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White matter fiber tracts for phonological processing

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PREFACE

The aim of this dissertation is to track and visualize fronto-parietal and interhemispheric white-matter pathways for two different phonological transformation processes: transformation based on prosodic, i.e. suprasegmental, information and transformation based on segmental information.

Structural connectivity between functionally defined fronto-parietal and interhemispheric language areas for these different aspects of phonological processing is investigated by means of a recently established probabilistic diffusion-tensor based tensor imaging method.

This neurocognitively motivated approach allows for in-vivo imaging of the most likely neuroanatomical pathways for specific language processes and embedding and discussing the findings in the context of existing models of large-scale networks for language processing.

In the introduction, the historical roots as well as the most recent models on large-scale language networks will be reviewed briefly and the functional role of frontal and parietal regions in language, specifically phonological processing, will be summarized. Furthermore, the findings of an fMRI study providing the seed regions for the tracking experiment are presented. This fMRI study investigated differential aspects of phonological processing; one based on suprasegmental the other on segmental features of speech.

In the methods and results section, the probabilistic fiber tracking method that was used in the study is explained and the results and visualizations of the fiber pathways are presented.

In the discussion, specific issues that were raised in the introduction are examined in relation to the results from the tracking experiment. Furthermore, the importance of the large-scale fronto-parietal pathways for phonological processing are discussed. Finally, the role of interhemispheric pathways for suprasegmental processing based on prosodic features of speech is explored with reference to disorders of prosody.

Table of contents

Table of figures

1. INTRODUCTION

1.1. From classical language areas to large-scale networks

In the framework of classical aphasiology, represented by the early works of Broca, Wernicke (1874), Lichtheim (1885) and later Geschwind (1965), which was chiefly based on the neurological and post-mortem study of aphasic patients, the arcuate fascicle was identified as the major neuroanatomical pathway that connects the frontal (Broca's area) and temporal (Wernicke's area) language regions. With modifications, this model is still alive and well in most textbook discussions of the neural basis of language to date.

Recently, with the advent of structural and functional neuroimaging this traditional fronto-parietal model of language processing as to be exclusively located in and interacting between Broca's and Wernicke's area has been modified and expanded by many lines of converging research methods like electrophysiological studies (ERP, EEG), neuroimaging (fMRI, PET, DTI) and lesion studies. Increasingly, for example, the important role of posterior temporal regions for language processing is appreciated and incorporated into neuroanatomical models of the neural language system as a large scale fronto-temporo-parietal network (see Shalom and Poeppel, 2008; Marslen-Wilson and Tyler, 2007; Tyler 2005, Opitz et al., 2007; Grodzinsky, 2006; Friederici, 2006a and b, 2004; Dronkers 2004; Hickok and Poeppel, 2007, 2004, 2000; Scott and Johnsrude, 2003; Wise et al., 2001, 1999; Scott et al., 2000; Mesulam, 1990; and many others).

1.2. Dual processing streams: A model for language processing?

From research on visual (Ungerleider and Mishkin, 1982), auditory (Rauschecker and Tian, 2000, Kaas and Hackett, 1999) and somatosensory (Dijkerman and de Haan, 2007) processing in non-human primates and humans it has become apparent, that sensory integration processes in the brain are organized along segregated processing streams.

In the visual domain, two streams of object processing have been described in the rhesus monkey, with the dorsal stream processing spatial information such as object position, size and orientation (“where”) and the ventral stream responsible for object recognition (“what”) (Ungerleider and Mishkin, 1982).

In the auditory domain, evidence from research on macaques suggests the existence of a dual, ventral-dorsal, auditory processing stream (Rauschecker and Tian, 2000). In this model, the dorsal stream is seen as spatial integration pathway (“where”) and connects caudolateral and caudomedial regions in the auditory cortex with the dorsolateral prefrontal cortex which can be routed either directly or indirectly via the posterior parietal cortex. The ventral stream (“what”) is considered to be a pattern or object processing route, connecting mediolateral and anterolateral regions in the macaque’s auditory cortex and ventrolateral prefrontal cortex via the parabelt cortex and areas in the anterior superior temporal gyrus. One important anatomical constraint of research on the macaque’s auditory processing system is that there are important anatomical differences between the macaque and the human brain in frontal and temporal regions; crucially, the macaque does not have a middle temporal gyrus (MTG) which seems to play an important role in language processing in humans (Vigneau et al., 2006).

Analogous to dual-stream models in the visual (Rauschecker et al., 1982) and auditory (Rauschecker and Tian, 2000) domain in non-human primates described above, Hickok and Poeppel (2007, 2004 and 2000) have proposed a dual-stream model of auditory speech processing in humans.

This dual-stream model consists of a ventral stream which maps speech sounds to lexical conceptual representations (“what”), and a dorsal stream which maps speech signals to articulatory networks (“how”). The ventral stream links the primary auditory cortex in posterior superior temporal gyrus (STG) with posterior parts of MTG and inferior temporal gyrus (ITG) – the “lexical interface” – which projects to the “combinatorial network” localized in anterior MTG and anterior inferior temporal sulcus (ITS) (Hickok and Poeppel, 2007, 2004). This large-scale processing network is assumed to be organized bilaterally with a left hemisphere (LH) preference. The dorsal stream, in turn, is mainly organized around the temporo-parietal junction, which is hypothesized to serve as “sensory-motor interface”, and areas in the frontal lobe involving BA 44 and premotor cortex which serve as an “articulatory network”. In a previous version of their model, the dorsal stream was suggested to reflect a basic ”where” system of spatial orientation (Hickok and Poeppel, 2000). More recently, Zaehle et al. (2008) found that the dorsal stream is involved in segmental sublexical processing, i.e. processing at the level of segments and syllables of speech, as well as the acoustic analysis of non-speech sounds.

Altogether, these findings suggest that the neural language processing system in humans may be organized along the same principles of functional and hierarchical segregation that govern other brain functions which is indicative of a general principle of organization across various processing domains.

1.3. Dorsal and ventral language-related pathways

In-vivo studies on white matter connections in the human brain using diffusion tensor imaging (DTI) have contributed to a more detailed understanding of the connectivity between regions implicated in language processing (Saur et al., 2008 [Fig. 1]; Makris and Pandya, 2008; Frey et al., 2008; Catani, 2005; Mori et al. 1999).

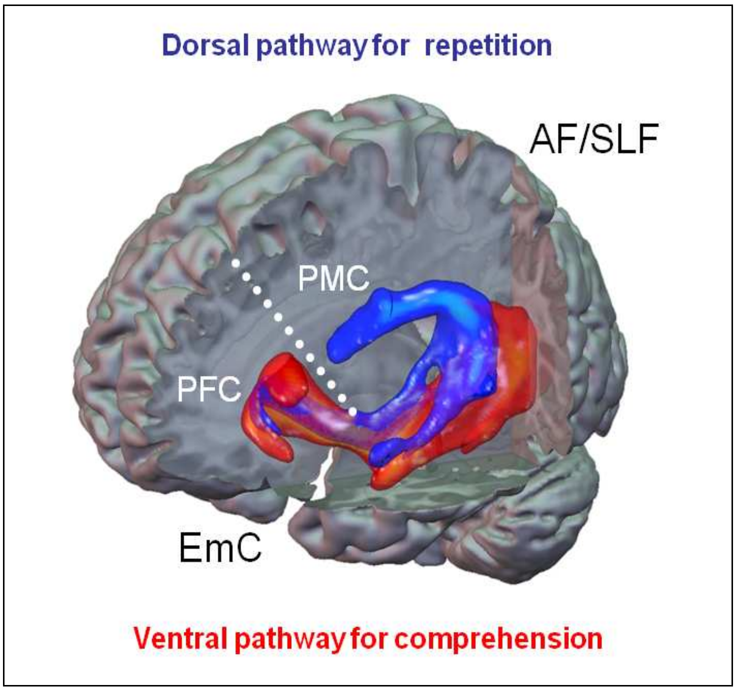

Figure 1 *Dorsal (blue) and ventral (red) pathway for language, modified from Saur et al. (2008); PMC=premotor cortex, PFC=prefrontal cortex, AF/SLF=arcuate fascicle/superior longitudinal fascicle, EmC=extreme capsule*

1.3.1. Dorsal language pathways

The arcuate fascicle, connecting temporal and inferior parietal cortex with the frontal lobe, is considered the classical language pathways in humans and, as a consequence, investigations concerning white matter fiber tracks for language processing have mainly focused on this white matter tract. It has been described in many recent, though mostly deterministic, DTI studies of the human white matter system in the brain (e.g. Catani et al., 2005, 2007).

A study by Catani et al. (2005) investigated the white matter pathways between perisylvian language areas in the left hemisphere, suggesting the existence of two parallel pathways that connect frontal and temporal regions. Apart from the well-known direct connection between Broca's area and Wernicke's area via the aforementioned arcuate fasciculus (AF), they describe an indirect route that connects temporal with parietal and parietal with frontal regions via a posterior (parieto-temporal) and anterior (parieto-frontal) segment of white matter tract. The findings of Catani et al. (2005) also suggest that, though highly interconnected, the inferior and parietal regions of Wernicke's area are dissociable anatomically. They take their model of direct and indirect connections between perisylvian language areas to lend support to a parallel distributed account of language processing that is performed by a network of distributed groups of neurons rather than specialized language centers as in the classical Broca-Wernicke-Lichtheim-Geschwind model.

This dorsal language pathway along the AF and superior longitudinal fascicle (SLF) is consistent with many recent DTI studies of the human brain (cp. Frey et al. 2008; Saur et al. 2008, Glasser, Rilling, 2008; Catani et al., 2007; Schmahmann, 2007;) such that the fact, that these fascicles connect the posterior temporal with the frontal lobe seems indisputable. However, two important caveats must be raised with respect to the tracking studies by Catani et al. First, they did not specify which specific sub-regions of the left inferior frontal gyrus (LIFG) are reached by these pathways and, second, using deterministic fiber tracking algorithms constrained by pre-defined regions-of-interest (ROI) is prone to false negatives, i.e. only fibers are detectable depending on the a priori information on the specified seeds.

In the study by Saur et al. (2008), in contrast, probabilistic fiber tracking was used to track connections between functionally defined language areas activated by prototypical language tasks, namely comprehension and repetition of speech. This approach allows for tracking of fiber pathways which is constrained only by the functional activation of language tasks and not by pre-conceived, and to some extent arbitrarily selected, regions. In this study the dorsal pathway between frontal and temporal regions of interest only reached pars opercularis of the inferior frontal gyrus - i.e. Brodmann Area (BA) 44. This finding is supported by evidence from studies in non-human primates, most importantly tracing studies in monkeys (Schmahmann, 2007; Schmahmann, Pandya, 2006) in which neither AF nor SLF reaches more ventro-lateral prefrontal regions like F5 (the homologues of BA 45 and BA 47 in humans). In spite of these converging lines of evidence on the importance and neuro*anatomical* characteristics of the dorsal language pathway, the *functional* significance of the AF/SLF fibers for language processing remains controversial.

1.3.2. Function of the dorsal pathway in language processing

Comparing repetition of pseudo words with words, Saur et al. (2008) delineated a fronto-temporal language network with activation temporal clusters in anterior and posterior STG and frontal clusters in premotor cortex (see Figure 2).

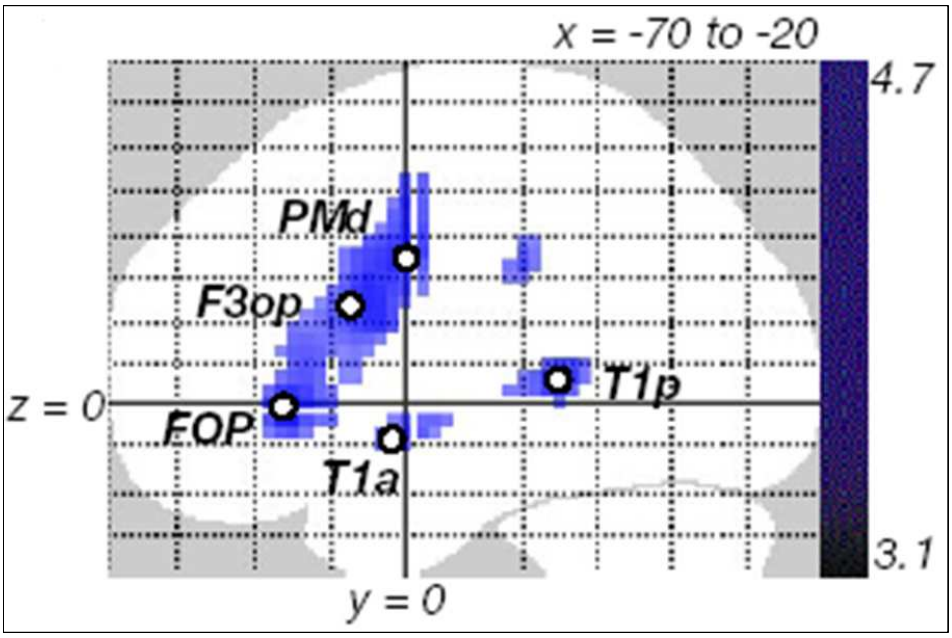

Figure 2 *Language network for repetition (Saur et al., 2008).*

Functionally, the activation in STG represents stages of pre-lexical processing during stimulus perception, whereas frontal regions are hypothesized to be necessary for preparing and planning of speech output, in this case repetition. From a processing point of view, the connection via the dorsal pathway is thought to be the route for mapping phonemic representations onto motor representations for articulation (cp. Hickok and Poeppel, 2004; Warren et al., 2005). This fronto-temporal interaction could also serve as means for frontal areas to map the planned motor output through mental representations of the sound structure (Indefrey and Levelt, 2004).

Finally, comparing DTI based tractography studies in the monkey and human brain, the AF also seems to play a crucial role in human language evolution as, for example, the prominent temporal lobe projection of the human arcuate fascicle is absent (or very small) in nonhuman primates (Rilling et al., 2008).

1.3.3. Ventral language pathways

Recent DTI tracking studies in the human brain have highlighted the importance of ventral fronto-temporal connections via the extreme capsule (EmC) for crucial aspects of language processing (Saur et al., 2008; Markis and Pandya, 2008; Frey et al., 2008; Anwander et al., 2007), specifically for comprehension of aurally presented speech (Saur et al., 2008).

Others argue, that an inferior occipito-frontal fascicle (Bello et al., 2008; Duffau et al., 2008; Powell et al., 2006) as well as the uncinate fascicle (Friederici et al., 2006a) are the crucial ventral temporo-frontal connection for language processing.

In support of DTI findings delineating the EmC as the crucial ventral pathway for language, autoradiographic tracing studies in monkeys (Schmahmann et al., 2007 and 2006; Petrides and Pandya, 2007) show that the EmC is the long association fiber bundle that provides temporo-frontal connection in these animals. These studies also show that only the homologues of the human BA 45 and BA 47 are reached by the ventral fiber bundles. In contrast to the premotor regions of interest in the experiment by Saur et al. (2008), the frontal operculum (FOP) (Fig. 1) is connected with the temporal lobe solely via the ventral pathway.

1.3.4. Function of the ventral pathway for language processing

In the above mentioned study by Saur et al. (2008), auditory speech comprehension, represented by contrasting meaningful normal sentences with meaningless pseudo sentences, involved a temporo-frontal processing network including middle and inferior temporal areas as well as ventrolateral prefrontal regions (including BA 45 and 47). The fronto-temporal interaction was provided structurally by a ventral pathway via the EmC and, in contrast to Catani et al. (2005), it was hypothesized that it is the disruption of this crucial ventral connection that may lead to transcortical sensory aphasia, i.e. poor comprehension of speech but intact repetition and production.

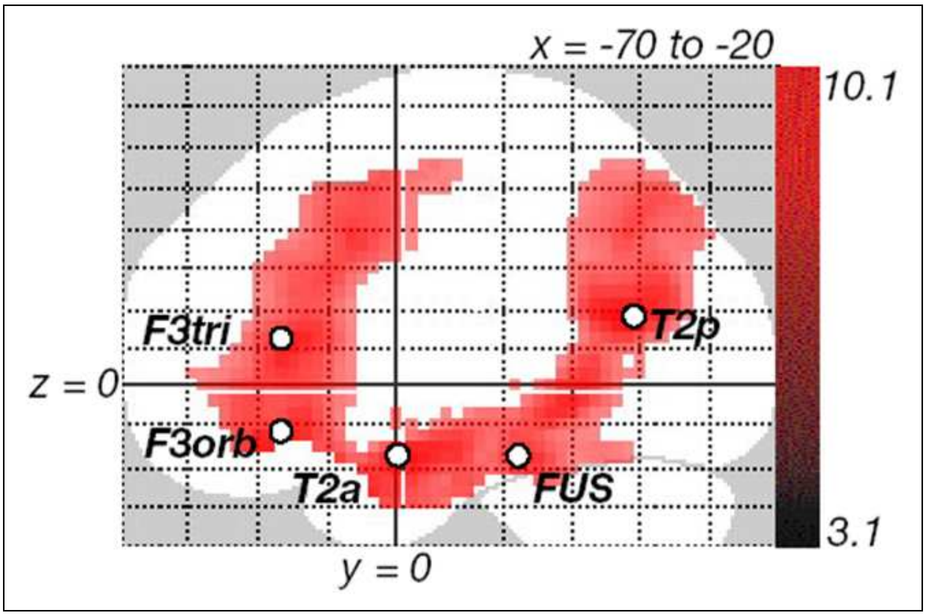

Figure 3 *Language network for comprehension (Saur et al., 2008).*

Furthermore, Saur et al. hypothesize, that the long association fibers connecting FOP and STG via the EmC may subserve a fronto-temporal "feedback system" (cp. Guenther et al., 2006) which could play a role in monitoring speech, in this case to control the sequencing of unknown - though legal - phonemes.

