The forgotten hemisphere

Right-hemispheric contributions to modality-independent phonological aspects of language processing in the healthy human brain

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List of Publications

The present dissertation is based on two review papers, a book chapter and four research papers. The latter are referred to in the text as studies 1-4.

Review 1 Siebner, H.R., **Hartwigsen, G.**, Kassuba, T. & Rothwell, J.C. (2009). How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. *Cortex 45 (9)*, 1035-1042.

Review 2 **Hartwigsen, G.**, Siebner, H.R. & Stippich, C. (in press). Preoperative functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS). *Current Medical Imaging Reviews.*

Book chapter **Hartwigsen, G.,** Kassuba, T. & Siebner, H.R. (2009). Combining transcranial magnetic stimulation with (f)MRI. In S. Ulmer & O. Jansen (Eds.), *fMRI - Basics and Clinical Applications* (pp.155-167). Heidelberg: Springer.

Study 1 Baumgaertner, A., **Hartwigsen, G.** & Siebner, H.R. (in revision). Modality-independent semantic, phonologic and perceptual word processing in the human brain. *Human Brain Mapping.*

Study 2 **Hartwigsen, G.**, Baumgaertner, A., Price, C.J., Koehnke, M., Ulmer, S. & Siebner, H.R. (under review). Efficient phonological decisions require both the left and right supramarginal gyri. A dual-site transcranial magnetic stimulation study. *Proceedings of the National Academy of Sciences of the USA.*

Study 3 **Hartwigsen, G.**, Price, C.J., Baumgaertner, A., Geiss, G., Koehnke, M., Ulmer, S. & Siebner, H.R. (in revision). The right posterior inferior frontal gyrus contributes to phonological word decisions in the healthy brain: evidence from dual-site TMS. *Neuropsychologia.*

Study 4 **Hartwigsen, G.**, Ulmer, S. Baumgaertner, A. & Siebner, H.R.
A frontal network for pseudoword repetition. *In preparation for Cerebral Cortex.*

Contents

1 Introduction

1.1 A brief historical overview

Language is the elementary mental capability that humans use to communicate. It involves the association of sounds and symbols with meaningful concepts and enables us to describe our external environment and articulate abstract thoughts. Moreover, our conception of the external world is "determined by our language" (Robins, 1952). The effective use of language requires the interaction of memory with sensory input and motor output systems (Price, 2000).

Since the days of Broca and Wernicke in the second half of the 19th century, research aims to define functional-anatomic models of language comprehension and production to describe the organisation of language in the human brain. The early models of language organisation were based on behavioural deficits in patients with brain lesions (e.g. Broca, 1861; Wernicke, 1874, see Shalom & Poeppel, 2008 for a review).

However, the results of deficit-lesion correlation studies are difficult to interpret since they often lack anatomical precision and are based on vague psychological constructs (see Shallice, 1988 for a review). For instance, neuropsychological profiles tend to be complex, involving more than one cognitive deficit. The full extent of the cognitive deficit may also be obscured following compensatory strategies adopted by the patient to overcome the deficits (i.e. cognitive reorganisation) or changes in the functional topography due to neuronal reorganisation (Thiel et al., 2006a). Likewise, pathological lesions (in contrast to experimental lesions) seldom conform to functionally homogenous neuroanatomical systems. Another critical limitation is the impossibility to distinguish whether the lost cognitive function is associated with the lesioned area or a disconnection of undamaged areas. Lesion deficit studies support the conclusion that neural systems intrinsic to the lesioned area, or the connections passing through that area, were necessary for the lost function.

One cannot infer that the damaged region was either sufficient for, or uniquely identifiable with that function. In contrast, functional neuroimaging studies on normal subjects provide the perfect complement in that the neural systems sufficient for one task compared to another can be identified (Price, 2000).

With the advent of modern functional imaging techniques such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), magnetoencephalography (MEG) or transcranial magnetic stimulation (TMS) in the late 20th century, a new decade of studies on language organisation in the human brain has

started focussing on the direct correlation between mental operations and indices of brain activity.

In contrast to the lesion-deficit approach, functional neuroimaging studies of both patients and healthy subjects are not limited to the assumption that cognitive processes or operations are confined to discrete anatomical regions but allow for the investigation of functional specialisation which emerges from the interaction between different areas (Price, 2000).

fMRI is increasingly being used to identify brain regions that are activated during language processing (Bookheimer, 2002; Costafreda et al., 2006). This information has been complemented by recent studies applying TMS to test if the stimulated cortex makes a critical contribution to the brain functions subserving a specific language task (Devlin & Watkins, 2007). While the relationship between task and functional activation as revealed by fMRI is correlative in nature, the neurodisruptive effect of TMS reflects a causal effect on brain activity (see 2.2 and 2.3 for a detailed description of fMRI and TMS). Results of time-sensitive measures such as EEG and MEG, on the other hand, are used to provide insight into the temporal aspects of the processes underlying language production and comprehension (Mehta, Jerger, Jerger & Martin, 2009; Salmelin & Kujala, 2006).

Recent functional-anatomic models of language processing are based on the results of investigations in healthy subjects. A profound understanding of language organisation in the healthy human brain is mandatory for the interpretation of activation changes due to reorganisation in patients. The use of a multimodal imaging approach combining different methods allows for an identification of brain areas being involved in specific language functions and enables the researcher to test whether this activation is of functional significance for a specific language function.

1.2 The structure of language processing: some basic linguistic functions

The current understanding of the structure of language processing distinguishes a set of different linguistic functions: these include separable processes related to the organisation of speech sounds (phonological processing), to the visual structure of written words (orthographic processing), to the meaning of linguistic tokens (semantic processing), to the structure of complex linguistic forms (syntactic processing), to the integration of phonological, semantic, and syntactic aspects of words (lexical processing), and to the

programming of speech motor acts (articulatory processing) (Poldrack et al., 1999). As the aim of this thesis is to investigate the neural correlates of phonological processing in the healthy human brain, the following sections focus on phonological aspects of single word processing.

1.2.1 What is phonology?

Phonology can be defined as the study of how sounds are organized and used in natural languages. Linguistic theories state that the phonological system of a language includes an inventory of sounds and their features, and rules which specify how sounds interact with each other (Katamba, 1989). In other words, phonology is concerned with the abstract set of sounds in a language which allows distinguishing meaning in the actual physical sounds one hears or speaks (Yule, 2006). Phonological processes are involved in the perception or production of syllables. Syllables are units for the organization of a sequence within a phonological system. A word can be divided into one or more syllables, for instance, the word "syllable" is composed of three syllables (i.e. *syl-la-ble*).
According to Katamba (1989), the syllable represents the "heart of the phonological representation". Syllables in turn can be divided into phonemes which are defined as the smallest contrastive units within the sound system of a language (i.e. /b/). A phoneme is the minimal unit that serves to distinguish between meanings of words (Féry, 2002).

1.2.2 Connectionist models of word processing

Because of the difficulties associated with the lesion-deficit model (see below for details), some cognitive models of the 20th century have primarily emphasised the complexity of linguistic functions rather than investigating their neurological principles. The proposed models focus on the healthy language system and describe the operations included in word processing. The connectionist or "parallel distributed processing" models emphasise that a large number of functions can emerge from a system with a limited number of highly interactive components. For instance, Seidenberg and McClelland (1989) argued that single word processing is based on orthographic, phonological and semantic processes that strongly interact with each other (Fig.1).

A key assumption of the model is that there is a single, uniform procedure for computing a phonological representation from an orthographic representation that is applicable to words as well as nonwords.

For example, orthographic processes influence phonologic processes during word reading since the written form of words typically provide cues to their syllabic structure (Adams, 1981). Hence, properties of speech such as syllables tend to be reflected by the orthography.

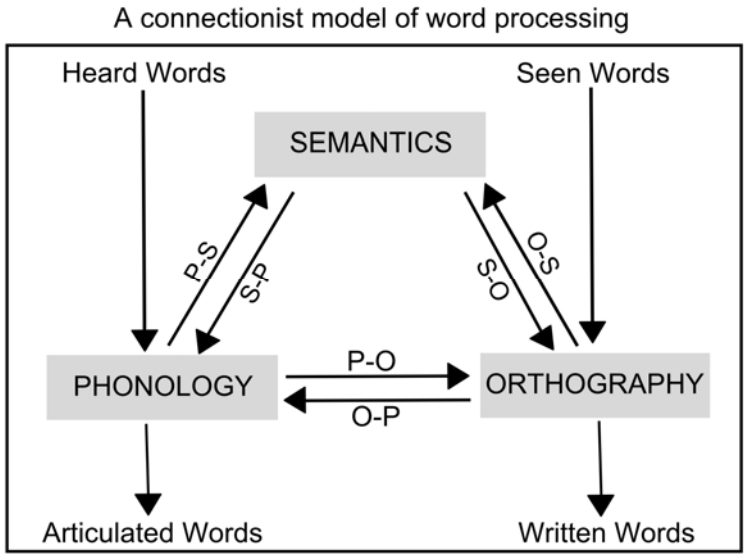

Fig.1 Connectionist model of word processing. The core aspects of word processing are connected and interact with each other. For instance, retrieving the phonology of a seen word from orthography can either occur via direct links (O-P) or indirectly via semantics (O-S, S-P). O: orthography, p: phonology, s: semantics (adapted from Seidenberg and McClelland (1989).

During a typical language task such as overt naming of a written word, the stimulus is first analysed orthographically. Then, the input's phonological code is computed and subsequently compiled into a set of articulatory-motor commands. Retrieving the phonological code from orthography can either occur via direct links or indirectly via semantics. Finally, the articulatory motor code is executed, resulting in the overt response.

According to this model, phonological dyslexia (i.e. a deficit for reading novel words) results from a disruption of the connection between orthography and phonology (Plaut & Shallice, 1993) and surface dyslexia (i.e. the deficit to read irregularly spelled words) results from a deficit in semantic processing (Plaut, McClelland, Seidenberg & Patterson, 1996). In contrast to the 19th century lesion-based models, the connectionist models place emphasis on distributed rather than modular processing. Yet, they are still not verified by neurophysiology. In this context, functional neuroimaging has the potential to redefine models of normal and abnormal language processing by providing appropriate neurological constraints. It can assess

whether there is a specialised neural system for a particular process or whether the implementation of that process is governed by patterns of distributed activity in neural systems that share other functions (Price, 2000).

1.3 Functional-anatomic models of language organisation

1.3.1 The classic model of cortical language representation

The first functional-anatomic model of cortical representation of language in the human brain dates back to the 19th century, when Broca reported a post-mortem study of a patient who had suffered from impaired language articulation (Broca, 1861). Since the patient's brain was damaged in the left inferior frontal gyrus, approximately corresponding to Brodmann's areas [BA] 44 and 45 (Amunts & Zilles, 2006), Broca reasoned that this area was contributing to the motor images of speech. Ever since "Broca's area" has been labelled the "core area" for language production. The work of Broca was complemented by Wernicke (1874) who reported another post-mortem study of a patient who had suffered from impaired language comprehension. In this patient's brain, damage was found in the left superior temporal gyrus – later referred to as "Wernicke's area" – which was associated with the auditory images of speech. In 1885, Lichtheim synthesized these two claims, predicting a (diffuse) connection between the two regions (Fig.2). Accordingly, it was assumed that damage to the white matter tracts that connect Broca's and Wernicke's areas (i.e. the arcuate fasciculus) results in a deficit of the repetition of heard speech with intact speech comprehension and production. For the next 150 years, language research was based on this "classic" model of language organisation (Demonet, Thierry & Cardebat, 2005).

This model was further developed by Geschwind (1965), adding "tertiary association areas", namely the angular and supramarginal gyri of the left inferior parietal cortex as a link between visual and auditory word forms. Accordingly, the resulting "Wernicke-Lichtheim-Geschwind" theory states that Wernicke's area is responsible for receptive language processing and is connected through the arcuate fasciculus with Broca's area, which is responsible for expressive processing. Tertiary association areas in the parietal lobe provide cross-modal associations underlying word meanings, while the arcuate fasciculus is viewed as being critical for word repetition (Geschwind, 1965).

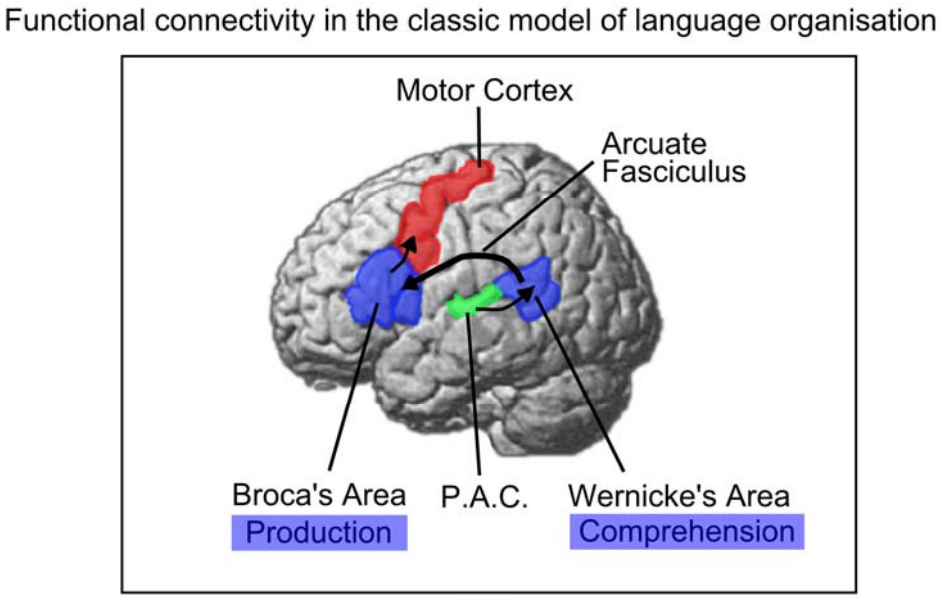

Fig.2 The "classic model" of cortical language representation in the human brain (following Geschwind, 1979). During the repetition of heard speech, input from the primary auditory cortex (P.A.C.) is mapped on Wernicke's area (associated with language comprehension) which is connected with Broca's area (associated with motor images of language production) in the left inferior frontal gyrus via the arcuate fasciculus. Broca's area is connected with the motor cortex serving the generation of speech output (adapted from Price, 2000).

