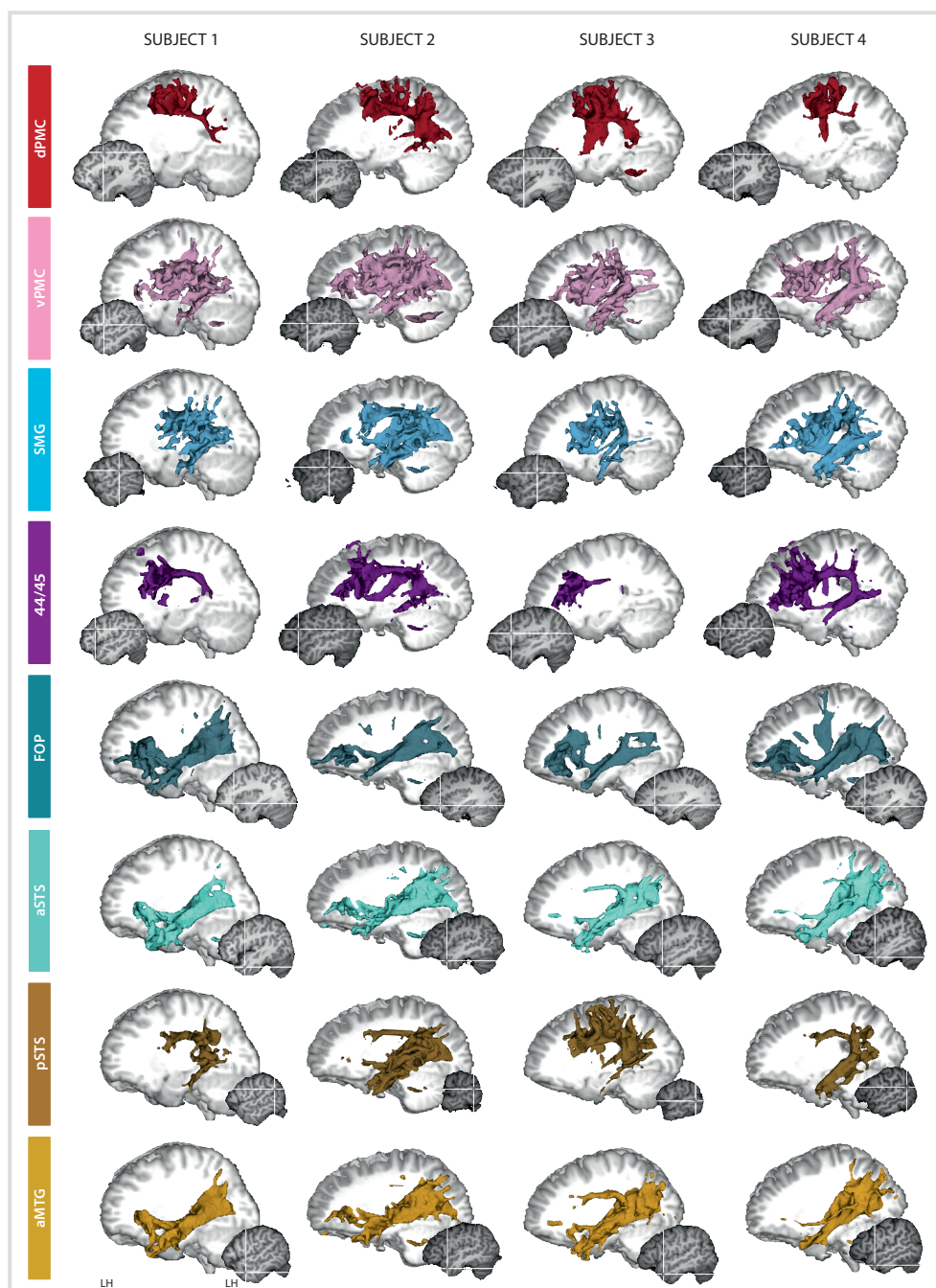


Figure 5.4: Fiber tractograms of four sample subjects. The individual seed points are represented using white crosshairs on individual slices. For abbreviations see page xv.

tract runs dorsally via the arcuate fascicle and connects supramarginal gyrus with middle STG and MTG, as well as with anterior insula following the inferior fronto-occipital fascicle.

Seed left BA 44/45 (activation cluster in complex syntax, repetition experiment): The fibers passing through Broca's area (BA 44/45) connect the region locally with pars opercularis and big parts of pars triangularis. Long fibers connect Broca's area, via the arcuate fascicle, with posterior portions of STG and STS. Additionally, a portion of the fibers passing through the seed connects Broca's area with the insular cortex. Other portions cross the midline to the contralateral hemisphere via the trunc of corpus callosum, connecting to the contralateral frontal lobe or follow the anterior thalamic radiation connecting to thalamus and brain stem structures.

Seed left frontal operculum (activation cluster in simple syntax, comprehension experiment): The fibers passing through the frontal operculum connect the region locally with the whole frontal operculum, rostral frontal pole and ventromedial prefrontal cortex. Long fibers connect the region following the inferior fronto-occipital fascicle and inferior longitudinal fascicle through the bottleneck of the extreme and/or external capsule and through temporal cortex with posterior temporal cortex and occipital cortex. Some fibers also run along the uncinate fascicle in anterior temporal direction. Additionally, a portion connects the frontal operculum, via the anterior thalamic radiation, with the thalamus and brain stem structures. Two other portions cross the midline to the ventromedial prefrontal cortex and occipital cortex, respectively, of the contralateral hemisphere via the splenium and genu of the corpus callosum, respectively.

Seed left anterior STS (activation cluster in simple syntax, repetition experiment): The fibers passing through anterior STS connect the region locally extensively with superior and middle regions of the temporal pole. Long distance fibers moreover form two bundles: one bundle running through the bottleneck of the extreme and/or external capsule following the uncinate fascicle to left and right ventromedial prefrontal cortices (via the genu of the corpus callosum); and a second running in posterior direction following the inferior longitudinal and inferior fronto-occipital fascicle to superior and middle posterior temporal cortex, as well as to occipital cortex. One portion also crosses the midline via the splenium of the corpus callosum to the contralateral occipital cortex.

Seed left posterior STS (activation cluster in sentence-level semantics, conjunction analysis): The fibers passing through posterior STS connect the region locally with other portions of the posterior STS, as well as with posterior STG and MTG. Long fibers connect the region ventrally via the SLF with middle portions of MTG and STG, as well as dorsally with the angular gyrus, and via the arcuate fascicle with precentral gyrus.

Seed left anterior MTG (activation cluster in word-level semantics, conjunction analysis): The fibers passing through the anterior MTG form two major tracts. One tract follows the inferior longitudinal fascicle and inferior fronto-occipital fascicle, extending to posterior temporal cortex and occipital cortex caudally. These fibers also cross hemisphere at the splenium of the corpus callosum and reach the contralateral occipital cortex. The other tract forms the uncinate fascicle and reaches ipsilateral orbitofrontal cortex and frontal pole.

5.4 Discussion

Aim and research question.

The present study aimed to reveal the different anatomy and different functional roles of the fiber tracts involved in language processing. Specifically, we investigated the human anatomy necessary for comprehending and repeating different aspects of syntactic and semantic information. We particularly asked the question: Can various fiber tracts involved in language processing be anatomically differentiated, and which fiber tract supports which specific linguistic function? Previously, there has been no consensus regarding which fiber tracts are involved in speaking and understanding, nor has there been any consensus about which aspects of language processing are supported by the different fiber tracts.

5.4.1 Dorsal fiber tracts

There are two different dorsal tracts.

Our main finding is that there are two dorsal fiber tracts involved in language processing that are functionally and anatomically separable: One fiber tract supports the mapping of auditory input to motor plans during repetition of speech, another transmits information relevant for the processing of syntactically complex structures. The first dorsal fiber tract (D1) involved in repetition connects the dorsal premotor cortex with the posterior MTG and branches out to the inferior parietal lobule, a region which was activated during repetition. This tract seems to have a direct fronto-temporal component, as well as an indirect fronto-parietal component which joins a parieto-temporal connection. Its direct component between the posterior temporal cortex and the premotor cortex was assigned to the SLF, its fronto-parietal component corresponds to the SLF II, and its parieto-temporal connection to the SLF-tp (see [Section 2.2.1](#)). The second dorsal fiber tract (D2), involved in processing complex syntax, is located inferior to D1 and connects BA 44 of Broca's area with the posterior STG directly. Such an inferior-running, direct connection between posterior temporal cortex and Broca's area corresponds to the AF (see [Section 2.2.1](#)).

Evidence for D1 being involved in repetition comes from Saur et al. (2008) and from studies on conduction aphasic patients that show deficits in repeating speech, and have lesions in their dorsal postcentral gyrus or their inferior parietal areas (see Buchsbaum et al., 2011). Also, in the present study, we observed branches of the D1 tract running to the postcentral gyrus and to the parietal lobule, thus corroborating an involvement of D1 in repetition. As D1 is left-lateralized in the current study, it seems that it primarily supports left-hemispheric language functions during repetition, as, for example, phonological processing and phonological working memory are located in the parietal cortex (Ravizza et al., 2004). Evidence for D2 being involved in processing complex syntax comes from artificial grammar learning studies and studies with primary progressive aphasia patients. White matter integrity in the arcuate fascicle and around left Broca's area was positively correlated with success in learning an artificial grammar (Flöel et al., 2009; Friederici et al., 2006a) and with performance in comprehending and producing complex syntactic structures (Wilson et al., 2011). Moreover, phylogenetic studies support the view that D2 is supporting an evolutionarily young and uniquely human function, i. e., higher linguistic processing, as it was found to be more pronounced in humans than in non-human primates, who are not able to process complex syntax (Rilling et al., 2008; Thiebaut de Schotten et al., 2012). Also ontogenetically, it has been shown that D2 is not present at birth and not yet fully pronounced in 7-year-old children, who still have problems in processing syntactically complex sentences (Perani et al., 2011; Friederici, 2012a; Brauer et al., 2011).

Evidence for
D1 and D2.

D2, as defined here, has to be distinguished from the pathway described by Catani and colleagues (2005), which terminated in what they called "Broca's territory", a region that encompasses more than only BA 44, and from the STG pathway described by Glasser and Rilling (2008), which mainly terminated outside BA 44, namely in the ventral premotor cortex (BA 6). In the present study, the ventral premotor cortex is connected to the supramarginal gyrus via a fiber tract previously described as the SLF III (see Section 2.2.1), as well as to the temporal cortex directly via a previously unnamed fiber tract (D3). Neither the ventral premotor cortex nor the supramarginal gyrus was, however, connected to BA 44 in our analysis. D3 thus seems to be different from D2, which terminates in BA 44 and which we suggest as corresponding to the arcuate fascicle and being involved in processing complex syntax. Hence, our additional tracking findings are in accordance with our interpretation of Catani et al.'s (2005) and Glasser and Rilling's (2008) results: They described the SLF III or D3 rather than the arcuate fascicle.

There is additionally
D3.

Also functionally, the SLF III and D3 were shown to be distinct from D2. On the one hand, the SLF III connecting the ventral premotor cortex and the supramarginal gyrus, was attributed a function in phonetic working memory during articulation (Maldonado et al., 2011; Duffau, 2008). On the other hand, a tract connecting the ventral

D3 is also
functionally distinct.

premotor cortex with the temporal cortex (which corresponds to D3), was attributed a function during sensory-to-motor mapping as a prerequisite for babbling (Perani et al., 2011). Contrary to other dorsal fiber tracts, this tract was shown to be already prominent at birth. It thus seems that D3, with its connections to the mouth area, is involved in a sub-function of repetition that is already present in newborns. In contrast, the fiber tract from the dorsal premotor cortex (D1), which we also delineated to be involved in repetition but which is not yet fully developed in newborns, seems to be involved in a sub-function of repetition that finally enables repetition of speech sequences, which newborns are still not able to perform. We thus speculate that D3 is involved in encoding of perceived phonetic and phonological information for motor output, which is necessary to support infant babbling and articulatory aspects later in life, whereas D1 is involved in the maintenance of the speech sequence in mind for motor output, an aspect of working memory that develops later during ontogeny than encoding (Thomason et al., 2009) in addition to having a role in auditory-input and motor-output mapping during speech repetition. This hypothesis is supported by the fact that D1 is connected to the posterior parietal cortex which was previously discussed as being involved in the maintenance phases of phonological working memory (Paulesu et al., 1993; Awh et al., 1996).

Interim summary
of dorsal tracts.

Taken together, our study solves the conflicting results of Friederici et al. (2006a) and Saur et al. (2008), with respect to the functional role of the dorsal fiber pathway, by demonstrating distinct dorsal pathways. Furthermore, our finding of different dorsal fiber tracts corroborates the model proposed by Friederici (2011), with the specification that the dorsal tract passing through Broca's area connects the frontal lobe with the posterior STG primarily, whereas a distinct superior direct and/or indirect tract connects the dorsal premotor cortex with the posterior MTG primarily. Both tracts are likely to variably continue inter-individually (and thus not be visible in our group results) to the anterior temporal regions, as well as connecting the superior and inferior temporal regions and the auditory cortex (e.g., Thiebaut de Schotten et al., 2012). The identification of a dorsal tract connecting to the MTG fits with the observation made by Glasser and Rilling (2008). However, they attributed a semantic role to the dorsal MTG pathway, because activation of the MTG has been reported frequently in fMRI studies on semantic processing. While, we do not argue against the MTG region being involved in semantic processing (as indicated by the semantic effects found in our fMRI analyses), we showed the dorsal pathway to the MTG to be involved in pure repetition, but not semantic processing. In contrast to Glasser and Rilling's conclusion, our conclusion is based on fMRI activations of the same subjects, on which both the fMRI analyses and the tracking was performed. We argue that, in order to map with motor plans, auditory information enters through connections via the MTG or the inferior parietal lobule into D1. The dorsal premotor cortex and surrounding areas, then probably subserve speech motor planning and control of repetition.

5.4.2 Syntactic and word-level semantic processing

A second finding of our study is that syntax is processed via both a dorsal and a ventral fiber tract, depending on the complexity of the syntactic structure. Our study reveals that syntactically complex structures are mediated dorsally via the arcuate fascicle, whereas syntactically simple structures are mediated ventrally, mainly via the inferior fronto-occipital fascicle and the uncinate fascicle. More specifically, we assume that the ventral fiber tracts support processing of local phrase structures or adjacent dependencies, and that this is a basic syntactic process which also applies during the comprehension of complex sentences. Additional processes that are required to understand complex sentences, but that are not necessary to understand simple sentences, like the analysis of distant or hierarchical dependencies, are supported by the dorsal fiber tract (Weiller et al., 2011; Friederici et al., 2006a).

Syntax is processed both dorsally and ventrally.

Our finding is corroborated by earlier fMRI based tractography studies on artificial grammar (Friederici et al., 2006a) and more recent studies showing that white matter integrity of both ventral and dorsal pathways is positively correlated with performance on a syntactic ambiguity task (Papoutsis et al., 2011), and performance on syntax comprehension (Griffiths et al., 2012; Rolheiser et al., 2011) and syntax production (Rolheiser et al., 2011) in stroke patients. Previously, most authors neglected the involvement of dorsal fiber tracts in syntactic processing (e.g., Saur et al., 2008) or did not investigate which kind of syntactic information (i.e., simple or complex structures) is processed dorsally, and which kind is processed ventrally (Papoutsis et al., 2011; Rolheiser et al., 2011).

Evidence for the finding.

Our finding is generally in line with the model by Friederici (2011) which assumes syntax to be supported by both dorsal and ventral fiber connections. However, based on the present results we can specify that in natural language processing, the relevant fiber tracts for processing of syntactically simple structures mainly seem to consist of the inferior fronto-occipital fascicle in addition to the uncinate fascicle, while processing syntactically simple structures in an artificial grammar environment was shown to involve mainly the uncinate fascicle (Friederici et al., 2006a).

Interim summary of syntactic processing.

The third main finding of the present study is that information relevant for word-level semantic processes is transmitted solely via ventral fiber tracts, encompassing the inferior fronto-occipital fascicle, the inferior longitudinal fascicle, and the uncinate fascicle. Also, cerebral electrostimulation studies suggest a semantic role for the inferior fronto-occipital fascicle (Mandonnet et al., 2007; Duffau et al., 2005) and, functionally compensable, the inferior longitudinal fascicle (Mandonnet et al., 2007) and the uncinate fascicle (Duffau et al., 2009). A recent tractography study on healthy participants strengthened the argument for the inferior longitudinal fascicle, and the fibers forming

Semantics is exclusively processed ventrally.

the inferior fronto-occipital fascicle, being involved in semantic processing (Wong et al., 2011). Our finding of bilateral semantic correlates, at least for repetition, supports this interpretation.

UF and IFOF for simple syntax, ILF also for semantics.

Remarkably, the ventral fiber tracts involved in semantic processing are overlapping but also different from the ventral fiber tracts involved in the processing of syntactically simple structures. The uncinate fascicle and fibers which run more superior through the bottleneck of the extreme and/or external capsule following the inferior fronto-occipital fascicle are stronger connected to the simple syntactic processing activation sites (anterior STS, frontal operculum) compared to the semantic activation site (anterior MTG). The inferior longitudinal fascicle, on the contrary, seems to be equivalently involved in transmission of semantic and simple syntactic information. Fibers specifically involved in the transmission of semantic information were found only locally in the middle temporal pole. Taken together, our findings are compatible with the model by Friederici (2011) insofar as semantic processing and simple syntactic processes are, at least partly, separable within the ventral pathway.