This study, together with other recent work (see e.g. Frey et al., 2008) demonstrates the function of at least two distinct routes for temporo-frontal interaction in language processing. This functional segregation of language pathways, however, may likely be a result of the experimental stimuli-related dissociation. In natural language processing like communication, the two pathways would be expected to interact closely to facilitate a maximal yield of information and verbal interaction.

1.4. Functional sub-systems of the fronto-parietal language network

As much as there is converging neuroanatomical and neurocognitive evidence that the neural language system is instantiated in a large scale, bilateral, fronto-temporo-parietal network, there is still considerable debate about the functional role of the various parts of the system for language processing.

Mainly, there is disagreement on the degree to which anatomically identifiable parts of the network can be related to dissociable linguistic aspects of spoken language comprehension and production like syntactic and semantic processing, inflectional morphology, as well as (sub)lexical phonemic processing with which the present study is concerned.

Before examining and discussing the fronto-parietal pathways in the context of phonological transformation processes during auditory-motor integration, it will be briefly reviewed what is known about the functional sub-systems involved – specifically left inferior frontal cortex and left parietal cortex.

1.4.1. Left inferior frontal cortex in language processing

Macroanatomy and cytoarchitecture of (left) inferior frontal cortex

The inferior frontal gyrus is one of three convolutions (the others being middle and superior frontal gyrus) which are divided by the convex surface anterior to the precentral gyrus. It is parcellated by branches of the lateral sulcus into three distinct parts: pars opercularis, pars triangularis and pars orbitalis (Fig. 4).

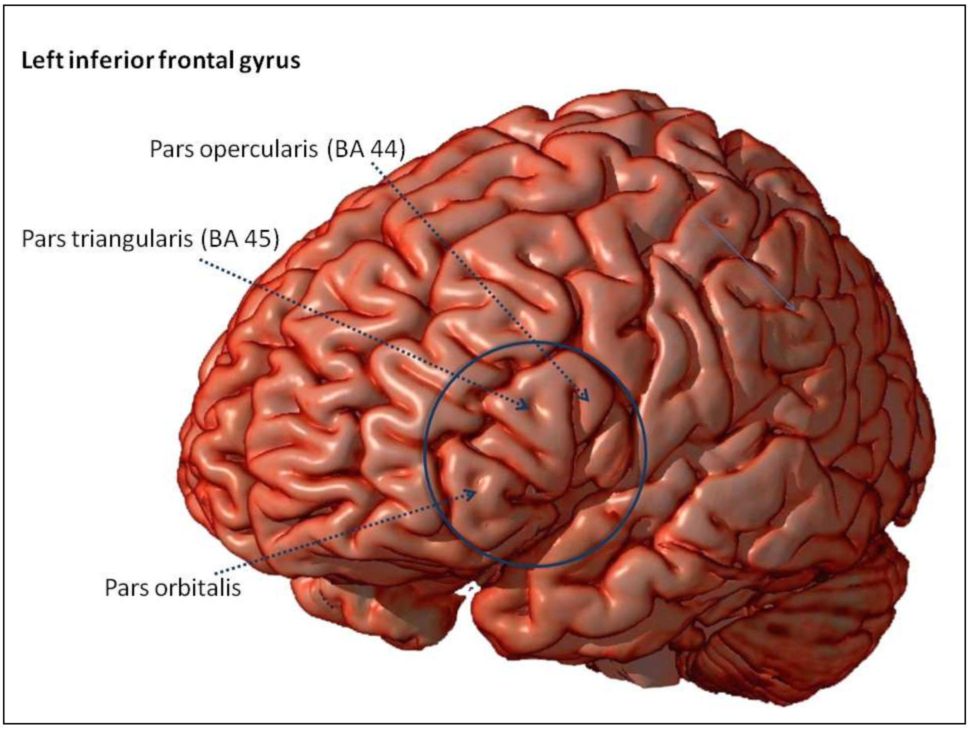

Figure 4 *Tripartition of IFG into Pars opercularis (BA 44), Pars triangularis (BA 45) and Pars orbitalis.*

In terms of cytoarchitecture, pars opercularis is largely occupied by BA 44 and pars triangularis by BA 45, the two of which comprise Broca's area. With respect to hemispheric asymmetries, Amunts et al. (1999) found differences between the left and right hemisphere in cytoarchitecture and volume as well as cell-packing density for BA 44 and to a lesser extent for BA 45 suggesting that BA 44 may be more lateralized than BA 45. Because of high inter-individual variability in macroanatomy as well as cytoarchitecture, Amunts et al. (1998) suggested the use of three-dimensional probability maps of areas 44 and 45 for analyzing structure-function relationships in these areas.

Functional role of BA 44 and BA 45 in language processing

The role of the left inferior frontal cortex, specifically BA 44 and BA 45 in auditory language processing is, to say the least, controversial (for review see Vigneau et al., 2006; Démonet et al., 2005). At one end of the research spectrum, it is being advocated that LIFG activity supports a variety of cognitive functions such as working memory (Lebedev et al., 2004; Waters et al., 2003; for meta-analyses see Owen et al., 2005; Miyake and Shah, 1999) or selection (Lebedev et al., 2004) and competition processes (Tippett et al., 2004), and is thus seen to be non-specific to language processing (Cooper, 2006; Ferstl et al., 2002; Kaan and Swaab, 2002; Thompson-Schill et al., 1997), lending support for more domain-general role of LIFG in executive processes.

At the other end, it is being advocated that LIFG is indeed crucially and specifically involved in language processing (Burton, 2009; Saur et al., 2008, Marslen-Wilson and Tyler, 2007; Tyler and Marslen-Wilson, 2007; Vigneau, 2006; Tyler et al., 2005; Ben Shachar et al., 2004; Rodd et al., 2005; Booth et al., 2002; Embick et al. 2000; Chee et al., 1999; and others).

In an early neuroimaging study using PET, Price et al. (1996), investigating the neural correlates of auditory word processing, found a functional division of Broca's area with BA 44 being preferentially involved in speech production and BA 45 in perception of single words. Based on a comprehensive review, Bookheimer (2002) advocates for a functional subdivision into three parts, a more dorsal part (superior posterior LIFG, BA 44/6), a middle part (middle portion of LIFG, BA 44/45) and an anterior-inferior part (inferior IFG, BA 45/47). This functio-anatomical tripartition, according to Bookheimer's and supporting findings (e.g. Thompson-Schill, 2005), goes along with a functional specialization in which the superior part is hypothesized to be preferentially involved in phonological, the middle part in syntactic and the inferior part in semantic processing (see also Shalom and Poeppel, 2008; Crinion et al., 2003, Dapretto et al. 1999).

With respect to phonological processing, the following findings are of particular interest. Using an overt picture-naming task during fMRI, Heim et al. (2002) found BA 44 to primarily supportive of phonological encoding. With respect to the role of Broca's area in speech production, Papoutsi et al. (2009), using event-related fMRI to investigate phonetic encoding and articulation hypothesized that LIFG (BA 44) is implicated in phonetic but *not* phonological encoding.[1] In addition, they postulate a functio-anatomical segregation of LIFG, pars opercularis (BA 44) into two subareas

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[1] The difference essentially being that phonetics is part of descriptive linguistic analysis investigating mostly the physical properties of speech sounds, whereas phonology studies language-specific systems of codes for decoding meaning in speech perception and encoding in speech production

with the dorsal part subserving phonological encoding and the ventral part phonetic encoding and possibly the transformation from phonological representations to articulation (cf. Hickok and Poeppel, 2000, 2004, 2007). Using an overt picture-naming task during fMRI, Heim et al. (2002) also found BA 44 to primarily supportive of phonological encoding.

Summarizing many neuroimaging studies on phonology, semantics and sentence processing in an extensive meta-analysis, Vigneau et al. (2006) suggested a functional segregation of the pars opercularis (BA 44) into an upper and a posterior part, the former devoted to phonological and the latter to syntactic processing. The dorsal part of the pars triangularis (BA 45), in turn, was preferentially involved in semantic processes in the studies reviewed in their meta-analysis.

Recently, Petrides (2008) suggested that BA 44, which has previously been shown to be involved in controlling the orofacial musculature (Petrides et al., 2005), is likely to be responsible for the higher-order articulatory control of speech production.

Regarding the time-course of interactions between frontal and temporo-parietal language areas in language production, Heim and Friederici (2003) have argued for a temporal primacy of LIFG areas over superior temporal / inferior parietal areas, opposite to the pattern observed in language comprehension by Thierry et al. (1999).

An important aspect of speech production concerns the difference between silent articulation (or „inner speech“) and imagery of speech which, in an early PET-study, have been examined by McGuire et al. (1996) who found increased activity during inner speech only in LIFG whereas temporal regions were only active during auditory imagery which suggests that subvocal internal rehearsal of speech might be regarded as an executive process whereas auditory imagery might be more akin to perceptive mechanisms.

To summarize, LIFG, BA 44 and BA 45 are involved to varying degree in phonological processes in speech production. Evidence from neuroimaging studies suggests that BA 44 seems to be involved in phonological and phonetic encoding processes as well as articulatory control whereas BA 45 seems to play a role in semantic aspects of language processing, in terms of processing possibly as an area that mediates top-down modulation on phonological coding routines.

1.4.2. Parietal cortex in language processing

Macroanatomy and cytoarchitectonics of inferior parietal cortex

The parietal cortex is subdivided into four major parts (Fig. 5), the parietal operculum (PO), the superior parietal lobule (SPL), the inferior parietal lobule (IPL) and the postcentral gyrus (PcG).

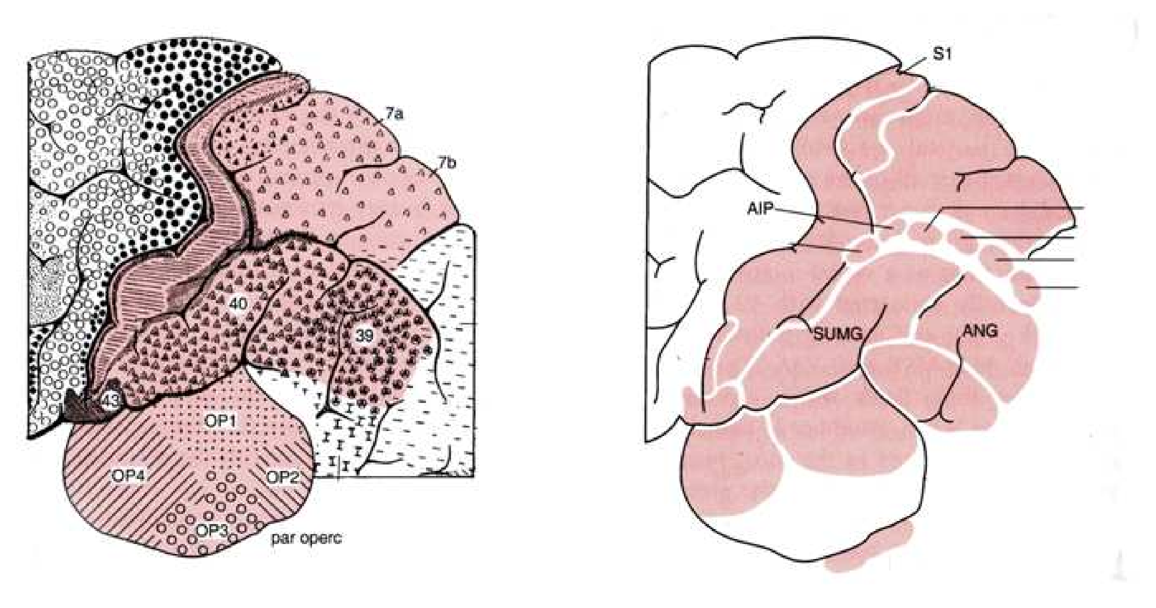

Figure 5 *Left parietal cortex with Parietal operculum (OP1-4), superior parietal lobule (BA 7a/b,) and inferior parietal lobule (IPL), with IPL comprising supramarginal gyrus, BA 40 (SUMG) and angular gyrus, BA 39 (ANG) divided by the intraparietal sulcus (AIP) and superior parietal sulcus including precentral gyrus (S1). Modified from Nieuwenhuijs et al., 2007.*

Following the early cytoarchitectonic classification of Brodmann (1909), inferior parietal cortex (IPC) comprises two distinct cytoarchitectonic areas: BA 39, which macroanatomically is called supramarginal gyrus and BA 40, called angular gyrus (Fig. 5). Though Brodmann's classification system is still in use today; even for the localization and attribution of activation maps in many functional neuroimaging studies, there is increasing evidence from more advanced methods of cytoarchitectonic mapping that IPC contains several more distinct areas and that there is no correspondence between macroanatomical landmarks and cytoarchitectonic borders (Caspers et al., 2006). Caspers et al. (2006) suggest that these differences in cortical microstructure could be related to functional specialization of IPC areas, a proposal which resonates well with the idea of IPC being a region of multimodal integration and mapping processes.

Functional attributes of parietal cortex: working memory and phonological short-term store

Generally, parietal regions especially inferior parietal lobule seem to play an important role in sensory-motor integration across a variety of processing domains like vision, attention and speech (Avillac, 2005).

In the context of mapping auditory input to articulation, with which the present study is concerned primarily, IPL seems to be preferentially involved in differential aspects of sublexical phonemic processing (Hickok and Poeppel, 2004; Caplan et al., 1995). However, there is a controversial and ongoing debate concerning the question of whether IPL and specifically SMG and IPS are more generally engaged in working-memory processes, what Baddeley (2003, 1992, 1986, 1966) conceptualized as the “short-term working memory loop”, or whether these areas subserve distinct computational sub-routines with a short-term phonological store as a specific subcomponent facilitating subvocal rehearsal, often called “articulatory loop” (for a review see Buchsbaum and D’Esposito, 2008) .

Evidence from early neuroimaging studies primarily using PET suggested that phonological tasks requiring short-term storage indeed engage left inferior parietal areas (Paulesu et al., 1993; Smith, 1995, 1996; Schuhmacher et al. 1996; Salmon et al. 1996; Awh et al. 1996; Jonides et al., 1998, summarized in fig. 6). Based on Baddeley’s model of an “articulatory loop” for phonological short-term store and a “subvocal rehearsal system” (Baddeley, 1992), the PET correlates of these systems were investigated.

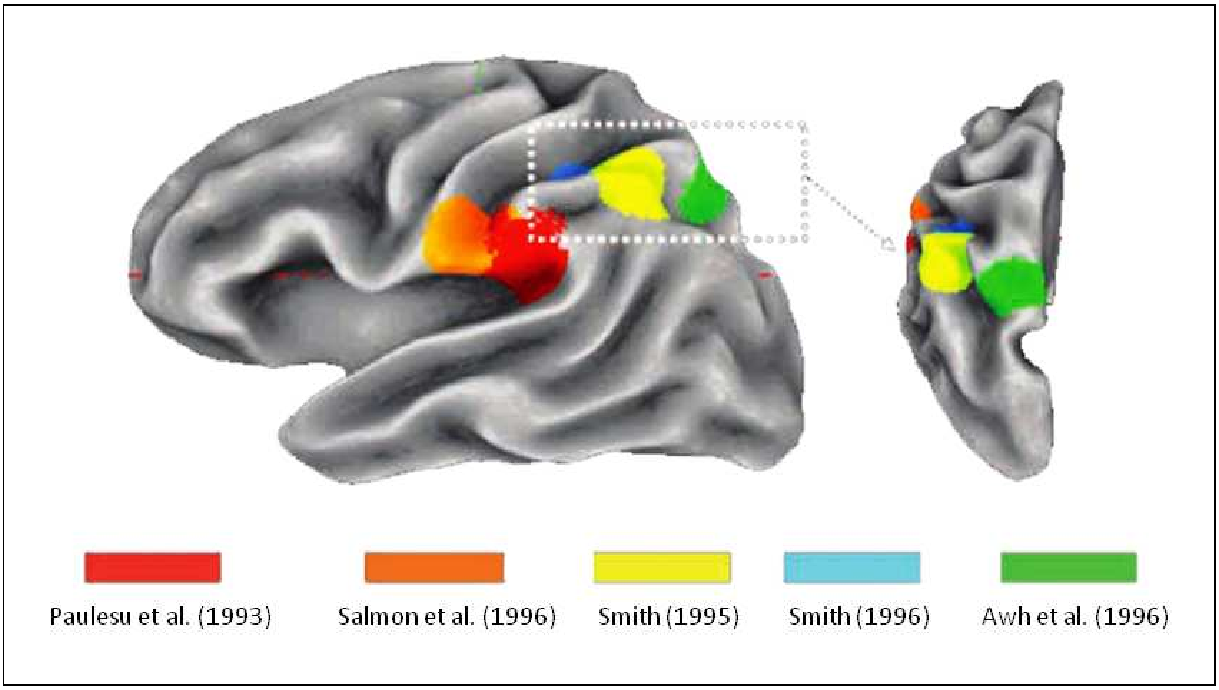

Figure 6 *The phonological store in the parietal lobe, evidence from five PET studies. Taken from Buchsbaum and D'Esposito, 2008.*

It was found, that short-term storage in the articulatory loop activated left inferior parietal areas whereas subvocal rehearsal activated Broca's area. Also using PET imaging, Démonet et al. (1994) found increased blood flow in the inferior part of the left primary motor cortex and in the supramarginal gyrus of IPL when comparing a phonological task with a lexical-semantic task which they assumed to engage verbal short-term memory, i.e. the articulatory loop as proposed by Baddeley.