Although this model has been clinically useful, it is both anatomically and psycholinguistically underspecified and no longer sufficient nowadays (e.g. Caplan, 2003; Demonet et al., 2005; Dronkers, Wilkins, Van Valin, Redfern & Jaeger, 2004; Poeppel & Hickok, 2004; Shalom & Poeppel, 2008).

It has been criticized that the effects of language disruption in anterior vs. posterior language areas do not follow the classic posterior-comprehension - anterior-expression dissociation. Rather, particularly within the frontal lobe, cortical stimulation mapping studies found areas specialized for semantic processing and phonology as well as articulation (e.g. Ojemann, Ojemann, Lettich & Berger, 1989).

Systematic investigations of patients with lesions in either Broca's or Wernicke's area did not reveal the assumed deficits in all patients (Dronkers et al., 2004; Schaffler, Luders, Dinner, Lesser & Chelune, 1993). On the other hand, behavioural deficits were not caused by a lesion in either Broca's or Wernicke's areas in all patients (e.g. Otsuki, Soma, Yoshimura, Koyama & Tsuji, 1996). Several anatomical correlation studies found little evidence of an exclusive association of the left inferior frontal gyrus with Broca's aphasia. For example, Alexander, Naeser and Palumbo (1990) and Dronkers (1996) found evidence of functional heterogeneity in the inferior frontal gyrus for different deficits among Broca's aphasics including those in articulation, syntax, and naming. Rather than indicating a high degree of variability in lesion location, the data show that multiple regions are involved in expressive language and that

only disruption to all of them produces the catastrophic breakdown of language as revealed in aphasics. As Broca's aphasia patients have a variety of seemingly diverse impairments, it is likely that these skills have different neural representations (Bookheimer, 2002).

1.3.2 Advanced functional-anatomic models of language organisation

1.3.2.1 An overview of recent models

In the last decades, a number of psycholinguistic models have been proposed for both language comprehension (e.g. Friederici, 2002; Hagoort, 2003; Hickok & Poeppel, 2000; 2004; 2007; Liberman, Cooper, Shankweiler & Studdert-Kennedy, 1967; Marslen-Wilson & Tyler, 1980; McClelland, 1991) and language production (e.g. Dell, 1986; Hickok & Poeppel, 2000; 2004; 2007; Indefrey & Levelt, 2004; Levelt, Roelofs & Meyer, 1999; Levelt, 2001). Some of these models focused on single word processing (e.g. Hickok & Poeppel, 2000; 2004; 2007; Indefrey & Levelt, 2004), while others implemented more complex processes such as sentence processing (e.g. Friederici, 2002; Hagoort, 2003).
Some functional imaging studies provide evidence for the existence of a shared fronto-temporal neural network engaged in the processing of phonological information in both language comprehension and production (Burton, Small & Blumstein, 2000; Heim & Friederici, 2003; Heim, Opitz, Muller & Friederici, 2003).
In the following sections, some of the leading recent models are discussed with respect to phonological single word processing. For detailed reviews and models on semantic processing, the reader is referred to Bookheimer (2002) and Price (2000) and to Friederici (2002) and Heim (2005) for syntactic processing.

1.3.2.2 Brain areas involved in phonological word processing

1.3.2.2.1 The role of Broca's area

Although Broca's area in the inferior frontal gyrus has been attributed the role of producing language for a long time (see above), a variety of functional imaging studies on both patients and healthy subjects provides evidence for the contribution of the inferior frontal gyrus to

both language production and language comprehension (Bookheimer, 2002). Moreover, it is now widely accepted that the role of Broca's area is not limited to language processing but also includes non-linguistic functions such as action perception (e.g. Grodzinsky & Santi, 2008).

It is currently debated whether Broca's area can be functionally divided into different subareas preferentially engaged in semantic and phonological word processing during both word comprehension and production (Costafreda et al., 2006; Poldrack et al., 1999).

Some functional imaging studies have explicitly shown common activations within the left inferior frontal gyrus (IFG) for both semantic and phonological processing (Barde & Thompson-Schill, 2002; Demonet et al., 1992; Gold & Buckner, 2002), raising the possibility that the IFG is necessary for both types of processing.

On the other hand, some studies directly comparing semantic and phonological processing found significant differences within the left IFG. For instance, phonological compared to semantic word judgement tasks revealed increased activation in the left posterior IFG (Burton, Diamond & McDermott, 2003; Devlin, Matthews & Rushworth, 2003; McDermott, Petersen, Watson & Ojemann, 2003). The opposite comparison of semantic with phonological word processing resulted in relatively stronger activation in the anterior part of the left IFG (e.g. Burton et al., 2003; Gitelman, Nobre, Sonty, Parrish & Mesulam, 2005; McDermott et al., 2003; Seghier et al., 2004). However, some studies found these differences only at a lenient statistical threshold (Otten & Rugg, 2001; Price, Moore, Humphreys & Wise, 1997; Roskies, Fiez, Balota, Raichle & Petersen, 2001).

Although the results of functional imaging studies are equivocal, a consensus has begun to emerge that there is an anterior-posterior division within the left IFG for semantic and phonological processing with more posterior portions (i.e. pars opercularis) being responsible for phonological decisions, and more anterior portions (i.e. pars orbitalis and triangularis) being responsible for semantic decisions (Costafreda et al., 2006; Gitelman et al., 2005; McDermott et al., 2003; Poldrack et al., 1999; Fig.3).

The functional segregation of the left IFG into subareas serving different aspects of language processing (i.e. phonology and semantics) can be complicated by automatic processing of task-irrelevant information during a specific language task. For example, even if a task requires only semantic information and thus engages the left anterior IFG, there may be some degree of automatic recruitment of phonological processes (engaging the left posterior IFG), although it is not required to perform the task (e.g. Bookheimer, 2002; McDermott et al., 2003; Poldrack et al., 1999).

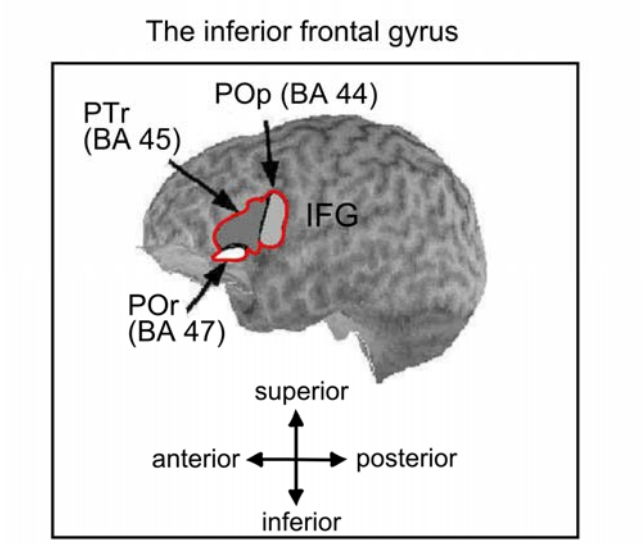

Fig.3 Subregions in the left inferior frontal gyrus (IFG) associated with language processing. The posterior part (pars opercularis [POp]) roughly corresponding to Brodmann's area 44 is associated with phonological processing. The anterior part (pars triangularis [PTr] and pars orbitalis [POr]) roughly corresponding to BA 45 and BA 47 is associated with semantic processing (adapted from Devlin et al., 2003).

The automatic processing of task-irrelevant information may partly explain the contradictory results revealed by functional imaging studies. More recent studies used transcranial magnetic stimulation (TMS) to investigate the functional anatomy of Broca's region (e.g. Aziz-Zadeh, Cattaneo, Rochat & Rizzolatti, 2005; Devlin et al., 2003; Gough, Nobre & Devlin, 2005; Kohler, Paus, Buckner & Milner, 2004; Nixon, Lazarova, Hodinott-Hill, Gough & Passingham, 2004). The use of repetitive TMS (rTMS) enables the researcher to test the functional significance of task-related activity patterns revealed by correlational methods such as fMRI. rTMS is able to disrupt neuronal processing in the targeted brain area which in turn may affect task performance, if the stimulated cortex makes a critical contribution to the brain functions subserving the task (Paus, 2005; Walsh & Cowey, 2000; see 2.3 for further details).
Devlin et al. (2003) investigated whether stimulation of the left anterior IFG (aIFG) interfered with semantic decisions such as deciding whether a visually presented word referred to a man-made (e.g. "kennel") or natural object (e.g. "dog"). Relative to no stimulation, rTMS significantly increased reaction times in the semantic task only, but not when participants focused on visual properties of the presented words. In contrast, Kohler et al. (2004) found that high-frequency online rTMS over the left but not right aIFG enhanced the accuracy of semantic word encoding in comparison to rTMS over parietal sites. The authors concluded that rTMS over the left aIFG might have triggered a more extensive processing of the stimulated items, underlining the important role of the left aIFG in episodic memory function. Although the results of Devlin et al. (2003) contrast with those of Kohler et al. (2004), both are consistent with the claim that the left aIFG is necessary for semantic processing.

The role of the left posterior IFG (pIFG) in phonological processing was examined by Nixon et al. (2004). The authors demonstrated that rTMS over the left pIFG interfered with a phonological working memory task. A word was presented on a computer screen (e.g. “knees”) and participants were asked to decide whether it sounded the same as a subsequently presented non-word (e.g. “neaze”) presented after a delay of 1-2 s. rTMS during the delay period selectively increased error rates of the phonological task, but not of a comparable visual working memory task. Aziz-Zadeh et al. (2005) investigated “covert speech arrest” which was measured in participants silently reading a visually presented word and counting its syllables. Again, rTMS over the left pIFG increased reaction times relative to unstimulated trials, consistent with a role of the pIFG in phonological processing. Taken together, these studies significantly extend previous neuroimaging results by demonstrating that the left aIFG is necessary for semantic processing while the left pIFG is engaged in phonological processing.

However, the TMS studies cited above do not differentiate between the two possibilities that both regions are necessary for both types of processing or that there is a subdivision with more anterior regions corresponding to semantic and more posterior regions to phonological processing since each of the single dissociations would be predicted by both accounts (Devlin & Watkins, 2007). Consequently, Gough et al. (2005) designed a TMS experiment to explicitly test a double dissociation between semantic and phonological processing in the left IFG. Two-letter strings were presented simultaneously on a computer screen and subjects had to decide whether they meant the same (e.g. “idea” and “notion”), sounded the same (e.g., “nose” and “knows”), or looked the same (e.g. “fwtsp” and “fwtsp”). Relative to no stimulation, rTMS over the left aIFG selectively increased reaction times when participants focused on the meaning of simultaneously presented words (i.e. their semantics) but not when they focused on the sound pattern of the words (i.e. their phonology). In contrast, the opposite dissociation was observed with stimulation over the left pIFG, which selectively interfered with the phonological task, but not with semantic decisions. Neither stimulation site affected the reaction times in the visual control task. Thus, the authors demonstrated for the first time a functional double dissociation for semantic and phonological processing within the left IFG as suggested by earlier functional imaging studies.

In a recent study, Anwander et al. (2007) used diffusion-weighted magnetic resonance imaging to test whether Broca’s area can be anatomically subdivided in vivo in the healthy human brain. The authors demonstrated that within Broca’s area, three subregions are discernable that were identified as putative BA 44 (pIFG), BA 45 (aIFG) and the deep frontal

operculum. These results indicate that the functional segregation within Broca's area is underpinned by an anatomical subdivision.

1.3.2.2.2 Networks for phonological word processing

To identify phonological aspects of language comprehension and production, a variety of tasks have been used in previous functional imaging studies including the repetition or articulation of syllables, the silent or overt reading or the repetition of pseudowords (i.e. pronounceable non-words without any associate meaning that can be pronounced on the basis of sublexical spelling-to-sound relationships such as "beudo"). Subjects were also required to attend to syllables or letters, to count the number of syllables a pseudoword or word encompassed or to discriminate whether two words or pseudowords rhymed or ended with the same sound. Phonological tasks usually aim at the identification of phonological aspects of language processing without accessing semantics (Graves, Grabowski, Mehta & Gupta, 2008).

While most studies focused on the role of the left pIFG in phonological processing (see above) some studies showed that phonological compared with semantic word processing also resulted in relatively strong activation in the supramarginal gyri (SMG) of the inferior parietal cortices bilaterally (Burton et al., 2003; Devlin et al., 2003; Price et al., 1997).