5.4.3 Sentence-level semantic processing

Sentence-level semantics involves AF and SLF-tp.

Lastly, the transmission of sentence-level semantic information, requiring the integration of semantic and syntactic information, is mainly supported by a dorsal pathway: Starting from the posterior STS, we obtained short-range connections to the STG and the MTG, and two long-range connections: one to the precentral gyrus, probably via the arcuate fascicle, and one to the angular gyrus, via the parieto-temporal SLF-tp (see the discussion about the nomenclature in Chapter 2). This tract's functional role is suggested to support syntactic-semantic integration, because the posterior STS is only activated when both syntactic and semantic information are available: The posterior STS was activated during semantic processes in the sentence environment, but not in the word list environment in the present study. Moreover, previous studies showed that superior temporal cortex is activated during natural grammar processing (Friederici et al., 2009; Bornkessel et al., 2005), but not during artificial grammar processing (Friederici et al., 2006a). Indeed, both the angular gyrus (Lau et al., 2008) and the posterior STS were previously hypothesized to play a role in syntactic-semantic integration.

The tracking is only indirect.

A limitation of the present study is that we cannot measure information transmission directly, but have to attribute the functional roles of fiber tracts indirectly. We tracked the fibers that run through a white matter area that was nearest to a functional activation peak. That this functional information is mediated via the observed fibers cannot be definitively demonstrated. However, as mentioned in the introduction, combining fMRI with DTI data is, at present, the best

noninvasive method for investigating the course and functional roles of fiber tracts.

5.5 Summary and Conclusion

In conclusion, the present study suggests the following model of the anatomy and functional roles of the fiber tracts involved in language processing (Figure 5.5):

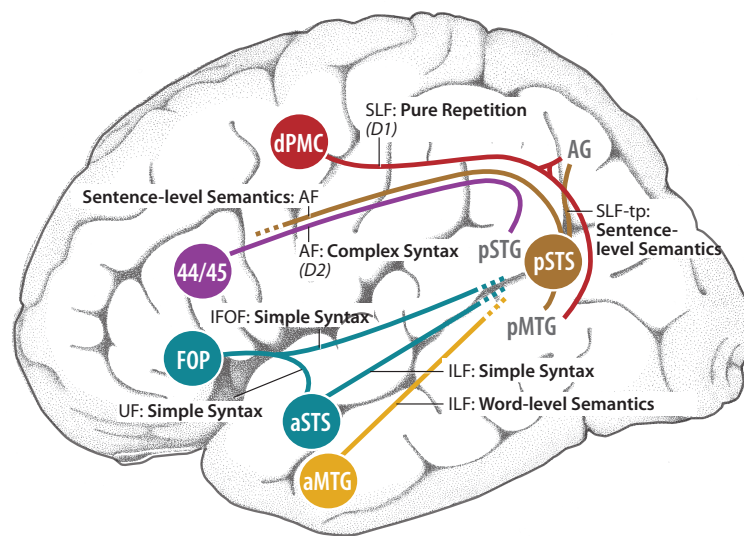


Figure 5.5: Simplified schematic outline of the model proposed by the tractography data of the present study. Lines represent the core long-distance left-hemispheric fiber tracts starting at the following seed regions: the dPMC (red), BA 44/45 (purple), the FOP (turquoise), the anterior MTG (yellow), and the posterior STS (ocher), laid on a rendered standard brain. Filled circles represent regions used as seed regions in the present study. Terminating regions are outlined; individual continuations of the tracts are however probable. Dotted lines are drawn if the continuations of the tracts are fanned out. D1, D2 = dorsal tracts as explained in Section 5.4. For other abbreviations see page xv.

Dorsally, one fiber tract (D1) connects the dorsal premotor cortex with the posterior MTG directly, or indirectly via the SLFII and the SLF-tp running through the parietal lobe, and is involved in mapping auditory input to motor plans during repetition. Another dorsal fiber tract (D2) connects BA 44/45 with posterior STG via the arcuate fascicle and is involved in processing syntactically complex structures. The arcuate fascicle also appears to be involved in the integration of syntactic and semantic information through branches to the posterior STS and the angular gyrus. Ventrally, the uncinate fascicle connects the anterior

Concluding
neurocognitive
model.

STS with inferior regions in the frontal lobe and is primarily involved in simple syntactic processing, as is the inferior fronto-occipital fascicle which connects posterior temporal regions with the frontal operculum. The inferior longitudinal fascicle connecting posterior with anterior temporal regions was demonstrated to be involved in both simple syntactic and word-level semantic processing.

Dorsally, repetition and complex properties, ventrally, simple properties are processed.

Taken together our findings indicate that, ventrally, “simple” linguistic properties, like word meanings and local syntactic structures, are transmitted between the temporal cortex and the inferior frontal cortex. Dorsally, “complex” linguistic properties, like sentence-level semantics and complex syntactic structures, are transmitted between the temporal cortex and the inferior frontal cortex. Additionally, there are phylo- and/or ontogenetically older dorsal tracts running from the temporal to the premotor cortex via the parietal cortex that play a role in mapping auditory input to motor plans, e. g., during repetition. The proposed model is based on a comprehensive study combined with a revealing statistical analysis; hence, it can serve as a reference for experiments investigating other cognitive functions and their supporting fiber tracts. Future studies will be useful to round off the model with respect to transmission of morphological and phonological information.

Chapter 6

Patient study: Language fiber tracts in edema patients

The tractability and integrity of fiber tracts within an edema, and the functional roles of long-range fiber tracts during language processing are controversial topics in the literature. In the present study, we pre- and postoperatively investigated the dorsal and ventral language fiber tracts of three patients initially presenting a peritumoral edema. We performed a test battery including experiments testing for (simple and complex) syntactic processing, as well as fiber tracking. We were successful in locating the tracts in the presence of an edema by lowering the fractional anisotropy threshold for streamline tractography. Moreover, the affected tracts demonstrated recovery after edema treatment and neurosurgery, both in terms of tractability and cognitive function. Concerning the functional roles of the arcuate, superior longitudinal, uncinate and inferior fronto-occipital fascicles, we found that the dorsal fiber tracts may be involved in the processing of complex syntax, whereas the ventral fiber tracts were involved in basic language functions.

Based, with modifications, on:

Gierhan, S. M. E., et al. (2012), "Tracking the language pathways in edema patients: Preliminary results.", In: "Informatik 2012", GI-Edition – Lecture Notes in Informatics. Bonn: Köllen Verlag.

Preface

Overview
of the chapter.

The tractography method which we applied on healthy participants (see [Chapter 5](#)) can only indirectly determine the functional roles of fiber tracts. Studying the language capacity of patients suffering from lesioned dorsal or ventral fiber tracts can provide more direct evidence as to which fiber tracts are essential for specific linguistic functions and which are dispensable or nonessential. Towards this aim, we designed a patient study which tests the language model by Friederici (2011) (see [Chapter 1](#)).

6.1 Introduction

Tractography
in patient studies.

In recent years, tractography of language fiber tracts has emerged as a valuable tool for presurgical planning of tumor resections (e.g., [Bello et al., 2008](#); [Mori et al., 2002](#); [Nimsky et al., 2005](#); [Papagno et al., 2011](#); [Yu et al., 2005](#))¹, intraoperative mapping of fiber tracts in order to achieve maximally safe tumor resection while preserving cognitive functions ([Bello et al., 2008](#); [Kuhnt et al., 2012](#); [Nimsky et al., 2005](#)), postoperative assessment (e.g., [Yu et al., 2005](#)), and the investigation of language deficits in tumor patients (e.g., [Bizzi et al., 2012](#)). Little is known, however, about the application of tractography in edema patients although patient studies can provide a good means for assessing which fiber tracts are essential for language processing and which are dispensable.

Study aim.

In the present study, we therefore aimed to clarify the use of pre- and postoperative tractography in edema patients, and to investigate, in a second step, which information fiber tracking can provide about the functional role of a tract during language processing. This has also direct implications for the prognosis and advisable extent of the tumor resection.

Hypotheses.

Concerning the application of tractography in edema patients we hypothesized the following: If a tract is affected by an edema preoperatively, but is tractable postoperatively after reduction of the edema, it must also have been present preoperatively, although masked by a reduced fractional anisotropy (FA) because of a high extracellular free water volume and reduced fiber volume due to the edema. If this proves true and is accompanied by a post-interventional symptomatic and behavioral improvement, then those cognitive functions are good candidates for the tract's functional role. Our hypothesis is supported by the finding that a vasogenic edema along a white matter tract can cause mild language impairments which can be completely reversed through edema treatment, hence suggesting an involvement of this tract in language ([Bizzi et al., 2012](#)). Concerning the specific functional

¹See [Bizzi \(2009\)](#) for an overview.

roles of the fiber tracts, we hypothesized, according to the model by Friederici (2011), processing of complex syntax to be a role of the arcuate fascicle (AF), speech repetition of the superior longitudinal fascicle (SLF) and/or the AF, simple syntactic processing of the uncinate fascicle (UF), and semantic processing to be a role of the inferior fronto-occipital fascicle (IFOF), also called the extreme capsule fiber system (ECFS).

To test our hypotheses, we studied three patients with peritumoral edemas pre- and postoperatively. We conducted both pre- and postoperatively fiber tracking and a battery of clinical tests and behavioral language experiments investigating the processing of complex and simple syntax during comprehension and repetition. We compared the results of the patients to those of healthy matched participants.

Methods of the present study.

6.2 Methods

6.2.1 Participants

We studied three patients (Pat01, Pat02, Pat03) pre- and postoperatively who showed a vasogenic edema around a brain tumor. Whereas the 62-year old Pat01 and the 46-year old Pat03 suffered from brain metastases, the 65-year old Pat02 suffered from a high-grade glioma (WHO IV). The tumor of Pat01 was located in the left anterior temporal lobe, and the tumors of Pat02 and Pat03 were located in the left parietal lobe. All patients presented with a pronounced vasogenic edema around the tumor which was treated with dexamethasone directly after admittance to the hospital. All patients reported problems in recalling words; Pat01 reported additionally disorientation and loss of appetite, Pat02 problems with his working memory, and Pat03 problems of arm coordination. All patients were male, right-handed and German native speakers who did not acquire a second language.

Three patients were studied.

Two groups of control participants were tested (Control group I (matched for Pat01 and Pat02): $n=9$; Control group II (matched for Pat03): $n=10$). The controls were healthy subjects without any neurological, psychiatric or language disorder that matched the patients in age (Control group I: 56–64 years; Control group II: 43–50 years), gender, handedness, native language, education, and second language acquisition (i. e., none before the age of 6).

Two control groups were studied.

All patients and healthy participants or adequate family members gave their written informed consent to participate in the study. The study was approved by the local ethical committee (University of Leipzig).

Approvals.

6.2.2 Experimental set-up

Pre- and
postoperative testing.

The patients were included into the study and first tested an average of 46 hours (range: 37–53 h) after admittance to the hospital. During the first testing session, all patients were exposed to decongestant medication. All patients underwent neurosurgery eight (Pat01), 12 (Pat02), and 14 days (Pat03) after admittance to the hospital. The patients were resubmitted to the neuropsychological testing 3–4 weeks after surgery (Pat01: 21 days; Pat02: 23 days, Pat03: 28 days). Each testing session lasted approximately two hours, during which the clinical and language tests were conducted. The order of behavioral tests was adjusted to the patients' ability. Additionally, anatomical brain scans were acquired before or after each session. For the behavioral testing of the control participants, the time of day, the intervals between sessions and tests, as well as the order of the tests were matched to the respective patients.

6.2.3 Behavioral tests and language experiments

Clinical tests.

A number of clinical tests were conducted for screening the general state of health and cognitive ability. We performed the d2 test to measure attention and concentration ability, the 3rd subtest of the German intelligence test "Leistungsprüfsystem" (LPS-3) to measure logical reasoning, as well as the forward and backward digit span tests (subtest 8) of the WIE 2006, the German adaptation of the WAIS-III to measure working memory capacity. To rule out a depression, a Visual Analog Scale (VAS) of the patient's mood, as well as the General Depression Scale (CES-D), that is the German version of the "Center for Epidemiological Studies Depression Scale", were conducted. To assess basic language capabilities, we performed the Token Test and the Repetition Test of the Aachen Aphasia Test (AAT).

Language
experiments.

Additionally, we performed two language experiments to specifically investigate the patients' abilities to repeat and comprehend German sentences of differing syntactic complexity. Stimuli and tasks were equivalent to the fMRI experiments that we performed in healthy participants (Chapter 3, Figure 3.2). However, in the patient study, only the meaningful stimulus material was used, and the patients and the healthy control subjects conducted the comprehension task during each trial of the comprehension experiment. Moreover, there was no rest period after the mini blocks. The trial design and timing characteristics were the same as in the studies on healthy participants.

6.2.4 Data analysis of the language experiments

Measures applied.

For the comprehension experiment, the percentage of correct button presses was assessed. For the repetition experiment, a repetition score per stimulus item was calculated in the following way: number of

correctly repeated words + 1 (if correct word order) + 1 (if no word was added) = a score of maximal 8 in case of correct repetition. These scores were then averaged over condition. All analyses were performed separately for each patient and the corresponding control group, as well as for each experiment (comprehension, repetition) using IBM SPSS Statistics (version 19).

The general ability to comprehend and repeat spoken sentences was assessed by comparing the ability of patients and control subjects to process simple sentences by means of one-sample t-tests. To determine the impact of the factor “syntactic complexity” on the repetition and comprehension performance of the control subjects, paired t-tests contrasting the performance on complex and simple sentences were calculated within the control groups. The control subjects’ difference between the two conditions (complex vs. simple sentences) was then tested against the patient’s difference using one-sample t-tests for both repetition and comprehension. This was done to see if the patient behaved significantly different from the controls, or, in other words, to see if the factor “syntactic complexity” had a different impact on the performance of the patient than on the performance of the control group, or if the patient’s performance is in a normal healthy range. The level of significance of all tests was set to 5 %.

Tests calculated.

6.2.5 MRI data acquisition and preprocessing

T1-weighted structural MPRAGE scans (TI=650 ms; TR=1300 ms; TR_A=10 ms; TE=3.5 ms; alpha=10°; FOV=256 x 240 mm²; 176 sagittal slices; spatial resolution = 1 x 1 x 1 mm³) and diffusion magnetic resonance imaging scans (TE=100 ms; TR=12.9 s; 128 x 128 image matrix; FOV=220 x 220 mm²; 88 axial slices (no gap); spatial resolution: 1.7 x 1.7 x 1.7 mm³, GRAPPA acceleration factor 2) were acquired on a whole-body 3 Tesla Siemens Verio magnetic resonance scanner (Siemens, Erlangen, Germany) equipped with an 32-channel head array coil. The diffusion sequence provided 60 diffusion-encoding gradient directions with a b-value of 1000 s/mm². Seven images without any diffusion weighting (b0) were obtained: one at the beginning of the scanning sequence and one after each block of 10 diffusion-weighted images as anatomical reference for offline motion correction.

Acquisition parameters.

The postoperative structural scan was reoriented to the sagittal intercommisural plane and the brain was segmented. The b0 images were used to estimate motion correction parameters of the diffusion magnetic resonance imaging sequence using the rigid-body registration (Jenkinson et al., 2002), implemented in FSL (FMRIB Software Library, University of Oxford, <http://www.fmrib.ox.ac.uk/fsl/>). We combined the motion correction for the diffusion magnetic resonance imaging data with the global registration to the T1 anatomy, corrected the gradient direction for each volume with the rotation parameters, and resampled the registered images to an isotropic voxel resolution

Analysis parameters.

of 1.7 mm. Finally, we computed the diffusion tensor, the three eigenvectors, and the FA value for each voxel (Basser et al., 1994). The preoperative structural image was matched to the postoperative brain volume using rigid-body registration, and the diffusion data was processed in the same way as the postoperative measurement.

6.2.6 Edema analysis

Segmentation and analysis of edema.

Edemas, tumors and resection cavities were manually segmented for each patient in the pre- and postoperative datasets using primarily the T2-weighted B0 images. The volume of the edemas, tumors and cavities were analyzed by summation of the affected voxels. The average FA within the edema was calculated by finding the arithmetic average of the FA of all voxels within the edema mask.

6.2.7 Fiber tracking

Tracking algorithm.

The diffusion tensor image was used for full-brain deterministic fiber tracking using an in-house implementation of the tensor deflection algorithm (Lazar et al., 2003) which deflected a computed streamline in each step by the local diffusion tensor and allowed for robust tracking in areas of low anisotropy. The algorithm was executed for all voxels within a brain mask which was created by shrinking the inner skull surface by 7 mm. This mask allowed us to reduce noisy endpoints of the streamlines. The examined fiber bundle was selected from the full-brain tracking using inclusion and exclusion masks adapted for each bundle.

Selection of mask regions.

Each bundle requires spatially distinct masks at two characteristic locations along the tract. For the dorsal fiber bundle (AF/SLF), one mask was placed in the temporal lobe near the temporoparietal junction and the second mask in the posterior frontal lobe (Catani et al., 2005; Mori et al., 2008). Streamlines crossing the extreme capsule and the thalamus were excluded. For the IFOF, one mask was placed in the frontal lobe and the other in the occipital lobe (Mori et al., 2008). Streamlines passing the thalamus were excluded. For the UF, one mask was placed in the rostral temporal lobe and the other in the inferior frontal lobe following the description of Ebeling & von Cramon (1992). The masks were individually adapted for each patient and control participant.

Adjustment of tracking.