In a further PET study, Jonides et al. (1996) also found posterior parietal areas specifically associated with the storage of "phonological codes" in verbal working memory. Schuhmacher et al. (1996), also in a PET study, showed that the fronto-parietal areas involved in processes representing verbal working memory are supramodal, i.e. independent of the input stimuli being visual or auditory.

Taking most of the evidence from early imaging studies on domain-independent working memory vs. phonological short-term store as reference point, Ravizza et al. (2004) investigated the notion of a dissociation of two parietal areas with fMRI; with dorsal inferior parietal cortex (IPC), or angular gyrus, assumed to respond to higher working-memory load and ventral inferior parietal cortex or supramarginal gyrus to information type (verbal/non-verbal). Interestingly, they did not find a clear representation of this dissociation reflected by neural correlates in fMRI, suggesting instead that dorsal IPC might rather play a role in modality-independent executive processes whereas ventral IPC was hypothesized to support phonological encoding.

Evidence from lesion studies too suggests that damage to the left inferior parietal area gives rise to deficits in verbal short-term memory (Shallice and Vallar, 1990; Vallar et al., 1997). In an fMRI study with aphasic patients, Caplan et al. (1995) reported that in speech perception the left supramarginal gyrus was implicated in phonemic processing. Investigating habituation and change detection in syllables and tones with fMRI, Celsis et al. (1999) interestingly found that SMG was specifically activated in the detection of changes in phonological stimuli.

Emphasizing the importance of lesion studies, Müller et al. (2006) picked up on the idea of a "phonological loop" consisting of a phonological short-term store associated with IPL and a subvocal rehearsal mechanism implemented in areas important for speech production, specifically LIFG and SMA. They argued that working-memory processes are organized along ventral and dorsal prefrontal cortex.

Finally, in their meta-analysis on functional imaging studies, Vigneau et al. (2006) found that most parietal clusters across different studies investigating phonological processing were located in left IPL and posterior superior SPL (see Fig. 7).

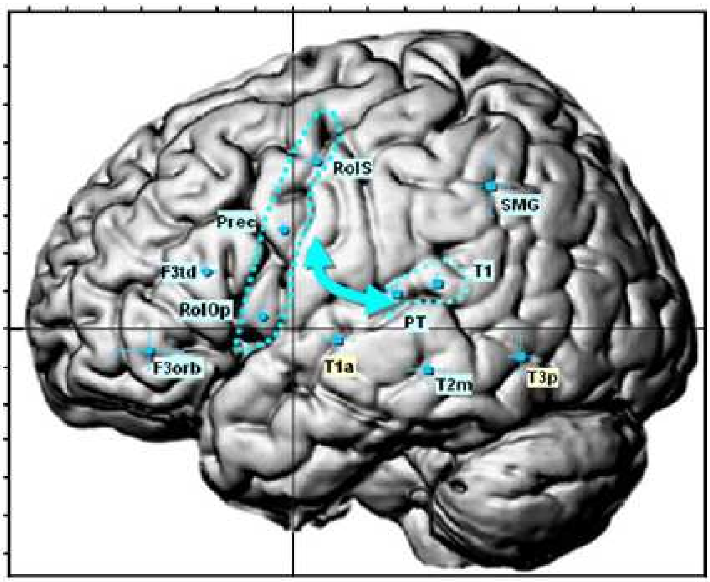

Figure 7 ***"**Phonological loop" from meta-analysis by Vigneau et al. (2006)*

1.4.3. Interhemispheric transcallosal fiber pathways

From a neuroanatomical point of view, any psycholinguistically and cognitively informed model of a bilaterally instantiated large-scale language network operating in parallel has to account for the interhemispheric structural connectivity of areas involved in language processing.

Structure and function of the Corpus callosum

The corpus callosum (CC) is one of two important commissural fiber systems (the other being the anterior commissure) which both develop ontogenetically from the commissural plate. It is a wide system of fibers interconnecting neocortical areas of the hemispheres. Macroanatomically, it is divided into a curved rostral part, called the *genu*, a middle part, called the *body* and a caudal part, the *splenium*. In terms of connectivity, commissural fibers can be *homotopic* that is interconnecting corresponding cortical areas, or *heterotopic*, interconnecting non-corresponding cortical areas.

Apart from its obvious importance in providing interhemispheric connectivity, the CC has often been investigated mainly with regard to questions of hemispheric specialization of functions, i.e. laterality (Galaburda and Rosen, 1990). Interestingly, as compared to other long-range fiber tracts, the CC quantitatively does not seem of major importance as a projection system (Schütz and Preißl, 1996). It has been estimated that the number of fibers of the CC ranges in the order of 10^8 while the number of cortico-cortical projections *within* one hemisphere alone is one order of magnitude higher at least (Schütz and Preißl, 1996).

Neurologically, the role of transcallosal transfer has been discussed in the context of e.g. apraxia syndromes (Watson and Heilman, 1983) as well as affective prosody in mixed transcortical aphasia (Speedie et al., 1984) and, maybe most prominently, in investigating neuropsychological dissociations that come about as a result of corpus callostomy in intractable epilepsy patients, usually referred to as split-brain patients (e.g. Gazzaniga and Sperry, 1967).

1.5. Phonological processes

In this subsection, important aspects of phonological processes will be reviewed and the fMRI experiment which formed the basis of the study presented in this dissertation is introduced.

First, prosody and segmentation, two specific aspects of phonological processing are introduced. Second, the design and results of the fMRI study that provided the seed points for tracking phonology-related language pathways are presented.

1.5.1. Phonology, prosody and segmentation

What is phonology?

Defining phonology from a neurocognitive and psycholinguistic point of view, it can be characterized as a neurally instantiated generative system (Jackendoff, 2002; Goldsmith, 1979; Chomsky and Halle, 1968) representing language forms (e.g. word forms), that acts as an interface (Jackendoff, 2007, 2002) for *de*coding lexical-semantic information from speech sounds, in the case of auditory comprehension, and *en*coding lexical-semantic information, in the case of speech production.

In speech production, specifically when producing single words, the conversion from a conceptual structure (i.e. meaning) to a word is generally viewed to proceed in a two-step process called *lexicalization* (Garrett, 1975; Levelt et al., 1999). In this process, a specific concept is first converted into an abstract form, specifying semantic and syntactic but not phonological information, called a *lemma* which is then, in a second step, specified phonologically in terms of articulation and stress, called *lexeme.*[2]

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[2] An important aspect of this predominant model of lexicalization that is much debated is the question of whether access to these two stages of processing is either discrete (Levelt, 1999), i.e. before a lexeme can be accessed the lemma has to be fully specified, or whether it is interactive, i.e. lexemes can be accessed before a lemma is fully specified (Rapp and Goldrick, 2000) .

Prosody and segmentation

In speech perception and comprehension, there are roughly two important kinds of information that are extracted by the hearer’s processing system in order to enable lexical access: (1) suprasegmental information, specifying the prosodic properties of speech sounds and (2) segmental information, facilitating the identification between distinctive speech units, i.e. phonemes.

If speech can be described physically as a more or less continuous stream of sounds that is perceived as a sequence of distinct - segmented - sounds, prosody encompasses the suprasegmental features of speech which are conveyed *perceptually* by pitch stress and duration and *acoustically* as changes in frequency, intensity and timing. The smallest prosodic unit of speech is the so-called phonological word (Bregman, 1990). Prosody is valuable in disambiguating words (consider “black bird“ and “blackbird“) as well as sentences (consider “He took the car.“ and “He took the car?“) a feature which is called *intrinsic prosody*. Furthermore, prosody enables a speaker to convey emotions and attitudes, a feature which is called *extrinsic or affective prosody.* Acoustically, affective prosody relies heavily on changes in fundamental frequency. Prosodic units are suprasegmental because they are not confined to any single segment; rather, they proceed in a hierarchy of higher levels of any utterance. These prosodic units are the actual phonetic spurts or chunks of speech. They do not in general correspond to grammatical units such as phrases, and clauses, though they may, and both can reflect how the brain processes speech.

Very little is known, however, about the neural mechanisms, pathways and interactions that govern prosodic processing in the human brain. Some insight may come from cases of prosodic pathology in cases of a- or dysprosody following brain damage, an aspect to which we will come back to in the discussion section.

In segmentation, the basic level of segmenting speech signals is the breakup and classification of the sound signal into a string of phonemes. Unlike writing, speech does not consist of a discrete sequence of sounds but rather a continuous stream of speech sounds interrupted by breathing and movements of the articulatory organs. The language processing system leads the hearer into perceiving boundaries between meaningful units of speech as pauses where, in reality, what is audible is a more or less continuous speech stream. Thus, segmentation of speech sounds in order to demarcate meaningful units and identify boundaries between words is a psychoacoustic illusion, albeit undoubtedly a very useful one. This effect is immediately tangible if one is immersed in a language never before heard, a case in which it is by no means easy to determine where one word ends and the next begins.[3]

Thus, there is an important difference, from a cognitive point of view, between the two types of information that are important in speech perception and comprehension in that prosody is fundamentally a property of the speech signal itself which facilitates decoding, whereas segmentation can be characterized more towards a specific kind of psychoacoustic processing routine in the hearer's neural language system.

1.5.2. Phonological processes revealed: an fMRI study

In order to investigate the *structural* routes for parieto-frontal interaction in phonological processes in the brain by means of a purely data driven probabilistic fiber tracking method (Saur et al. 2008, Kreher et al. 2008), it is necessary to first *functionally* define the brain network involved in differential aspects of phonological processing.

To define this phonological network, the results from a sophisticated scanning experiment investigating the neural correlates of two specific phonological processes, one based on manipulating suprasegmental (in this case prosodic) information and one based on manipulating segmental information, were used.[4] The aim of that fMRI study was to reveal which brain networks are involved in naturally occurring phonological processes requiring an explicit phonological manipulation (with little processing demands on working memory) while minimizing lexical-semantic interference by operating at the level of pseudo-words.

The material consisted of two different sets of aurally presented speech stimuli, designed to dissociate two different phonological processes: suprasegmental and

---

[3] Apparently something which is, to some extent, much less difficult for infants early in life.

[4] The fMRI experiment was conducted by the research group of Annette Baumgärtner, PhD, Institut für Systemische Neurowissenschaften, Universitätsklinikum Hamburg-Eppendorf. The following section is based on information provided by Dr. Baumgärtner and her colleagues (also cf. to Peschke et al. 2009, in press).

segmental transformation, the former was called "prosodic" the latter "segmental" in the experiment

The first group of stimuli, were intended to elicit a phonological transformation process of prosodic features based on a shift of stress and was hence called "prosodic processing" (abbr. "PROS"). The stimuli consisted of 36 bisyllabic pseudocountries and 36 corresponding pseudolanguages. The phonological and prosodic structure of the items was derived from real examples of countries and languages in German like “Kuba” → “kubanisch” (engl.: “Cuba” → “Cuban”). Considering that "standard" German often has a trochaic structure, the pseudocountries were stressed on the *first* syllable (e.g. /'doga/) whereas the pseudolanguages were stressed on the *second* syllable (e.g. /do'ganisch/). This change in stress placement is a natural process in spoken German.

The second group of speech stimuli in the transformation condition was hypothesized to elicit a phonological process which was called "segmental transformation" (abbr. SEGM). This material contained 36 bisyllabic pseudo-nouns including the German definite article “der” and 36 corresponding three-syllable pseudo-diminutives with the prefixed German definite article “das”. These items were phonologically derived from real German nouns and corresponding diminutives, for example, “der Ball” -> “das Bällchen” (engl.: “the ball” - “the small ball”) or “der Bach” -> “das Bächlein” (engl.: “the stream” -> “the streamlet”). Note that this transformation from a noun to a diminutive in standard German typically requires a mutation from a vowel to a vowel modified by a diacritic - an *umlaut* (“der Mall” -> “das Mällchen”). The change from vowel to umlaut in the transformation of a pseudo-noun into a pseudo-diminutive is a naturally occurring process in German and was dubbed "segmental transformation" because transformation is mainly based on segmenting the target word.

The fMRI experiment consisted of two different tasks: overt repetition and transformation.

(1) In the repetition task (REPEAT) participants had to repeat the speech stimuli as accurately as possible.

(2) In the transformation task (TRANSFORM), items had to be transformed depending on the phonological process as described in the previous section. In case of the PROS condition, a pseudo-country had to be transformed into the according pseudolanguage. The intention was to elicit a change of stress from

the first to the second syllable, something which the participants were not instructed of. In the case of the SEGM condition, a pseudo-noun had to be transformed into the according pseudo-diminutive. This task was designed to initiate a segmental vowel change. This vowel mutation was also not explicitly explained to the participants.

The design and time course of the stimulus presentation are illustrated in Fig. 8 (see also Appendix)

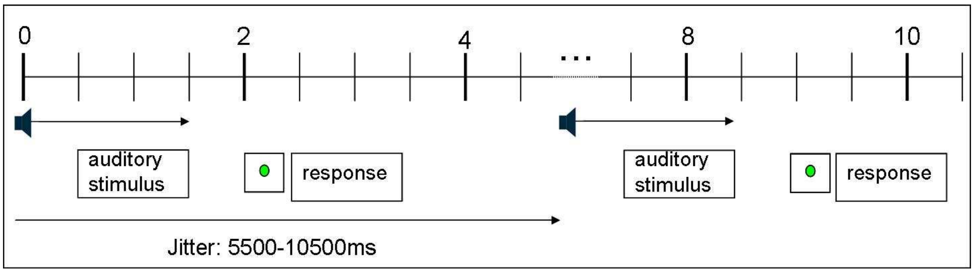

Figure 8 *Time course and design of fMRI experiment (courtesy of Peschke et al., 2009, submitted)*

Behavioral results (see Appendix for more details)

There was a significant main effect of task with more phonological errors in the transformation compared to the repetition task which can be explained by additional cognitive processing demands because of the phonological manipulation during transformation. Not surprisingly, this higher demand resulted in more phonological substitutions. In most cases, however, only a single phonetic feature of one phoneme was affected. Furthermore, subjects showed less phonological errors in the segmental compared to the prosodic condition although the segmental processing effectively included one syllable more as source of phonological error in the repetition condition. Considering the accuracy of the transformation processes, subjects showed almost perfect performance. There were no differences between segmental and prosodic transformation in degree of accuracy which suggest similar difficulty of both conditions. In analogy to the stimuli, the response duration was significantly higher in the SEGM compared to the PROS condition.

fMRI results

fMRI results were derived from 23 healthy subjects. Of all possible subtractive or conjunction analyses in the fMRI experiment, two contrasts were of particular interest to the tracking experiment and will hence be shown in more detail.

First, the activations from the contrast of prosodic transformation minus prosodic repetition are shown (Fig. 9-10). Recall that this contrast was hypothesized to reflect the neural correlates of suprasegmental phonological processes based on prosodic transformation through a shift in stress placement (remember „Dóga“ → „Dogánisch“).

Second, the contrast segmental transformation minus segmental repetition will be considered (Fig. 11-17). Remember that this contrast was hypothesized to reflect the neural correlates of phonological transformation based on segmentation of the target word through a vowel mutation by producing pseudo-diminutives (consider „der Mall“ → „das Mällchen“).