In a recent meta-analysis, Vigneau et al. (2006) identified left-hemispheric brain regions associated with phonological processing of language. The authors found a large variability of activation clusters across studies (Fig.4A) which was attributed to the variety of different tasks and control conditions being used in the 45 studies included. Nevertheless, the authors defined two networks dedicated to speech sound production and perception, respectively: a fronto-temporal auditory-motor network and a fronto-parietal loop for phonological working memory (Fig.4B).

The auditory-motor network for speech coordination encompasses areas involved in sensory-motor control, including an upper motor area for mouth motion control, a lower premotor area in the precentral gyrus dedicated to pharynx and tongue movement and a sensory-motor integration region in the Rolandic operculum. The clusters were extracted from studies using different tasks such as covert and overt articulation of phonemes, syllables, letters or pseudowords as well as word repetition and silent rehearsal of letters during working memory tasks.

The phonological working memory loop connects a cluster in pars triangularis of the inferior frontal gyrus with the supramarginal gyrus in the parietal cortex. These areas were activated during the repetition of words or pseudowords, the counting of syllables and the identification of syllables in presence of a low signal-to-noise ratio.

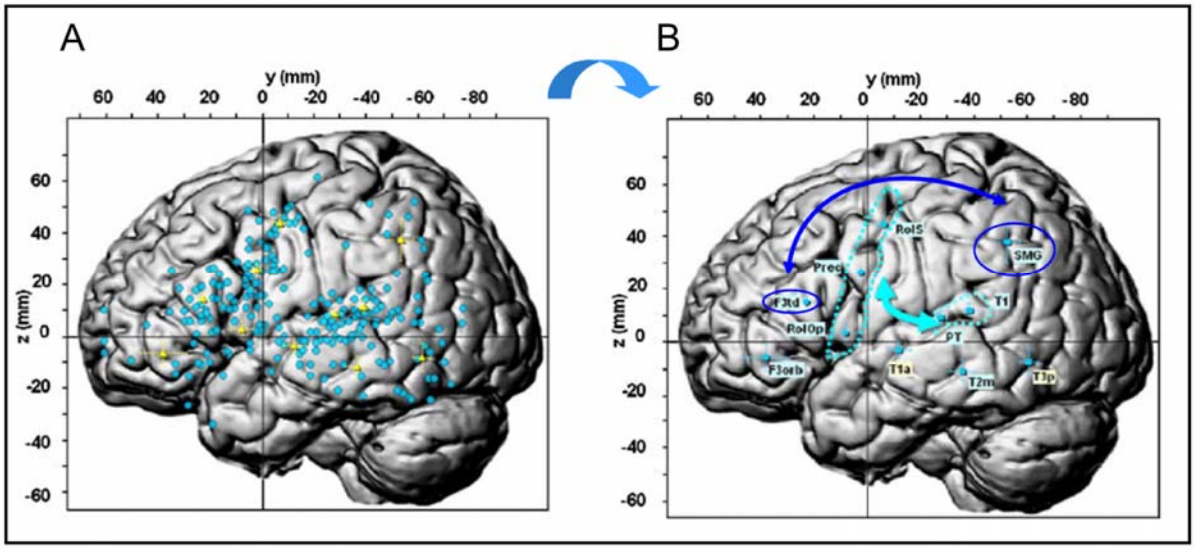

Fig.4 Networks for phonological word processing. A. Phonological clusters from different studies. Sagittal surface map of 247 activation peaks issued from 45 studies on phonological processing (turquoise); clusters are segregated by an algorithm for spatial classification and their standard error on the y and z axes (yellow). B. The auditory-motor network (in turquoise) includes motor and premotor clusters along the precentral sulcus in the frontal lobe and auditory unimodal planum temporale and superior temporal clusters in the temporal lobe. The phonological working memory loop (in blue) connects pars triangularis in the anterior inferior frontal gyrus with the supramarginal gyrus in the parietal cortex. F3td: pars triangularis; Prec: precentral gyrus; PT: planum temporale; RolOp: Rolandic operculum; RolS: Rolandic sulcus; SMG: supramarginal gyrus; T1: superior temporal gyrus (adapted from Vigneau et al., 2006).

While the role of the SMG in phonological working memory processes is well established from both lesion and functional imaging studies (e.g. Buchsbaum & D'Esposito, 2009; Devlin et al., 2003; Dewarrat et al., 2009; Martin, Wu, Freedman, Jackson & Lesch, 2003; McDermott et al., 2003; Mummery, Patterson, Hodges & Price, 1998; Price et al., 1997; Vandervliet et al., 2008; Wilde, 2009), the involvement of the anterior inferior frontal gyrus (i.e. pars triangularis) is surprising since this area has been considered to subserve semantic processing while a more posterior aspect of the left IFG was associated with phonological processing (see above).

1.3.2.3 The dual stream model of language processing

Based on the results of functional imaging studies (e.g. Buchsbaum, Hickok & Humphries, 2001; Hickok et al., 2000; Hickok, Buchsbaum, Humphries & Muftuler, 2003), Hickok & Poeppel suggested a functional-anatomic model of language processing that distinguishes neuroanatomically segregated routes for semantic and phonological word processing (Hickok & Poeppel, 2000; 2004; 2007). Their model is based on an analogy between the visual and the auditory processing streams: The separation of the visual stream into at least two substreams is well established. A ventral stream, connecting occipital with temporal areas is responsible for visual object recognition (the "what" stream), and a dorsal (occipital-parietal) stream is involved in the visual representation of spatial attributes (the "where" stream) and supports visuomotor integration functions (Milner & Goodale, 1995).

According to Hickok and Poeppel (2004; 2007), the auditory stream for language processing is similarly organized: A ventral stream, projecting from the bilateral core auditory cortices to various temporal lobe regions, is involved in auditory recognition and processes speech signals for comprehension. The ventral stream maps "sound onto meaning". A dorsal stream, projecting from the bilateral auditory cortices to temporo-parietal and frontal lobe articulatory networks, is the interface between auditory and motor processing and maps "sound onto articulatory-based representations" (Fig.5). The dorsal stream is thus engaged in phonological aspects of language processing while semantic aspects are subserved by the ventral stream.

The framework posits that early cortical stages of language perception involve auditory fields in the bilateral superior temporal gyrus (STG). This cortical processing system then diverges into the ventral and dorsal stream. The ventral stream projects ventro-laterally toward posterior middle temporal gyrus which serves as an interface between sound-based representations of speech in the superior temporal gyrus (STG again bilaterally) and widely distributed conceptual representations.

The dorsal stream projects dorso-posteriorly involving a region in the posterior Sylvian fissure at the parieto-temporal boundary (Sylvian-parietal-temporal [area Spt]), and ultimately projects to frontal regions. Area Spt is involved in translating acoustic speech signals into articulatory representations in the frontal lobe, which is essential for speech development and normal language production. Under normal circumstances, both pathways interact as described in Figure 5. While the dorsal stream is proposed to be strongly left-hemispheric dominant, the ventral stream is more bilaterally distributed.

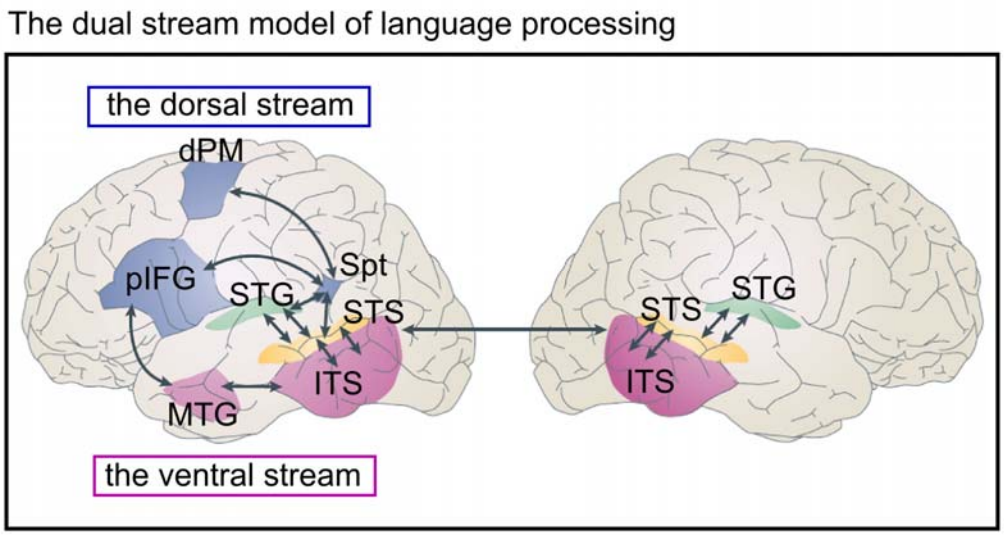

Fig.5 Anatomic locations of the dual stream model components. Green: Areas in the dorsal STG are proposed to be involved in spectro-temporal analyses. Yellow: The bilateral posterior STS is implicated in phonological-level processes. Blue: The dorsal stream. The posterior region (area Spt) is proposed to be a sensorimotor interface. The anterior locations (pIFG and dPM) correspond to portions of the articulatory network. Pink: The ventral stream. The posterior regions, posterior MTG and ITS correspond to the lexical interface, which links phonological and semantic information. The anterior locations correspond to the proposed combinatorial network. dPM: dorsal premotor cortex, ITS: inferior temporal sulcus, MTG: middle temporal gyrus, pIFG: posterior inferior frontal gyrus, Spt: Sylvian-parietal-temporal, STG: superior temporal gyrus, STS: superior temporal sulcus (adapted from Hickok and Poeppel, 2007; see text for further details).

A task that consecutively activates the dorsal stream is the verbal repetition of heard speech during which access to a motor-based representation is necessary (Hickok & Poeppel, 2004). The results of Buchsbaum et al. (2001) support the notion of a network mapping sound onto articulation: In that study, subjects listened to and covertly rehearsed blocks containing three multi-syllabic pseudowords each during fMRI. Activation was found in left area Spt, and an area at the border between left superior temporal gyrus and sulcus (STG /STS) as well as in BA 44 of the inferior frontal gyrus and in the left premotor cortex. Area Spt and BA 44 were tightly correlated in their activation time-course. These activity patterns were attributed to working memory processes during the rehearsal of the pseudowords (Hickok & Poeppel, 2004). It has been argued that area Spt located by Buchsbaum et al. (2001) and labelled by Hickok et al. (2003) may correspond both anatomically and functionally to the anterior part of the supramarginal gyrus (SMG) in the parietal cortex (Shalom & Poeppel, 2008).

The activation of the dorsal stream during phonological working memory processes connecting area Spt and the inferior frontal gyrus fits well with the phonological working memory loop identified by Vigneau et al. (2006). A meta-analysis by Jobard, Crivello and Tzourio-Mazoyer (2003) also suggests a role of both the left pIFG and SMG during phonological working memory processes. It should be noted, however, that the inferior frontal

areas proposed by Hickok and Poeppel (2000; 2004; 2007) and Jobard et al. (2003) are located posterior to those identified by Vigneau et al. (2006) and are thus more in line with studies assuming a role of the left pIFG in phonological processing (i.e. Gitelman et al., 2005; Gough et al., 2005; McDermott et al., 2003; Poldrack et al., 1999; see above).

The claim of a strongly left-hemispheric dominant dorsal stream for phonological processing is consistent with lesion studies emphasizing the importance of left rather than right frontal and temporo-parietal areas for phonological processing in right-handed patients (e.g. Dewarrat et al., 2009; Price, 1998; Thiel et al., 2006a; Vandervliet et al., 2008; Wade, Hewer, David & Enderby, 1986; Wilde, 2009). However, a left-hemispheric dominant dorsal stream contrasts with previous functional imaging studies on healthy subjects showing a bilateral activation of the supramarginal gyrus when right-handed participants made phonological in contrast to semantic word decisions (e.g. Buchsbaum & D'Esposito, 2009; Devlin et al., 2003; Martin et al., 2003; McDermott et al., 2003; Mummery et al., 1998; Price et al., 1997). A left-hemispheric dominant dorsal stream also contradicts the results of Seghier et al. (2004) suggesting that phonological processing is more bilaterally distributed while semantic processing is rather left-lateralized.

It has also been criticized that the dual stream model has little explicit to say about the frontal lobe, including Broca's area and its subdivisions (Shalom & Poeppel, 2008).

In a recent study, Saur et al. (2008) used combined functional magnetic resonance imaging and diffusion tensor imaging-based tractography to identify the most probable anatomical pathways connecting brain regions preferentially associated with either semantic or phonological processing during different language tasks. The authors demonstrated that the repetition of heard pseudowords is subserved by a dorsal stream connecting the superior temporal lobe and premotor areas in the frontal lobe (including the left pIFG) via the arcuate and superior longitudinal fascicle.

In contrast, higher-level language comprehension (i.e. listening to normal sentences compared to meaningless pseudo-sentences) is mediated by a ventral pathway connecting the middle temporal lobe and the ventrolateral prefrontal cortex via the extreme capsule (Fig.6). The results of this study support the notion of a functional-anatomic subdivision of the language system into a dorsal stream mapping sound onto articulation and a ventral stream mapping sound onto meaning.