To adapt the tracking algorithm to the low anisotropy within the edema, the threshold of the FA was lowered to 0.075. This value allowed tracking of fibers within the edema and excluding the tumor area and the ventricles. Lowering the FA threshold without any additional processing might, however, introduce false positive connections. Therefore, to eliminate streamlines leaving the bundle of interest, the tracking was performed in an adapted two step approach. First, the

fiber bundle of interest was selected, and the volume of the bundle was computed by selecting all voxels which were crossed by at least two streamlines. In this way, spurious single streamlines were excluded. Second, this mask was dilated by 1 mm and the streamline tracking was performed again within this limited volume. Finally, the same masks were applied again and the final bundle was extracted.

6.3 Results

6.3.1 Edema development

For each segmented edema region, the volume was calculated. Postoperatively, the volume of the edema was significantly reduced by 79–95 % in all patients (see Table 6.1). Also, the tumor volume was reduced. The mean FA in the region that was preoperatively affected by the edema increased postoperatively: slightly for Pat01, but tremendously for Pat02 and Pat03 (Table 6.2).

Edema volume reduced postoperatively.

Table 6.1: Development of the edema and tumor volume in the three patients studied, as well as postoperative volume of the resection cavity. Reduction is given in percent.

	Volume of edema [mm ³]			Volume of tumor [mm ³]		Volume of cavity [mm ³]
	Pre	Post	Reduction	Pre	Post	Post
Pat01	65366	3564	94.55	14583	4685	3700
Pat02	115124	24654	78.58	33076	0	16543
Pat03	81847	5237	93.60	4988	0	8733

Table 6.2: Development of the FA values in the region preoperatively identified as edematous.

	Mean FA preoperatively in edema	Mean FA postoperatively in edema region (segmented preoperatively)	Increase [%]
Pat01	0.210	0.225	7.13
Pat02	0.120	0.237	97.15
Pat03	0.147	0.263	78.17

6.3.2 Behavioral results of the clinical tests

The analysis of the d2 test revealed attention and concentration deficits for all three patients: Their numbers of processed items and their concentration performance were pre- and postoperatively more than one standard deviation below the means of the age matched control groups.

Attention and concentration of all patients were affected.

They ameliorated slightly postoperatively. Pat02's scores were below the scores of the other two patients. (See Table 6.3 for exact values.)

Table 6.3: Results of the d2 test. For the control subjects, average values are given, and standard deviation is given in brackets. Asterisks indicate results more than one standard deviation below the mean of the controls. d2-tn = total number of items processed; d2-cp = index of concentration performance.

	Preoperatively/1st session		Postoperatively/2nd session	
	d2-tn	d2-cp	d2-tn	d2-cp
Pat01	242*	105*	279*	113
Pat02	no data	no data	163*	63*
Control I	371.3 (62.96)	129.6 (22.55)	396.9 (68.93)	136.3 (24.18)
Pat03	231*	101*	250*	104*
Control II	469.9 (44.57)	178.5 (15.33)	472.1 (63.35)	183.4 (23.82)

Logical reasoning was affected, but improved postoperatively.

The LPS-3 was employed as a measure of the ability of logical reasoning (see Table 6.4). The control group of Pat01 and Pat02 demonstrated a mean of 20.7 (SD = 6.52) correct responses in the first session and improved to 23.7 (SD = 6.56) correct responses in the second session, while the control group for Pat03 scored higher with a mean of 29.2 (SD = 4.32) correct responses in the first session and 29.1 (SD = 4.65) correct responses in the second session. All three patients performed more than one SD below the mean of the control groups in the respective sessions, except for Pat01 who performed as good as his control group postoperatively. All patients improved their performance postoperatively: Pat02 was not able to complete the LPS-3 preoperatively, but had 10 correct answers postoperatively. Both, Pat01 and Pat03 improved from 16 (Pat01) and 22 (Pat03) correct responses preoperatively to 24 correct responses at the postoperative testing.

Table 6.4: Results of the LPS-3 test. For the control subjects, average values are given, and standard deviation is given in brackets. Asterisks indicate results more than one standard deviation below the means of the control groups.

	Preoperatively/ 1st session	Postoperatively/ 2nd session
Pat01	16*	24
Pat02	no data	10*
Control I	20.7 (6.52)	23.7 (6.56)
Pat03	22*	24*
Control II	29.2 (4.32)	29.1 (4.65)

Patients' working memory capacity was partially impaired.

The patients' forward digit spans ranged from 4 (Pat01) to 6 digits (Pat03) preoperatively, and ameliorated one digit postoperatively (see Table 6.5). The backward digit spans ameliorated from 3 digits preoperatively to 4 (Pat01) and 5 digits (Pat03) postoperatively. For Pat02, the Digit Span Test could not be acquired preoperatively; postoperatively, he showed a forward digit span of 5 digits, and a backward digit span

of 3 digits. Compared to the controls, Pat01 deviated from his control group, i. e., he did worse than his control group (more than one standard deviation below the controls' mean), regarding the forward digit span at both sessions but not regarding the backward digit span (see Table 6.5 for control group values). Pat02 did worse than his control group at both sessions and in both measures. Pat03 was only worse than his control group regarding the preoperative backward digit span. Postoperatively, he did as good as his control group.

Table 6.5: Results of the digit span test. For the control subjects, average values are given, and standard deviation is given in brackets. Asterisks indicate results more than one standard deviation below the means of the control groups. Fwd = forward digit span level; Bwd = backward digit span level.

	Preoperatively/ 1st session		Postoperatively/ 2nd session	
	Fwd	Bwd	Fwd	Bwd
Pat01	4*	3	5*	4
Pat02	no data	no data	5*	3*
Control I	6.3 (1.00)	4.0 (1.32)	6.4 (1.24)	4.2 (.83)
Pat03	6	3*	7	5
Control II	6.6 (.97)	5.0 (1.25)	7.2 (1.03)	5.1 (1.1)

None of the patients and control subjects presented a depressive disorder, as revealed by the German version of the CES-D and a Visual Analog Scale for Depression. Only Pat02 showed signs of a depressive mood according to the CES-D postoperatively, while his results on the Visual Analog Scale for Depression indicated no such condition.

No participant was depressive.

The evaluation of the Token Test of the AAT revealed that Pat02 had a severe language disorder preoperatively, but not postoperatively. Pat03 and Pat01 showed no or only a very mild disorder pre- and postoperatively. According to the results of the Repetition Test of the AAT, all patients showed only a very mild or no language disorder. However, this test was not conducted for Pat02 preoperatively.

Pat02's language abilities improved.

6.3.3 Behavioral results of the language experiments

In the language experiments, the control groups performed very well. In the comprehension experiment, they correctly answered on average 84.3 % of the simple sentences and 70.8 % of the complex sentences. In the repetition experiment, they had average scores of 7.84 on the simple sentences and 7.83 on the complex sentences (from a total score of 8.0). On both experiments, the younger and more highly educated control group performed slightly better than the other control group (see Figure 6.1; and Table 6.6 for details).

Both control groups performed well on the language tests.

The patients had a wide range of starting points in terms of performance (see Figure 6.1, and Table 6.6, Table 6.7, Table 6.8).

Table 6.6: Descriptive statistics of the language experiments of the patients and their control groups per session: Comprehension accuracy and repetition scores on simple and complex sentence conditions, as well as the difference values between performance on simple and complex sentences (simple–complex) are given. The comprehension accuracy is given in percent. The numbers of the repetition experiment indicate the repetition score (see Section 6.2.4; maximal value if everything was repeated correctly was 8.0). For the control subjects, the average values are given, standard deviation in brackets. Subimposed numbers indicate session number.

	Comprehension			Repetition		
	simple	complex	simple–complex	simple	complex	simple–complex
Pat01 _{pre}	no data	no data	no data	7.42	5.84	1.58
Pat01 _{post}	80	64	16	7.78	7.42	.36
Pat02 _{pre}	no data	no data	no data	no data	no data	no data
Pat02 _{post}	no data	no data	no data	7.12	4.73	2.38
Controls I ₁	82 (9)	65 (6)	17 (10)	7.89 (.09)	7.73 (.26)	.16 (.24)
Controls I ₂	81 (8)	71 (8)	10 (9)	7.85 (.14)	7.77 (.17)	.10 (.09)
Pat03 _{pre}	85	67	19	7.93	6.89	1.04
Pat03 _{post}	84	67	18	7.89	6.13	1.76
Controls II ₁	87 (7)	70 (10)	17 (9)	7.86 (.10)	7.92 (.08)	-.06 (.10)
Controls II ₂	87 (9)	77 (11)	10 (7)	7.75 (.24)	7.89 (.11)	-.13 (.26)

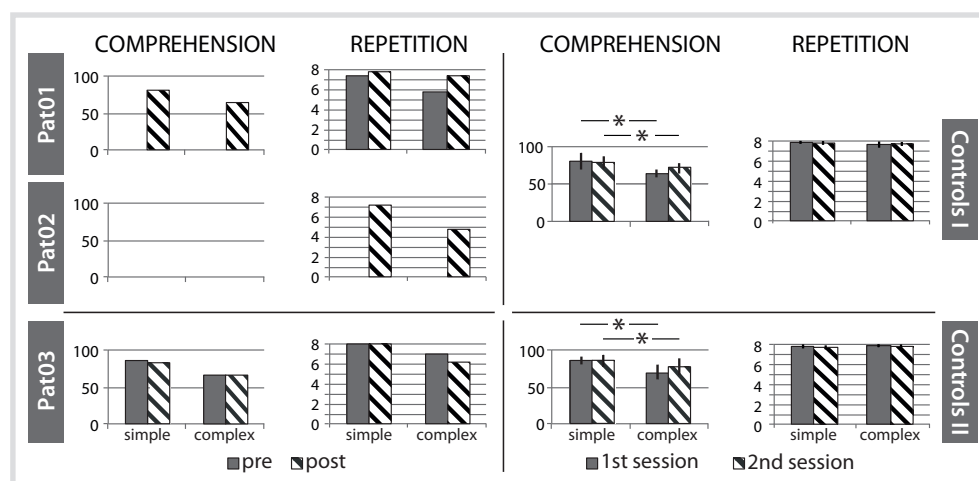


Figure 6.1: Results of the behavioral language experiments per patient/control group per session: Comprehension accuracy and repetition scores on simple and complex sentence conditions are given. The comprehension accuracy is given in percent. The numbers of the repetition experiment indicate the repetition score (see Section 6.2.4; maximal value if everything was repeated correctly was 8.0). Significant differences are marked with an asterisk (paired t-tests, two-tailed, level of significance = 5 %), error bars indicate standard deviation.

Pat01 was not able to perform the comprehension experiment preoperatively (Table 6.6), and performed significantly worse than his control group at the repetition experiment (Table 6.8). His performance improved postoperatively and was comparable to the control group for both the repetition and comprehension experiment. In the comprehension experiment, both the control group and the patient were influenced by syntactic complexity at both sessions, in that they comprehended complex sentences significantly worse than simple sentences (see Table 6.7, Table 6.8). The patient performed equal to his control group. Also in the repetition experiment, the control group performed worse on complex sentences than on simple sentences at both sessions; these differences, however, were not significant. The patient, on the contrary, was much more influenced by syntactic complexity, especially preoperatively, meaning that he repeated complex sentences much worse than simple sentences. His performance on repeating complex sentences greatly improved postoperatively. His performance on repeating simple sentences also improved slightly: The patient already performed well preoperatively but significantly worse than his control group, whereas the patient performed equally well as his control group postoperatively.

Pat01 improved in comprehension and repetition, especially during repetition of complex sentences.

Table 6.7: *Complex vs. simple sentence processing during comprehension and repetition in the control groups: significance values (p-values) of paired t-tests (two-tailed) between the two conditions (complex vs. simple sentences) are given. This was done to measure how much the healthy control groups are influenced by syntactic complexity. Subimposed numbers indicate session number. Significant differences are marked using asterices: * $p < .05$, ** $p < .01$, *** $p < .001$.*

	Comprehension	Repetition
Controls I₁	.001***	.076
Controls I₂	.009**	.308
Controls II₁	.000***	.081
Controls II₂	.002**	.137

Pat02 was not able to accomplish the language experiments preoperatively, and could only accomplish the repetition experiment postoperatively (Table 6.6). He performed significantly worse than his control group when first exposed to the repetition task, on both simple and complex sentences (Table 6.8). In contrast to his control group, the patient was heavily influenced by syntactic complexity (see Table 6.7, Table 6.8).

Pat02 was influenced by syntactic complexity during repetition.

Pat03, on the contrary, performed very well on the language experiments (Table 6.6), and his general ability to comprehend and repeat language (i.e., when only simple conditions are studied) did not differ significantly from that of his control group, neither pre- nor postoperatively (Table 6.8). In fact, he performed slightly better than his control group on repeating simple sentences. Repeating complex sentences, however, was worse than repeating simple sentences, both pre- and postoperatively. This is in contrast to his control group

Pat03 was pre- and postoperatively influenced by syntactic complexity during both experiments.

Table 6.8: Patients' performance compared to control groups' performance on the behavioral language experiments (comprehension and repetition). Shown are the results (p-values) of t-tests (two-tailed) comparing the performance on simple sentences ("General performance") of the patients with the performance of their respective control groups. This was done to compare the patients' general performance to comprehend and to repeat with healthy normal performance. Furthermore ("Syntactic complexity"), the results of t-tests comparing the accuracy difference between simple and complex sentences (simple-complex) of the patients with the difference of the respective control group are shown. These tests were performed to analyze and compare how much the patients and control groups were influenced by syntactic complexity. Pat01's post-operative comprehension performance was contrasted against the control group's comprehension performance during the first session as it was the patient's first exposure to the comprehension task. Asterisks indicate significance level: * $p < .05$, ** $p < .01$, *** $p < .001$.

	Comprehension		Repetition	
	General performance	Syntactic complexity	General performance	Syntactic complexity
Pat01 _{pre}	no data	no data	.000***	.000***
Pat01 _{post}	.463	.869	.151	.005**
Pat02 _{pre}	no data	no data	no data	no data
Pat02 _{post}	no data	no data	.000***	.000***
Pat03 _{pre}	.437	.439	.065	.000***
Pat03 _{post}	.346	.006**	.105	.000***

who did even slightly better on repeating complex than on repeating simple sentences. In other words, syntactic complexity had a strong impact on the patient's ability to repeat sentences, both pre- and postoperatively; the matched healthy controls, in contrast, were not influenced by syntactic complexity in their ability to repeat sentences (see Table 6.7, Table 6.8). During comprehension, on the contrary, both the matched healthy controls and the patient were influenced by syntactic complexity during both sessions. The controls, however, demonstrated a learning effect, meaning that they were less influenced by syntactic complexity during the second session compared to the first session. The patient, on the contrary, was equally strongly influenced by syntactic complexity during both sessions.

6.3.4 Tracking results

Table 6.9: Development of edema infiltration of the tracts: Percent of traced streamlines that were affected by the edema. For abbreviations see page xv.

	Preoperatively	Postoperatively
Pat01 – UF	100	0
Pat01 – IFOF	100	0
Pat02 – AF/SLF	100	96
Pat03 – AF/SLF	99.28	0

Pat01: At least IFOF recovered.