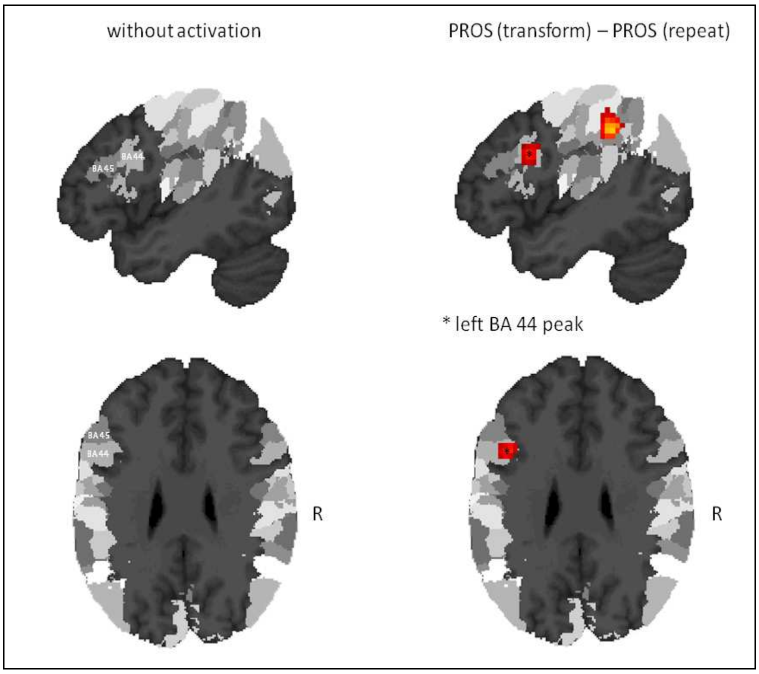

Figure 9

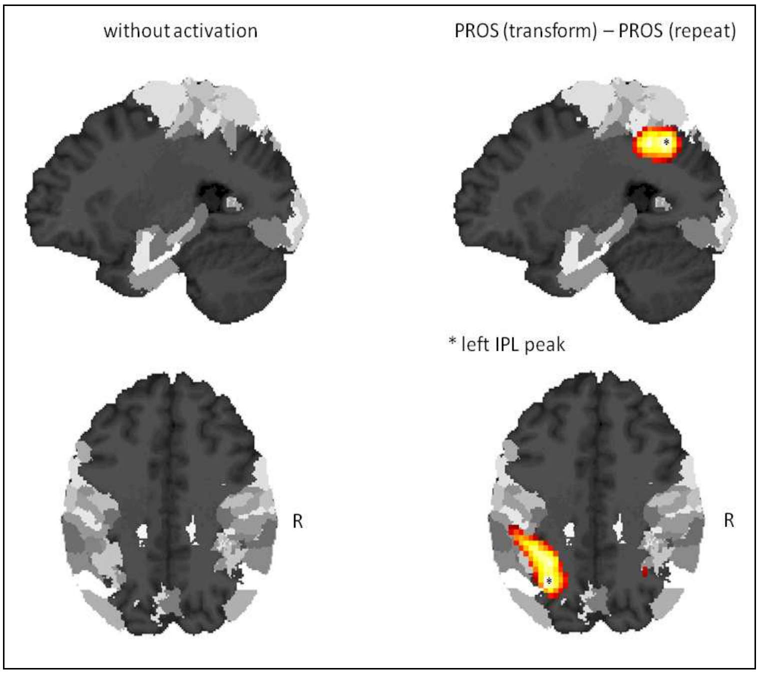

Figure 10

Figure 9 and 10 *SPM activation maps (p<0.001) for PROS(transformation) – PROS(repetition) from the fMRI experiment by Peschke et al. (2009, submitted). Main peaks of activation that were used for the tracking experiment were: left inferior frontal gyrus, pars opercularis (BA 44) [Fig. 9] and left parietal lobe, inferior parietal lobule/intraparietal sulcus [Fig.10]. No significant clusters of activation were found in the right hemisphere.*

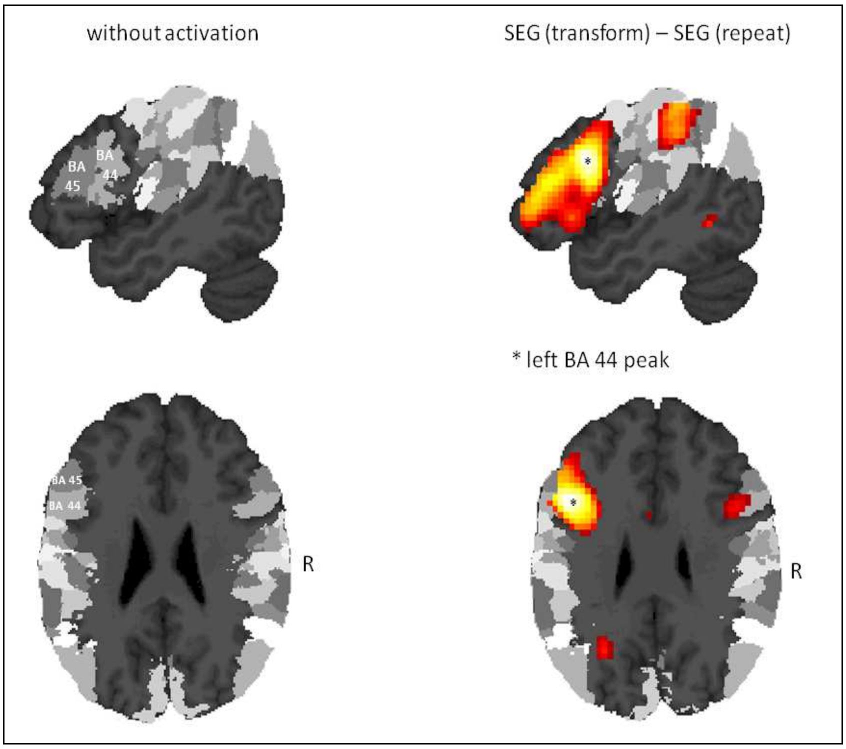

Figure 11

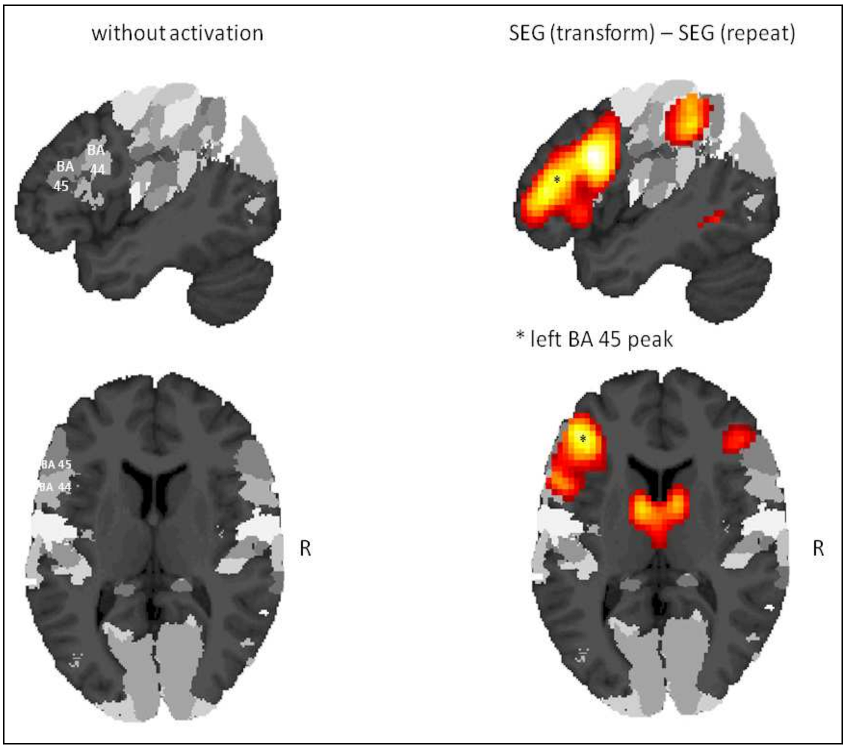

Figure 12

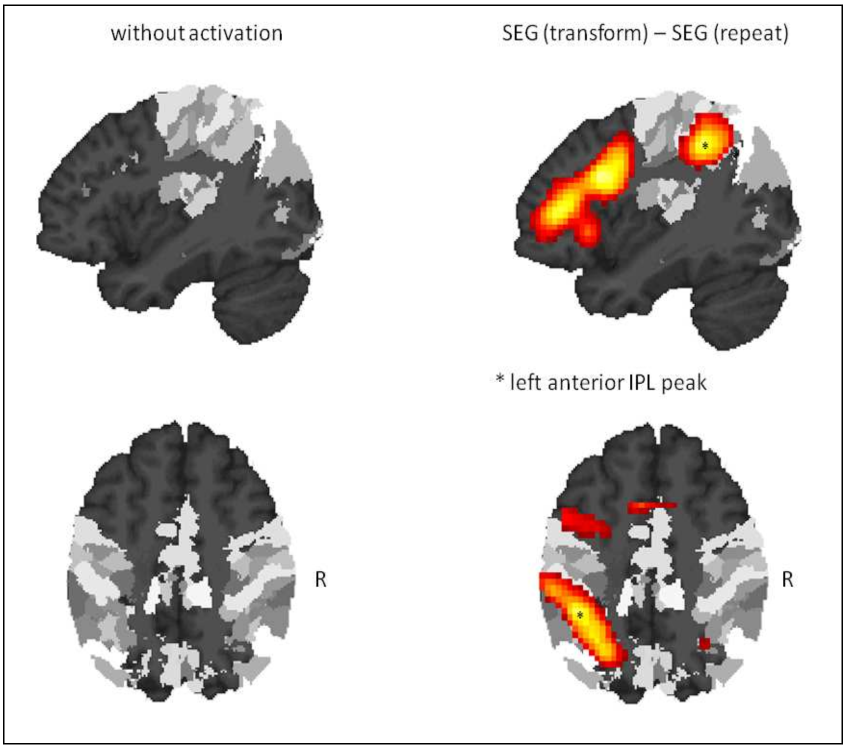

Figure 13

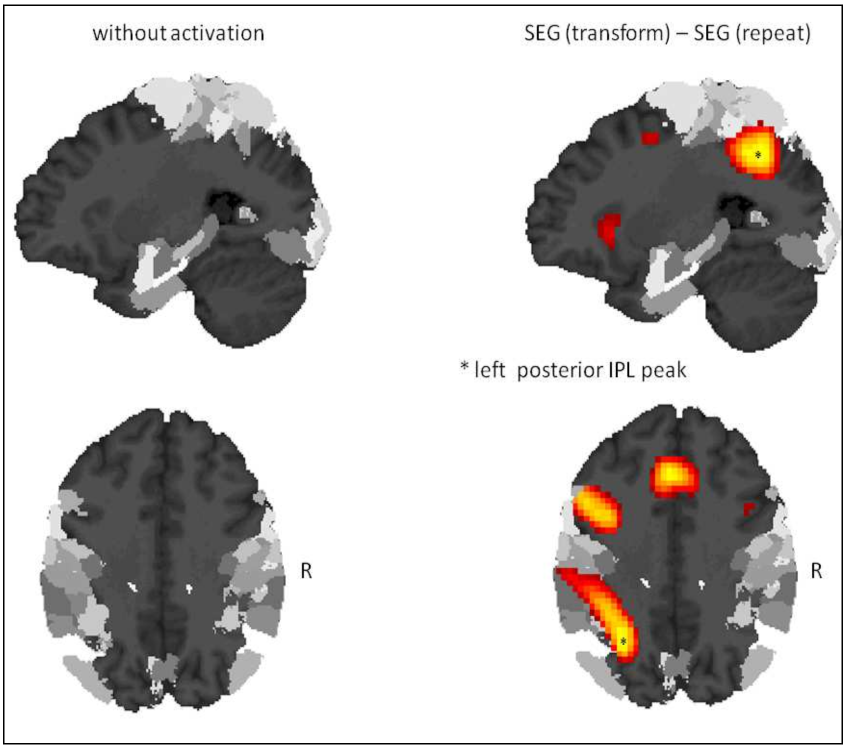

Figure 14

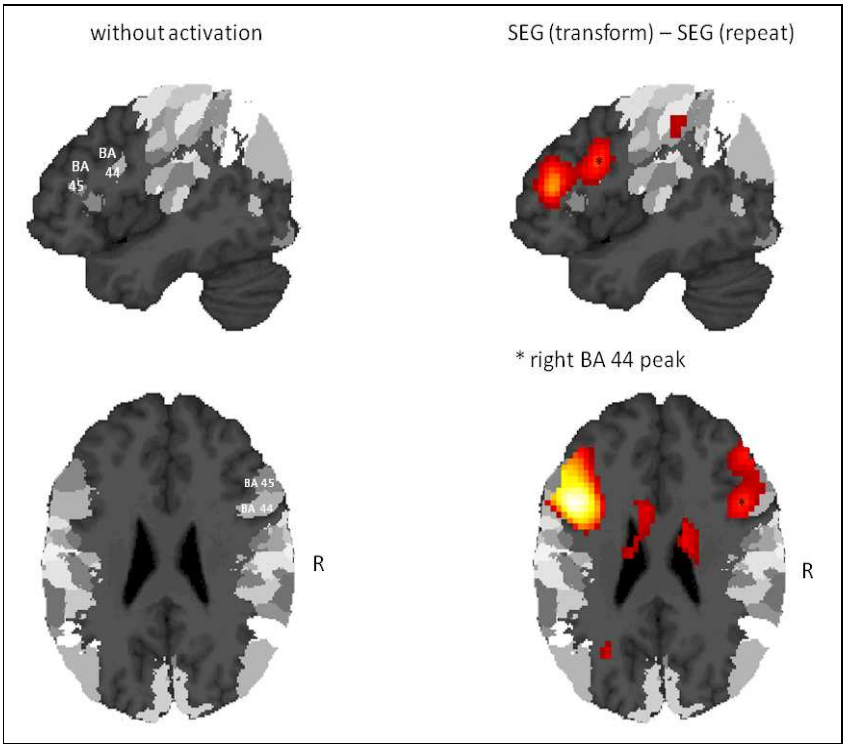

Figure 15

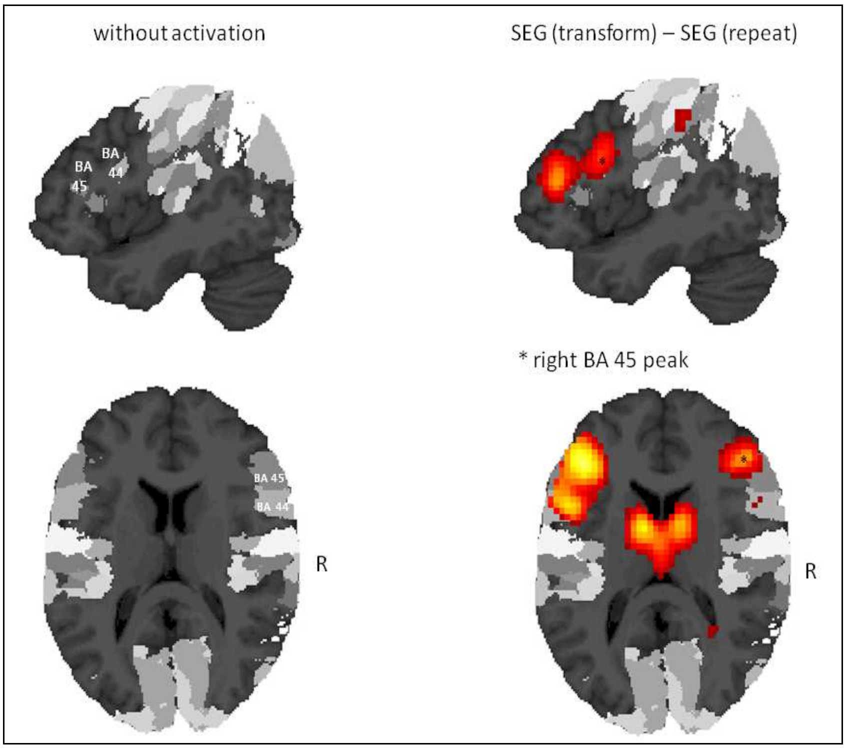

Figure 16

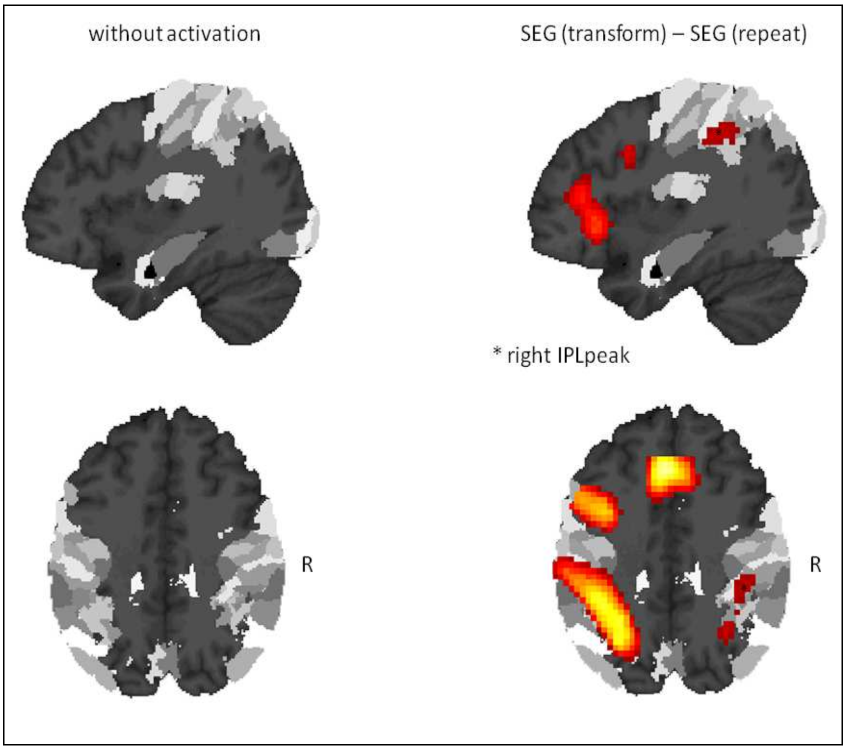

Figure 17

Figures 11-17 *SPM activation maps (p<0.001) for SEG(transform) – SEG(repeat) from the fMRI experiment by Peschke et al. (2009, submitted). Main peaks of activation that were used in the tracking experiment (see also Table 1) were: left inferior frontal gyrus: pars opercularis (BA 44) [Fig. 11], pars triangularis (BA 45) [Fig. 12]; in the left parietal cortex: anterior [Fig. 13] and posterior [Fig. 14] inferior parietal lobule, intraparietal sulcus (IPS). In the right hemisphere, main peaks of activation were: right inferior frontal gyrus: pars opercularis (BA 44) [Fig. 15], pars triangularis (BA 45) [Fig. 16]; in the right parietal cortex: inferior parietal lobule, intraparietal sulcus [Fig. 17]. Composites of activations created by the author with the SPM-based* Anatomy toolbox*.*

Prosodic transformation (Fig. 9 and 10), when contrasted with repetition, elicited a strongly left lateralized fronto-parietal activation pattern with the inferior frontal activations predominantly confined to BA 44 and the parietal activations comprising parts of inferior parietal lobule, intraparietal sulcus (IPS).