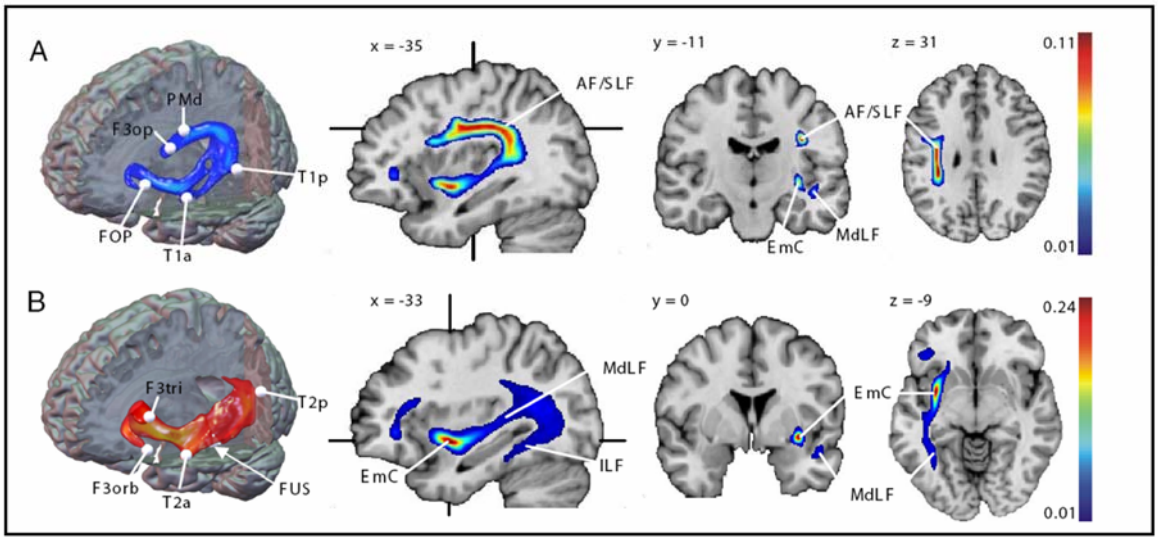

Fig.6 Dual pathway networks for language based on fibre tracking results. Composite fibre networks subserving pseudoword repetition (A) and sentence comprehension (B); averaged across the pairwise connections of 33 subjects. Three-dimensional tractography renderings visualize the spatial orientation of both networks. Crosshairs on sagittal sections indicate the orientation of the coronal and axial section. Maximum PIBI (probability index forming part of the bundle of interest) values are given at the top of the colour bar. AF/ SLF: arcuate and superior longitudinal fascicle, EmC: extreme capsule, MdLF / ILF: middle and inferior longitudinal fascicle. F3orb/tri/op: pars orbitalis, triangularis and opercularis of the LIFG; FUS: fusiform gyrus; PMd: dorsal premotor cortex, T1a/p: anterior and posterior superior temporal gyrus; T2a/p: anterior and posterior middle temporal gyrus (from Saur et al., 2008).

1.3.2.4 A functional-anatomic model of language production

Indefrey and Levelt (2004) aimed to identify the "core" areas for language production in a meta-analysis including 82 functional imaging studies on word production. Areas consistently activated during language production tasks (i.e. pseudoword or word reading, word generation and picture naming) included the bilateral (pre-) supplementary area, the left posterior inferior frontal gyrus, the left insula, the left precentral cortex and additional temporal and subcortical areas. These results were complemented by a review on the time course of activations gained from different studies using magnetoencephalography (MEG).

The authors found some areas consistently activated for word production as well as perception (e.g. passive listening to words or pseudowords), including temporal areas and the posterior inferior frontal gyrus. This finding is in line with the proposal of a shared fronto-temporal network engaged in the processing of phonological information in both language comprehension and production (Burton et al., 2000; Heim & Friederici, 2003; Heim et al., 2003).

Based on these results, the authors proposed a psycholinguistic functional-anatomic model of word production (Fig.7). According to this model, word production involves five main types

of linguistic representations: First, a lexical concept is created in the middle temporal gyrus (approximately 175 ms after stimulus presentation). The second step is the generation of a target lemma (i.e. an abstract conceptual form or representation, see Rickheit, Herrmann & Deutsch, 2003) which also takes place in the middle temporal gyrus (around 250 ms after stimulus presentation). A lexical phonological output code is then built and spelled out into segments in the posterior middle and superior temporal gyrus (around 330 ms). During lexical phonological code retrieval, rules which require morphological information are recalled from the mental lexicon (see Mohanan, 1986 for further details). The speaker accesses the phonological codes for all of the target word's morphemes. For instance, when the lemma "goat" has the syntactic diacritical feature "pl", indicating that the target is the plural form of the word, then two phonological codes will be retrieved, one for the stem and one for the plural inflection (i.e. /goUt/ and /s/, respectively). For the irregular word 'sheep', only one code will be retrieved (i.e. /Si:p/). Afterwards, a syllabified phonological output is generated in the posterior inferior frontal gyrus (around 455 ms). Finally, an articulatory score is formed in the inferior precentral and postcentral gyri (around 600ms).

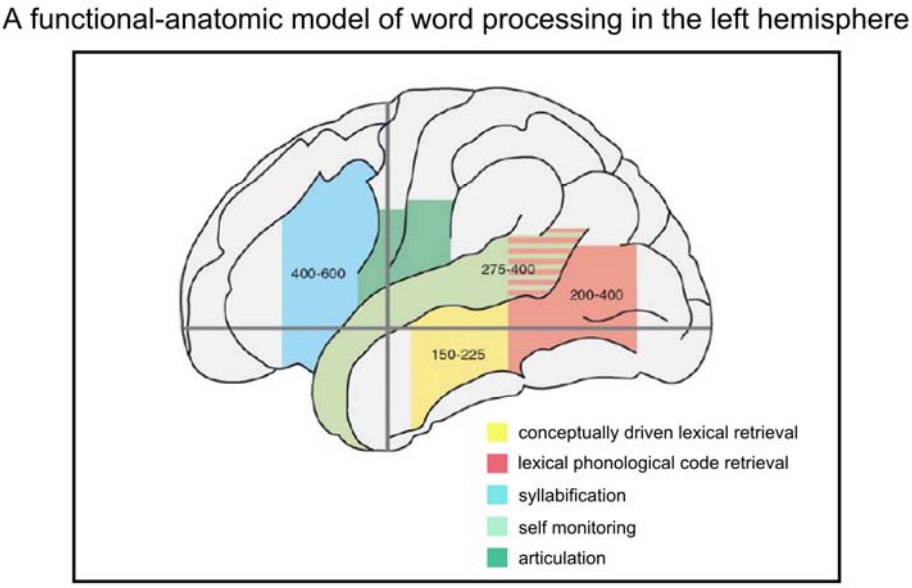

Fig.7 Brain areas involved in word production. Lexical retrieval and lemma selection are associated with activation of the middle temporal gyrus (yellow), phonological code retrieval occurs in the posterior middle and superior temporal gyrus (red), syllabification takes place in the posterior inferior frontal gyrus (blue), self monitoring in the bilateral middle and posterior superior temporal gyri (light green) and articulation in the inferior precentral and postcentral gyri (dark green). The numbers indicate the time windows (in milliseconds) during which the regions are activated (see text for details). Further regions involved in phonetic encoding and articulation include the right sensorimotor cortex, the right supplementary motor area and the left and right cerebellum (not shown) (adapted from Indefrey and Levelt, 2004).

According to Indefrey and Levelt (2004), another important process during language production is self-monitoring: Self-monitoring activates bilateral middle and posterior superior temporal gyri and involves an internal loop, taking as input the phonological word, i.e. the output of syllabification, as well as an external loop, taking as input the acoustic speech signal of the own voice. The earliest activation of these areas may be expected immediately after the first spelled-out segment is used for the production of a phonological word, approximately after 355ms. The self-monitoring mechanism prevents the system from producing erroneous outputs (Heim et al., 2003).
For a detailed review on the time course of reading as revealed by MEG, see Salmelin (2007).

In the following section, the phonological aspects of language production assumed in the model of Indefrey and Levelt (2004) are described in more detail.
In contrast to real word production, the production of a pseudoword isolates sublexical phonological aspects of word production without accessing semantic aspects (Graves et al., 2008). Accordingly, the model proposed by Indefrey and Levelt (2004) predicts that the sublexical phonological processing during pseudoword reading or repetition starts with the encoding or syllabification of a stimulus (i.e. the incremental clustering of the pseudoword's segments in syllabic patterns or the separation into syllables) in the left pIFG. Syllabification activates an abstract segmental representation, whereas in the subsequent stages of phonetic encoding and articulation motor representations are built up and the task is executed. This is supported by the results of Salmelin, Schnitzler, Schmitz and Freund (2000) who used MEG to define the spatiotemporal activation patterns in overt reading. Their results show that an early articulatory based phonological encoding of single words takes place in the left IFG. A recent study by Sahin, Pinker, Cash, Schomer and Halgren (2009) also supports the notion that phonological encoding engages the left IFG at about 450 ms after stimulus presentation. According to their results from intracranial electrophysiology, the IFG is involved in phonological, phonetic and articulatory programming.
The next step in the model is phonetic encoding or articulatory preparation (i.e. the transformation of syllables into motor action instruction or "syllable scores") which includes activation of the right supplementary motor area and the cerebellum. The final articulation of the stimulus is associated with the ventral premotor cortex as well as sensorimotor areas. The MEG results of Salmelin et al. (2000) also suggest that left and right motor and premotor areas and the supplementary motor areas are activated during the motor preparation for oral output and actual vocalization.

The proposed role of the pIFG in phonological aspects of word production is well in line with the dual stream model (Hickok & Poeppel, 2000; 2004; 2007). It also converges with Broca's idea of an inferior frontal language production area (Broca, 1861). In terms of its proposal of the temporal lobe, the model of Indefrey and Levelt (2004) again fits with the hypotheses articulated in the dual stream model. This supports the notion that perception and production data at the single-word level of analysis yield comparable functional-anatomic assignments (Burton et al., 2000; Heim & Friederici, 2003; Heim et al., 2003).
However, it has been criticized that the model does not include assumptions about the contribution of parietal regions such as the supramarginal gyrus to language production (Shalom & Poeppel, 2008).

1.4 The role of the right hemisphere in language processing

1.4.1 Cerebral dominance

A dominant role of the left hemisphere in language processing has consequently been proposed since 1836 when Dax put forward the "doctrine of cerebral dominance", a model in which the ability of language is controlled by the cerebral hemisphere contralateral to the preferred hand (cited in Penfield & Roberts, 1959). Today, there is consensus about the dominance of the left hemisphere in language processing (e.g. Lindell, 2006; Shalom & Poeppel, 2008; Thiel et al., 2006a; Winhuisen et al., 2007) and most of the functional-anatomic models of language processing focus on the role of the left hemisphere (see above).
Knecht et al. (2000a; 2000b) demonstrated that handedness is strongly correlated with hemispheric language dominance in healthy subjects. The incidence of right-hemispheric language dominance was found to increase linearly with the degree of left-handedness. The authors showed that individual handedness is a predictor for hemispheric dominance in language processing. Given that right-handers are both more common and more predictably lateralized than left-handers, most studies focus on the investigation of healthy right-handed subjects (Lindell, 2006). Yet the fact that the left hemisphere is the superior language processor does not necessarily imply that the right hemisphere is completely lacking linguistic ability.

1.4.2 Right-hemispheric language involvement in patients

Lesion studies have shown that language difficulties follow left rather than right-hemispheric lesions (e.g. Dewarrat et al., 2009; Gling, Gloning, Haub & Quatember, 1969; Hecaen, Mazars, Ramier, Goldblum & Merienne, 1971; Ozeki et al., 2008; Patterson & Hodges, 1992; Price, 1998; Sakurai et al., 1998; Vandervliet et al., 2008; Wade et al., 1986; Wilde, 2009). According to Lindell (2006), language deficits following right-hemispheric damage may be more subtle than those following left-hemispheric damage and may thus be more difficult to detect.

Functional imaging studies, however, have demonstrated language-related activation of right-hemispheric areas in patients with left-hemispheric damage (Raboyeau et al., 2008; Saur et al., 2006; Thiel et al., 2001; Winhuisen et al., 2005; 2007). These activation patterns have been reported in patients suffering from aphasia after left-hemispheric stroke (Heiss, Kessler, Thiel, Ghaemi & Karbe, 1999; Karbe et al., 1998; Ohyama et al., 1996) as well as in tumor patients (Holodny, Schulder, Ybasco & Liu, 2002; Meyer et al., 2003; Schlosser et al., 2002; Thiel et al., 2001).

It is a matter of debate whether this activation is essential for language performance or represents "maladaptive" over-activation reflecting disinhibition rather than functioning of right-hemispheric regions due to infarction of left-hemispheric areas (e.g. Martin et al., 2004; Martin et al., 2009; Naeser et al., 2005a). Some studies implicated that the (temporary) recruitment of homologue areas in the right hemisphere after left-hemispheric stroke is associated with language improvement (Saur et al., 2006; Thiel et al., 2006a; Winhuisen et al., 2005). In contrast, other studies have shown improved language recovery in aphasic patients following suppression of neuronal processing in the non-lesioned right hemisphere with transcranial stimulation techniques (Andoh & Martinot, 2008; Martin et al., 2009; Naeser et al., 2005a; Naeser et al., 2005b). The behavioural improvement after inhibition of right-hemispheric activation has been interpreted as a suppression of maladaptive over-activation which in turn may have allowed for a better modulation in the remaining left-hemispheric networks (Naeser et al., 2005a). It has also been suggested that right-hemispheric activation after left-hemispheric stroke may reflect an up-regulation of non-linguistic cognitive processing (van Oers et al., 2010).