In Pat01, the UF and the IFOF were studied, as the localization of the tumor in the left anterior temporal lobe was most likely to affect these tracts. The resulting fiber tracts are illustrated and compared to

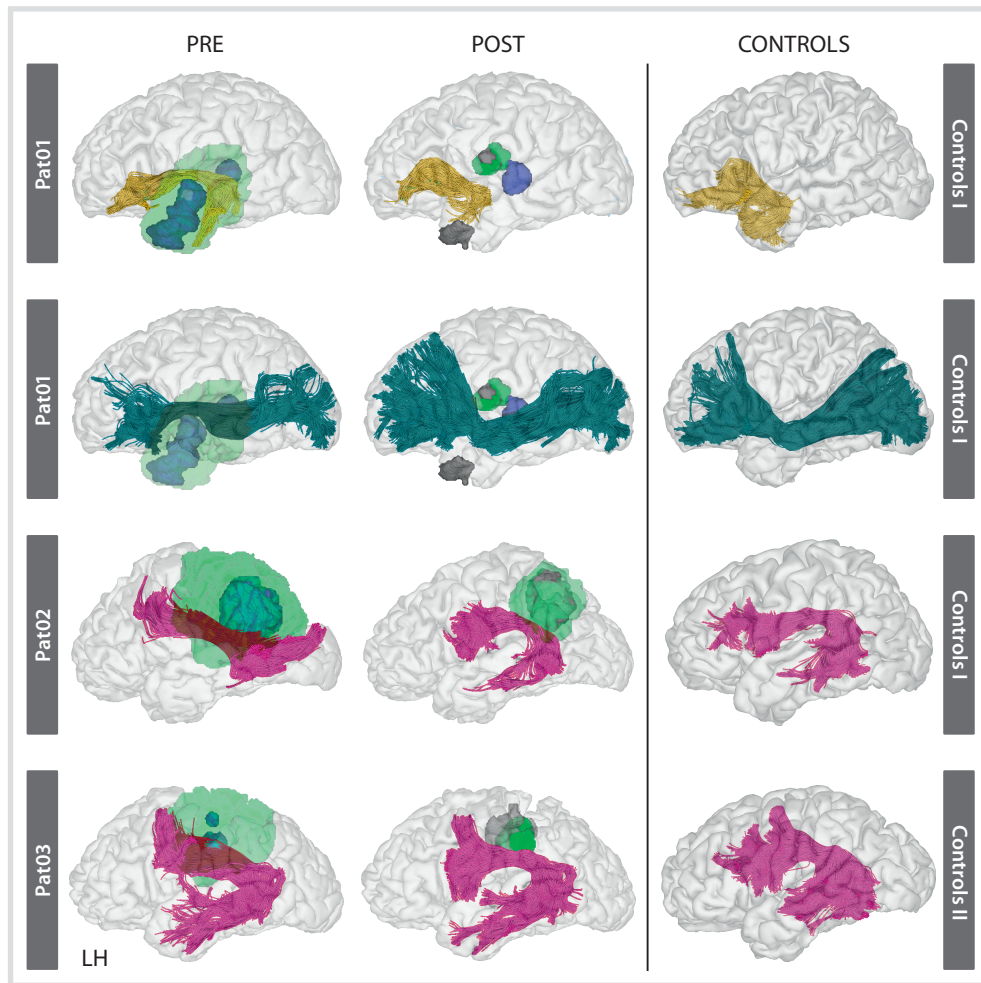


Figure 6.2: Results of pre- and postoperative fiber tracking per patient and for sample subjects of the respective control groups. Fibers are displayed in 3D figures as streamtubes: uncinate fascicle (yellow), inferior fronto-occipital fascicle (turquoise), and arcuate/superior longitudinal fascicle (reddish purple). Edema is shown in green, tumor in blue, resection cavity in gray.

a healthy control subject in [Figure 6.2](#). Preoperatively, both tracts were affected by the edema at every point of the transverse section whereas they were completely unaffected by the remaining edema postoperatively ([Table 6.9](#)). The volume of the tracts developed differently: Whereas the UF volume decreased postoperatively, the IFOF volume increased and reached the average volume of the control group's tract ([Figure 6.3](#)). Both tracts demonstrated a postoperatively increased FA which was near the FA value of the control group's fiber tract, at least for the UF ([Figure 6.4](#)). The FA values of the extra-edematous parts of both tracts were roughly the same pre- and postoperatively, as was the postoperative mean FA of the complete fiber tract. At least in case of the

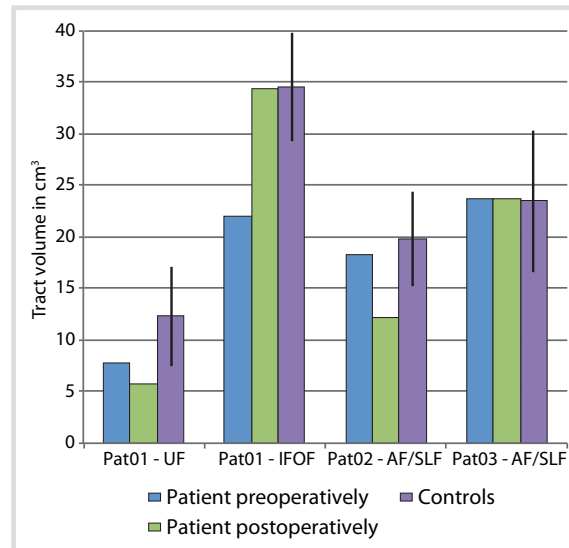


Figure 6.3: Volume of each tract per patient/control group in cm^3 . Error bars represent standard deviation. For abbreviations see page xv.

UF, these values were comparable to the UF's average FA of the control subjects. These FA values suggest that the fiber tracts were functioning again after treatment. This is also suggested, at least for the IFOF, when comparing the course of the recovered fibers with the course of the fibers in the control group which appear similarly (Figure 6.2).

Pat02: AF/SLF only slightly recovered.

In Pat02, the dorsal fiber tracts, encompassing probably the AF and/or the SLF, were studied. Preoperatively but also postoperatively, the fiber bundle was affected by the edema at almost every point of the transverse section (Table 6.9). Whereas the bundle's volume was equivalent to that of the control group, the volume was postoperatively considerably decreased (Figure 6.3). The FA of the parts of the tracts that were located within in the edema preoperatively was very low, but, at both data points, high in the parts of the tract located outside the edema. The outside FA was comparable to the postoperative mean FA of the complete tract which was, however, still more than one standard deviation below the FA of the control group's tract (Figure 6.4). Taken together, the AF/SLF bundle of Pat02 was still affected by the edema postoperatively, but to a lesser extent then preoperatively. This is reflected in higher postoperative FA values that are, however, significantly below those of the healthy control group, probably as the tract is still affected by the edema (Figure 6.2).

Pat03: AF/SLF recovered.

In Pat03, the AF/SLF was studied, too. The fiber bundle was affected by the edema preoperatively at almost every point of the transverse

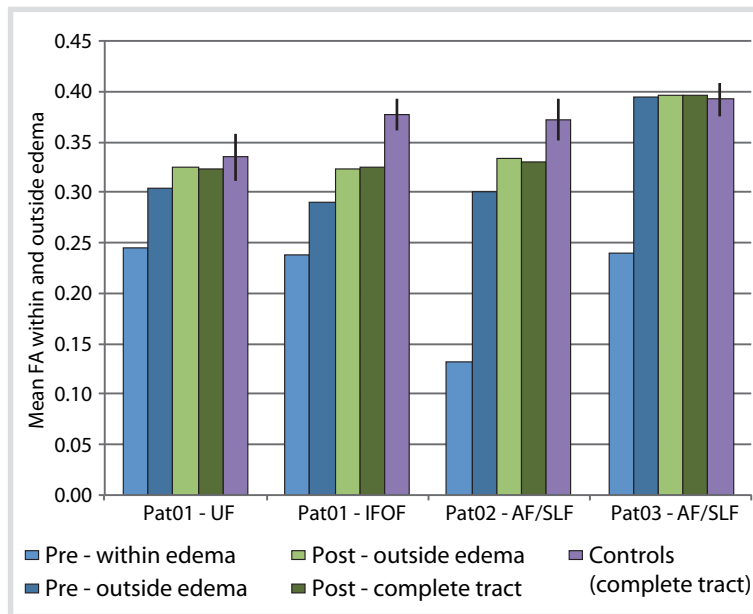


Figure 6.4: Mean FA of those parts of the bundles located within and outside the edema, and mean FA of the complete bundle, per bundle per patient (blue, green), respectively per control group (lavender). Represented are the average FA of those bundle parts located within the edema preoperatively (light blue), the average FA of those bundle parts located outside the edema preoperatively (dark blue), the average FA of those bundle parts located outside the postoperatively remaining edema (light green), the average FA of the complete fiber bundle postoperatively (dark green), as well as the average FA of the complete fiber bundle of the control subjects (averaged over subjects). Error bars represent standard deviation. For abbreviations see page xv.

section (Table 6.9), which is reflected in a low FA of those parts of the tract that are located within the edema preoperatively. Postoperatively, the bundle was unaffected by the edema and also the FA values were comparable to those of the matched control group's tract (Figure 6.4). The volume and the profile of the bundle were pre- and postoperatively remarkably similar to the volume and the profile of the healthy control group's bundle (Figure 6.3 and Figure 6.2).

6.4 Discussion

In the present study, we examined pre- and postoperative fiber tracts in edema patients to investigate the amount of fiber recovery within an edema, and the functional roles of dorsal and ventral language fiber tracts. We hypothesized that a postoperatively tractable fiber pathway is also existent and anatomically intact preoperatively, and should be traced by using an appropriate tracking algorithm combined with a reduced FA value as threshold. If this were the case, this would have

Overview
of the study.

direct implications for the presurgical planning and the amount of resection during neurosurgery. Moreover, we hypothesized that we can make claims about the functional roles of fiber tracts by additionally studying the clinical symptoms: If a certain cognitive function is symptomatic preoperatively but recovers postoperatively, the preoperatively affected but postoperatively recovered fiber tract should be involved in this function. This would directly impact the prognosis of the patient with regard to the cognitive functions he can perform after neurosurgery and treatment of the edema.

Lowering the FA threshold enables tracking through an edema.

With regard to the first hypothesis, our data indeed show that it is possible to do reasonably robust fiber tracking through an edema. The long-range fiber tracts that proved present postoperatively could be traced preoperatively when lowering the FA threshold to 0.075 and using a tensor deflection tractography algorithm in the three patients. A similar finding was achieved earlier for tractography through tumor tissue (Akai et al., 2005). Thus, it is highly recommended to lower the FA threshold in the process of presurgical planning. Doing this, the neurosurgeon could be saved from resecting white matter which may regain function again after intervention. Lowering the FA threshold, however, might result in false positive tractography results as shown in Pasternak et al. (2009). The tracking result must therefore be interpreted with caution. Thus, we only discuss the central parts of the fiber tracts which appear to be more robust than peripheral tract parts. An alternative method for fiber tracking in edema is free water elimination using a multiple compartments model (Pasternak et al., 2009). This approach produces increased FA values in the edema but needs additional constraints to stabilize this process and is less robust than the single tensor fit we used.

White matter function can recover through treatment.

Our data furthermore indicate that the white matter may recover through edema treatment. In all patients, the average FA of the fiber bundles that preoperatively passed through the edema increased postoperatively after reduction of the edema volume by around 78–95 %. This improvement was accompanied by an improvement of the cognitive behavior, suggesting that the recovered white matter had regained function. Reasons for the recovered white matter function after neurosurgery could be, apart from a mild improvement in the general state of health, both reduced edema volume as result of the edema management, as well as reduced pressure as result of the resection of the tumor. Moreover, other parts of the brain could have taken over the functional role of the respective tract within the scope of plasticity processes, thus explaining the functional improvements. However, it is rather unlikely that plasticity takes place within four to six weeks without special training (see Duffau, 2006). Rather, the high potential for the recovery of white matter through neurosurgery and edema treatment is an important argument for retaining as much of the white matter as possible during resection.

Taken together, it appears that the tracts are not destroyed by the edema but that only their functions are suppressed preoperatively due to the edema, with a high probability of recovery postoperatively. Comparing (recovered) postoperative with (bad or missing) preoperative behavior thus enables determination of the functional role of a tract.

Method for acquiring functional roles of fiber tracts.

Concerning the functional roles of the ventral language fiber tracts, the UF and the IFOF, we investigated one patient (Pat01) who showed a tumor and an edema in the anterior temporal cortex, covering the UF and the IFOF, which were discussed as being involved in comprehension of simple syntax (Friederici et al., 2006a; Wilson et al., 2011) and semantic processing (Mandonnet et al., 2007; Saur et al., 2008). Both the UF and the IFOF showed higher FA values postoperatively. The patient's behavioral results demonstrated an improvement in both repeating and comprehending simple sentences. We explain the behavioral improvements with a recovery of the ventral language pathways, which we assign to word-level semantic as well as simple syntactic processes occurring during both comprehension and repetition of sentences. Thus, it seems that intact ventral language pathways, i. e., intact UF and/or IFOF, are relevant for performing basic language processes, like handling word meanings or simple syntactic structures. This is underpinned by the observation that Pat03 demonstrated intact basic language functions while demonstrating intact ventral pathways. It is, however, also possible that a slight improvement in the general state of health of Pat01 accounts for the improvements in the language experiments.

UF and IFOF are associated with basic language abilities.

Concerning the functional roles of the dorsal language fiber tracts, the AF and the SLF, we investigated two patients (Pat02, Pat03) who showed a tumor and an edema in the parietal cortex, covering the AF and/or the SLF, which were discussed as being involved in comprehension and production of complex syntax (Friederici et al., 2006a; Wilson et al., 2011), and speech repetition (Saur et al., 2008). However, the extent of the edemas and/or the pressure of the tumors were too pronounced to affect the AF or the SLF separately. We can, therefore, only speculate about the functional roles of both tracts in conjunction, not individually.

Acquiring the functional roles of the dorsal tracts.

In Pat02, the ability to repeat and comprehend recovered only slightly. He repeated complex sentences significantly worse than simple sentences, performed overall worse than his control group and could not perform the comprehension experiment at any time. His behavioral performance is, though, in accordance with his tractography results: The patient's dorsal bundle was still postoperatively affected by the lesion. In Pat03, repetition and comprehension performance were already good preoperatively, and did not change dramatically postoperatively. It is however remarkable that Pat03 generally performed worse on complex than on simple sentences in both experiments at all data points. This performance is deviant from the performance of the healthy control group.

AF and/or SLF may be associated with complex syntax.

Handling complex syntax is sensitive to an intact brain system.

From this state of affairs we cannot conclude about the functional roles of the dorsal fiber tracts: Despite a good recovery of the dorsal language fiber tracts in Pat03, the ability to perform complex sentences remained impaired. It may be that the AF and/or the SLF is involved in and even necessary for the processing of complex syntax, which would corroborate the finding of Friederici et al. (2006a). However, the present study shows that the AF and/or the SLF are not sufficient for processing complex syntax. Possibly, an intact cognitive system is a prerequisite for proper processing of complex syntax. Processing complex syntax seems to be very sensitive to changes in the brain following injuries and to depend more than other functions on an intact cognitive system.

6.5 Summary and Conclusion

Ventral tracts support basic linguistic functions, dorsal tracts complex linguistic functions.

We demonstrated that it is possible to trace a fiber tract that passes through an edema. Moreover, we showed that recovered diffusivity values in a tract preoperatively affected by an edema go along with recovered cognitive behavior through edema treatment and neurosurgery. The ventral running UF and/or IFOF demonstrated involvement in basic language processes. The dorsal running AF and/or SLF may be involved in the processing of complex syntax, with processing of complex syntax being, however, very sensitive to pathological changes in the brain. Our findings are based on three patients only, thus requiring further studies. Moreover, cases that show a clearer segregation of the affected tracts, and/or of the ability to repeat and process complex syntax would push forward our understanding of language fiber tracts.

Chapter 7

General discussion

Preface

The following sections first recapitulate the context of the presented pieces of work ([Section 7.1](#)). Second, they summarize and discuss the results from the perspective of different linguistic functions ([Section 7.2](#)). This is followed by some remarks concerning the newness, importance and generalizability of the findings ([Section 7.3](#)), as well as limitations of the presented studies ([Section 7.4](#)). The chapter closes with an overview of open questions ([Section 7.5](#)), and provides some concluding remarks ([Section 7.6](#)).

Overview
of the chapter.

7.1 Summary of the studies

The present work aimed at investigating the anatomy and functional roles of fiber tracts involved in phonological and motor aspects of speech repetition, as well as in syntactic and semantic aspects of both sentence repetition and comprehension. Specifically, the fiber tracts supporting complex syntactic, simple syntactic, word-level semantic and sentence-level semantic processing were investigated. For this purpose, the existing literature was reviewed, and several empirical studies on both healthy and affected adults were conducted.

Research question.

[Chapter 2](#) first reviewed the available literature concerning the anatomy and functional roles of fiber tracts involved in auditory language processing. Although several studies have been conducted in recent years, there is still much disagreement and confusion concerning the course, the nomenclature and the functional roles of language fiber tracts. The chapter therefore concluded with a neurocognitive model

Literature review.

(Figure 2.3) demonstrating—based on what is currently known—the most probable course and functional roles of the language fiber tracts.¹

Motivation for the empirical studies.

Although there is already a certain basis on which a neurocognitive model can be formulated, the empirical evidence for the model is still sparse; for nearly each functional role, the basis consists of a few studies only. Thus, we performed additional empirical studies to further elucidate the anatomy and functional roles of the fiber tracts involved in auditory language processing. We conducted two related fMRI studies in healthy participants (Chapter 3, Chapter 4) that served as basis for a tractography study (Chapter 5), and performed a second tractography study in edema patients of which the results were correlated with the patients' behavioral performance (Chapter 6). All these studies addressed the neural correlates of speech repetition and comprehension.

fMRI studies.

The first fMRI study (Chapter 3) investigated the key brain regions supporting syntactic and semantic processes during sentence comprehension in healthy participants. Specifically, those brain regions that process syntactic structures of differing complexity were examined, as well as those that process word meanings and the overall sentence meaning. The second fMRI study (Chapter 4) investigated the key brain regions supporting phonological and motor aspects, as well as syntactic and semantic processes during sentence repetition, and compared the results with the results from sentence comprehension.

Tractography study on healthy participants.

The key brain regions then served as starting points for fiber tracking (Chapter 5) to investigate the fiber tracts supporting these various cognitive functions. The chapter concluded with a new neurocognitive model (Figure 5.5) describing the course and functional roles of the fiber tracts involved in the investigated aspects of language processing: pure repetition, processing of simple and complex syntax, as well as processing of word-level and sentence-level semantics.

Tractography study on patients.

The patient study (Chapter 6) finally examined repetition and comprehension of sentences of varying syntactic complexity in patients with affected ventral (one patient) and dorsal pathways (two patients). The patients suffered from a brain tumor plus surrounding edema which were treated medicinally and neurosurgically. The treatment was thought to curtail the lesion and to recover the functioning of the fiber tracts. To study the functional roles of the fiber tracts, behavioral tests and tractography were applied before and after the treatment. The behavioral abilities the patients lacked before recovery of the fiber tracts were compared to the abilities they demonstrated after recovery of the fiber tracts in order to infer the functional roles of the tracts. The results of the patient study represent another piece of empirical evidence for the functional roles of language fiber tracts.

¹Some of these tracts and functional roles have also been suggested in the four pathway model of Friederici (2011) on the basis of which we formulated the hypotheses for the presented empirical studies.

7.2 Results and Discussion

In the following sections, the main results of the present thesis will be summarized and interpreted in light of the two suggested neurocognitive models (Figure 2.3, Figure 5.5), and discussed along with the contributions of the patient study. The key points of the discussion are illustrated in condensed form in Figure 7.1.