In the segmental transformation task (Fig. 11 to 17), when contrasted with repetition, a bilateral fronto-parietal pattern was found with peak activations in the left and right inferior frontal gyrus (BA 44 and 45) as well as in both IPL/IPS (more extensively in the left than in the right hemisphere).

1.6. Hypotheses

Summarizing the diverse findings from the studies reviewed above there is indeed converging evidence that IPL and IFG are involved in a variety of phonological processes.

Based on the evidence from the studies reviewed above and the results from the fMRI experiment, we hypothesize that:

> (1) inferior parietal cortex connects to inferior frontal areas via dorsal and ventral pathways, with
>
> (1a) the dorsal pathway necessary for mapping phonological information from phonological short-term store in parietal regions to the frontal articulatory network (bottom-up processing) and
>
> (1b) the ventral route as a possible route for top-down modulation, e.g. morpho-syntactic or semantic processes, which might occur more in the segmental transformation task
>
> (2) the transcallosal fiber pathways connect homotopic parietal and frontal regions and facilitating interhemispheric interactions and are critical for phonological processing which will be examined with reference to disorders of prosody

2. METHODS

2.1. Subjects

DTI analyses were performed on 20 subjects. All subjects were native speakers of German without any history of serious medical, neurological or psychiatric illness, or hearing loss (mean age=34,25 years, age range 20-69 years, eight females). Hand preference was tested with the 10-item version of the Edinburgh Handedness Inventory (Oldfield, 1971), 10 subjects were identified as having left hand preference, 10 as having right hand preference. The subjects were chosen to have a balanced left/right hand preference in order to eliminate possible structural lateralization effects from the DTI analysis. The images were acquired as part of a previous study (see Saur et al., 2008) approved by the Ethics Committee of the University Clinic of Freiburg. All subjects gave written informed consent.

2.2. MRI data acquisition

DTI data, with a 63 direction tensor imaging protocol, were acquired on a 3T Siemens TIM Trio scanner. A total of 70 scans with 69 slices using a diffusion-sensitive spin-echo EPI sequence with CSF suppression and with 61 diffusion-encoding gradient directions (b-factor = 1,000 s/mm), 9 scans without diffusion weighting, voxel size = 2 x 2 x 2 mm^3, matrix size = 104 x 104 pixel^2, TR = 11.8 s, TE = 96 ms, TI = 2.3 s). During reconstruction, scans were corrected for motion and distortion artifacts based on a reference measurement.

2.3. Tracking procedure

2.3.1. Definition of seed regions

The seed regions (see also Fig. 9-17) for the probabilistic fiber-tracking were extracted from the t-maps of the fMRI random effects analyses from the transformation experiment by Peschke et al. (2009, submitted). In the contrasts of interest, i.e. PROS(transform)-PROS(repeat) and SEGM(transform)-SEGM(repeat), the peak voxel in the significant (p<0.001) activation clusters was identified, resliced to the native space of each subjects' DTI data and enlarged to a sphere with a radius of 4 mm each containing 33 seed voxels.

cond.	**name**	**MNI (x y z) coordinates**	**region**
PROS	pros_left_BA44	-45 12 27	left inferior frontal gyrus, pars opercularis, BA 44
	pros_left_IPL	-27 -51 39	left inferior parietal lobule / intraparietal sulcus
SEGM	seg_left_BA44	-48 12 27	left inferior frontal gyrus, pars opercularis, BA 44
	seg_left_BA45	45 39 9	left inferior frontal, gyrus, pars triangularis, BA 45
	seg_left_aIPL	-39 -42 45	left anterior inferior parietal lobule / intraparietal sulcus
	seg_left_pIPL	-27 -60 36	left posterior inferior parietal lobule / intraparietal sulcus
	seg_right_BA44	45 12 24	right inferior frontal gyrus, pars opercularis, BA 44
	seg_right_BA45	45 36 12	right inferior frontal gyrus, pars triangularis, BA 45
	seg_right_IPL	36 -42 45	right inferior parietal lobule / intraparietal sulcus

***Table 1** Seed voxels from the fMRI experiment that were used for the probabilistic fiber tracking; MNI=Montreal Neurological Institute (the coordinate space in SPM), PROS=prosodic transformation condition, SEGM=segmental transformation condition from fMRI experiment*

2.3.2. Probabilistic tracking

First, the effective self-diffusion tensor (DT) was computed from the movement and distortion corrected diffusion-weighted imaging dataset (Basser et al., 1994).

DTI data were analyzed using a novel method of pathway extraction (Kreher et al., 2008) implemented in a Matlab-based software (*DTI&Fiber Toolbox,* http://www.uniklinik-freiburg.de/mr/live/arbeitsgruppen/diffusion_en.html).

A Monte Carlo simulation of Random Walks (MCRW) similar to the Probabilistic Index of Connectivity (PICo) method (Parker et al., 2003) was used to calculate the probabilistic maps for each seed region separately. This DTI-based probabilistic MCRW experiment was extended to preserve the information about the main traversing directions of the propagated trajectories in each voxel, which is used when combining the probability maps (see below). The number of propagated trajectories was set to 10^5 and maximal fiber length was set to 150 voxels. The tracking area was restricted to a white matter mask to avoid tracking across anatomical borders. To ensure contact of the cortical seed regions with white matter, a rim of grey matter was included in the mask.

2.3.3. Multiplication

Region-to-region anatomical connectivity between two seed spheres was computed using a recently developed combination of probability maps (Kreher et al., 2008). On a computational level, this combination is based on a *multiplication*, which takes the main traversing trajectory of the random walk into account. Walks starting from seed regions may face in opposing directions (*connecting fibers*) or merge and face in the same direction (*merging fibers*). Within the pathway connecting two seed regions, the proportion of connecting fibers should exceed the proportion of merging fibers. Using this directional information during the multiplication, merging fibers are suppressed and connecting fibers are preserved (Kreher et al., 2008).

This method enables the extraction of the most probable direct pathway between two seed regions without using a priori knowledge about the putative course. The resulting values represent a voxel-wise estimation of the probability that a voxel is part of the connecting fiber bundle of interest (represented by a "probability index forming part of the bundle of interest" [PIBI]). To identify the most probable parieto-frontal association tracts, all parietal maps were combined permutatively with all frontal maps in the respective context (prosodic or segmental transformation).

2.4. Post-processing

The combined maps were scaled to the range between 0 and 1, spatially normalized into standard MNI space, and smoothed with an isotropic 3 mm Gaussian kernel.

Group maps for each region-to-region connection were computed by averaging the combined maps from all subjects, resulting in 20 mean maps. Composite networks for segmental transformation were computed by averaging the mean maps defined in each experiment. Thus, voxels represent the arithmetic mean of the PIBI from all contributing probability maps. To remove random artifacts, only voxels with PIBI values of >0.0145 were displayed, which excludes 95% of the voxels with PIBI $>10^{-6}$. This value was generated empirically from the distribution observed in a large collection of preprocessed combined probability maps (see also Saur et al., 2008).

condition	name	tracking
PROS	pros	left IPL with left BA 44
SEGM	seg_left_1	left ant. IPL with left BA 44
	seg_left_2	left ant. IPL with left BA 45
	seg_left_3	left post. IPL with left BA 44
	seg_left_4	left post. IPL with left BA 45
	seg_right_1	right IPL with right BA 44
	seg_right_2	right IPL with BA 44
	seg_interhemispheric_1	left ant. IPL with right IPL
	seg_interhemispheric_2	left post. IPL with right IPL
	seg_interhemispheric_3	left BA 44 with right BA 44
	seg_interhemispheric_4	left BA 45 with right BA 45

Table 2 *Summarizes the seed-to-seed probabilistic fiber tracks that were analyzed.*

2.4.1. Visualization

The resulting tracks were visualized using the above mentioned Matlab-based *DTI&Fiber Toolbox* (for sections in 2D) and the tool *FancyRender* (for 3D images).

3. RESULTS

3.1. Fiber pathways for prosodic transformation

Fig. 18 illustrates the fronto-parietal fiber pathway connecting the left IPL, intraparietal sulcus seed with the left BA 44 seed from the activations from prosodic transformation when contrasted with repetition.

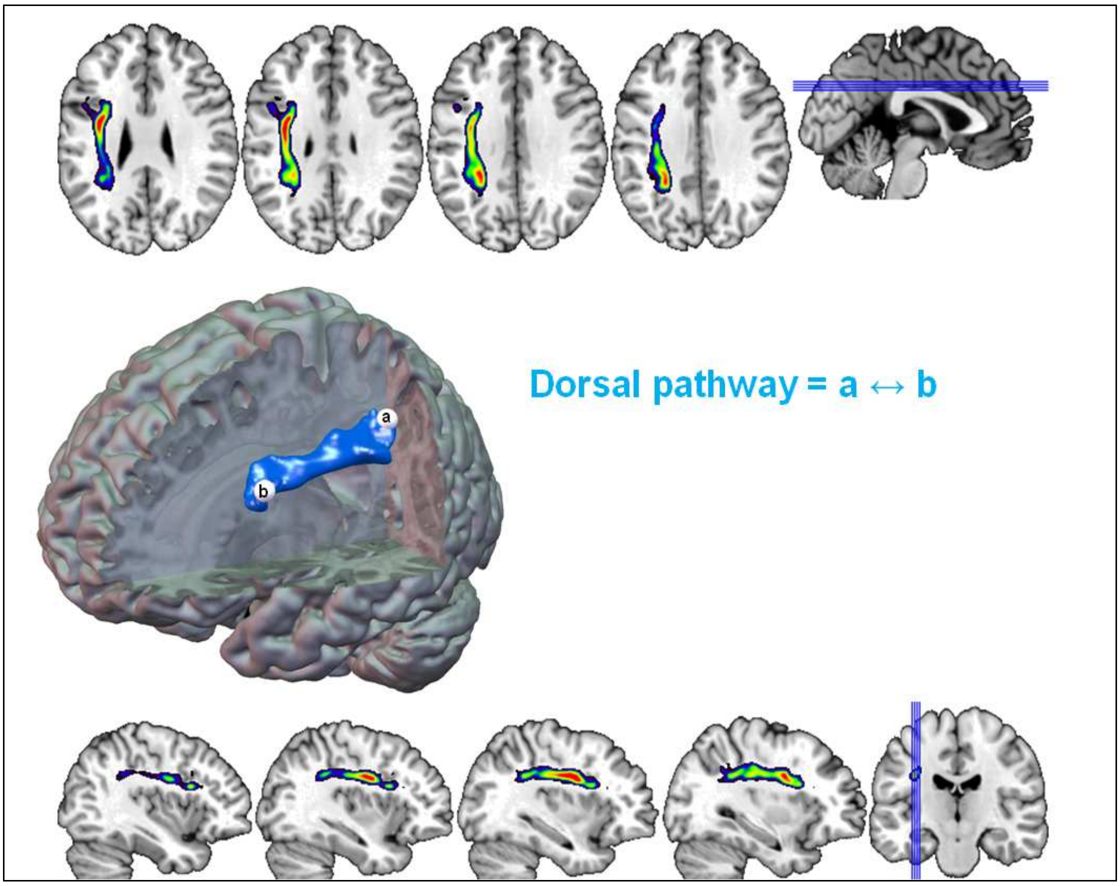

__Figure 18__ Left hemispheric fiber network for prosodic transformation displayed as mean map of 20 subjects. Three-dimensional tractography rendering (light blue) visualizes the spatial orientation of the network. Seed spheres: a=inferior parietal lobule, intraparietal sulcus [x=-27, y=-51, z=39], b=inferior frontal gyrus, BA 44 [-45 12 27].

Fronto-parietal connectivity between IPL/IPS and BA 44 in the left hemisphere is exclusively provided by a dorsal pathway, most likely via the superior longitudinal fascicle III. According to Schmahmann and Pandya (2006), the SLF (which has long been thought to be identical with the AF) consists of three distinct bidirectional subcomponents (SLF I-III). Parietal projections, investigated by autoradiography (Petrides and Pandya, 1984) in monkeys, have shown that the SLF I originates in the posterior parietal region and caudal superior parietal lobe and connects mainly to supplementary motor areas (Schmahmann, 2007). The SLF II fibers start in the IPL and project dorsally and medially along the AF fibers to end in dorsal frontal BA 6, 8 and 46 (Schmahmann, 2007). Finally, the SLF III fibers, have their source in the rostral part of the IPL as well as in the parietal operculum and proceed through the parietal opercular white matter and terminate in ventral parts of BA 6 and BA 44, the anatomical equivalent to the human LIFG, pars opercularis, BA 44 (Schmahmann, 2007). These SLF III fibers have also been found in-vivo in recent high-angular DTI studies (Frey et al., 2008; Makris et al., 2005) which also confirmed that the AF and SLF fibers can be distinguished by DTI.

3.2. Fiber pathways for segmental transformation

For the seeds from the segmental transformation condition, when contrasted with repetition, a bilateral dorsal and ventral system of fiber pathways providing fronto-parietal-connectivity was found (Fig. 19 for the left hemisphere and Fig. 20 for the right hemisphere).

In the left hemisphere, the dorsal pathway, connecting anterior and posterior inferior parietal lobule, intraparietal sulcus with inferior frontal gyrus, pars opercularis (BA 44), like the dorsal pathway in prosodic transformation, is provided by SLF III fibers.

The ventral pathway, however, connects the anterior and posterior inferior parietal lobule, intraparietal sulcus with the IFG, pars triangularis (BA 45).

Emerging from the anterior or posterior intraparietal sulcus seeds (aIPL and pIPL); the fibers first run ventrally before joining the middle longitudinal fascicle (MdLF) and then connect to inferior frontal gyrus, pars triangularis (BA 45) via the extreme capsule (EmC). A temporal association tract, the middle longitudinal fascicle (MdLF) contributes fibers to the EmC, which runs in the white matter of the superior temporal lobe. The resulting composite fiber tract of EmC and MdLF thus provides parieto-temporal-frontal connectivity via a ventral route.

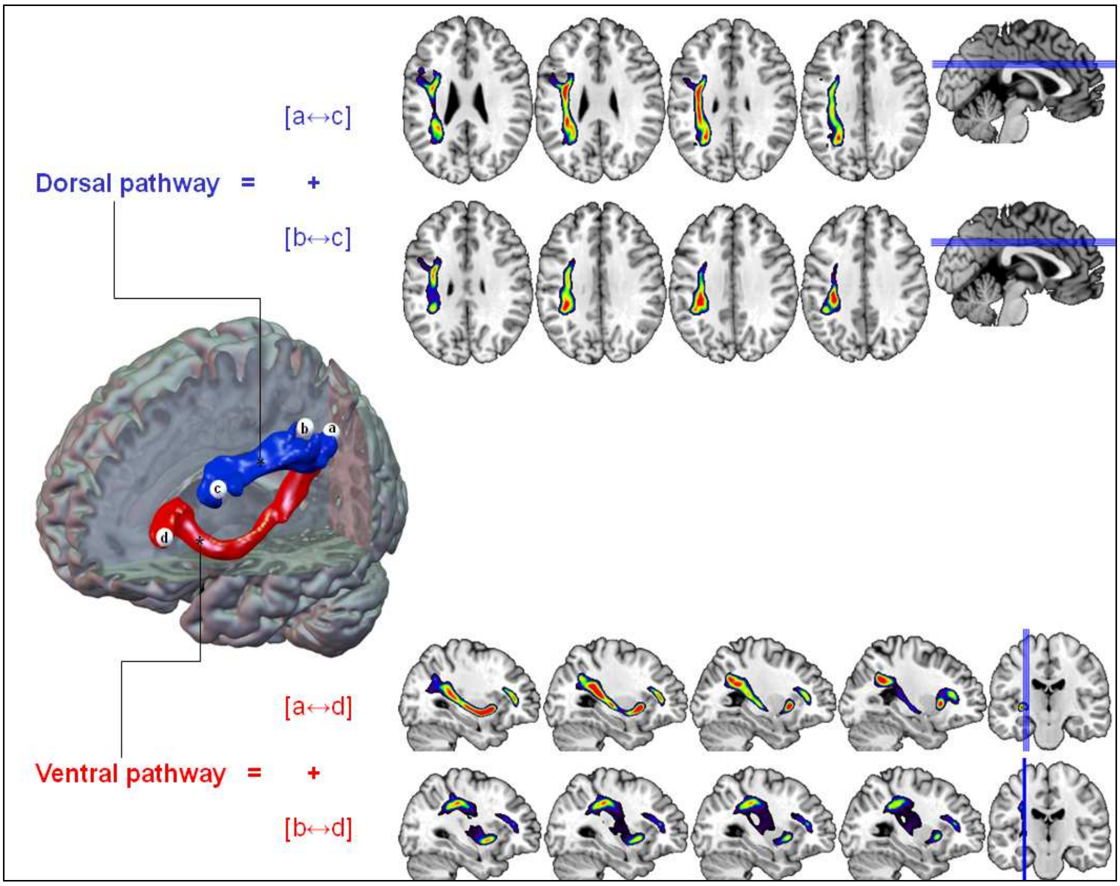

Figure 19 *Combined left hemispheric fiber network for segmental transformation identified in a random effects analysis (p <0,01) containing all connections of all subjects (n=20). Three-dimensional tractography rendering visualizes the spatial orientation of the segregated dorsal (blue) and ventral (red) pathways. Seed spheres: a=posterior inferior parietal lobule, intraparietal sulcus [-39 -42 45]; b=anterior inferior parietal lobule, intraparietal sulcus [-27 -60 36]; c=inferior frontal gyrus, BA 44 [-48 12 27]; d=inferior frontal gyrus, BA 45 [45 39 9].*

In the right hemisphere (Fig. 20), fronto-parietal fiber connections essentially mirror the left hemispheric connections, with a dorsal pathway connecting posterior IPL/IPS with the right homologue of BA 44 and a ventral pathway projecting from IPL/IPS to BA 45 via the MdLF/EmC fiber system.