Thiel et al. (2006a) aimed to identify factors which determine successful compensation of lost language function after brain lesions. The authors used combined positron emission

tomography (PET) and rTMS in right-handed patients with brain tumors of the left hemisphere. rTMS was applied over the left and right aIFG during a verb generation task. Patients as well as healthy control subjects showed increased reaction times during verb generation when rTMS was applied over the left aIFG, indicating that the left hemisphere still remained essential in patients. Some patients also showed increased reaction times after TMS over the right hemisphere (right TMS-positive patients). In accordance with the TMS-results, both normal subjects and right TMS-negative patients had significantly higher left IFG activation than right IFG activation during PET.

In right TMS-positive patients, no difference between left and right IFG activation was observed. The shift of language function to the right hemisphere was positively correlated with disease duration and language performance. In patients with rapidly progressive lesions, no right-sided language function was detected by TMS and language performance was linearly correlated with the lateralization of language related brain activation to the left hemisphere.

The authors concluded that the faster progressing disease in right TMS-negative patients compared to right TMS-positive ones left them less time for successful integration of right-hemispheric areas. Thus, only patients with slowly progressing brain lesions recovered right-sided language function as detected by TMS. According to Thiel et al. (2006a), their results indicate that time is an essential factor for the successful integration of the right hemisphere in the language network and for a compensation of the loss of left-hemispheric language function.

Based on the results of repeated functional MRI examinations from the acute to the chronic phase in 14 aphasic patients, Saur et al. (2006) developed a model of language recovery after stroke that postulates three stages: a strongly reduced activation of remaining left language areas in the acute phase (0-4 days after stroke) is followed by an early up-regulation of the language system with recruitment of homologue (right-hemispheric) language zones in the subacute phase (2 weeks after stroke), which correlates with language improvement. Thereafter, a normalization of activation is observed, with activation increases in left-hemispheric areas and decreases in homologue right-hemispheric regions, possibly reflecting consolidation in the language system in the chronic phase (4-12 months after stroke).

This suggests that a temporary recruitment of the intact right hemisphere improves recovery after stroke. It remains unclear, however, whether right-hemispheric activation reflects reduced trans-hemispheric inhibition due to altered left-hemispheric functioning.

If this was the case, the up-regulation in left-hemispheric areas with gradual recovery could reflect a regained inhibitory influence of the left hemisphere, resulting in a decrease of right-hemispheric activation (Saur et al., 2006).

1.4.3 Right-hemispheric language involvement in healthy subjects

Functional imaging studies have shown right-hemispheric activation in both language comprehension and production tasks in healthy subjects (e.g. Ackermann & Riecker, 2004; Buchsbaum & D'Esposito, 2009; Chee, O'Craven, Bergida, Rosen & Savoy, 1999; Devlin et al., 2003; Kemeny, Ye, Birn & Braun, 2005; Martin et al., 2003; McDermott et al., 2003; Mummery et al., 1998; Poldrack et al., 1999; Price et al., 1997; Shibahara, 2004; Tremblay, Monetta & Joanette, 2004). Some studies found that right as well as left pIFG are activated when healthy right-handed subjects perform phonological tasks (Chee et al., 1999; Devlin et al., 2003; Gitelman et al., 2005; Poldrack et al., 1999; Shibahara, 2004; Tremblay et al., 2004).

Gitelman et al. (2005) showed task specific activation patterns in the right hemisphere for phonological and semantic processing: While the right (along with the left) IFG was consistently activated during a phonological task when subjects decided whether two presented words were homophones, a semantic task (i.e. the decision, whether two words were synonyms) revealed activation of right and left temporal areas.

Other studies demonstrated that both the left and right supramarginal gyri (SMG) are activated when healthy right-handed participants make decisions about the sounds of words (i.e. their phonology) compared to decisions about their meanings (i.e. their semantics).

In a review, Bookheimer (2002) proposed that the right hemisphere is primarily involved in more complex aspects of language processing such as the interpretation of the figurative, contextual, or connotative meaning of a sentence which involves right posterior temporal regions (i.e. the right-hemispheric homologue of Wernicke’s area). However, the studies cited above along with the results of Heim et al. (2003) and Turkeltaub, Eden, Jones and Zeffiro (2002) implicate that the right hemisphere is also involved in the processing of phonological (and to a lesser degree semantic) aspects of single words. A recent study by Seghier et al. (2004) suggests task-specific differences in right-hemispheric involvement during language processing. The authors found functional activation patterns that were more left lateralized for semantic than phonological processing.

It needs to be born in mind, however, that the task-related activation of the right hemisphere revealed by functional imaging studies may be incidental to performance (i.e. redundant processing, Price & Friston, 2002) and does not prove the functional significance of right-hemispheric activation in language processing.

1.5 Summary and remaining questions

Recent studies and functional-anatomic models of language processing defined different networks for phonological and semantic aspects of word comprehension and word production. In general, phonological activation clusters were located posterior to semantic clusters and a strong interaction between parietal and (posterior) inferior frontal areas has been proposed during phonological word processing.
Although consensus is emerging on the contribution of left-hemispheric parietal and frontal areas to phonological processing, it remains unclear, which areas precisely contribute to efficient phonological processing. While most of the previous studies used functional magnetic resonance imaging to identify areas involved in specific tasks, this correlational approach does not allow testing the functional significance of task related activity.

Lesion studies have shown that phonological difficulties follow left rather than right-hemispheric lesions (e.g. Dewarrat et al., 2009; Ozeki et al., 2008; Vandervliet et al., 2008). The temporary recruitment of homologue areas in the right hemisphere after left-hemispheric stroke, however, may improve recovery (Saur et al., 2006; Thiel et al., 2006a; Winhuisen et al., 2005).
The functional significance of right-hemispheric activation during phonological processing in healthy subjects remains to be determined. Previous studies lack a systematic investigation of right-hemispheric activation in healthy subjects. Although some studies reported activation in right-hemispheric areas (Burton et al., 2003; Devlin et al., 2003; Price et al., 1997), most investigations focused on left-hemispheric contributions to phonological processing. Accordingly, studies using transcranial magnetic stimulation have tested the functional relevance of left but not right-hemispheric areas so far (e.g. Gough et al., 2005; Nixon et al., 2004; Romero, Walsh & Papagno, 2006). Consequently, functional-anatomical models of language have been developed to include left but not right-hemispheric areas for phonological processing (e.g. Hickok & Poeppel, 2000; 2004; 2007).

Another issue that has not received much attention yet is the dependence of task-related activity on the sensory modality used for stimulus presentation. While the core substrates of language processing should be modality-independent, most studies focused on the unimodal presentation of either visual or auditory stimuli. Thus, it remains unclear whether the areas involved in phonological word processing are modality-independent.

2 Methodological background and considerations

2.1 General considerations

The majority of studies have used functional magnetic resonance imaging to investigate the neural correlates of language processing. In the following sections, functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) are discussed more in detail since both methods were used in the empirical studies described in section 3.

2.2 Functional magnetic resonance imaging (fMRI)

2.2.1 BOLD fMRI

Blood oxygen level dependent (BOLD) functional magnetic resonance imaging is “probably the most widely used functional imaging technique” (Ogawa, Menon, Kim & Ugurbil, 1998). For a detailed review of the physiological substrates and technical issues, see Logothetis, Pauls, Augath, Trinath & Oeltermann (2001) or Logothetis (2008).

Studying brain functions with fMRI usually refers to the use of BOLD fMRI. This method provides a means for the non-invasive investigation of specific functions of the human brain without exposing the subject to ionizing radiation such as positron emission tomography (PET). Brain functions are measured indirectly, but with high spatial resolution via local hemodynamic changes in “functional areas”, i.e. in regions of the human brain which control important functions such as voluntary movements, language or memory (Hartwigsen, Siebner & Stippich, in press; see Appendix III). To this end, the corresponding neuro-functional systems must receive targeted stimulation, which is usually done by using specific stimulation paradigms.

BOLD fMRI takes advantage of the relationship between blood flow and neuronal activity: The stimulation leads to increased synaptic activity in the functional area with increasing energy and oxygen consumption of the activated neurons, which is not only met but overcompensated by local hemodynamic changes: regional cerebral blood volume, blood flow, and blood oxygen content are rising. In BOLD fMRI, the blood itself serves as an intrinsic contrast agent rendering the intravenous administration of paramagnetic contrast agents or radioactive substances unnecessary (Kwong et al., 1992; Ogawa, Lee, Kay & Tank,

1990). The different magnetic properties of oxygenated haemoglobin and deoxygenated haemoglobin are exploited to produce image contrast: Neuronal activity requires oxygen for energy generation. This oxygen is extracted from the blood and leads to a change from oxy- to deoxyhaemoglobin, which increases the local susceptibility and thus decreases the signal intensity in T2*-weighted images (Kwong et al., 1992; Ogawa et al., 1990; Ogawa et al., 1992). Finally, decrease in deoxygenated blood due to an inflow of new oxygenated blood (luxury perfusion) leads to a signal intensity increase in T2*-weighted images (Ernst & Hennig, 1994; Frahm, Kruger, Merboldt, & Kleinschmidt, 1996).

By statistical correlation of the measured BOLD signal time course to the hemodynamic response function, those areas of the brain can be identified which exhibit task-synchronic hemodynamic changes (Bandettini, Wong, Hinks, Tikofsky & Hyde, 1992). Even if the physiology of the underlying neurovascular coupling is not yet conclusively understood, there is very good agreement between the localization of the BOLD signal and the actual site of neuronal activation (Logothetis et al., 2001). Because of the low signal-to-noise ratio, similar trials must be carried out repeatedly during fMRI in order to obtain enough BOLD signal for statistical purposes.

The temporal resolution capability of fMRI is lower compared to electrophysiological measures such as electroencephalography (EEG), or magnetoencephalography (MEG). For paradigms in block design, the temporal resolution corresponds to the length of the blocks (typically >15 s). With event-related measurements, a temporal resolution of less than 100 ms may be achieved (Buckner et al., 1996). However, in contrast to MEG and EEG, the functional localization is more precise due to the direct relation of the obtained images to the surface anatomy, providing a spatial resolution in the millimetre range (for further details see Kim & Ogawa, 2002; Kim & Ugurbil, 2003).

2.2.2 Implications for the investigation of language production

Overt language production during fMRI can produce motion-induced signal artefacts that may confound the activation signals of interest. Artefacts may include signal voids, blurring or distortion, which can mask brain activations (Barch et al., 1999), while artefactual changes that are correlated with the stimulus can be mistaken for true brain activation or deactivation.

Thus, fMRI investigations on language production often used covert (i.e. silent) language paradigms as a substitute to overt language paradigms (e.g. Lurito, Kareken, Lowe, Chen &

Mathews, 2000; Rauschecker, Pringle & Watkins, 2008; Wildgruber, Ackermann & Grodd, 2001). A common assumption behind the use of covert speech is that it involves all of the processes and neural mechanisms of overt speech with the exception of the final motor execution stage. However, it has been demonstrated that overt and covert speech do not produce the same patterns of neural activation in the core language areas (e.g. Barch et al., 1999; Huang, Carr & Cao, 2002; Numminen & Curio, 1999; Shuster & Lemieux, 2005). For instance, left inferior frontal activation is not typically observed in silent reading (Salmelin, 2007). Further, the use of covert speech does not allow for the control of task performance.

A variety of methods have been developed to solve the problem of articulation-induced artefacts. Some of these take advantage of the fact that the BOLD response typically lags behind the speech response by several hundred milliseconds. This long-lag hemodynamic effect allows for the use of event-related designs (Buckner et al., 1996; Friston et al., 1998). The fact that the BOLD effect is delayed relative to the stimulus onset allows the researcher to disregard activity registered at the initiation of the task when movement artefacts might occur during overt speech production. Birn, Bandettini, Cox & Shaker (1999) suggested that the use of brief (less than 2 seconds) stimuli in event-related designs provides a method of identifying different temporal profiles of signal variations associated with BOLD and motion-induced signals. It has thus been argued that event-related fMRI may become the method of choice in the functional neuroimaging of language (Dogil et al., 2002). Other studies discarded the images acquired during motion to eliminate the functional data contaminated by motion (Riecker, Wildgruber, Dogil, Grodd & Ackermann, 2002; Wilson, Saygin, Sereno & Iacoboni, 2004). However, this approach is limited by the fact that the behaviour of interest must be short to ensure that the motion-induced signal changes do not overlap the hemodynamic response function (Gracco, Tremblay & Pike, 2005).

Huang, Rothwell, Edwards and Chen (2008) suggested that the combination of immobilization techniques with advanced motion correction algorithms is a reliable alternative. A different approach is the use of silent intervals in volume acquisition which has been demonstrated to produce robust activation patterns during overt language production even when block-designs were used (Eden, Joseph, Brown, Brown & Zeffiro, 1999; Gracco et al., 2005).

2.3 Transcranial magnetic stimulation (TMS)

2.3.1 A general introduction

Functional imaging studies can map activation changes during specific tasks, yet they provide no proof whether these changes are functionally relevant. TMS provides a means for the investigation of the functional relevance of such activation changes. In principle, there are two different possibilities to apply TMS to investigate cognitive processes: **Online TMS** is given during a task to perturb intrinsic neuronal activity in the stimulated area (i.e. the "virtual lesion" approach, see below). An important advantage of TMS-induced lesions relative to studies of structural lesions (e.g. acute stroke) is that there is insufficient time for functional reorganization to occur during TMS and thus, the acute "lesion" effect should not be substantially confounded by any recovery process (Walsh & Cowey, 1998; 2000). In contrast, **offline TMS** is applied before a task to induce a lasting suppression of neuronal excitability in relevant areas. This conditioning approach bears some analogies to acute stroke, because inhibitory offline TMS gives rise to an acute adaptive reorganization within the non-stimulated functional loops of the (language) networks to compensate for TMS-induced suppression of neuronal activity in those components of the network that have been perturbed with TMS (Siebner & Rothwell, 2003).