7.2.1 Speech repetition

The literature review (Chapter 2) suggested that SLF III mediates articulatory aspects of repetition, SLF-tp mediates phonological aspects, and a direct or indirect temporo-frontal connection to dorsal PMC, probably encompassing SLF II, mediates further aspects of repetition, e. g., motor planning and control.

Literature review:
Fiber tracts involved
in repetition.

Our empirical findings support these tracts as being involved in phonological, phonetic and/or motor aspects of speech repetition. We revealed the left ventral PMC, the supramarginal gyrus, and the dorsal PMC as key regions for pure repetition, i. e., speech repetition that is free from semantic content and syntactic structure, which only represents phonological, phonetic and motor processes (Chapter 4). Tracking from these regions delineated two long-range fiber tracts as involved in pure repetition (Chapter 5): One inferior running tract connects the ventral PMC with the temporal cortex and sends out branches to the supramarginal gyrus. It is composed of the SLF III connecting the ventral PMC with the supramarginal gyrus, and a parieto-temporal part connecting the supramarginal gyrus with the temporal cortex. A superior running tract (which we called D1) connects the dorsal PMC with the posterior MTG, and sends out branches to the AG. It is composed of the fronto-parietal SLF II and the parieto-temporal SLF-tp. The present methodology cannot decide if these pathways also comprise fibers which connect the frontal and temporal cortices directly, as the study by Saur and colleagues (2008) suggested.

Tractography studies:
Fiber tracts involved
in repetition.

The SLF III, connecting ventral premotor cortex with supramarginal gyrus, was attributed an articulatory function (Maldonado et al., 2011; Duffau, 2008) whereas the functional role of the tract connecting supramarginal gyrus with temporal cortex is not yet clear (see Section 2.2.1). Notably, these parieto-temporal fibers could also be part of a direct tract connecting ventral PMC with the temporal cortex. Such a tract has been demonstrated to be existent already in newborns, and to be still present in the adult brain (Perani et al., 2011). This ventral PMC tract with its connections to the mouth area was attributed a function in sensory-to-motor mapping. More specifically, infants are already able to babble and to imitate the sounds of adults while being limited in their verbal working memory capacity (Thomason et al., 2009). Therefore, we argue that it is encoding aspects of sensory-to-motor

Inferior dorsal tracts
may support
articulation and
encoding for
repetition.

mapping which is supported by this ventral PMC tract connecting ventral premotor cortex to the temporal cortex and/or by that part of the tract that connects supramarginal gyrus with temporal cortex.

Superior dorsal tracts may support maintenance for repetition.

D1, on the contrary, which we also delineated as being involved in repetition, is not yet fully developed in newborns (Perani et al., 2011). D1 thus seems to support a sub-function of repetition that newborns are not yet able to perform which may be the maintenance of phonetic and phonological information in mind for motor output, an aspect of working memory that develops late during ontogeny (Thomason et al., 2009). This hypothesis is supported by the fact that the dorsal premotor tract is connected to the posterior parietal cortex which has been discussed being involved in the maintenance phases of phonological working memory (Paulesu et al., 1993; Awh et al., 1996).

Summary.

In sum, speech repetition is primarily supported by dorsal fiber tracts. An inferior tract connecting the ventral premotor cortex via the supramarginal gyrus with the temporal cortex may subserve articulation and encoding of phonetic and phonological information for motor output. This tract comprises the fronto-parietal SLF III and a parietal-temporal component, but may also comprise fibers directly connecting the ventral PMC with the temporal cortex. A superior tract connecting the dorsal premotor cortex via the angular gyrus with the posterior temporal cortex may subserve speech motor planning and control aspects of repetition, as well as the maintenance of phonetic and phonological information in mind for motor output. This tract comprises the fronto-parietal SLF II and the parietal-temporal SLF-tp, but may also comprise fibers directly connecting the dorsal PMC with the posterior temporal cortex.

7.2.2 Simple syntactic processing

Literature review: Simple syntax is supported by UF and/or IFOF.

The literature review in Chapter 2 suggested that simple syntactic processing is supported by ventral fiber tracts, i.e., the UF and/or the IFOF. The empirical evidence for that is, however, sparse. Some authors actually suggest that ventral tracts are dispensable when it comes to syntactic processing, implying that syntactic information is primarily transmitted dorsally (Wilson et al., 2012).

Healthy participants: Simple syntax is primarily supported by UF and IFOF.

Our studies on healthy participants corroborate the assumption of ventral tracts being involved in simple syntactic processing. We revealed the left frontal operculum (during sentence comprehension, see Chapter 3) as well as the left anterior STS (during sentence repetition, see Chapter 4) to be key areas for simple syntactic processing. Fiber tracts connecting to these areas are the UF, the IFOF, as well as the ILF (see Chapter 5). We observed the UF and the IFOF to be primarily dedicated to simple syntactic processing, whereas the ILF, on the contrary, was dedicated to both simple syntactic processing and semantic pro-

cessing, i. e., the tract connected equally strongly to the key areas for simple syntactic and semantic processing.

Our patient study strengthens these findings by suggesting that, for the processing of simple syntax, ventral pathways are essential: The patient—demonstrating impaired ventral tracts but intact dorsal tracts—performed worse on simple syntactic structures than his healthy controls, and worse than postoperatively when his ventral pathways were recovered. Ventral pathways seem therefore to be essential for processing simple syntax. This is contrary to the statement that ventral pathways are dispensable for simple syntactic processing (Wilson et al., 2012). This statement is based on patients who demonstrated primary progressive aphasia which is a slowly progressive degeneration disorder. Therefore, these patients may have gradually got used to the degeneration and non-availability of the ventral pathways resulting in the use of dorsal pathways for simple syntactic processing, whereas our patient demonstrated that the ventral pathways are essential for simple syntactic processing in non-chronic patients whose brain networks could not yet rearrange, as well as in the healthy brain. However, we have to add that our patient also performed poorly on other cognitive tests preoperatively. It is thus possible that not the impairment of his ventral pathways, but his poor general state of health accounted for his poor performance, also on simple syntactic structures. With the present patient case we, hence, cannot determine whether ventral pathways are dispensable or essential for processing of simple syntax.

Patient study:
Ventral pathways are essential for simple syntax.

Taken together, we showed that the left frontal operculum as well as anterior superior temporal regions process simple syntax. These cortical regions are connected with other brain regions primarily via the UF and IFOF, but also via the ILF. These tracts are, hence, good candidates for the mediation of simple syntactic processes. If these ventral tracts are constantly not available, dorsal tracts may take over simple syntactic processing.

Summary.

7.2.3 Complex syntactic processing

The literature review in Chapter 2 suggested the AF to subserve complex syntactic processes. The AF was defined as directly connecting Broca's area, i. e., primarily BA 44, to the posterior temporal cortex.

Literature review:
Complex syntax is supported by AF.

Our studies on healthy participants corroborate this finding with respect to sentence repetition: A border region between the left BA 44 and BA 45 was active during repetition of complex syntactic structures, and was directly connected to the posterior STG via the AF. We are the first to describe the AF as being involved in complex syntactic processes during repetition. Our study, however, could not make any conclusions about the fiber tracts involved in complex syntactic processing during

Healthy participants:
Complex syntax during repetition is supported by AF.

comprehension (see for a discussion of this issue and possible solutions [Section 7.4.1](#)).

Patient study:
Complex syntax is
sensitive to
brain integrity.

Our patient study also relates complex syntactic processing to the dorsal pathways: Both dorsally affected patients were heavily influenced by syntactic complexity, i. e., they performed worse on syntactically complex sentences than on syntactically simple sentences, during both repetition and comprehension (as far as could be assessed). Although the patients were still influenced by syntactic complexity postoperatively, despite a good recovery of the dorsal tracts in both patients, this does not necessarily mean that the dorsal pathways are not supporting complex syntactic processing. Rather it appears that such a high-level linguistic function as the processing of syntactically complex structures is very sensitive to pathological changes in the brain. In other words, proper complex syntactic processing seems to depend on the full integrity of the AF and/or on the overall integrity of the cognitive system.

Summary.

We conclude that Broca's area in the left hemisphere, i. e., primarily BA 44, supports the processing of syntactically complex structures which is mediated by the AF connecting Broca's area directly with the posterior superior temporal cortex. Processing syntactically complex structures seems to be sensitive to the complete integrity of the AF.

7.2.4 Word-level semantic processing

Literature review:
IFOF is a crucial tract
for semantic
processing.

The literature review suggested that semantic processing is subserved by the IFOF and other ventral fiber tracts. These other tracts were, however, proposed to be dispensable, meaning that their semantic functions can be compensated by the IFOF.

Healthy participants:
ILF is strongly
involved in word-level
semantic processing.

In line with the literature review, our studies on healthy participants showed that word-level semantic processing is subserved by ventral fiber tracts, exclusively. We eliminated the left anterior MTG as a key region for word-level semantic processing which we demonstrated to be connected with inferior frontal and posterior temporal regions via the UF, the ILF and the IFOF. Compared to simple syntactic processing, word-level semantic processing demonstrated stronger ILF connections, i. e., the white matter voxels that constitute the ILF demonstrated a stronger connectivity with the cortical key region for word-level semantic processing (i. e., the anterior MTG) than with the cortical key regions for simple syntactic processing (i. e., the frontal operculum and the anterior STS). The UF and the IFOF, on the contrary, were stronger connected to the key regions for simple syntactic processing than to the key region for word-level semantic processing. However, all these key regions demonstrated connections to all three ventral tracts. It is thus possible and suggests itself that word-level semantic processing is also supported by the IFOF and/or the UF and not only by the ILF, as was put forward by the literature. The present tractography

study is, unfortunately, not capable of deciding which of the ventral tracts is dispensable, which is necessary, or which is essential for word-level semantic processing. Although connectivity strengths may give a hint, the tract most strongly connected to a cortical key region (the ILF in our case) may not necessarily be the essential one but could likewise be the one that is used most often. Additionally, a fiber tract may be essential for more than one linguistic function (the UF or the IFOF in our case), although it demonstrates different connectivity strengths to the key brain regions supporting these linguistic functions. A patient study could decide the essential tract for word-level semantic processing if it were capable of differentiating between the adjacent ventral tracts. Our patient study, however, did not test for semantic processing as we felt using pseudoword stimuli would put too much effort on the patients.

Taken together, the present data suggest that word-level semantic processing is supported exclusively by ventral fiber tracts that connect the left anterior MTG to the posterior temporal and frontal regions: the UF, the ILF, and the IFOF. Which of these tracts are essential, and which are dispensable has to be decided in further studies.

Summary.

7.2.5 Sentence-level semantic processing

No previous study reported the fiber tracts involved in sentence-level semantic processing, which we take to be the building up of an overall sentence meaning through upload and integration of syntactic and semantic information (see [Figure 3.1](#)). Our studies eliminated the left posterior STS as a key region for sentence-level semantic processing. This region proved to be connected to the superior and middle temporal cortex locally, as well as to the precentral gyrus via the AF, and to the angular gyrus via the SLF-tp. We interpret the strong local connections of the posterior STS with the MTG to be used for interconnection with lexical-semantic processing sites, e.g., in the anterior MTG. Dorsally, sentence-level semantic processing seems to rely, at least partly, on the same pathway as does complex syntactic processing. This pathway, the AF, may be used by the posterior STS to access syntactic information in frontal syntactic processing sites for integration with semantic information. Additionally, the posterior STS demonstrated connections to the angular gyrus via a pathway (SLF-tp) previously reported in a few studies to be responsible for phonological processing and speech repetition (see [Section 2.2.1](#)). We argue that the SLF-tp, together with the SLFII, may be responsible for maintenance of phonological information in mind (see [Section 7.2.1](#)). Via the SLF-tp, the relevant phonological information is probably held in working memory until all necessary information is available. Local temporal connections, the AF, as well as the SLF-tp may work together to enable proper sentence-level semantic processing in the posterior STS.

Sentence-level semantic processing is supported by pSTS via AF, SLF-tp, and local connections.

In sum, the connections of the posterior STS suggest that this key region for sentence-level semantic processing accesses semantic informa-

Summary.

tion via local temporal connections, and syntactic information via the AF. Moreover, the phonological information is held in mind through connections to the angular gyrus via the SLF-tp.

7.2.6 General organization of the language network

Language uses long-range fiber tracts.

We successfully delineated cortical brain regions of language processing to be connected to other cerebral lobes via long-range fiber tracts. Although we cannot measure the actual information flow, it is more than likely that information is effectively transmitted by these long-range fiber tracts between these cortical regions, given the brain's economic mode of operation. The fiber tracts probably support linguistic functions through transmission of linguistic information, thereby affording cognitive computations like encoding, maintenance, or access of information. In doing so, they are sustained by short-range connections between cortical areas of the same cerebral lobe.

Differentiation of dorsal and ventral makes anatomical and functional sense.

The long-range fiber tracts have been grouped into dorsal and ventral tracts (see [Chapter 1](#)). Our studies endorse that this classification is anatomically real. Moreover, they demonstrate that it is a classification that also functionally holds true. Whereas “complex” linguistic information is transmitted dorsally between the temporal and the frontal cortex, “simple” linguistic information was shown to be transmitted ventrally. Moreover, phylo- and/or ontogenetically older tracts connecting the temporal and the premotor cortex via the parietal cortex seem to support the encoding and maintenance of phonological information for mapping onto motor plans, as well as articulation and speech motor planning and control.

There is more than one dorsal and one ventral language fiber tract.

Both the literature review and our studies clearly support the assumption that there is more than one dorsal and one ventral fiber tract involved in auditory language processing. We were able to show that these tracts are both anatomically and functionally differentiable.

7.2.7 Summary

From discussing the results of the present work, the following picture of the anatomy and functional roles of language fiber tracts emerges (as is visualized in [Figure 7.1](#)):

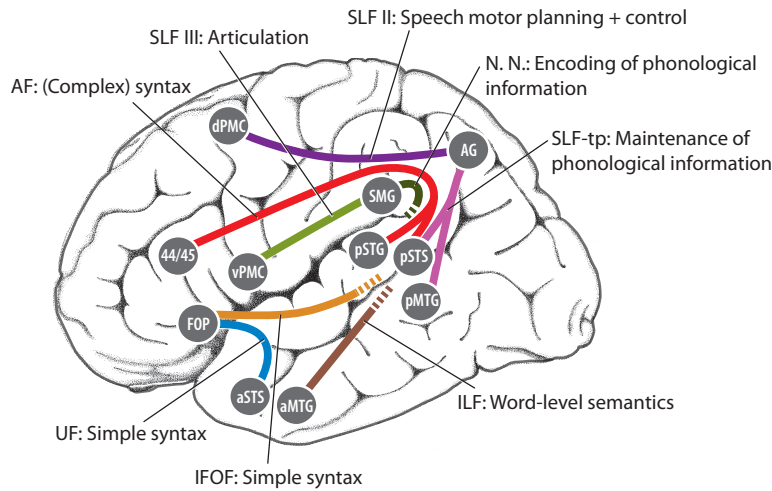


Figure 7.1: Neurocognitive model as outlined in the literature review (Chapter 2) enriched with the results from the empirical experiments of the present thesis. The results are presented in condensed form on a schematic left hemisphere: Some indirect tracts may encompass direct fibers; local connections, as well as branching terminations are not shown. See, for a more detailed description of the results, Section 7.2. For abbreviations see page xv.

- **Phonological, phonetic and motor aspects of speech repetition** are supported by dorsal fiber tracts, exclusively. These are the inferior running SLF III and a parieto-temporal component connecting supramarginal gyrus with temporal cortex, as well as the superior running SLF II and SLF-tp. Both inferior and superior tracts may also comprise fibers connecting frontal and temporal cortex directly without relay stations in the parietal cortex. Different functional roles have been proposed for the tracts: maintenance of phonological information, speech motor planning and control for the superior tracts, encoding of phonological information and articulation for the inferior tracts.
- **Simple syntactic processing** is supported by ventral fiber tracts, connecting to frontal operculum and anterior STS, i. e., primarily the IFOF and/or UF. Further studies are needed to decide on the necessity of the different tracts, also compared to dorsal tracts.
- **Complex syntactic processing** is supported by the AF connecting Broca's area to posterior superior temporal cortex directly. This could also be shown for complex syntactic processing during repetition. Our patient study suggests that proper processing of complex syntactic structures may depend on the complete integrity of the cognitive system.
- **Word-level semantic processing** is exclusively supported by ventral fiber tracts of which the IFOF and/or ILF may be the crucial ones, connecting the key region for word-level semantic processing in the anterior MTG with posterior temporal and frontal brain regions.

- **Sentence-level semantic processing** relies on the activation of the left posterior STS together with its local connections to lexical-semantic regions in the MTG, as well as long-range connections to syntactic regions in the frontal cortex via the AF, and verbal working memory regions in the parietal cortex via the SLF-tp.
- **Generally**, the language network relies on several short-range as well as long-range fiber tracts that connect the temporal and frontal cortices dorsally and ventrally, but that also connect with the parietal and occipital cortices. These language fiber tracts have been shown in the present thesis to be both anatomically and functionally differentiable, with the dorsal pathways supporting primarily “complex” linguistic functions, as well as verbal working memory and speech repetition, and the ventral pathways supporting primarily “simple” linguistic functions.

7.3 Newness, importance and generalizability of the findings

Newness
of the findings.