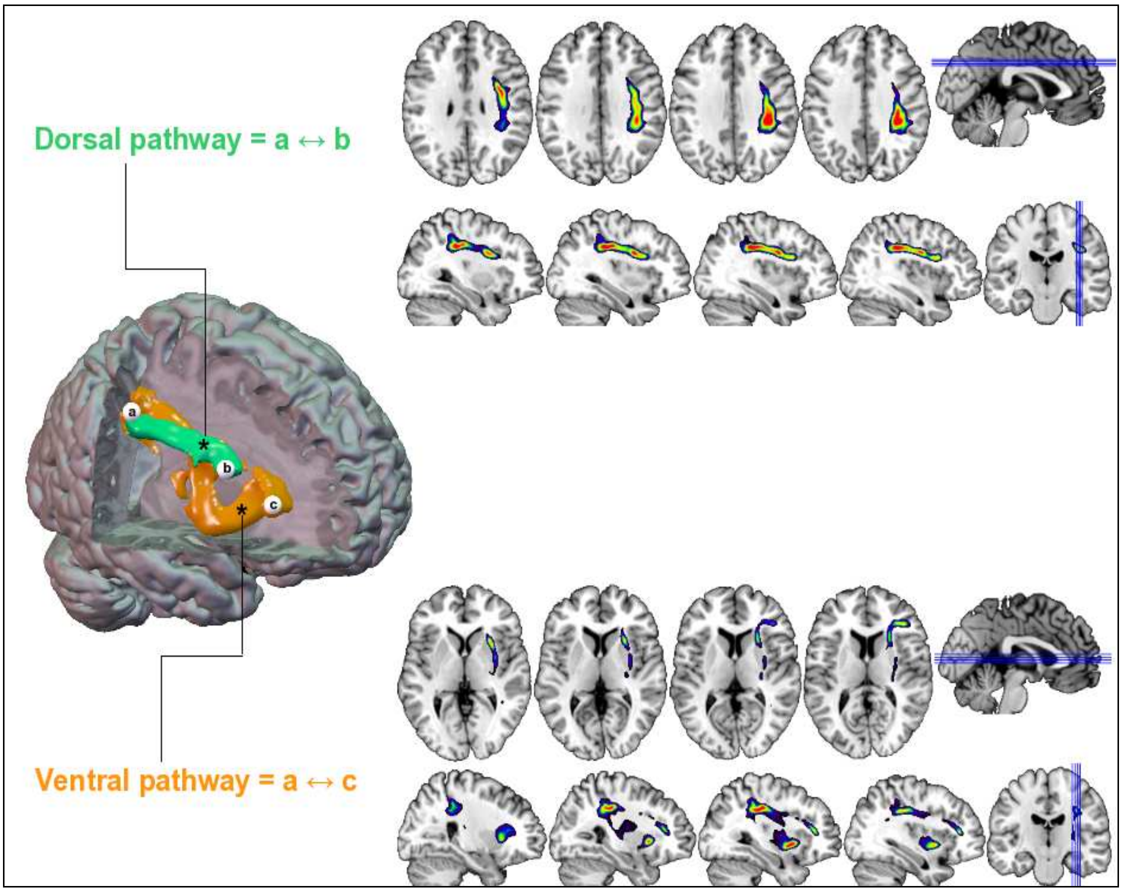

***Figure 20** Combined right hemispheric fiber network for segmental transformation identified in a random effects analysis (p <0,01) containing all connections of all subjects (n=20). Three-dimensional tractography rendering visualizes the spatial orientation of the segregated dorsal (light green) and ventral (orange) pathways. Seed spheres: a= inferior parietal lobule, intraparietal sulcus [36 -42 45]; b= inferior frontal gyrus, BA 44 [45 12 24]; c=inferior frontal gyrus, BA 45 [45 36 12].*

3.3. Interhemispheric transcallosal fiber pathways

Fig. 21 and 22 show the transcallosal fiber pathways from the tracking experiment connecting left and right parietal seed regions (Fig. 21) and left and right frontal regions (Fig. 22).

The interhemispheric parietal pathways (Fig. 21) are aligned close together in the splenium of the CC (and radiation) with the connections between the left posterior parietal to the right parietal seed running more caudally and the connection between the left anterior parietal to right anterior parietal seed more rostral.

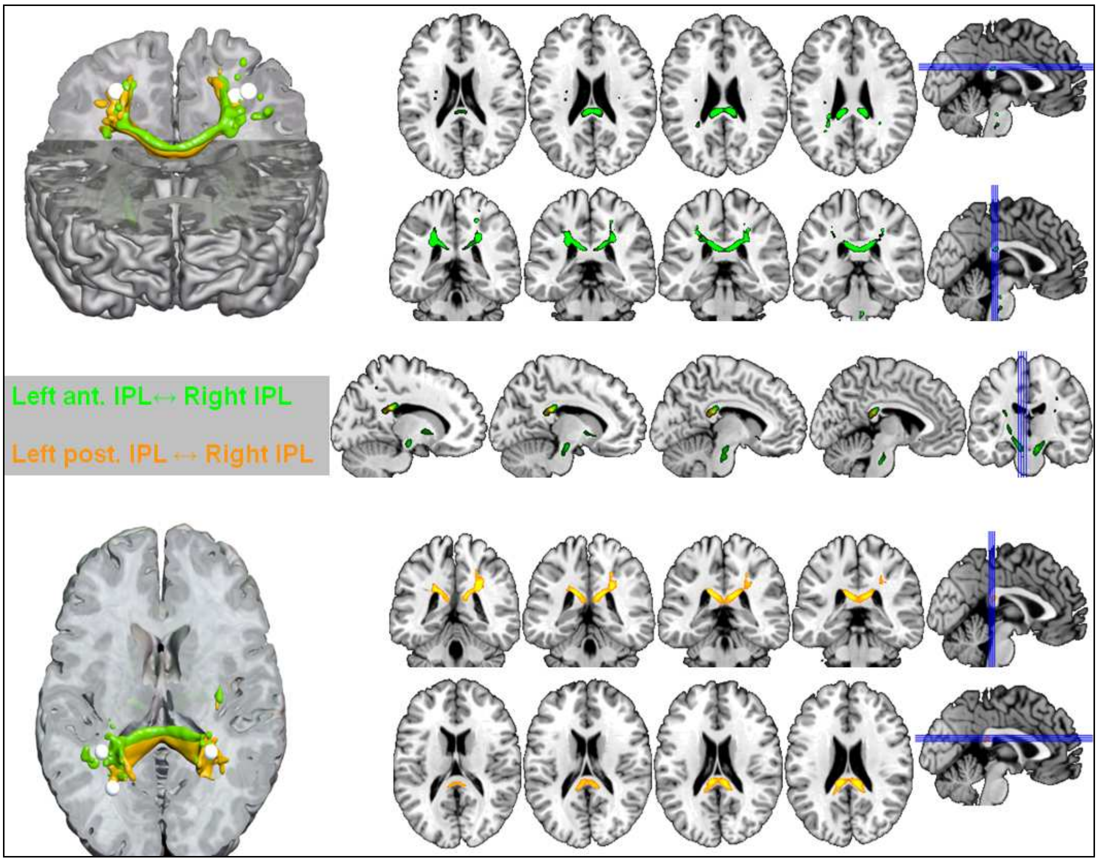

Figure 21 *Combined inter-hemispheric fiber network for segmental transformation identified in a random effects analysis (p <0.01) containing all connections of all subjects (n=20). Shown in orange are transcallosal connections between left hemispheric posterior inferior parietal lobule and right hemispheric inferior parietal lobule. In green, transcallosal connections between left anterior parietal lobule and right hemispheric inferior parietal lobule are shown.*

The interhemispheric frontal pathways (Fig. 22) too are oriented closely together, with the connection between left BA 44 and its right hemispheric homotopic area running through the body of the CC and the connections between left BA 45 and its right homotopic area crossing more rostrally in the genu.

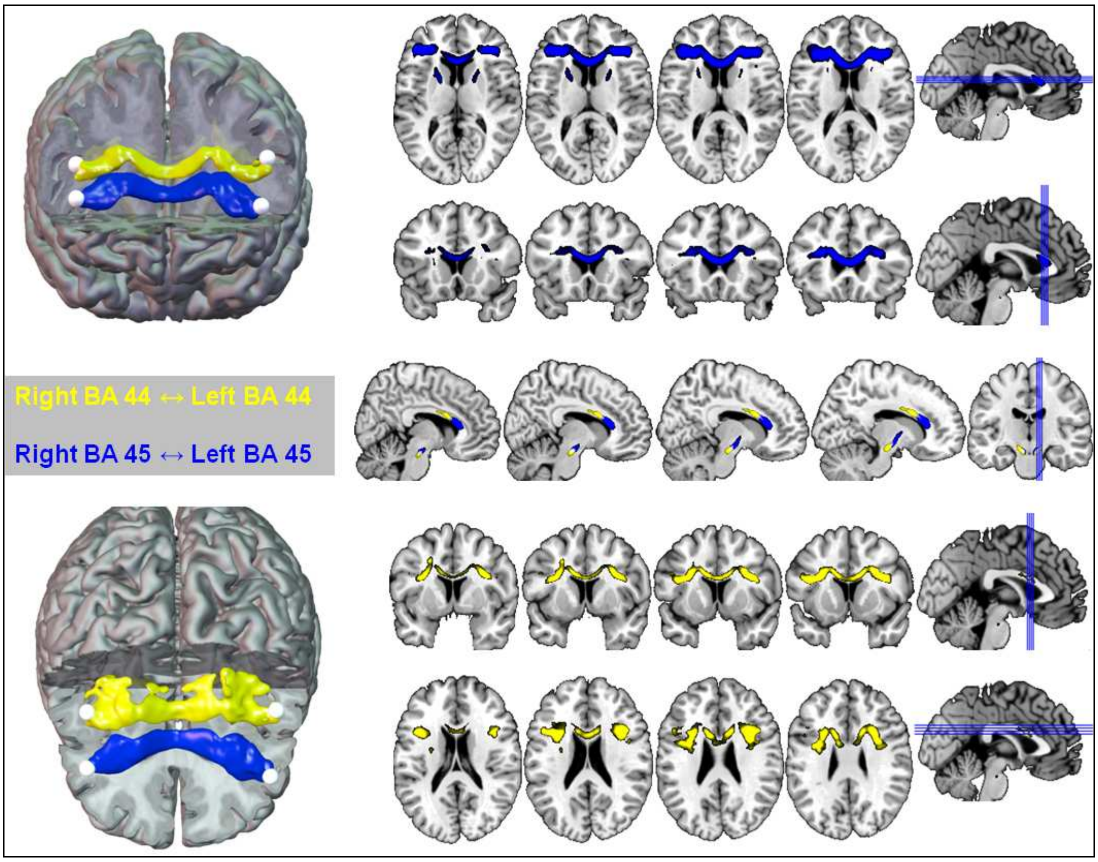

Figure 22 *Combined inter-hemispheric transcallosal fiber network for segmental transformation identified in a random effects analysis (p <0.01) containing all connections of all subjects (n=20). Shown in yellow are interhemispheric connections between left hemispheric BA 44 and its right hemispheric homotopic area. In blue, transcallosal connections between left hemispheric BA 45 and its right hemispheric homotopic area are shown.*

4. DISCUSSION

The goal of the study presented here was to track and visualize fronto-parietal fiber pathways subserving experimentally dissociable aspects of phonological processing. In the following discussion we come back to the issues that were raised in the introduction and put the findings from the tracking experiment into a neurocognitively motivated framework of language processing with special emphasis on neuroanatomical and processing constraints on fronto-parietal interaction in phonological transformation processes.

First, we will establish that from a cognitive point of view, phonology can be regarded as a generative system with a parallel processing architecture that is to some degree independent from syntax and semantics, though highly interactive.

Then, the findings from the tracking experiment, showing a dual pathway system for fronto-parietal interaction, will be discussed and related to this cognitive account in order to formulate a theoretically motivated and neuroanatomically informed model of how different phonological processing routines might be realized in the neural language system. This approach will be discussed against the backdrop of already existing neuroanatomical and neurocognitive models on language processing focusing on phonological issues, specifically Hickok and Poeppel (2007, 2004), Jackendoff (2007, 2002), Nadeau (2001) and Vallar (1997).

Finally, the findings from the interhemispheric trackings will be interpreted and discussed with respect to implications for neurological disturbances of intrinsic and extrinsic prosodic features of speech, commonly referred to as a- and dysprosody.

4.1. Phonology as a generative system with a parallel architecture

In recent years, many researchers from diverse fields have attempted to systematically narrow the gap between mainly cognitively motivated accounts on language processing and models mainly driven by neuroanatomical constraints and neurological data from lesion studies (Hickok and Poeppel, 2007, 2004, Marslen-Wilson and Tyler, 2007; Saur et al., 2006, Wise, 2003).

With respect to phonology, one of the major theoretical developments in conceptualizing processing of phonological units was the insight, that phonology, like syntax, is a hierarchical and generative system *sui generis* (Jackendoff, 2007, 2002; Chomsky and Halle, 1968) that is organized in a parallel processing architecture. Because in this "parallel architecture" account (Jackendoff, 2007) syntax and phonology are assumed to operate in parallel and to some extent independently (though highly correlated), such a processing systems requires principles, or interface rules, that account for functional interactions between these sub-systems.

However, any coherent cognitive model of language processing in general and phonological processing in particular should be embedded in and be coherent with a neuroanatomical framework that puts certain restraints on possible structure-function relationships between sub-components of the respective processing systems.

Starting with the assumption then that functionally phonological processing is a parallel, interactive (and to some extent iterative) routine we will now review how this model can be effectively constrained by evidence from functional and structural neuroanatomical studies and models.

4.2. Dorsal and ventral fronto-parietal pathways in suprasegmental and segmental processing

In the following, we will first discuss the findings from the fiber tracking experiment in the context of previously established models of phonological processing as presented in Fig. 23. We will then address possible reasons for the dissociation of segmental transformation into different pathways for fronto-parietal connectivity and interaction.

4.2.1. Models of phonological processing: accounts from cognitive psychology vs. cognitive neuroscience

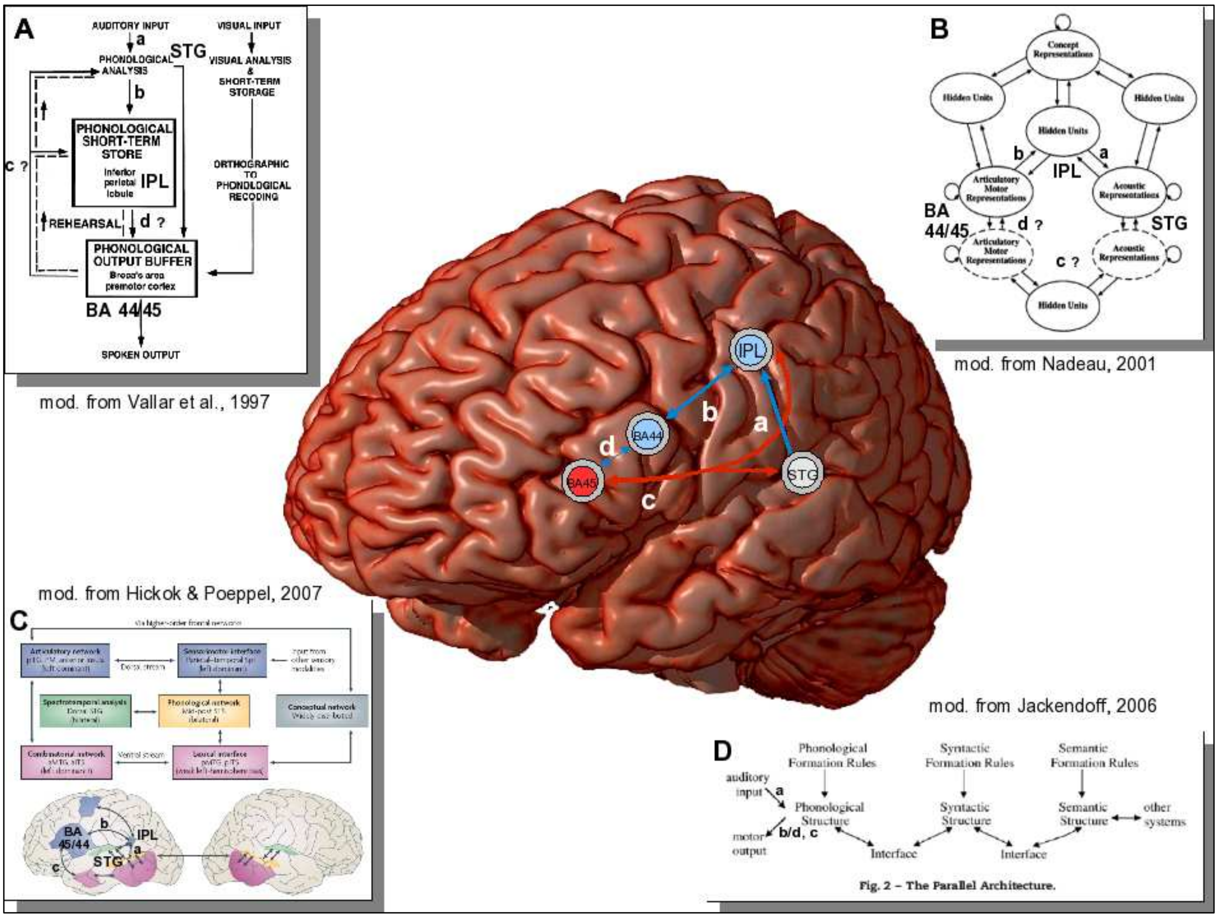

Figure 23 *Model of phonological processing pathways in the left hemisphere involving primary auditory cortex in the superior temporal sulcus and gyrus (abbr. STG), inferior parietal lobule (IPL) and inferior frontal gyrus, BA 44 and 45. Small letters (a), (b), (c) and (d) relate to connectivity and specific functions that are conveyed by the pathways between these areas. The four panels with capital letters (A), (B), (C) and (D) show important processing models, where the areas and functions from the main figure are related to specific processing stages of the respective models. Coloured arrows illustrate the pathways, a dorsal parieto-frontal (blue) and a ventral parieto-temporal-frontal (red) pathway.*

Figure 23 illustrates the principal components of the phonological processing system: the primary auditory cortex with superior temporal gyrus (STG) for acoustic analysis of the speech signal (phonetic decoding) and posterior superior temporal gyrus (STG) for phonological decoding (Hickok and Poeppel, 2007; Spitsyna et al., 2006; Uppenkamp et al., 2006, Warren et al., 2005); the IPL, supramarginal gyrus/intraparietal sulcus, acting as either a specific phonological short-term store or more domain-independent working memory loop; and frontal, mainly premotor area

BA 44 as articulatory network (Hickok and Poeppel, 2007, 2004) or phonological output buffer (Vallar et al., 1997).