In summary, online and offline TMS represent complementary approaches: While online TMS acutely disrupts a specific language function, offline TMS impairs cortical processing beyond the time of stimulation and thus can be used to induce and examine acute reorganization within the language system.

2.3.2 The "virtual lesion" approach

The following section is based on the "special-issue" research report (see Appendix I):

Siebner, H.R., Hartwigsen, G., Kassuba, T. & Rothwell, J.C. (2009). How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. *Cortex* 45 (9): 1035-42.

In this review, some important features of TMS are summarized and their implications for investigations on brain-behaviour relations with "neurodisruptive" online TMS (i.e. TMS during a task) are discussed.

TMS provides a method of stimulating the human brain through the intact skull without producing significant discomfort (Barker, Jalinous & Freeston, 1985). The basic principles of TMS have been covered in recent reviews (e.g. Amassian & Maccabee, 2006; Bestmann, 2008; Pascual-Leone, Walsh & Rothwell, 2000; Ziemann et al., 2008). TMS uses a magnetic field to "carry" a short lasting electrical current pulse into the brain where it stimulates neurones, particularly in superficial regions of the cortex. A high intensity TMS pulse causes a synchronised high-frequency burst of discharge in a relatively large population of neurones that is terminated by a long lasting GABAergic inhibition. The combination of artificial synchronisation of activity followed by depression effectively disrupts perceptual, motor and cognitive processes in the human brain. This transient neurodisruption is often referred to as "virtual lesion" (Pascual-Leone et al., 2000). The behavioural consequences induced by the temporal perturbation of ongoing neuronal activity can be used to characterize the specific contribution of the stimulated area to a distinct cognitive function (Jahanshahi & Rothwell, 2000; Walsh & Rushworth, 1999). If the stimulated area is critically involved in the cognitive task, then performance may be impaired or slowed which is usually measured as increased error rates or reaction times. If the area is not essential, then TMS either has no effect or may even facilitate task performance. For instance, TMS can suppress visual perception of briefly presented trigrams when a single TMS pulse is applied to the occipital cortex 80-100 milliseconds after stimulus onset (Amassian et al., 1989).

Such effects are usually created by applying a single pulse or a short high-frequency train of stimuli to the cortical area of interest during an experimental task. The approach is now widely used in cognitive neuroscience to interfere with a wide range of brain functions, including perception, motor execution, or higher-level cognitive processes such as language functions (Pascual-Leone et al., 2000).

It is usually argued that if a TMS pulse affects performance, then the area stimulated must provide an essential contribution to the behaviour being studied (see above). However, there is one exception to this: the pulse could be applied to an area that is not involved in the task but which has projections to the critical site. Activation of outputs from the site of stimulation could potentially disrupt processing at the distant site, interfering with behaviour without having any involvement in the task.

Three features are important when considering the “virtual lesion” effect. First, the electrical pulse induced in the brain is very short lasting. A typical monophasic pulse current rises to a maximum and has reversed towards zero in about 200 µs (e.g. Terao & Ugawa, 2002). This leads to highly synchronous activation of neurones. Second, the stimulation is not focal. With a conventional figure-of-eight coil, the effective area of stimulation is several square centimetres. The third important feature of TMS is that the magnetic field falls off very rapidly with distance from the TMS coil. The exact relation depends on the size of the coil, but for a typical coil, the field at a distance of 4 cm may be only about 30% of that at the coil surface (Weyh & Siebner, 2007). This means that superficial areas of cortex are easy to stimulate, but those deep in a sulcus or far from the scalp surface have a much higher threshold.

Experiments in the motor cortex have measured the strength-duration relationship of the pulses that are needed to evoke electromyographic activity in contralateral muscles. This relates the duration of the induced electrical current to the amplitude needed to evoke a response of a given size. The form of the curve suggests that TMS stimulates axons, and not cells because axons are most efficiently activated by a short duration pulse whereas cells require longer pulses. Exactly which axons are stimulated is not known. However, whichever they are, it is thought that excitation occurs in the grey matter of the cortex rather than in the subcortical white matter (Edgley, Eyre, Lemon & Miller, 1997) since the former is nearer the scalp surface and has a lower electrical resistance than the underlying white matter.

It is still poorly understood which set of axons is initially activated by the electrical field induced by TMS. Factors such as the degree of axonal myelinisation, the cell type, and the presence of large bending axons are all known to have an important influence. At the present time it is safe to conclude that the electrical field preferentially excites the axons of a subset of neurones in the stimulated cortex.

The effects of TMS are not limited to the stimulated area. There are two ways in which TMS at one site can influence activity at another site. First, the stimulus might directly change activity in axonal projections to other areas. This would lead to synaptic activity in the target zone and directly change patterns of activity in that structure. Since many cognitive operations are processed by ongoing interactions within spatially separate networks, TMS at one node in the network can also lead to changes in distant zones even if they are not directly connected to the stimulated site.

Within the brain, cortico-cortical interactions via directly connecting pathways have been successfully studied by stimulating two cortical motor areas with TMS (two-site TMS as opposed to single-site TMS). For instance, a TMS pulse given to one primary motor cortex can influence the excitability of the primary motor cortex in the opposite hemisphere (Di Lazzaro et al., 1999; Ferbert et al., 1992). The effect may be facilitatory or inhibitory depending on the intensity of stimulation.
Cortico-cortical synapses are thought to be excitatory and glutamatergic, so that inhibitory effects are presumably mediated via an interneuron in the receiving area. The conclusion is that behavioural effects of a TMS pulse may not only be due to activation at the site of stimulation but also to direct inputs to remote areas of cortex. As at the site of stimulation, the mechanism of these remote effects depends on stimulus intensity.

The combination of a TMS-induced artificial neural synchronisation plus a long lasting inhibitory postsynaptic potential is the main evidence for the ‘‘virtual lesion’’ effect. Together they prevent the continuation of any ongoing neural activity that might have been of behavioural relevance. The size of the neural population that is affected will depend on the stimulus intensity and the intrinsic excitability of the neurones (see Siebner, Hartwigsen, Kassuba & Rothwell, 2009; Appendix I for more details).

2.4 Combining fMRI with TMS

This section is based on the following book chapter (see Appendix II):

Hartwigsen, G., Kassuba, T. & Siebner, H.R. (2009). Combining transcranial magnetic stimulation with (f)MRI. In S. Ulmer & O. Jansen (Eds.), *fMRI - Basics and Clinical Applications* (pp.155-167). Heidelberg: Springer.

2.4.1 Why combine fMRI with TMS?

Combined fMRI and TMS gives access to non-invasive measuring of stimulation effects on the brain with a high spatial (fMRI: spatial resolution in the millimetre range) and temporal (single-pulse TMS: temporal resolution in the order of milliseconds) resolution.
Regarding fMRI, a critical question is whether the BOLD signal really captures the TMS induced changes in regional neuronal activity. Allen, Pasley, Duong and Freeman (2007)

combined optical imaging with electrophysiological recordings of neuronal activity in the visual cortex of cats to show that TMS-induced changes in neural activity are readily reflected by cerebral hemodynamics. Further, the quantitative coupling between TMS-evoked neural activity and cerebral hemodynamics was present over a range of stimulation parameters. These results underline the usefulness of combined fMRI-TMS approaches.

2.4.2 Different combinations of fMRI and TMS

An interesting approach is to give TMS while subjects are performing a particular task during fMRI (i.e. concurrent fMRI and TMS, Fig.8A). Several concurrent fMRI-TMS studies demonstrated that TMS can evoke changes in neural activity in remote connected cortical and subcortical areas (Bestmann, Baudewig, Siebner, Rothwell & Frahm, 2005; Bohning et al., 1999; Ruff et al., 2008). Distant changes in the BOLD signal can even occur in the absence of consistent signal changes in the stimulated area (Bestmann, Baudewig, Siebner, Rothwell & Frahm, 2004). This suggests that transsynaptic spread of excitation from the stimulated to connected brain areas has a major contribution to neuronal stimulation that is induced by TMS in the human brain.

For example, Bestmann et al. (2005) applied short trains of rTMS over the left premotor cortex during fMRI. TMS produced an increase in the BOLD signal in the stimulated cortex and connected areas. Since the premotor TMS train did not produce overt muscle movements, it was concluded, that these BOLD signal changes resulted from cortical stimulation rather than from somatosensory feedback activation.

Concurrent fMRI-TMS also opens up the possibility to examine how TMS interacts with intrinsic task-related activation and how these TMS-induced changes in task-related activity relate to changes in behaviour.

TMS and fMRI can also be separated in space and time. In this case, TMS is given outside the MRI suite before or after fMRI.

When TMS precedes fMRI, a conditioning session of repetitive TMS (rTMS) is applied before fMRI to induce an acute reorganization in functional brain networks which can be subsequently mapped with fMRI (Fig.8B). This condition-and-map approach can be used to study the changeability of functional brain networks. The conditioning effects of rTMS on regional neuronal activity can be detected by comparing task-related activation before and

after TMS. For example, O'Shea, Johansen-Berg, Trief, Gobel and Rushworth (2007) used fMRI in healthy right-handed subjects to probe short-term reorganization in right dorsal premotor cortex after rTMS-induced disruption of neuronal processing in the dominant left dorsal premotor cortex specialized for action selection. Low-frequency rTMS specifically increased activity in right premotor cortex and connected medial premotor areas during action selection without affecting behaviour. Based on additional experiments it was claimed that this increase in activity reflects compensatory short-term reorganization that helps to preserve behaviour after the "neuronal challenge" induced by rTMS.

Alternatively, fMRI can be performed first to localize brain areas that are involved in a given task. Based on the spatial information offered by fMRI, focal TMS can then be applied in a consecutive session outside the MR scanner to precisely target a specific area during the task (Fig.8C).

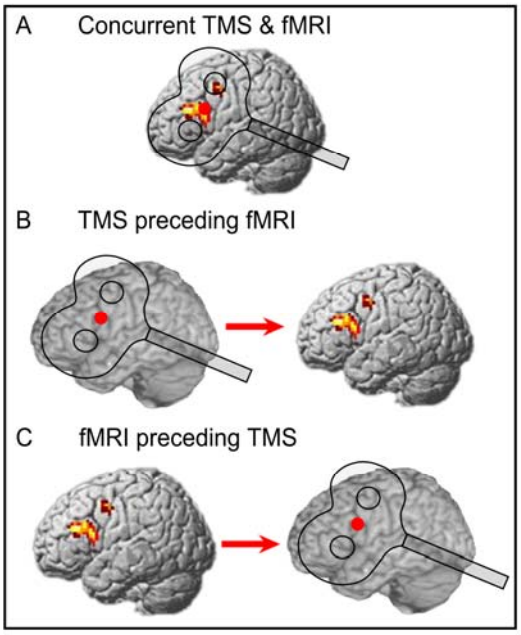

Fig.8 Combined fMRI and TMS. Relative timing of fMRI and TMS determines the application of combined fMRI-TMS. **A** fMRI and TMS can be performed interleaved, (i.e. concurrently) to investigate immediate effects of TMS on brain functions. Alternatively, fMRI and TMS can be separated in time. **B** TMS preceding fMRI can be used to probe the lasting effects of TMS conditioning on brain functions. **C** fMRI preceding TMS is usually used to identify appropriate sites for focal TMS (adapted from Hartwigsen, Kassuba and Siebner, 2009).

For instance, functional MRI can be used to functionally localize the optimal site for TMS. Participants usally first perform a specific task during fMRI. The individual peak activation can then be identified and superimposed on the structural image of the subject's brain. Finally, frameless stereotaxy allows for the placement of the TMS coil over the fMRI defined functional area. If TMS impairs task performance it can be inferred that the stimulated cortex makes a critical contribution to the task (e.g. Amassian et al., 1989; Ashbridge, Walsh &

Cowey, 1997). This fMRI-guided TMS approach is more precise than relying on structural anatomical landmarks because it takes into account the inter-individual variability of the functional representation of brain areas (Sparing, Buelte, Meister, Paus & Fink, 2008).
An alternative strategy uses the results of a previous fMRI study that has used the same or a similar experimental task. The stereotactic coordinates of task-related peak activation in the area of interest define the site of stimulation. The individual site of stimulation is determined by using the inverse of the normalisation transformation and transforming the coordinates from standard to "individual" space. This strategy was used in study 2 and 3 of the empirical studies in section 3. For a detailed review of combined TMS and fMRI see Hartwigsen et al. (2009); Appendix II.