Many aspects of the present thesis are novel: Since the last reviews about language fiber tracts have been published, numerous new studies have been conducted. These studies are included in the extensive overview that is presented in the current thesis about the recent literature dealing with the anatomy and functional roles of language fiber tracts. The thesis also systematically considered, for the first time, the various nomenclatures used in the literature. In an fMRI study, the key brain regions were investigated that are activated by phonological and motor, semantic and syntactic processes during sentence repetition. In sentence repetition, no previous study had ever examined the neural correlates of these linguistic processes. Moreover, the tractography study on healthy participants that was presented in the current thesis directly compared, for the first time, the fiber tracts involved in repetition and comprehension. Additionally, no study before compared different linguistic sub-processes of repetition and comprehension, i. e., simple syntactic, word-level and sentence-level semantic processing.

Importance
of the findings.

With the data from the present thesis, hitherto conflicting results of Saur et al. (2008) and Friederici et al. (2006a) can be solved. The results from healthy participants were lined with patient data, and ended in a neurocognitive model that can be used as basis for further research. Thus, the results of the current thesis can provide a guide and reference for all researchers—linguists, as well as psychologists or neuroscientists—working in the field of language and brain connectivity.

Generalizability
of the findings.

It is imaginable that the findings from language processing will lead to a more general understanding of how the brain works. It recently becomes more and more clear that the brain does not produce cognitive skills using cognitive enclaves. Rather, cognitive skills seem to

arise from the interaction of various cognitions using various neural networks. Thus, understanding the language network is an important piece of a puzzle that may further elucidate our understanding of the brain's general mode of operation.

7.4 Limitations

The following section outlines some of the limitations that are inherent to the presented studies and the methodology used. Moreover, it presents some possibilities for extending the results that may enable a completion of our understanding of the language network.

7.4.1 Measuring syntactic complexity in comprehension

In the current thesis, the studies on healthy participants could not reveal neural correlates of syntactic complexity during language comprehension. The studies used a probe verification task (listening to complex sentences and answering an auditory probe from time to time) during sentence comprehension, as shown in [Chapter 3](#). This task seemed to be very difficult, preventing deep processing of the syntactic structure while leading to enhanced working memory or cognitive control efforts. We discuss an alternative task along with an evaluation of it in [Appendix A](#).

Absence of syntactic complexity effects in sentence comprehension.

7.4.2 Methodological issues

The results of the present thesis are based on a profound literature review, on a patient study, as well as on a comprehensive within-subjects investigation of the key brain regions and fiber tracts involved in language processing combined with a revealing statistical analysis. The fMRI based tractography method we used in this latter study, however, comprises several methodological limitations. These are outlined in the following sections.

Methodological limitations of fMRI based tractography.

The result of probabilistic tractography is a tractogram that illustrates the connectivity strengths of all connections that pass through a specific predetermined seed region. However, this tractogram does not demonstrate which of these fibers or fiber tracts are actually used by the gray matter of the seed region for transmission of information. More specifically, it remains undetermined which fibers or fiber tracts are used for transmission of the specific linguistic information that we located to be processed in the seed region, and not for transmission of other information that may also be processed in the seed region. Other methods, for example functional connectivity methods, are also not capable of illustrating the fibers in use. However, these methods can at least demon-

Which tracts are functionally used?

strate which (probably connected) cortical brain regions communicate with each other for bringing about a specific cognitive function. It may, however, be the case, that the investigated brain areas do not communicate directly but that the communication is mediated via another brain region or several other brain regions that were not part of the tested model of brain regions. Therefore, functional connectivity studies have to be combined with structural connectivity studies.

How is the information flow?

Fiber tractography—in the way it can be applied at present to the intact human brain—cannot measure the direction of the information flow, nor can it measure the order in which the brain regions are used. One possibility to deduce the direction and the order of the information flow is to transfer results from invasive connectivity and tracer studies on non-human primates to the human brain, additionally consulting structural connectivity studies in humans. Other possibilities to deduce and formulate models about the direction and the order of the information flow are time-sensitive methods that can be directly applied to the human brain, as, for example, effective connectivity methods (e.g., Dynamic Causal Modeling), magnetoencephalography or auditory evoked potentials. Ideally, these methods are combined with structural connectivity methods as only these can provide the anatomy of the pathways the information flows. From results of time-sensitive and non-human primate studies, Rauschecker (2011), for example, concluded that the information flow between the frontal and the temporal cortex via the parietal cortex is probably bidirectional: The parietal cortex receives sensory information from the temporal cortex, as well as motor preparatory information from the frontal cortex, and matches both types of information to enable language processing. The information is postulated to be anatomically transmitted via connections between the posterior superior temporal region and the parietal cortex, as well as via connections between the ventral PMC and the parietal cortex.

7.4.3 Possible extensions

Other fMRI designs enrich the language network.

fMRI-based tractography is an indirect method for mapping cognitive functions onto the white matter anatomy. It thus depends on the quality and specificity of the fMRI designs used. This is illustrated by the number of parameters that can lead to choosing different seed regions and finally to delineating different fiber tracts as being crucial for language processing, such as the choice of stimuli, factors, e.g., prosodic or morphological processing, contrasts that are performed, tasks, or modalities that are investigated, for example visual language processing. The results of the present thesis, hence, are constrained by the factors and tasks that were investigated.

Right-hemispheric functions enrich the language network.

Using fMRI designs that focus on right-hemispheric language functions would enrich our understanding of the language network. In the present thesis, we primarily reported left-hemispheric fiber tracts. The

dominance of the left hemisphere in our findings is partly due to the fact that language is primarily supported by the dominant hemisphere (usually the left hemisphere in right-handed subjects) whereas the right hemisphere only supports a few language functions. The fMRI designs of the current work, however, only addressed those linguistic functions that are primarily supported by the left hemisphere, as was demonstrated by the results. If we would have investigated other linguistic functions, like prosody, for example, also right-hemispheric brain regions and fiber tracts would probably have enriched the obtained language network (Friederici, 2011).

The fiber tracts that were examined and reported in the current thesis were primarily long-range fiber tracts. Short-range connections, however, should not be neglected because it is very likely that the numerous existing short-range connections are used for local communication and transmission of information between adjacent brain regions. In addition to the long-range fiber tracts, short-range connections should be included in the neurocognitive models of the future to extend our understanding of the language network.

Short-range connections enrich the language network.

7.5 Open questions

From the results of the present thesis, there emerge and remain several interesting open questions, from which a few are outlined in the following sections. More empirical studies, new and creative designs, as well as advancements of the present methodology are required to answer these questions.

- What is the precise functional role of the SLF II during speech repetition? Is D1 a direct or an indirect fiber tract?
- What is the precise functional role of the fiber tract connecting the supramarginal gyrus with the temporal cortex? Is it part of an indirect tract connecting the ventral premotor cortex via the supramarginal gyrus with the temporal cortex, or is the ventral premotor cortex also directly connected with the temporal cortex?
- Is language production supported by the same fiber tracts as language repetition?
- Are different simple syntactic processes (see Figure 3.1) mediated by different fiber tracts? Do the UF and the IFOF support different simple syntactic processes?
- To what extent is the AF different from fiber tracts supporting verbal working memory? If different, how does the AF interact with fiber tracts and brain regions supporting verbal working memory?
- How are the long-range fiber tracts interconnected, and how are they connected to other brain areas via short-range pathways?

How is the right hemisphere integrated into the language network found in the present studies?

- How does the network of auditory language processing overlap with other language modalities, e. g., visual language processing?
- What is the direction and the timeline of the information flow?
- Do the fiber tracts have more general functional roles that can be applied to different cognitive skills, e. g., linearization vs. hierarchization, automaticity vs. control, bottom-up vs. top-down processing, integration vs. identification?

7.6 Conclusions

Concluding remarks.

The current thesis investigated the anatomy and functional roles of fiber tracts supporting auditory language processing. Specifically, the brain regions and fiber tracts supporting speech repetition and different semantic and syntactic processes during both sentence repetition and comprehension were examined. The results demonstrate that there are several—anatomically and functionally differentiable—long-range fiber tracts in the brain that enable humans to speak and to comprehend language. These tracts can be grouped into dorsal and ventral fiber tracts connecting temporal and frontal cortex, with dorsal tracts supporting “complex” linguistic functions, and ventral tracts supporting “simple” linguistic functions. Additionally, there are important long-range tracts connecting the frontal and temporal cortices with the parietal and occipital cortices which have also been demonstrated to support language processing, e. g., during speech repetition. Other carefully conducted studies on healthy participants and patients, as well as advancements and combinations of the different connectivity methods are necessary to further elucidate the brain networks that enable humans to speak and to comprehend language.

Appendix A

Behavioral picture study

A.1 Introduction

In a previous study (Chapter 3), we investigated the neural correlates of syntactic complexity by contrasting complex with simple sentences. However, subjects performed below chance level on the probe verification task, especially in meaningless conditions, probably reflecting that the task was too difficult to allow for a deep or fine-grained syntactic analysis. Therefore, we tried to design a new task reinforcing syntax processing, and came up with a speech-picture-matching task (with “speech” implying either sentences or word lists), which included the same stimuli as in the previous study.

Motivation
for the study.

The current chapter describes the methods and results of a behavioral pretest using this new task. The experimental design, including participant restrictions, auditory stimulus material, trial design, and experimental setup remained the same as in the previous study to ensure comparability. Here, we tested for an above chance level performance on the complex syntactic conditions as well as on all other conditions. Moreover, we tested for a potential follow-up fMRI study that the conditions did not differ in task difficulty, measured by accuracy, but only in syntactic complexity.

Aims.

An ideal task for measuring the processing of syntactically complex structures during sentence comprehension would have to generate above chance level accuracy results in order to be sure that the syntactic structures of the sentences have been effectively processed by the participants. Moreover, the activations in response to complex syntactic processing have to be contrasted with those in response to simple syntactic processing. Therefore, both types of syntactic structures should be equally difficult to process. For comparison with the brain correlates of simple syntactic processing, the task should

Constraints
of the ideal task.

also be applicable to word lists which contain no syntactic structure so that the correlates of simple syntactic processing can be eliminated by contrasting the activations in response to simple syntactic processing with those in response to processing of non-syntactic structures. In order to compare these correlates of different syntactic processing to semantic processing, the ideal task should also be applicable to both real word as well as pseudoword stimuli.

Methods of the present study.

We tried to design such a task by using the auditory stimuli that we employed in the presented studies (Figure 3.2) together with pictures (see Figure A.1), and asking the participants to compare what they hear to what they see. The pictures represented two labeled persons acting on each other in an abstract way, as well as an oriented line above one of the persons (for the word list stimuli). The meaning of either the abstract action or the oriented line was learned by the subjects at the beginning of each trial. Moreover, the subjects were instructed which order of appearance of the nouns in a word list would match the picture. Doing so, the same task could be applied for sentence and word list stimuli of both real words and pseudowords, i. e., comparison of the position of one oriented element (action arm or oriented line) in a picture with the structure of a sound string, which means understanding of the syntax in case of sentence stimuli (see the detailed description of the methods below).

A.2 Methods

A.2.1 Participants

32 participants were tested.

We tested 32 healthy adult right-handed German native speakers (50 % female), aged on average 23.91 years ($SD = 2.92$; range: 18–31 years) who gave their written informed consent to participate in the study which was approved by Ethics Committees (University Leipzig).

A.2.2 Design, stimulus material and task

Design and auditory stimuli.

As the studies before, the present study had a 3×2 design with the factors syntax (complex/simple/missing) and semantics (meaningful/meaningless). We applied a speech-picture-matching task to the same auditory stimuli as used in the previous studies, i. e., syntactically complex and simple sentences, as well as syntax-free word lists, all formed by using real words or pseudowords as stimuli (see Figure 3.2).

Visual stimuli and task.

For each auditory stimulus, the visual stimulus (see Figure A.1) consisted of two labeled stickmen, one in a passive default posture (arms vertically down), and one in an acting posture (with one arm being ei-

ther diagonally up or diagonally down), with an oriented line above one of the stickmen. The participants were told to judge whether what they see matches what they hear, i. e., whether the picture depicts what they hear. To judge the correctness of the heard nouns, the participants had to read the labels below the stickmen. To judge the correctness of the abstract action, the participants learned the current meaning of the action at the beginning of each trial before the presentation of the actual stimuli. In the case of word list stimuli, the participants were told that picture and auditory stimulus match if the stickman that has the oriented line on top of it is mentioned first in the word list. The oriented line also represented the monosyllabic noun included in the word lists instead of the verb. To judge the correctness of this monosyllabic noun, which was not labeled, the participants learned the current meaning of the oriented line at the beginning of each trial before the presentation of the actual word list stimulus. Each stickman consisted of seven yellow lines. The middle arm of one stickman was always the acting arm. The acting arm and the oriented line above the stickmen appeared randomized in one of two possible orientations. The side of the acting stickman as well as of the oriented line was counterbalanced across conditions.

We additionally added auditory filler stimuli, in which one word (either a noun or verb) was exchanged so that the participants not only had to attend to the order of the words but also to its content. These filler stimuli were included to ensure that the participants were processing each stimulus completely. Half of all stimuli matched, half mismatched the auditory material. The participants were carefully trained on the task before the experiment.

Filler stimuli.

A.2.3 Procedure

During the behavioral testing, the participants were presented with the visual stimuli via a computer monitor, and the auditory stimuli via speakers. Brightness and sound level was kept constant across all participants. We presented six conditions with 32 trials each plus 48 filler stimuli, i. e., 240 trials altogether, in randomized order. There were five breaks which were distributed regularly in the course of the experiment. After the experiment, the participants had a short break before they filled in a questionnaire about the experiment and did a digit span test (WIE 2006).

Experimental set-up.

Each trial started with a jittered black screen of 500–1500 ms. After that, a learning picture was presented for 2000 ms. To catch participants' eye movement subjects had to focus their eye gaze on a fixation cross for 500–1500 ms before the visual stimulus and the auditory stimulus were presented together for approximately 3000 ms, followed by a maximum of 2000 ms black screen. For response, the participants pressed one of two buttons (counterbalanced across subjects), as soon as they knew whether the auditory and visual stimuli matched. At maximum, the trial had a length of 12 s.

Trial design.

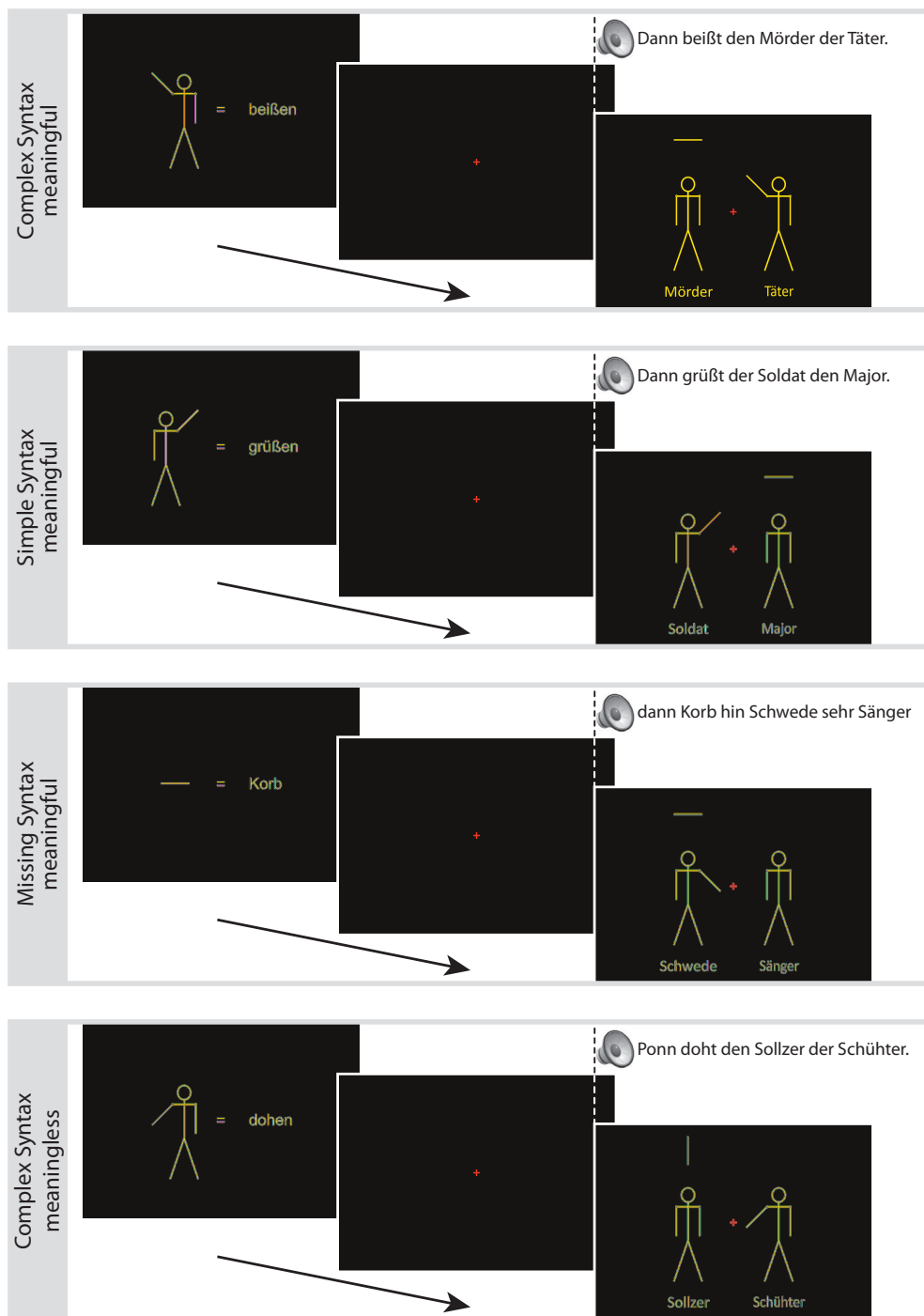
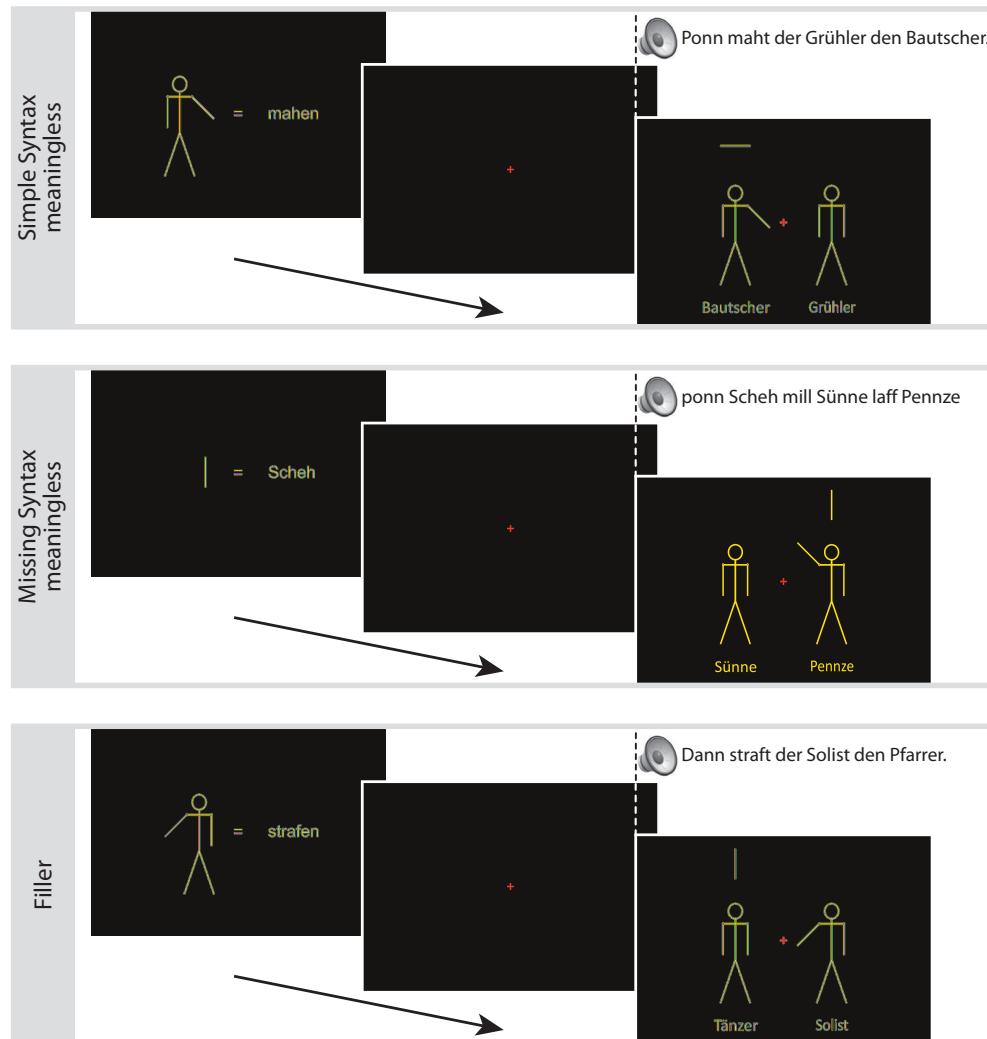