Importantly, in terms of explanatory mechanisms and frameworks, the models summarized in this figure differ substantially from each other. The accounts of Vallar et al. (1997) and Nadeau (2001) and to some extent (Jackendoff, 2007, 2006) are mainly motivated by investigating interactions between *functionally* defined components of the phonological processing system from a cognitive psychology point of view, without particular reference to or explanatory need for how these components are neurally instantiated.

Taking an approach which is more grounded in cognitive neuroscience, the widely discussed and somewhat prevalent model on language processing by Hickok and Poeppel (2007, 2004), on the other hand, does indeed provide not only a psycholinguistically and cognitively motivated account but also incorporates a neuroanatomical framework in which their dual-processing model is realized. One particularly appealing feature of this neurocognitive model is that it permits for the prediction of differences between the streams in computational complexity (e.g. sampling rate) and degree of higher-level modulation of lower-level features as well as making predictions on the effect of neurological damage on the functional integrity of the processing streams.

In accounting for the structure-function relationships in phonological transformation processes, we are adopting a similar neurocognitively motivated approach for relating the findings from the fMRI experiment and the DTI tracking data to the cognitive and psycholinguistic models on phonological processing discussed before.

4.2.2. The functional role of dorsal and ventral pathways in phonological transformation processes

As we have seen from the behavioral data, participants in the fMRI study showed no significant differences in terms of response onset or accuracy between the prosodic and segmental transformation task[5]. Thus, differences in the neural processing system as revealed by fMRI should be attributable, to some extent, either to

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[5] Though differences between PROS and the control and SEGM and the control were significant

differences between intrinsic properties of the stimuli or the underlying cognitive processing routines (that do not yield detectable behavioral differences).

With respect to the properties of the stimulus material used, the SEGM stimuli were significantly longer than the PROS stimuli (and as a consequence the overall response duration from onset to offset was longer as well). This may result in a higher overall working memory / phonological short-term storage load for the SEGM condition, which may explain the more extensive and generally greater activations in IPL areas. However, most studies that have shown an involvement of components of the dorsal phonological pathway (i.e. BA 44 and IPL) were studies with a high processing-load on working memory (Heim et al., 2005, Buchsbaum and D'Esposito, 2008), which may implicate, that working memory demands alone do not necessitate a ventral fronto-parietal pathway, rather the dorsal pathway seems sufficient to accommodate fronto-parietal interaction based on incremental processing demands in working memory (and analogously phonological short-term store). This, in turn, requires some further explanation why the SEGM condition elicited inferior parietal areas that do connect to BA 45 via a ventral pathway. One possibility is that fronto-parietal connectivity is ultimately driven by the IFG area involved in a particular process, or in other words, the ventral pathway is only engaged when BA 45 is involved in a particular operation. This notion is supported by the fact that in the defining experiment by Saur et al. (2008), temporo-frontal interaction via a ventral pathway was only provided when BA 45 was reached. Therefore, we will have to examine whether there are any salient differences in properties of the stimulus material or cognitive processing demands between the SEGM and PROS condition that would explain a preferential involvement of BA 45 in the segmental task.

From a psycholinguistic point of view, the pseudo-diminutives of the SEGM condition (recall “der Mall” → “das Mällchen”) have some particularly interesting features that differ from the PROS stimuli. First, they are prefixed by the German definite article “der”, which becomes “das”, a process that constitutes a relevant morpho-syntactic change.[6] Furthermore, the SEGM transformation also entails a change in gender from "der Mall" (male, nominative) to "das Mällchen" (neuter, nominative).

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[6] Note that, while not prominent in English, morphological cases feature saliently in German influencing the type of definite article that applies in a particular construction:

case	*male*	*female*	*neuter*	*plural*
nominative	der	die	das	die

Interestingly, morpho-syntactic processes (Marslen-Wilson and Tyler, 2007; Indefrey et al., 2001; Embick et al., 2000) as well as processing of gender determinants (Padovani et al., 2005; Hernandez et al., 2004; Heim et al., 2002) have both been functionally attributed to LIFG, which could explain why the SEGM transformation yielded more extensive activations in left anterior IFG than the PROS condition and also showed some right IFG activation.

Furthermore, the definite articles “der” is also a lexical word which, together with the pseudo-noun, builds a (pseudo)-noun phrase which, speculatively, is likely to engage the bilateral lexical-semantic ventral processing system with the definite article as a lexical lead-in. This, in turn, could also explain why only the seeds from the SEGM condition are connected with BA 45 via a ventral pathway – the route for lexical-semantic processing in comprehension (Saur et al., 2008). By inference, this would naturally lead to the conclusion, that BA 45 is preferentially involved in lexical-semantic aspects of language processing.

Fig. 24 shows a summary of all activation clusters from the previously mentioned meta-analysis by Vigneau et al. (2006). In this analysis, BA 45 seems indeed to be more often elicited by paradigms that exert syntactic and lexical-semantic processing demands, whereas BA 44, especially caudal parts of BA 44, seems to be preferentially involved in paradigms that require phonological processing.

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genitive	des	der	des	der
dative	dem	der	dem	den
accusative	den	die	das	die

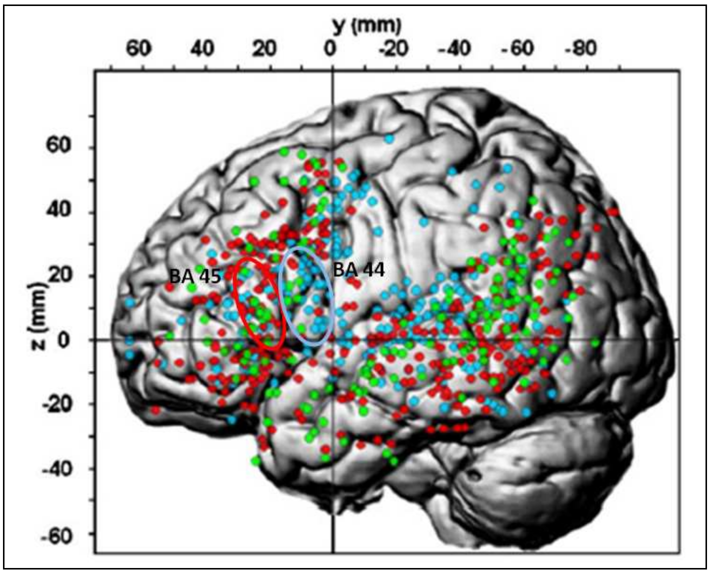

Figure 24 *Modified figure from Vigneau et al. (2006). The meta-analysis shows phonological activation clusters in light blue, syntactic clusters in green and semantic clusters in red. BA 44 and BA 45 were delineated by the author. As can be seen, BA 45 comprises a mostly syntactic and semantic clusters whereas BA 44 comprises mostly phonological clusters caudally and some syntactic clusters rostral.*

This finding, incidentally, resonates well with the previously mentioned proposal by Bookheimer (2002), suggesting an anatomical tripartition of LIFG goes along with a functional specialization in which the dorsal part (BA 44) is involved in phonological, the middle part (BA 44/45) in syntactic and the inferior part (BA 45/47) in semantic processing (for supporting evidence see also Thompson-Schill, 2005; Crinion et al., 2003). With respect to non-familiar speech sounds, like pseudo-words that were used in the present fMRI study, Scott and Johnsrude (2003) speculated that repetition of unfamiliar words or non-words is likely to depend on the ability to store a sequence of sounds over a short period of time, which they functionally attributed to posterior STS (following Wise 2003 and Wise et al., 2001).

More recently, the function of the left inferior parietal lobule and even some subcomponents of this cortical area have become the focus of further investigations using electrophysiological methods as well as fMRI. In a comprehensive review, Gottlieb et al. (2007) proposed that a specific part of IPL, the lateral intraparietal sulcus, acts as a multimodal integration area that binds information from different cognitive domains in a topographically organized fashion thus acting as an interface between cognition and action. This, of course, accommodates the results from this fMRI experiment on phonological transformations which also engaged the left and right intraparietal sulcus.

Thus, the segregation of fronto-parietal white-matter pathways into dorsal and ventral pathways suggests a functio-anatomical dissociation for different phonological processing routines. We hypothesize, that in terms of neurocognitive processing, the dorsal pathway seems to act as a fast, bottom-up route for mapping suprasegmental and segmental phonemic information from phonological working-memory in IPL to the inferior-frontal articulatory network, whereas the ventral pathway could be important for top-down modulation of phonological transformation processes as required in segmental transformation.

4.3. Interhemispheric transcallosal fiber connections

Only the segmental transformation, when contrasted with repetition, yielded significant right hemispheric activations (Fig. 11-17). Thus, interhemispheric transcallosal fiber pathways could only be tracked from these seed regions. However, we will see that the *absence* of right frontal activation in the prosodic transformation task is also particularly noticeable with respect to the dissociation between intrinsic and extrinsic features of prosody and their possible neural realization.

Interestingly, the transcallosal fiber pathways between the left and right IFG showed a homotopic pattern of connectivity and the fiber systems were clearly segregated and aligned in a rostral (BA 45) to caudal (BA 44) gradient in the body and genu of the CC. These findings are entirely consistent with recent studies using probabilistic high-angular resolution diffusion imaging tractography (Chao et al., 2009) and conventional DTI tractography (Park et al., 2008). Methodologically, callosal fibers show high reliability in fiber tracking procedures and are among the most well-aligned fibers in the brain (Park, 2008).

In order to investigate some functional implications of transcallosal transfer between left and right inferior frontal areas (and to some extent interparietal connectivity) we will discuss these findings in the following section in the context of particular disorders of speech processing – usually referred to as a- or dysprosody, though we will see that this terminology is somehow a mixed bag which will have to be conceptualized in the framework of the processing routines described so far.

4.4. Disorders of prosody: reduced and altered prosodic quality of speech

In the fMRI study that provided the functional basis of investigating white matter fiber pathways for phonological processes, prosody was one important feature that was modulated in order to engage the phonological en- and decoding system.

There seems to be a dissociation of different aspects of prosodic processing, particularly, *intrinsic* and *extrinsic* (i.e. *affective*) prosody in terms of hemispheric lateralization, with rhythmic features and stress placement (intrinsic prosody) most likely instantiated in left frontal areas and emotional aspects of prosody (affective prosody) most likely processed in right hemispheric homotopic areas (Heilman, 1984).

The first anecdotal report on a patient, though not published, with a disturbance of what we today call prosodic features of speech, was a case of foreign-accent-syndrome in conjunction with right hemiparesis by the French neurologist Marie in 1907 (Ackermann, 1993). Later, Pick (1919) published the first detailed description of foreign-accent-syndrome as consequence of brain damage (Ackermann, 1993). It took almost 30 years, before in 1947 the Norwegian neurologist Monrad-Kohn developed what we today would perhaps call a patholinguistic model of prosodic disturbances – differentiating *aprosody* from *dysprosody* - based on four qualities of prosodic speech: stress placement, rhythm, speed of speaking and pitch shifting.[7] In

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[7] „An analysis, of spoken language reveals the following elements, all necessary - if not of equal importance - to normal speech: choice of the correct words and their precise articulation; correct inflection of the words; correct placing of the words in the sentences; correct placing of stress upon syllables *and words* within the sentence (including prolongations); natural rhythm, pauses and rate of speaking (rhythm and speed should perhaps be listed as two different elements); natural shifting of pitch from syllable to syllable and from word to word, some being pronounced on a higher, some on a lower note, varying from sentence to sentence (the pitch rising and falling, gradually or abruptly); accompanying mimicry and gesture. The last four elements, except mimicry and gesture, constitute, what I propose to call the prosodic quality of speech.“ p. 405.

this paper, he presented a case of foreign-accent-syndrome in a 30 year old woman who, following traumatic brain injury, suffered left frontal brain damage with hemiplegia of the right side and global aphasia. During the course of recovery she developed a prosodic disturbance leading to a foreign accent (her Norwegian sounding like German, which in 1941 surely was no small nuisance) mixed with residual aphasia with paraphasias and jargon. The ability for correct placing of pitch and stress on syllables and words was called „prosodic faculty“ by Monrad-Kohn. He goes to great lengths to distinguishing between *alteration* and *loss* of prosody, the former which he subsumes under *dysprosody* and the latter under *hypo-* or *aprosody*.

Importantly, this early classification into dys- and aprosody has been modified and extended. As Ackermann et al. (1993) have pointed out, foreign-accent-syndrome is by far not the only phenomenological manifestation of disturbed prosody. Already well before the first conceptual classification of prosodic disturbances, Brissaud (1894), observed the monotonous manner of speech of some aphasic patients, which led him to propose a distinction between aphasia based on disturbed intonation (“aphasie d’intonation”) and disturbed articulation (“aphasie d’articulation”).

Ross (1981, 2008), in turn, resurged the term “aprosodia” to describe various syndromes of impaired affective prosody following right-hemispheric damage. In drawing an analogy to the clinical subtyping of aphasia types, he postulated eight theoretical subtypes of aprosodia: motor, sensory, global, conduction, anemic, transcortical motor, sensory and mixed aprosodia (Fig. 26). It was hypothesized, that lesions in the right hemisphere were sufficient to produce each of the aprosodia subtypes.[8]

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[8] „[…] their functional-anatomic organization in the right hemisphere (mirrors) that of propositional language in the left.“

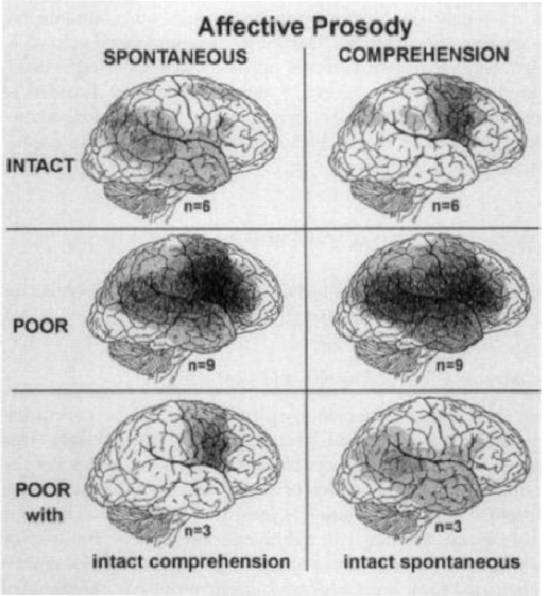

Figure 25 *Symptom-lesion mapping in disorders of affective prosody from Mesulam (2000).*

As Stringer and Hodnett (1991) have pointed out, most cases of aprosodia in the literature have indeed been localized to right-hemispheric brain damage (de Bleser 1985; Bell, 1990).[9] However, since Ross‘ original definition of aprosodia was based on cases of disturbed *emotional* aspects of prosody, or affective prosody, his classification of prosodic disturbances (and as a consequence most case reports based thereupon) were more or less deemed to associate aprosodia with mainly right-hemispheric damage. The predicted syndrome of *transcortical motor aprosodia* from Ross‘ classification in analogy to transcortical motor aphasia (Freedman, 1984), however, features much less frequently in the clinical literature and is more often associated with (medial) frontal lobe lesions in the *left* hemisphere, for example following infarction of the left anterior cerebral artery territory (Taubner et al., 1999; Heilman et al., 1984; Alexander and Schmitt, 1980).