2.5 Preoperative fMRI and TMS of language function

In the clinical setting, both fMRI and TMS are being increasingly used to map changes due to reorganisation after stroke or slowly progressive brain lesions in patients (e.g. Heiss et al., 2003; Martin et al., 2009; Saur et al., 2006; Thiel et al., 2006a; Winhuisen et al., 2005; see 1.4.2). TMS has a potential for diagnostic purposes (Kobayashi & Pascual-Leone, 2003) or as a therapeutic tool for neuropsychiatric disorders such as depression (George et al., 2003; Lisanby, Kinnunen & Crupain, 2002).
fMRI and TMS can also be used for the localization of critical cortical areas before brain surgery in preoperative settings. Since both techniques offer a great potential to improve the accuracy of preoperative planning and facilitate decision-making regarding the extent and exact location of surgical resections, the preoperative use of fMRI and TMS in the language system is described more detailed. The next section is based on the following review article (see Appendix III):

Hartwigsen, G., Siebner, H.R. & Stippich, C. (in press). Preoperative functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS). ***Current Medical Imaging Reviews.***

This review discusses the use of fMRI and TMS in presurgical settings. Preoperative fMRI of motor and language function represents the best established and best validated clinical application of BOLD fMRI (Desmond et al., 1995; Jack et al., 1994). For instance,

preoperative fMRI can be used to investigate tumor related aphasia. In this context, it is necessary to exclude that the tumor has affected structures that belong to the "classic" model of language, i.e. Broca's area of the left inferior frontal gyrus, Wernicke's area of the left superior temporal gyrus or the arcuate fascicle connecting both regions (see 1.3.1). Surgical damage to those structures will result in severe and persisting language deficits. Consequently, preoperative fMRI of language function focuses on robust and reproducible localization of Broca's and Wernicke's area and on reliable language lateralization. To this end, a set of various paradigms is usually applied covering different linguistic aspects (Stippich et al., 2003). Comparable localization should be available from different paradigms to achieve reproducibility as an important prerequisite for the diagnostic use of preoperative language fMRI (Rutten, Ramsey, van Rijen, Noordmans & van Veelen, 2002a; Rutten, Ramsey, van Rijen & van Veelen, 2002b). fMRI-based language lateralization is highly variable between paradigms as well as measurements and patients. Despite these limitations, fMRI is clinically feasible to determine language lateralization, if the results of multiple paradigms point towards the same direction (Hirsch et al., 2000; Ramsey, Sommer, Rutten & Kahn, 2001; Rutten et al., 2002a; Stippich et al., 2007).

Preoperative language fMRI also allows to reduce the number of invasive diagnostic measures prior to treatment and to better stratify patients for intraoperative cortical mapping and awake craniotomies (Binder et al., 1996; Lehericy et al., 2000; Rausch et al., 1993; Roux et al., 2003).

Numerous studies demonstrated the reliable identification of hemispheric language dominance with fMRI (Binder et al., 1996; Frost et al., 1999; Szaflarski et al., 2002). However, the areas identified in different studies of language processing have varied markedly, likely due to the use of different paradigms and post-processing techniques.

In a recent review, Baxendale (2002) compared the results of fMRI and Wada testing (Wada & Rasmussen, 1960) obtained from 70 patients having undergone both fMRI and Wada testing as reference procedure to determine language dominance. With the exception of one study (Worthington et al., 1997), which showed a comparatively low concordance of only 75%, all other studies report impressive concordance rates at or near 100% between the two techniques despite the use of different language tasks and Wada test protocols (Benbadis et al., 1998; Binder et al., 1996; Yetkin et al., 1998).

In addition to information on lateralization, fMRI has the potential to provide detailed maps of the intrahemispheric localization of critical language areas as revealed by comparison of

fMRI activation and intraoperative electrocortical stimulation (IES). For instance, Rutten et al. (2002a) compared the results of fMRI quantitatively with IES mapping in thirteen patients. In eight of these patients, critical language areas were detected by IES, and in seven out of eight patients sensitivity of fMRI was 100% (i.e. fMRI correctly detected all critical language areas with high spatial accuracy). This indicates that such areas could be safely resected without the need for IES. On the other hand, on average only 51% of fMRI activations were confirmed by IES, resulting in a low specificity of fMRI. This study illustrates some of the current problems of basing clinical decisions on fMRI activation maps. Different language-related paradigms activate a different set of brain regions and a combination of various tasks is necessary to achieve high sensitivity in identifying critical areas (Ramsey et al., 2001).

Several studies demonstrated that TMS provides a means for preoperative planning and decision making in epileptic surgery candidates (Kamida et al., 2003; Vitikainen et al., 2009) or tumor patients (Kaminogo et al., 1999; Krings et al., 1997; Krings et al., 2001).
However, few studies used TMS for preoperative mapping of higher cognitive functions. Pascual-Leone, Gates and Dhuna (1991) were the first who applied TMS in a preoperative setting to induce speech-arrest in six presurgical epilepsy patients. The authors tested whether TMS could be used as a non-invasive alternative to the Wada test. Short trains of repetitive TMS (rTMS) at different rates were applied over several scalp positions around the perisylvian cortex in both hemispheres. rTMS over the left but not right inferior frontal cortex (i.e. Broca's area) produced reproducible speech arrest 4-6 s after stimulation when subjects counted aloud. Wada test revealed left-hemispheric language dominance in these patients, suggesting that the rTMS induced speech arrest offered a non-invasive alternative for the determination of language dominance. Other studies, however, failed to replicate these promising results: Jennum, Friberg, Fuglsang-Frederiksen and Dam (1994) reported that rTMS induced complete speech arrest in only 14 of 21 preoperative patients. Michelucci et al. (1994) also called into question the reliability of rTMS for the determination of language dominance. In their study, rTMS only induced speech arrest in 7 of 14 epilepsy patients.
A systematic investigation of stimulation intensity and rate in healthy subjects by Epstein et al. (1996) may explain the inter-study variability: Although higher stimulation rates induced stronger effects of speech arrest, lower rates of 4-8 Hz were more reliable. Since higher frequencies produced prominent facial and laryngeal muscle contractions and discomfort, speech arrest was more difficult to determine. In another study with healthy subjects, Epstein et al. (1999) demonstrated that low-frequency 4 Hz rTMS also interfered with reading and

spontaneous speech. When comparing the reliability of 4 Hz rTMS with the Wada test in preoperative epilepsy patients, rTMS indicated left-hemispheric language dominance in 12 of 16 patients while the Wada test showed left dominance in all patients. Further, results from Wada test were a better predictor of postoperative language impairment.
These results call into question the reliability of rTMS for the preoperative determination of language dominance. However, when comparing Wada test and TMS, one should bear in mind that the Wada test affects brain functions over a large region in one hemisphere for several minutes while TMS disruption is far more focal and transient. Studies in healthy subjects have suggested that different sites within Broca's area can be targeted with rTMS to induce speech arrest and that more anterior sites may correspond more closely to the results of Wada testing (Aziz-Zadeh, Iacoboni, Zaidel, Wilson & Mazziotta, 2004; Stewart, Walsh, Frith & Rothwell, 2001).

In conclusion, fMRI is feasible for clinical routine neuroimaging and provides important diagnostic information noninvasively that is otherwise unavailable. Yet the number of studies on presurgical language fMRI is still limited, and the results are heterogeneous. fMRI has at least the potential to help reducing the number of invasive diagnostic measures needed.
The reliability and accuracy of preoperative TMS, on the other hand, remains to be determined. Given the complementary information that is provided by the various brain mapping techniques, the integration of different non-invasive imaging methods such as fMRI and TMS or EEG / MEG and TMS will be most useful in the context of preoperative planning.

3 Summary of the empirical studies

3.1 A general introduction to the empirical studies

Based on the partly contradictory results of previous studies, the overall aim of this thesis was **to investigate the neural substrates of phonological aspects of language comprehension and production in the healthy human brain. Of interest was particularly the contribution of right-hemispheric areas to these processes.** More specifically, this thesis addresses the following questions:

1. Which areas contribute efficiently to phonological in contrast to semantic aspects of single word comprehension?
2. Is the contribution of the right hemisphere necessary during phonological single word processing?
3. Does the contribution of these areas depend on the sensory modality used for stimulus presentation (i.e. auditory vs. visual)?
4. Which areas contribute efficiently to phonological aspects of single word production?
5. Is the contribution of these areas dependent on the modality used for stimulus presentation?

To answer these questions, four different studies were designed: Study 1 aimed to delineate brain regions involved in phonological compared to semantic word judgements on visually as well as auditorily presented words with fMRI. Study 2 tested the functional significance of these results with TMS. The experimental design allowed us to compare the contribution of both the left and right hemisphere to phonological word judgements in healthy subjects. Study 3 was guided by the results reported in the literature and used TMS to investigate the functional contribution of right- as well as left-hemispheric inferior frontal regions to phonological word judgements.

Finally, study 4 focused on language production. This study was designed to delineate brain regions involved in phonological aspects of word production by contrasting the overt repetition of pseudowords with real words during fMRI.

The combined use of fMRI and TMS in these studies allowed for the investigation of brain functions with high spatial and temporal resolution.

In the following sections, the main results of these studies are briefly summarized. For more details, please see Appendix IV-VII.

3.2 Study 1. Modality-independent semantic, phonological and perceptual word processing in the human brain

Although a large number of functional imaging studies can be found in the literature designed to identify the neural substrates of word processing and its linguistic subcomponents in the healthy brain, most of the previous studies focused on unilateral processing of either auditory or visual word stimuli.

These studies have demonstrated that phonological and semantic aspects of word comprehension engage distinct networks in the brain, with semantic aspects resulting in more anterior and more left lateralized activation compared to phonological judgements (for meta-analyses, see Costafreda et al., 2006; Vigneau et al., 2006).

Direct comparisons of phonological and semantic word judgement tasks resulted in relatively stronger activation of the supramarginal gyri bilaterally (Burton et al., 2003; Devlin et al., 2003; Price et al., 1997) and the left posterior inferior frontal gyrus (Burton et al., 2003; Devlin et al., 2003; McDermott et al., 2003).

In contrast, semantic compared to phonological word processing revealed increased activation in the anterior part of the inferior frontal gyrus (e.g. Burton et al., 2003; Gitelman et al., 2005; McDermott et al., 2003; Seghier et al., 2004). Most of the studies cited above presented stimuli only visually (e.g. Devlin et al., 2003; Gitelman et al., 2005; McDermott et al., 2003; Price et al., 1997; Seghier et al., 2004). Other studies have examined either phonological (e.g. Burton et al., 2003; Cohen, Jobert, Le Bihan & Dehaene, 2004) or semantic word processing (e.g. Chee et al., 1999; Marinkovic et al., 2003) in both the auditory and the visual modalities, but none of these studies directly compared phonological and semantic processing within the same subjects. Therefore, it remains to be determined which regions in the brain specifically contribute to phonological or semantic word processing in a modality-independent fashion.

This fMRI study was designed to delineate areas in the human language system subserving modality-independent processing of word phonology and word semantics. During fMRI, participants had to make phonological and semantic decisions on the same set of heard or written words.

We expected to find activation in the left posterior inferior frontal gyrus (pIFG) and bilateral supramarginal gyri (SMG) for phonological compared to semantic processing independent of the sensory modality used for stimulus presentation.

In contrast, modality-independent semantic word decisions compared to phonological word decisions should activate anterior regions, especially the left anterior inferior frontal gyrus (aIFG).
In addition to the phonological and semantic tasks, we included a perceptual control task to capture neuronal activity patterns involved in the processing of perceptual, non-linguistic features that are inherent in auditorily and visually presented word stimuli. The influence of such stimulus-inherent, non-linguistic perceptual stimulus characteristics on the resulting activation pattern might be particularly relevant when using fMRI to draw conclusions about potential reorganisation processes in the language system after left-hemispheric brain damage.

This study used a two (modality: spoken vs. written words) by three (task: phonological, semantic and nonlinguistic) event-related within-subject factorial design. Participants performed three tasks in both the auditory and the visual modality on the same set of concrete German nouns. In the phonological task, subjects categorized the words as having two or three syllables via button press. The semantic task consisted of deciding whether a word represented a natural or man-made item. Two perceptual decisions were included as nonlinguistic tasks. In the perceptual auditory task, subjects decided whether or not there had been a decrease in vocal pitch towards the end of the word. In the perceptual visual control task, subjects decided whether or not font size had decreased towards the end of the word.

Analyses of the behavioural data revealed increased error rates for the perceptual relative to both other tasks. A two-way repeated measures ANOVA on reaction times showed that subjects responded significantly faster for the perceptual visual task compared to both visual linguistic tasks (i.e. significant task by modality interaction). A main effect of modality indicated overall shorter reaction times for visual than auditory presentation.

As expected, we found distinct activation patterns for the functional imaging data of phonological compared to semantic word processing and vice versa.
Phonological compared to semantic decisions resulted in strong activation increases in the bilateral SMG for both auditory and visual word stimuli. In contrast, semantic decisions showed stronger activation of pars triangularis in the aIFG as compared to phonological decisions independent of the modality of stimulus presentation. Finally, non-linguistic perceptual decisions compared to both linguistic tasks revealed a maximal change of activation in pars opercularis of the right pIFG.

Our findings are consistent with the proposal of an anterior-posterior gradient for semantic and phonological processes, respectively. Modality-independent semantic computations preferentially engaged the left aIFG, while phonological computations, independent of modality, were preferentially processed bilaterally in posterior areas, specifically the SMG.

Within the same group of subjects, we showed for the first time the bilateral activation of the SMG during phonological decisions compared to semantic decisions. This finding confirms and extends previous results of a supramarginal involvement in phonological processes based on visual stimuli (Devlin et al., 2003; McDermott et al., 2003; Price et al., 1997). We also found a task-specific activation of the SMG for phonological decisions on both visually and auditorily presented words. The observation that the functional involvement of the SMG in phonological judgements extends beyond the constraints of a given modality leads us to propose that the SMG forms a modality-independent core area for phonological processing.