Figure A.1: For caption and continuation see next page.



Continuation of Figure A.1. Illustration of the stimuli and the trial design of the behavioral picture study. Depicted are the core aspects of each trial only, in their chronological order. For each condition and for the fillers, one example is given. The visual stimulus after the fixation cross picture is presented simultaneously with the auditory presentation of the sentence/word list which is written here only for illustration purposes. Notice that the first four depicted trials match, whereas the following three trials mismatch. Literal English translations (ACC = accusative, NOM = nominative; PW = pseudoword): Then bites the_{ACC} murderer the_{NOM} offender. – Then greets the_{NOM} soldier the_{ACC} major. – Then basket toward Swede very singer. – Ponn(PW) doht(PW) the_{ACC} sollzer(PW) the_{NOM} schühter(PW). – ponn(PW) maht(PW) the_{NOM} grühler(PW) the_{ACC} bautscher(PW). – ponn(PW) scheh(PW) mill(PW) sünne(PW) laff(PW) pennze(PW) – Then punishes the_{NOM} soloist the_{ACC} priest. (instead of “dancer” as labeled beneath the stickman)

A.2.4 Data analysis

Tests performed. Data analysis was done using IBM SPSS Statistics (version 19). We performed t-tests to test for the performance against a chance level of 50 % by comparing the accuracy means of each condition with a test value of 0.5. To test for the difficulty of the task we calculated a repeated measurements ANOVA (level of significance 5 %) with the factors syntax (simple, complex, missing) and semantics (meaningful, meaningless). For post-hoc tests, we performed Bonferroni corrected paired-samples t-tests.

A.3 Results and Discussion

Results of a pretest. We found that the subjects did process the stimuli much better than in our previous task (Chapter 3), i.e., they also demonstrated better comprehension of the sentences. In all conditions—meaningful and meaningless—subjects answered significantly above chance level (see Table A.1).

Table A.1: Mean percent correct responses and statistical analysis against chance level. Asterisks represent values that are significantly different from chance level (test value = 0.5; $p < .001$). SD = standard deviation.

	Mean	SD	T-value
Complex Syntax meaningful	93.36*	10.25	23.93
Simple Syntax meaningful	95.47*	7.39	34.81
Missing Syntax meaningful	79.06*	9.04	18.18
Complex Syntax meaningless	88.67*	10.43	20.97
Simple Syntax meaningless	92.11*	9.12	26.13
Missing Syntax meaningless	79.22*	8.62	19.17

ANOVA results. A repeated-measurements ANOVA revealed a significant main effect of semantics ($F_{1,31} = 29.39$; $p < .001$), meaning that the participants' accuracy when answering meaningful conditions was better than their accuracy when answering meaningless conditions. Likewise, the ANOVA revealed a significant main effect of syntax ($F_{2,30} = 21.97$; $p < .001$), meaning that the participants performed better on simple conditions than on complex conditions and missing conditions. There is also a significant interaction between the factors semantics and syntax ($F_{2,30} = 5.37$; $p < .05$).

Post-hoc tests. Post-hoc analysis of the repeated measurements ANOVA (Figure A.2) revealed no significant difference between the accuracy of answering meaningful simple and complex sentences ($t(31) = 1.45$; $p > .05$), as well as no significant difference between word lists of meaningful and meaningless conditions ($t(31) = -0.139$; $p > .05$). All other comparisons differed significantly (see Table A.2). This means

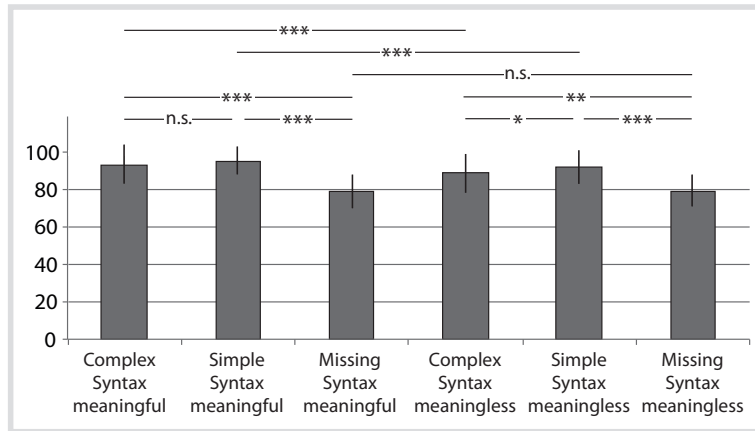


Figure A.2: Post-hoc results of the behavioral picture study. Syntactically complex sentences, syntactically simple sentences and word lists, containing meaningful or meaningless words (see Figure 3.2 for sample stimuli) were contrasted in paired-samples t-tests. Asterisks indicate significance level: * $p < .05$, ** $p < .01$, *** $p < .001$. n.s. = not significant.

that answering meaningful simple and complex sentences did not differ in difficulty; potential differences in the brain would thus be solely attributable to the difference in syntactic structure. Unfortunately, subjects performed significantly better on these conditions compared to the performance on the word list condition and compared to the performance on meaningless stimuli (see Table A.2). Also, meaningless simple sentences were answered significantly better than meaningless complex sentences ($t(31) = 2.317$; $p = .027$).

Table A.2: Post-hoc analyses of several conditions. Asterisks indicate significance level: * $p < .05$, ** $p < .01$, *** $p < .001$. mful = meaningful; mless = meaningless; simple = simple sentences; complex = complex sentences; missing = word lists.

	T-value	p-value
Simple_mful vs. Complex_mful	1.449	.157
Simple_mful vs. Missing_mful	7.354	.000***
Complex_mful vs. Missing_mful	5.918	.000***
Simple_mless vs. Complex_mless	2.317	.027*
Simple_mless vs. Missing_mless	5.461	.000***
Complex_mless vs. Missing_mless	3.857	.001**
Missing_mful vs. Missing_mless	-.139	.891
Simple_mful vs. Simple_mless	4.337	.000***
Complex_mful vs. Complex_mless	6.242	.000***

To eliminate this obvious difference in task difficulty between meaningful and meaningless stimuli, one could think of familiarizing subjects with the pseudowords before the experiment so that the meaningless conditions are becoming equally easy as the meaningful

Potential changes to the general conditions.

conditions. To ease all conditions, one could additionally think of including only those subjects as participants that have a high working memory load, because the working memory capacity positively correlated with the performance on complex sentences (correlation of digit span measures with accuracy on meaningful/meaningless complex sentences: $r = .64/.63$). Another option to ease the task would be to eliminate the filler stimuli used. This means that subjects would only have to attend to the structures but not to the correspondence of the words they hear and see.

Outlook.

Changing these settings should be tested in the future. If this leads to good performance in all conditions and to same difficulty of all conditions (i. e., non-significant differences between the conditions), the task and settings could be taken for an fMRI and tractography study that investigates the key regions and fiber tracts supporting syntactic complexity during language comprehension as compared to the key regions and fiber tracts supporting simple syntactic processing and semantic processing.

Appendix B

Tables

B.1 Tables relating to literature review (Chapter 2)

Table B.1: Overview of the dorsal tracts reported in language-related fiber tracking studies (see for illustration Figure 2.1). Studies appear in chronological order, following date of publication access; * = seed region.

Study	Method	Distant cortical areas connected via long-range fiber tract	Functional role in language processing assigned by the authors	Tract name assigned by the authors
<i>Makris et al. (2005), Cereb Cortex</i>	Bottleneck single-ROI approach, terminations are based on animal literature	caudal-lateral prefrontal regions (dorsal BA 6/46)	-	SLF II/AFh
		vPMC, ventral PFC (ventral BA 6/44)	(i) articulation	SLF III
		SMG	(i) reception and modulation of audiospatial information	AFv
		pSTG		
<i>Parker et al. (2005), Neuroimage</i>	Double-ROI approach	BA 44*	pSTG*, mSTG	(i) comprehension of intelligible speech
		pSTG*	BA 40 (SMG)	(i) processing segmental information
<i>Catani et al. (2005), Ann Neurol</i>	Bottleneck single-ROI approach, Double-ROI approach (for partitioning)	"Broca's territory" (BA 44)	"Wernicke's territory" (pSTG/MTG)	(i) phonologically based language functions
		"Broca's territory" (vPMC)	"Geschwind's territory" (IPL)	(i) semantically based language functions
		"Geschwind's territory" (IPL)	"Wernicke's territory" (pMTG/STG)	(i) semantically based language functions
				AF, direct pathway
				AF, indirect pathway, anterior segment
				AF, indirect pathway, posterior segment

Continuation of Table B.1.

Study	Method	Distant cortical areas connected via long-range fiber tract	Functional role in language processing assigned by the authors	Tract name assigned by the authors
<i>Croxson et al. (2005), J Neurosci</i>	Bottleneck double-ROI approach	dorso-lateral* and dorso-medial* PFC (including dPMC)	-	SLFII
		post. ventro-lateral PFC (BA 44)*	-	SLFIII
<i>Friederici et al. (2006b), PNAS</i>	Single-ROI approach with fMRI for seeding	BA 44*	m/pSTG	processing of syntactic complexity
<i>Powell et al. (2006), Neuroimage</i>	Single-ROI approach with fMRI for seeding	Broca's area*	SMG, pSTG and pMTG	verbal fluency, verb generation
<i>Anwander et al. (2007), Cereb Cortex</i>	Single-ROI approach with parcellation by means of clustering	BA 44*, vPMC	parietal cortex, temporal cortex	-
		BA 45*	parietal cortex, temporal cortex	-
<i>Glasser & Rilling (2008), Cereb Cortex</i>	Bottleneck single-ROI approach; Double-ROI approach (for partitioning)	BA 44 and 6	pSTG (BA 22)	(i) phonological processing
		BA 44; parts of BA 45, 6, 9	pMTG (BA 21/37)	(i) lexical-semantic processing
				STG-pathway of AF
				MTG-pathway of AF

Continuation of Table B.1.

Study	Method	Distant cortical areas connected via long-range fiber tract	Functional role in language processing assigned by the authors	Tract name assigned by the authors
<i>Frey et al. (2008), J Neurosci</i>	Double-ROI approach	pars opercularis (BA 44)*	-	SLF III
		BA 44*	-	AF
		dorsolateral BA 8 and rostral BA 6 (dPMC)*	-	AF
<i>Saur et al. (2008), PNAS</i>	Multi-ROI approach with fMRI for seeding	PMC (BA 6)*, pars opercularis*	mapping sound to articulation	MDLF and SLF III/AF
<i>Hua et al. (2009), Cereb Cortex</i>	Multi-ROI approach, population-averaged	Broca's area (BA 44)	-	SLF
<i>Bernal & Altmann (2010), Magn Reson Imaging</i>	Bottleneck single-ROI approach	precentral gyrus (premotor and motor cortex)	involved in, but not necessary for language	SLF and AF
<i>Saur et al. (2010), Neuroimage</i>	Multi-ROI approach with fMRI for seeding	pars opercularis*, dPMC*	phonological processing	AF/SLF

Continuation of Table B.1.

Study	Method	Distant cortical areas connected via long-range fiber tract	Functional role in language processing assigned by the authors	Tract name assigned by the authors
<i>Galantucci et al. (2011), Brain</i>	Bottleneck single-ROI approach; Double-ROI approach (for partitioning); Lesion mapping (for functional role determination)	frontal and opercular areas	syntactic processing, articulation	SLF II
		frontal and opercular areas	syntactic processing, articulation	SLF III
		frontal areas	syntactic processing, articulation	AF (SLF IV)
		pMTG/STG	phonological processing, auditory-motor-mapping	SLF, temporo-parietal part
		temporo-parietal region*	auditory-motor-mapping	SLF I
<i>Wong et al. (2011), J Neurosci</i>	Single-ROI approach with fMRI for seeding	postcentral gyrus		
<i>Martino et al. (2011), J Anat</i>	Multi-ROI approach compared with post mortem fiber dissection	pFOP	-	SLF, horizontal
		pMTG	-	SLF, vertical
		pFOP	-	AF or deep SLF

Continuation of Table B.1.

Study	Method	Distant cortical areas connected via long-range fiber tract	Functional role in language processing assigned by the authors	Tract name assigned by the authors
<i>Thiebaut de Schotten et al. (2012), Cortex</i>	Double- and multi-ROI approaches	pSFG and MFG (BA 6, 8, 9)	ant. IPS and AG (BA 39 and 40)	-
		IFG (BA 44, 45, 47)	IPS and IPL, pSTG	-
		IFG (BA 44, 45), inf. precentral gyrus (BA 6), pMFG/IFG (BA 8, 9, 44, 45)	pSTG (BA 41 and 42) and PMTG/ITG (BA 21, 22 and 37)	auditory-/visual-motor-mapping
<i>Griffiths et al. (2012), Cortex</i>	Double-ROI approach with fMRI for seeding	BA 44*	pMFG*	syntactic processing
				AF

Note.
 AFh = horizontal portion of arcuate fascicle; AFv = vertical portion of arcuate fascicle; (i) = authors used inference to deduce the functional roles; N.N. = nomen nescio. For further abbreviations see page xv.

Table B.2: Overview of the ventral tracts reported in language-related fiber tracking studies (see for illustration Figure 2.2). Studies appear in chronological order, following date of publication access; * = seed region.

Study	Method	Distant cortical areas connected via long-range fiber tract	Functional role in language processing assigned by the authors	Tract name assigned by the authors
<i>Parker et al. (2005), Neuroimage</i>	Double-ROI approach	BA 44*	ATL, pSTG*	UF or superior part of extreme capsule
<i>Croxson et al. (2005), JNeurosci</i>	Bottleneck double-ROI approach	central* and lateral* orbitofrontal cortex	-	UF
		lateral orbitofrontal cortex* and ant. ventro-lateral PFC (BA 45)*	-	EmC
<i>Friederici et al. (2006b), PNAS</i>	Single-ROI approach with fMRI for seeding	FOP*	ATL	UF
<i>Powell et al. (2006), Neuroimage</i>	Single-ROI approach with fMRI for seeding	pSTG*	STG, MTG, occipital lobe, ATL, frontal areas	IFOE, ILF
<i>Antwanger et al. (2007), Cereb Cortex</i>	Single-ROI approach with parcellation by means of clustering	BA 45*	posterior temporal cortex	IFOE and ILF
		FOP*	posterior temporal cortex	IFOE and ILF
		FOP*	ATL	UF
<i>Frey et al. (2008), JNeurosci</i>	Double-ROI approach	pars triangularis* (BA 45)	mSTG/STS*	EmC
		pSTG/STS*	ventral post. IPS*	MdLF and ILF

Continuation of Table B.2.