This syndrome of prosodic alteration, which following the vestiges of Monrad-Kohn should perhaps be more coherently called *transcortical motor dysprosody*, seems to fit well with the conceptual distinction between *extrinsic* and *intrinsic* prosody which has been introduced here. In the fMRI paradigm used in this study the decisive

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[9] „Of the more than 30 cases of aprosodia that have appeared in the literature, most have had lesions in the predicted areas […] However, less is known about the localization of the lesion producing transcortical motor aprosodia (TMA).“ p. 90.

parametric difference in the prosodic stimuli before and after transformation (recall Dóga → Dogánisch) was a difference in stress placement - a feature of intrinsic prosody.

With respect to damage to callosal fibers connecting left and right LIFG Klouda et al. (1988) have reported about a patient with hemorrhagic lesion of the anterior part of the CC without damage to cortical projection areas. This study is particularly interesting because an assessment of the prosodic quality of the spontaneous speech of the patient was done over a follow-up period of one year. The patient initially showed a complete (extrinsic) aprosody which recovered substantially throughout the follow-up period.

Thus, it could be inferred, that intrinsic prosodic features of speech should be affected more by damage to left inferior frontal regions (and possibly the dorsal parieto-frontal pathway), whereas lesions of right inferior cortex should disturb extrinsic prosodic features of speech, specifically affective prosody. It should be noted, however, that this hypothesis of course is based on two different *kinds* of arguments with different evidentiary value. One is grounded in positive evidence from lesion studies of right hemispheric frontal areas reviewed above, that clearly show that damage in these areas leads to disturbance of extrinsic, i.e. emotional, prosodic quality of speech. The argument from the fMRI transformation experiment, in turn, suggests, *ex negativo*, that the *absence* of right hemispheric activity in transformation based on suprasegmental features of speech implicates that intrinsic prosody might preferentially be processed in the left hemisphere.

4.5. Summary

To summarize, the results of the tracking experiment which were functionally motivated by the fMRI transformation experiment, together with the findings from previous research discussed above, suggest that suprasegmental and segmental processing are instantiated in a large-scale fronto-parietal network with segregated ventral and dorsal pathways for segmental transformation.

The segregation into dorsal and ventral pathways for segmental transformation could be either suggestive for a functio-anatomical dissociation for this particular kind of phonological transformation processes or a result of concurrent engagement of the lexical-semantic ventral processing route as a result of the segmental stimuli forming a pseudo noun phrase. In terms of cognitive processing routines, the dorsal pathway seems to act as a fast, bottom-up route for mapping suprasegmental and segmental phonemic information from phonological short-term store in IPL/IPS to the inferior-frontal articulatory network, whereas the ventral pathway could be important for top-down, possibly lexical-semantic, modulation, in this case of segmental transformation.

With respect to interhemispheric connections, rostral transcallosal projections provide connectivity between homotopic inferior frontal areas and caudal projections between left and right parietal areas. As has become apparent from the research discussed above, the homotopic interhemispheric transcallosal projections between left hemispheric BA 44, 45 and their right hemispheric homologues as well as interparietal connections in providing pathways for functional interaction seem to play an important role for the functional integrity of the phonological processing system. However, it remains to some extent unknown, whether interhemispheric transfer is a necessary prerequisite for intact phonological processing. To date, very little data on the effect of transient or permanent damage of callosal fibers with respect to extrinsic and intrinsic prosodic features of speech is available. The previously mentioned study by Klouda et al. (1988) is particular interesting in this respect, as the longitudinal follow-up of a patient with hemorrhagic damage to the anterior CC showed a remarkable recovery from complete aprosody though the CC, presumably, did not recover structurally.

4.6. Zusammenfassung

Die Ergebnisse der probabilistischen Traktographie der Faserverbindungen zwischen kortikalen Arealen für phonologische Verarbeitung, welche durch ein Sprachexperiment mittels funktioneller Kernspintomographie (fMRT) definiert wurden, zeigen, dass phonologische Transformationsprozesse in einem Netzwerk mit zwei unterschiedlichen Verbindungswegen für die Interaktion zwischen frontalen und parietalen Arealen verwirklicht sind.

Ein dorsaler Weg über das Fasersystem des Fasciculus arcuatus und Fasciculus longitudinalis superior verbindet inferior-parietale Areale links mit dem linken Gyrus frontalis inferior, Brodmann-Areal (BA) 44 und ein ventraler Weg über das Fasersystem der Capsula extrema verbindet inferior-parietale Areale links mit dem linken Gyrus frontalis inferior, BA 45.

Die beiden Fasersysteme zeigen eine funktionelle Segregierung, wobei der dorsale Weg hinreichend für phonologische Transformation basierend auf einer Betonungsverschiebung (suprasegmentale Transformation) ist und der ventrale Weg notwendig für phonologische Transformation welche auf Segmentierung basiert (segmentale Transformation) ist.

Hinsichtlich der neurokognitiven Prozesse ist anzunehmen, dass der dorsale Weg vorwiegend als schnelle, sogenannte „bottom-up“, Route für das Weiterleiten segmentaler und suprasegmentaler phonemischer Information dient, während der ventrale Weg eine Route für die exekutive Modulation, oder “top-down“ Kontrolle, mittels lexikalisch-semantischer Information darstellt.

Die ebenfalls untersuchten interhemisphärischen Faserverbindungen zwischen kortikalen Arealen für phonologische Transformation zeigen, dass transkallosale Projektionsfasern homotope Areale (z.B. BA 44 links mit BA 44 rechts) direkt miteinander verbinden. Auf der neurokognitiven Ebene kann die Interaktion zwischen homotopen Arealen, insbesondere inferior frontal, wichtig für unterschiedliche Arten prosodischer Störungen infolge eines neurologischen Schadens sein.

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6. APPENDIX

6.1. Methods of fMRI experiment

6.1.1. Stimulus presentation

The visual cues were presented centrally on a dark background. They were projected onto a screen located at the top of the head coil and viewed by the subjects via a mirror. The auditory stimuli were presented via an MR-compatible electrodynamic headphone with a built-in dual-channel microphone (MR ConFon GmbH, Magdeburg, Germany, http://www.mr-confon.de) for the combined presentation and recording of speech. Subjects responses were recorded with the sound recording software PhonOr implemented in the ConFon system which automatically preprocesses the dual channel recordings by reducing the whole frequency spectrum of the scanner noise by 20dB in relation to the speech signal. Vocal response recordings had to be customized in order to synchronize them with the recordings of scanner pulses and stimulus onsets. To this end, scanner pulses were recorded in two different channels: once they were routed to the standard presentation software which also recorded stimulus onsets, and once they were fed into the vocal response recording channel as an additional signal. This procedure ensured perfect synchronization of the general presentation parameters with the recording of vocal responses. Vocal responses were recorded by ConFon running on a Samsung R65-T5500 Canspiro laptop situated outside of the scanner room, and saved as wavfiles. The volume for the auditory presentation was set to a comfortable level individually for each subject in a preceding test scan. The task sequence was controlled by a PC running "Presentation" software (Neurobehavioral Systems, www.neurobehavioralsystems.com).

6.1.2. Experimental Design

The study was designed as a 2x2 full-factorial design with the factors *task* and *phonological process*. The experiment contained eight runs, four for each task (REPEAT and TRANSFORM), of whom two comprised the PROS and SEGM condition, respectively. Thus, there were two runs for repetition of the prosodic and segmental material, respectively, and two runs for the transformation of the prosodic and segmental material. The phonological process remained constant within a run. Thus, subjects did not have to switch between the prosodic and segmental stimuli. Every run was composed of 36 experimental trials and had a length of about 5.5 minutes each. Half of the 36 trials were bisyllabic and the other half were three-syllable pseudowords. The sequence of tasks and phonological processes was pseudorandomized, with the restriction that maximally two runs of one task or phonological process could occur in a row and that each run appeared almost equally often in all positions across subjects. The order of the pseudowords within a run was pseudorandomized, in a way that maximally three mono- and bisyllabic words, respectively, occurred in a row. The trial sequence was fixed within runs for all subjects. The experiment took a total of about 50 min to complete for each participant.

Both groups of stimuli consisted of 36 bisyllabic and 36 three-syllable items in each case. The speech material was spoken by an experienced male native German speaker and was recorded in a soundproof environment. Mean duration of the PROS material was 824 ms (range 544-1136 ms; SD: 177 ms) and mean duration of the SEGM material was 954 ms (range 639-1288 ms; SD: 170 ms). There was a significant difference in duration between both speech stimuli groups with a longer duration for the SEGM material ($t = -4,49$; $DF = 142$; $p < 0,0001$). This difference is a result of a short speaking pause between the additional article and the noun in the segmental condition on the one hand and possibly a dissimilar phonetic structure of both stimuli groups on the other hand. The sound intensity of all stimuli was set to 80dB.

To prepare the subjects for the beginning of an auditory stimulus, each trial started with the presentation of a visual cue (symbol of a loudspeaker) which was presented 500 ms before the onset of each auditory stimulus until the offset of the auditory stimulus. As a sign to start to speak, a green dot was presented 500 ms after the offset of the auditory stimulus for 300 ms. Subjects were instructed to speak by the time the green dot disappeared. During the rest of the trial the screen remained dark. The SOA was jittered in an interval of between 5.5 and 10.5 seconds.

6.1.3. Data acquisition and image preprocessing

Imaging was conducted using a 3T Siemens magnetic resonance imaging system, acquiring around 1520 volumes in total. For each subject, functional T2-weighted gradient-echo echo-planar images were obtained from 26 axial slices (3 mm thickness, no gap, TR 1720 ms, TE 30 ms, flip angle 80°, field of view 216 x 216 mm2, matrix 72 x 72) oriented parallel to the anterior and posterior commissure. Furthermore, a 3D high-resolution (1 x 1 x 1 mm voxel size) T1-weighted structural MRI (MPRAGE) was acquired for each subject. Head movement was restrained within the head coil by circumaural headphones fitting tightly into the head coil and by tight foam padding. Additionally, subjects were instructed to minimize head movement. The microphone was placed centrally to the mouth as closely as possible without touching the lips.

The processing and analysis of imaging data was performed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing included slice timing, realignment and un-warp, coregistration between the individual structural T1-weighted image and the EPI- images, and segmentation of the structural images. The resulting estimated spatial normalization parameters were then applied to the series of functional images, which were subsequently resampled to a voxel size of 3 x 3 x 3 mm and finally smoothed using a 10 mm full-width at half-maximum isotropic Gaussian kernel.

6.1.4. Behavioral data: analyses and results

The first step in vocal response analysis was to determine the accuracy of responses in the REPEAT and TRANSFORM task, using the sound editing software ‘Audacity’. Verbal responses were evaluated independently by two raters (CP and a second rater who was not familiar with the goal of the study) for accuracy, using the criterion that only words without any audible phonetic or phonological distortions were rated as accurate. Mean concordance between raters was 0.8 (Cohen’s Kappa), which constitutes substantial interrater agreement by convention (Landis & Koch, 1977). Whenever the raters differed, the respective tokens were rated by a third person. The inclusion criterion was set to a minimum of 80% correct responses. Next, we performed an error analysis. The number of phoneme substitutions was examined separately for each item. When the target item had been produced with a phonemic substitution, the number of substituted phonetic features of the respective phoneme was counted and described in terms of type of error.

In case of the TRANSFORM task the accuracy of the transformation additionally was analyzed. More precisely, regarding the PROS material, the transformation only was correct when word stress was changed from the first to the second syllable or vice versa. The transformation of the SEGM material was rated as accurate when a vowel mutation occurred.

Next, word duration (in ms) was measured in two ways. For the first analysis, only responses (a) without any iteration, correction or delay within the utterance and (b) in the case of the TRANSFORM task only with correct transformations were included. This analysis should give an unaffected outline of response duration differences between conditions. The on- and offset of each of these responses was determined by visual and auditory inspection of the speech wave. The duration of individual responses was then calculated by subtracting the onset from the offset of the response. For the second kind of analysis, the duration of the whole process of repetition and transformation, respectively, was measured for each event from stimulus onset to speech offset. Since this analysis represents differences between stimuli durations, response latencies and response durations altogether, it is important for the interpretation of the functional data.

The last step was to measure the response latency of each item by calculating the time interval from the offset of the green dot to vocal response onset.

All participants reached a satisfactory level of phonological and phonetic accuracy, with a group mean of 86.8% correct responses across conditions (range 80.6-93.1%, SD: 3.7%). A repeated-measures ANOVA with task and phonological process as factors revealed a significant main effect of task ($F(1,21) = 51.24$; $p < 0.000$), a significant main effect of phonological process ($F(1,21) = 9.91$; $p < 0.005$) and a significant task by phonological process interaction ($F(1,21) = 10,48$; $p < 0.005$). With respect to the accuracy of responses, participants achieved an overall 81.8% correct responses for the transformation tasks. The post-hoc analysis showed higher accuracy for the REPEAT task (mean: 91.8% correct) than for the TRANSFORM task (mean: 81.8% correct). The SEGM condition, participants showed higher accuracy (mean: 88.9% correct) than in the PROS condition (mean: 84,7%), however, a paired t-test showed no significant difference in transformation accuracy between both phonological processes. Also there were no significant differences in response latency between segmented and prosodic transformations.

There was a significant main effect of task with more phonological errors in the transformation compared to the repetition task which can be explained by additional cognitive processing demands because of the phonological manipulation during transformation. Not surprisingly, this higher demand resulted in more phonological substitutions. In most cases, however, only a single phonetic feature of one phoneme was affected. Furthermore, subjects showed less phonological errors in the segmental compared to the prosodic condition. This effect could be caused by the additional article in the segmental condition, which appeared with every stimulus in this condition and was not error-prone. Thus, the segmental processing effectively included one syllable less as source of phonological error. Considering the accuracy of the transformation processes, subjects showed almost perfect performance. There were no differences between segmental and prosodic transformation in degree of accuracy which suggest similar difficulty of both conditions.

In analogy to the stimuli, the response duration was significantly higher in the SEGM compared to the PROS condition. This difference was explained by Peschke et al. (2009, submitted) by the different phonetic structures of the items in both phonological processes. Additionally, the article in the SEGM condition causing a speech pause between article and noun could contribute to this effect. The second analysis of response duration considered the whole duration from stimulus onset to speech offset and is crucial for the interpretation of the functional activation. As in the first analysis, the only significant effect was seen for the phonological processes with higher durations for the SEGM than for the PROS condition. This result is not surprising as that analysis involves the differences in duration of the stimuli and the responses. Effects on functional activation differences are explained later.

There were no significant correlations between the behavioral parameters, indicating that the results were not confounded by potential speed-accuracy trade-off effects. Accordingly, subjects with shorter response latencies did not make more errors when repeating the stimuli.

6.1.5. Functional imaging data

Statistical analyses of the functional imaging data were performed in two steps. In a first level analysis, a statistical model was computed for each subject. Therefore, the process of repetition and transformation, respectively, was defined as one event lasting from stimulus onset to vocal response offset, and entered as sole variable into the model. This regressor was convolved with a canonical hemodynamic response function (HRF) as implemented in SPM5. As intrasubject stimulus correlated motion was corrected by using unwarp for the preprocessing of the images, the realignment parameters were not inserted into the model. Voxel-wise regression coefficients for the variable of interest were estimated using the least-squares method within SPM5, and statistical parametric maps of the t statistic (SPM{t}) were generated. Next, we computed the main effects of each condition in the 2x2 factorial design (REPEAT_PROS, REPEAT_SEGM, TRANSFORM_PROS, TRANSFORM_SEGM).

In a second-level analysis, the contrast images of the first-level analysis for each subject were used to perform a group analyses. Therefore, the contrast images of the four conditions were entered into a within-subject ANOVA model with the additional factor subject, including a correction for non-sphericity. All of the analyses were computed within this model.

To identify areas of common activation due to repetition and transformation of pseudowords across the phonological processes, both contrast images of REPEAT and TRANSFORM, respectively, were submitted to a conjunction analysis under the conservative conjunction null hypothesis, using a threshold of $p < 0.05$ (FWE corrected).

In a next step, areas sensitive to the additional phonological manipulation independent of the phonological process were identified. Therefore, differential contrasts comparing TRANSFORM with REPEAT were computed for both phonological processes separately and combined in a conjunction analysis under the conjunction null hypothesis, using a threshold of $p < 0.05$ (FDR corrected). To verify these results the reverse contrast was computed by combining the differential contrasts of REPEAT versus TRANSFORM, (computed separately for both phonological processes) in a conjunction analyses, using the same threshold. To get a more detailed view of processes concerning phonological manipulations as a function of the phonological process, the differential contrasts comparing TRANSFORM with REPEAT were analyzed for PROS and SEGM separately, using a threshold of $p < 0.05$ (FDR corrected).

To answer the question of a possible lateralization of the transformation process, we computed a differential contrast within the ANOVA comparing the contrast images of PROS with those of SEGM and vice versa for the transformation task. Since only the half of the events are included in this analysis, the statistical threshold was set to $p < 0.001$ (uncorrected).

Additionally, interactions between the two factors 'task' and 'phonological process' were computed. Therefore, it was analyzed where the difference between TRANSFORM and REPEAT is greater for one of the phonological processes. The statistical threshold for both analyses was set to $p < 0.05$ (FDR corrected).

All of the above analyses were computed for the entire volume of 26 slices. Anatomical localization of activation peaks was done by using the SPM Anatomy Toolbox Version 1.3b (Eickhoff et al., 2005). Spatial references are given in Montreal Neurological Institute (MNI) coordinates.