Study	Method	Distant cortical areas connected via long-range fiber tract		Functional role in language processing assigned by the authors	Tract name assigned by the authors
<i>Saur et al. (2008), PNAS</i>	Multi-ROI approach with fMRI for seeding	pars orbitalis*, pars triangularis*	fusiform gyrus*, pMTG*, aMTG*	mapping sound to meaning	ILF and MdLF and EmC
		FOP*	aSTG* and pSTG*	monitoring processes during repetition	EmC
<i>Makris et al. (2009), Cereb Cortex</i>	Bottleneck single-ROI approach	temporal pole (BA 38)	pSTG, AG (BA 39)	transmission of linguistic information	MdLF
<i>Hua et al. (2009), Cereb Cortex</i>	Multi-ROI approach, population-averaged	ant. inferior frontal lobe (BA 10)	occipital lobe (BA 18, 19)	-	IFOF
		ant. inferior frontal lobe (BA 10)	temporal pole (BA 38)	-	UF
		temporal pole (BA 38)	occipital lobe (BA 18, 19)	-	ILF
		mSTG/STS	AG	(i) language comprehension	MdLF
<i>Makris & Pandya (2009), Brain Struct Funct</i>	Bottleneck single-ROI approach	frontal operculum, pars triangularis, orbitofrontal gyrus	mSTG/STS, AG	(i) language expression	EmC

Continuation of Table B.2.

Study	Method	Distant cortical areas connected via long-range fiber tract	Functional role in language processing assigned by the authors	Tract name assigned by the authors
<i>Saur et al. (2010), Neuroimage</i>	Multi-ROI approach with fMRI for seeding	FOP*	pSTG*	phonological processing
		aSTG*	pSTG*	phonological processing
		pars opercularis*	pMTG*	semantic processing
		pars orbitalis*	pMTG*	semantic processing
		pars orbitalis*	aMTG*	semantic processing
<i>Wong et al. (2011), J Neurosci</i>	Single-ROI approach with fMRI for seeding	temporo-parietal region*	anterior insula	semantic processing
		temporo-parietal region*	MTG	semantic processing
<i>Martino et al. (2011), J Anat</i>	Multi-ROI approach compared with post mortem fiber dissection	frontal lobe	occipital lobe, SPL, temporo-basal area	IFOF
		medial and lateral orbitofrontal gyrus	temporal pole, aSTG, aMTG	UF
		fusiform gyrus	occipital lobe	ILF, medial
		temporal pole	occipital lobe	ILF, lateral

Continuation of Table B.2.

Study	Method	Distant cortical areas connected via long-range fiber tract		Functional role in language processing assigned by the authors	Tract name assigned by the authors	
Sarrubbo et al. (2011), Brain Struct Funct	Double- and multi-ROI approaches	Pars triangularis, pars orbitalis		SPL, occipital extra-striate cortex, Fusiform area	(i) semantic processing	superficial IFOF
		MFG, dorsolateral PFC	SPL, occipital cortex, Fusiform area	(i) semantic elaboration of language, visual cognition and conceptualization	deep IFOF, posterior component	
		MFG, lat. orbitofrontal cortex	SPL	(i) multimodal sensory-motor integration, motor planning	deep IFOF, middle component	
		basal orbitofrontal cortex, frontal pole	occipital cortex, fusiform area	(i) emotional and behavioral aspects	deep IFOF, anterior component	
		medial fronto-orbital region (BA 11), frontal pole (BA 10), aSFG (rostral BA 9)	occipital lobe (BA 18, 19)	(i) reading, semantic processing	IFOF	
Thiebaut de Schotten et al. (2012), Cortex	Double- and multi-ROI approaches	orbitofrontal cortex (BA 11 and 47) and frontal pole (BA 10)	sup. temporal pole (BA 38)	-	UF	
Griffiths et al. (2012), Cortex	Double-ROI approach with fMRI for seeding	BA 45*	pMTG*	syntactic processing	ECFS	

B.2 fMRI results of the comprehension experiment (Chapter 3)

Table B.3: fMRI comprehension study: Results of the fMRI main effects.

Region	Hemisphere	BA	MNI peak coordinate [mm]	z-score	Extent in voxels
<i>p < .05, FWE-corrected</i>					
Parametric syntax effect (complex syntax > simple syntax > missing syntax)					
posterior IFS (7.0 % of cluster in BA 44)	L	6	-33 2 34	5.33	26
n/a	L	n/a	-24 -37 34	5.21	26
n/a	R	n/a	21 -43 34	5.20	29
frontal operculum (5.6 % in BA 45; 0.6 % in BA 44)	L	47	-45 26 2	5.19	29
posterior STS	L	37	-63 -55 10	5.15	13
Semantic main effect (meaningful > meaningless stimuli)					
anterior MTG	L	20	-54 -10 -18	6.63	82
▷ anterior STS	L	21	-51 8 -26	5.58	
IFG (pars orbitalis) (1.4 % in BA 45)	L	47	-48 29 -2	5.25	33
IFG (medial pars opercularis) (13.9 % in BA 44; 1.1 % in BA 45)	L	48	-42 11 14	5.00	34
posterior MTG/STS	L	21	-63 -55 14	4.81	11
posterior IFS	L	44	-36 5 34	4.45	1

Note.

For abbreviations see page xv. Brodmann areas are based on Brodmann map as provided by MRICroN (<http://www.mccauslandcenter.sc.edu/micron/micron/>). Percentages of areas are based on Jülich Probability Maps (as provided by Anatomy Toolbox, Eickhoff et al. (2007)).

Table B.4: fMRI comprehension study: Results of the differential effects of syntactic processing. A hash key indicates regions used as seed regions in the tractography study on healthy participants.

Region	Hemisphere	BA	MNI peak coordinate [mm]			z-score	Extent in voxels
<i>p</i> < .001, <i>k</i> ≥ 16							
Simple Syntax for Meaningful sentences (Simple syntax > missing syntax)							
anterior insula (14.0 % in BA 45; 4.4 % in BA 44)	R	47	30	29	-6	6.29	858
frontal operculum # (4.8 % in BA 45; 3.1 % in BA 44)	L	47	-33	29	-6	5.29	627
n/a	L	n/a	-36	-49	22	5.17	706
▷ posterior STS	L	37	-60	-58	14	4.93	
lingual gyrus	R	18	24	-88	-2	4.58	324
posterior STG	R	22	60	-49	18	4.35	233
parahippocampal gyrus	L	37	-24	-34	-6	4.33	101
parahippocampal gyrus	R	37	24	-34	-6	4.03	133
n/a	L	37	-33	-58	-6	3.72	23
n/a	R	n/a	18	-43	30	3.71	99
supplementary motor area	R	32	6	17	46	3.63	34
Conjunction (Simple > missing syntax) & (Complex > missing syntax)							
posterior IFS (4.5 % in BA 44)	L	48	-36	14	30	4.00	39
posterior IFS (26.1 % in BA 44; i. e., 2 % activated)	R	44	48	8	30	3.96	16
frontal operculum (23.2 % in BA 45; 11.0 % in BA 44)	L	45	-45	20	6	3.93	87
precuneus/IPS	L	n/a	-18	-46	30	3.92	69
anterior insula (10.6 % in BA 45; 1.0 % in BA 44)	R	45	42	23	6	3.79	35
precuneus	R	n/a	18	-34	34	3.69	30
Complex Syntax for Meaningful sentences (Complex syntax > simple syntax)							
posterior IFS	L	6	-30	5	38	3.65	17

Note.

For abbreviations see page xv. Brodmann areas are based on Brodmann map (as provided by [MRICroN](#)). Percentages of areas are based on Jülich Probability Maps.

Table B.5: fMRI comprehension study: Results of the differential effects of semantic processing.

Region	Hemisphere	BA	MNI peak coordinate [mm]			z-score	Extent in voxels
<i>p</i> < .001, <i>k</i> ≥ 16							
Semantic effect for Word lists (Meaningful > meaningless word lists)							
anterior MTG	L	21	-51	8	-26	4.99	135
Semantic effect for Simple sentences (Simple meaningful > meaningless sentences)							
posterior IFS (13.7 % in BA 45; 3.5 % in BA 44)	R	45	45	23	18	5.03	382
IFG (pars orbitalis) (10.1 % in BA 45; 1.8 % in BA 44)	L	47	-42	29	-6	4.36	301
▷ posterior IFS	L	48	-42	20	18	4.34	
▷ anterior IFS	L	47	-27	47	2	3.34	
posterior STS	L	n/a	-63	-55	18	4.33	40
anterior MTG	L	21	-57	-7	-18	4.24	37
Semantic effect for Complex sentences (Complex meaningful > meaningless sentences)							
posterior IFS (1.0 % in BA 6; 0.7 % in BA 44)	L	44	-33	5	34	5.63	476
▷ posterior STS	L	39	-36	-52	26	3.51	
n/a	R	n/a	21	-43	38	4.44	117
anterior MTG	L	20	-54	-10	-18	4.42	39
precentral gyrus	R	6	36	-13	46	4.41	322

Note.

For abbreviations see page xv. Brodmann areas are based on Brodmann map (as provided by [MRIcroN](#)). Percentages of areas are based on Jülich Probability Maps.

B.3 fMRI results of the repetition experiment (Chapter 4)

Table B.6: fMRI repetition study: Statistics and main peak coordinates of the fMRI contrast “pure repetition”. A hash key indicates regions used as seed regions in the tractography study on healthy participants.

Region	Hemisphere	BA	MNI peak coordinate [mm]	z-score	Extent in voxels
<i>p</i> < .05, FWE-corrected					
Pure word repetition (meaningless > meaningful word lists)					
supplementary motor area	L	6	-9 5 58	Inf	2665
▷ cingulate gyrus	L	32	-6 17 42	Inf	
▷ anterior insula	L	48	-27 20 2	Inf	
▷ cingulate gyrus	R	24	6 26 22	7.63	
▷ thalamus	L	n/a	-18 -10 14	7.28	
▷ anterior insula	R	48	36 17 -2	7.11	
▷ pallidum	L	n/a	-15 5 6	7.10	
▷ supplementary motor area	R	6	12 5 62	6.91	
▷ dorsal premotor cortex #	L	6	-39 -4 50	5.63	
ventral premotor cortex # (50.1 % in BA 44)	L	6	-51 5 14	6.62	73
supramarginal gyrus # (52.3 % in OP1; 43.4 % in PFop)	L	48	-60 -22 22	5.92	40
cerebellum	R	n/a	36 -61 -30	5.78	24
inferior parietal sulcus (61.4 % in Area 2; 22.2 % in 7PC; 5.6 % in 7A; 5.3 % in hIP3)	L	7	-30 -49 54	5.20	10

Note.

For abbreviations see page xv. Brodmann areas are based on Brodmann map as provided by MRICroN. Percentages of areas are based on Jülich Probability Maps (see Caspers et al., 2008; Eickhoff et al., 2007, for abbreviations of these).

Table B.7: fMRI repetition study: Results of the fMRI main effects.

Region	Hemisphere	BA	MNI peak coordinate [mm]	z-score	Extent in voxels
<i>p</i> < .05, FWE-corrected					
Parametric syntax effect (complex syntax > simple syntax > missing syntax)					
anterior MTG	L	20	-54 -7 -18	7.04	167
▷ anterior STS	L	20	-45 11 -26	6.40	
posterior STS	L	39	-57 -61 22	6.68	187
posterior STS	R	39	57 -64 18	5.61	21
posterior insula	L	48	-33 -16 -2	5.29	12
parahippocampal gyrus	L	30	-27 -28 -18	5.13	25
Semantic main effect (meaningful > meaningless stimuli)					
angular gyrus	L	39	-51 -64 22	7.10	244
anterior MTG	L	20	-57 -10 -22	6.35	68
posterior cingulate gyrus	L	23	-6 -46 34	5.95	112
dorsomedial prefrontal cortex	L	32	-9 53 30	5.16	36
middle MTG	L	37	-63 -46 -6	5.13	15

Note.

For abbreviations see page xv. Brodmann areas are based on Brodmann map as provided by MRICroN.

Table B.8: fMRI repetition study: Results of the differential effects of syntactic processing. A hash key indicates regions used as seed regions in the tractography study on healthy participants.

Region	Hemisphere	BA	MNI peak coordinate [mm]	z-score	Extent in voxels
<i>p</i> < .05, FWE-corrected					
Simple Syntax (Simple syntax > missing syntax)					
anterior MTG	L	20	-54 -7 -18	6.30	64
▷ anterior STS #	L	20	-45 11 -26	4.82	
posterior insula	L	48	-33 -22 2	5.04	17
angular gyrus	L	39	-54 -64 22	4.92	30
Complex syntax (Complex syntax > simple syntax)					
STS	L	21	-48 -37 -6	5.08	11
IFG # (54.2 % in BA 45; 42.4 % in BA 44)	L	44	-54 20 22	4.51	8

Note.

For abbreviations see page xv. Brodmann areas are based on Brodmann map as provided by MRICroN. Percentages of areas are based on Jülich Probability Maps.

Table B.9: fMRI repetition study: Results of the differential effects of semantic processing.

Region	Hemisphere	BA	MNI peak coordinate [mm]	z-score	Extent in voxels
<i>p</i> < .05, FWE-corrected					
Semantic effect for Word lists (Meaningful > meaningless word lists)					
posterior MTG	L	37	-60 -46 -6	5.46	109
▷ middle MTG	L	20	-54 -22 -10	5.18	
Semantic effect for Simple sentences (Simple meaningful > meaningless sentences)					
angular gyrus	L	39	-51 -61 22	6.50	173
anterior MTG	L	21	-60 -10 -22	5.23	24
precuneus	L	23	-3 -49 34	5.04	14
dorsomedial prefrontal cortex	L	32	-9 53 30	5.03	8
Semantic effect for Complex sentences (Complex meaningful > meaningless sentences)					
angular gyrus	L	39	-48 -64 18	7.71	328
precuneus	L	23	-9 -49 34	6.52	188
anterior MTG	L	20	-57 -10 -22	6.01	68
dorsomedial prefrontal cortex	L	32	-9 53 30	5.87	214
anterior MTG	R	21	57 -7 -18	5.20	36
posterior MTG	L	37	-63 -46 -6	5.00	8
angular gyrus	R	21	54 -58 22	4.66	12

Note.

For abbreviations see page xv. Brodmann areas are based on Brodmann map as provided by [MRICroN](#).

B.4 Overlap of the comprehension and repetition experiment (Chapter 5)

Table B.10: Statistics and main peak coordinates of the conjunctions between the comprehension and repetition experiment. A hash key indicates regions used as seed regions in the tractography study on healthy participants.

Region	Hemisphere	BA	MNI peak coordinate [mm]	z-score	Extent in voxels
$p < .01, k \geq 11$ (uncorrected)					
Simple Syntax					
posterior STS/AG	L	39	-54 -61 22	2.74	44
Complex Syntax					
n.s.					
Word-level Semantics					
anterior MTG #	L	21	-51 8 -26	2.82	33
Sentence-level Semantics					
anterior MTG	L	20	-54 -10 -18	3.10	22
posterior STS #	L	n/a	-63 -55 18	2.56	11

Note.

For comprehension, only meaningful stimuli were contrasted.

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BIBLIOGRAPHIC DETAILS

Sarah M. E. Gierhan

Brain networks for language

Anatomy and functional roles of neural pathways supporting language comprehension and repetition

Fakultät für Biowissenschaften, Pharmazie und Psychologie Universität Leipzig

Dissertation

173 pages, 239 references, 24 images, 21 tables

The current thesis presents the anatomy and functional roles of fiber tracts involved in auditory language processing. It aimed at anatomically differentiating the course of the fiber tracts, as well as examining whether the fiber tracts can be differentiated functionally. Specifically addressed were the gray and white matter structures that underlie complex and simple syntactic processing, as well as word- and sentence-level semantic processing during both language comprehension and repetition, as well as phonological, phonetic and motor aspects of speech repetition.

The thesis first provides a literature review which introduces methods for accessing fiber tracts and discusses the precise course of different fiber tracts along with their proposed functional roles during auditory language processing. Second, the review is followed by two functional magnetic resonance (fMRI) experiments investigating the key brain regions of different linguistic functions during sentence comprehension and repetition. The resulting brain regions were then used in a tractography study to investigate the fiber tracts supporting the above mentioned linguistic functions in healthy adults. Finally, the functional roles of ventral and dorsal fiber tracts were studied in patients who demonstrated preoperatively lesioned, and postoperatively recovered fiber tracts.

The findings corroborate the existence of several anatomically differentiable ventral and dorsal fiber tracts. They furthermore suggest a functional differentiation into ventral fiber tracts supporting “simple” linguistic functions, and dorsal fiber tracts supporting “complex” linguistic functions, as well as working memory and speech repetition functions. Taken together, the present thesis can provide a detailed and comprehensive neurocognitive model of fiber tracts involved in auditory language processing that outruns the existing models and solves hitherto conflicting results.

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Sarah Gierhan
Leipzig, den 22. August 2012

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