A bilateral parietal involvement in phonological processing of auditory input has been suggested in previous neuroimaging studies using an auditory rhyme identification task (Burton et al., 2003) or similarity judgements on auditorily presented nonwords (Strand, Forssberg, Klingberg & Norrelgen, 2008). The modality-independent phonological activation of the SMG strongly suggests that phonological processing preferentially engages dorsal stream components within the human language system as recently proposed by Hickok and Poeppel (2000; 2004; 2007), and that this engagement applies to auditory as well as visual stimuli.

Instead of the predicted activation in pIFG for phonological processing, we found a small cluster of activation in the left precentral gyrus bordering the ventral premotor cortex. One potential explanation for this finding is that semantic as well as phonological decisions activated the pIFG due to automatic processing of task-irrelevant information (Gough et al., 2005). For example, even if a task requires only phonological information (and thus engages the pIFG), skilled readers may automatically access semantic information as well (engaging the aIFG), although it is not required to perform the task (MacLeod, 1991; Price, Wise & Frackowiak, 1996; Van Orden, Johnston & Hale, 1988). Thus, the pIFG may have been activated for both the phonological and the semantic task.

However, our finding of left precentral activation is in accordance with prior studies suggesting that left precentral (i.e., BA 6) and parietal (i.e. BA 40) activation reflects unique preferential engagement for phonological compared to semantic processing (Gold et al. 2005). It is also in good agreement with prior reports of left pIFG activation extending into the left

precentral gyrus (Devlin et al. 2003; McDermott et al. 2003). Left precentral activation during phonological processing as required by syllable decision has been linked to subvocal articulation (Price et al. 1997). In the present study, such strategies may have contributed to phonological processing both in the auditory as well as in the visual modality.

Our results further demonstrate that the anterior aspect of the left IFG has a modality-independent capability for semantic processing which is strongly left-lateralized. This finding substantiates the central role of the left aIFG as core region for semantic processing. In good agreement with the present results, the left aIFG was activated during semantic processing of both words and pictures in a previous fMRI study (Mechelli, Josephs, Lambon Ralph, McClelland & Price, 2007). The fMRI results support the notion that the left aIFG may subserve the modality-independent convergence of semantic information that is fed into the aIFG through separate visual and auditory word processing pathways via the ventral language processing stream (see Hickok & Poeppel, 2000; 2004; 2007).
Finally, our findings show distinct and modality-independent involvement of right posterior inferior frontal areas in the processing of non-linguistic perceptual features of auditory (i.e. changes in pitch) and visual (i.e. changes in font size) word stimuli. This result is consistent with previous reports of the role of right inferior frontal areas in vocal pitch processing. Zatorre, Evans, Meyer and Gjedde (1992) found that right-hemispheric mechanisms appear to be crucial in attending to vocal pitch, and suggested that the right prefrontal cortex may be part of a distributed network involved in maintenance of pitch information in auditory working memory. This interpretation fits well with the demands of our experimental task. Interestingly, however, the present findings suggest a right frontal sensitivity to stimulus aspects beyond the auditory modality, for example changes in the visual surface structure of written stimuli. Our findings highlight the need to critically examine specific perceptual characteristics of verbal stimuli when, for example, interpreting activation in the Broca homologue as being purely linguistic.

To summarize, our findings suggest that phonological, semantic and nonlinguistic word processing rely partly on discrete circuits, each of which may depend on separate neural subsystems. A better understanding of the functional anatomy supporting these linguistic components will greatly assist in planning targeted neuromodulatory intervention, in order to identify the function of critical convergence zones for phonological and semantic processing in the language network.

3.3 Study 2. Efficient phonological decisions require both the left and right supramarginal gyri. A dual-site transcranial magnetic stimulation study

In our first study, we showed bilateral activation of SMG during phonological in contrast to semantic aspects of single word processing. This study was designed to test the functional significance of these activation patterns.

In agreement with our functional imaging results, previous neuroimaging studies have found that both the left and right SMG are activated when right-handed participants make phonological compared to semantic decisions on visually or auditorily presented words (e.g. Buchsbaum and D'Esposito, 2009; Devlin et al., 2003; Martin et al., 2003; McDermott et al., 2003; Mummery et al., 1998; Price et al., 1997). This contrasts with the results of several lesion studies demonstrating that phonological difficulties follow left rather than right temporo-parietal lesions (e.g. Dewarrat et al., 2009; Ozeki et al., 2008; Price, 1998; Sakurai et al., 1998; Vandervliet et al., 2008; Wilde, 2009). Thus, the functional significance of right SMG activation remains unclear. The apparent discrepancy between functional imaging and lesion studies could have arisen for several reasons.

One possibility is that right SMG activation during phonological decisions is redundant but might contribute to some extent when the left SMG is damaged. The alternative possibility is that both the left and the right SMG contribute to efficient phonological processing in healthy right-handed individuals but the consequences of right SMG damage are more subtle and therefore not typically detected in a neuropsychological investigation (e.g. Lindell, 2006).

In this study, we tested these two hypotheses using online TMS (i.e. TMS during a specific task). TMS was applied over either the left SMG, the right SMG or both the left and right SMG simultaneously during modality-independent (i.e. auditory and visual) phonological word processing.

We hypothesized that if right supramarginal activation during phonological decisions is redundant, then reaction times or error rates would only increase when online TMS was applied over the left SMG but not the right SMG. In contrast, if the right SMG also contributes to phonological decisions, then task specific reaction times or error rates should also increase with TMS over the right SMG. By comparing unilateral to bilateral TMS, we were able to investigate whether the left and right SMG can compensate for one another. If both the left and the right SMG are equally necessary for efficient phonological decisions, then the effect of TMS should be the same irrespective of whether it is applied unilaterally or

bilaterally. In contrast, if phonological decisions are possible with either the left or the right SMG, then the effect of TMS over both the left and right SMG should be greater than the effect of TMS over either the left or right SMG alone (see Price & Friston, 2002).

The experiment initially had a 3x3x2x2 factorial design with three different tasks (phonological, semantic and perceptual) and three TMS sites (left, right, and bilateral stimulation over the SMG) in two modalities (auditory and visual) for two groups (real TMS group vs. sham TMS group). However, the perceptual task was excluded from further analyses since preliminary investigations in the sham group indicated that this task was not comparable to the linguistic ones with respect to reaction times and error rates.
Subjects were randomly assigned to the real TMS group or the sham TMS group. An identical set of two- and three- syllable German nouns were presented in each of the three tasks in both the auditory and visual modalities. This study used the same tasks and stimuli as our fMRI study (see above for details).

The placement of the TMS coils over the SMG was guided by frameless stereotaxy. Stereotactic coordinates for the left and right SMG were obtained from group activation data of our previous fMRI study (see study 1). The experiment consisted of an auditory and a visual run for each subject. During each run the three blocked tasks were presented. Each task started with a verbal or written instruction of the task and consisted of 120 trials for each condition, with a trial-duration of three seconds. Stimulation intensity was set to 90% of individual resting motor threshold of the left primary motor hand area.
During each experimental trial, a four-pulse train of biphasic pulses was applied at a rate of 10 Hz over the left, right or bilateral SMG 100 ms after word onset. Trials with left, right and bilateral TMS (40 each) were pseudorandomly intermingled. In the sham group, ineffective TMS was applied (control condition).

The first analysis tested whether real relative to sham TMS differentially influenced reaction times (RT) for the three stimulation sites with a three-way repeated-measures ANOVA. We used the difference in RT between the phonological and semantic task as dependent measure.
The real TMS group showed longer RT relative to the sham TMS group when making phonological judgements (main effect of group). The relative delay of phonological decisions in the real TMS group was present with unilateral real TMS of the left or right SMG as well as bilateral real TMS of the left and right SMG. Real TMS caused a relative delay of

phonological judgements on visual and auditory stimuli to a similar degree. Accordingly, the task-specific increase in RT during phonological decisions did not interact with either stimulation site or stimulus modality. A main effect of modality indicated that the overall difference in RT between phonological and semantic decisions was greater for auditorily than visually presented words across both groups.

A four-way repeated measures ANOVA of mean reaction times including the additional factor task (phonological vs. semantic) confirmed that real TMS selectively delayed phonological processing. Real TMS compared to sham TMS significantly increased RT for the phonological but not the semantic task independent of the stimulated hemisphere. This effect was present for both modalities but stronger for auditorily than visually presented words. Reaction times were again significantly longer for auditory than visual word stimuli across both groups and all conditions (main effect of modality). Overall, real TMS produced changes in error rates that paralleled the changes in reaction times.

A second experiment was designed to assess the intensity-dependence of the behavioural "lesion" effect induced by unilateral real TMS over the SMG on phonological judgements. Five subjects from the real TMS group received real TMS over the left or right SMG at four different stimulation intensities (55, 60, 70 and 90% of individual RMT). Subjects performed the phonological task again while receiving TMS over the left or right SMG in two sessions. Both sessions consisted of four blocks of different TMS intensities including 30 trials of the phonological task each. Repeated measures ANOVA revealed a main effect of intensity, indicating that the highest intensity (90% of RMT) increased mean RT of phonological judgements compared to all other intensities. This intensity effect was comparable for left and right SMG TMS. Overall, mean RT were longer for auditorily than visually presented words. Error rates were not significantly different between the different conditions.

The results of this study provide strong evidence that both the left and right SMG are required for efficient phonological processing of auditorily and visually presented words in healthy right-handed subjects. Our findings confirm and extend previous investigations (e.g. Romero et al., 2006) by showing that the right SMG contributes to phonological processing; and that both SMG are important for phonological decisions on auditorily as well as visually presented words.

In previous studies, TMS usually affected either reaction times or error rates (Devlin et al., 2003; Gough et al., 2005; Nixon et al., 2004). In our experiments, TMS increased both, providing evidence for a strong "virtual lesion" effect independent of the stimulation site. The concurrent increase in both measures also excludes a non-specific speed-accuracy trade-off.

Real TMS over the left, right or both SMG had a specific effect on phonological judgements without affecting semantic judgements. The stronger RT-increase for the phonological compared to the semantic task in the real TMS group indicates that both SMG contribute to phonological word processing. The disruptive effect of real TMS was present for both stimulus modalities, confirming a modality-independent role of the SMG in phonological processing. Nevertheless, the lesion effect of real TMS was stronger for auditorily than visually presented words. It is possible that auditory phonological encoding was more difficult than visual encoding and could therefore be more easily disrupted by TMS. However, the longer RT for auditory compared to visual stimuli in both groups and tasks most likely resulted from the fact that responses were measured from word onset (see Cohen et al., 2004).

We found that the effect of TMS over the right SMG was as great as that to the left SMG or both SMG. This lesion pattern suggests that the right and left SMG are two crucial nodes of the same functional system and thus, "lesioning" one node is already sufficient to disrupt the integrative function of the system. This hypothesis is supported by our second experiment (TMS with different intensities over the left and right SMG) showing that the sensitivity of the left and right SMG to the disruptive effect of TMS was identical.

In patient studies, damage to the right hemisphere is not typically associated with deficits in phonological processing (e.g. Wilde, 2009), however, there is a lack of studies directly comparing phonological deficits after left versus right supramarginal lesions.

The discrepancy between our study and previous patient data may be due to differences in the time scale of functional reorganization. In our study, TMS was applied online during task performance, leaving the language system no time to develop adaptive plasticity. This may be different in patients with chronic structural lesions where massive reshaping of the language network occurs during recovery (Saur et al., 2006). Alternatively, the phonological tests used in previous studies might have lacked sensitivity to detect subtle phonological deficits in patients with right-hemispheric parietal stroke (e.g. Lindell, 2006).

An alternative explanation of our results is that unilateral TMS over the right SMG might have produced its detrimental effect on phonological processing not by disrupting neuronal

processing in the stimulated SMG but by activating transcallosal inputs from the right to the left SMG (Siebner et al., 2009). These transcallosal inputs might have activated inhibitory circuits or added “noisy” activity in the left SMG and thereby interfered with phonological processing in the left SMG. This interpretation would be in line with previous studies demonstrating significant acute remote effects of TMS in contralateral homotopic areas (Bestmann et al., 2008; Irlbacher, Voss, Meyer & Rothwell, 2006; Thiel et al., 2006b). However, several considerations render this explanation unlikely. Neurophysiological studies of the primary motor cortex showed that TMS over the ipsilateral motor hand area has much stronger excitatory and longer lasting inhibitory effects on regional excitability as opposed to the transcallosally induced effects induced by TMS over the contralateral motor hand area (Kobayashi & Pascual-Leone, 2003). The threshold for inducing transcallosal inhibitory effects is also considerably higher than for inducing intracortical inhibition with the coil placed over the motor cortex (Ferbert et al., 1992; Kujirai et al., 1993). Therefore, the effect size of a lesion effect should be stronger and the threshold for inducing a lesion effect should be lower with ipsilateral than contralateral TMS using the same stimulation intensity. Furthermore, there is little evidence from previous studies that transcallosal excitation spread to the homologue parietal area makes a substantial contribution to the behavioural effects obtained with TMS. Indeed, many studies found a specific deterioration in task performance with unilateral TMS over one hemisphere but not over the homologue area in the other hemisphere (Cattaneo, Silvanto, Pascual-Leone & Battelli, 2009; Gobell, Rushworth & Walsh, 2006; Sack et al., 2007). The fact that most previous studies revealed a clear asymmetric sensitivity of the right and left parietal cortex to TMS lesioning argues against a significant contribution of transcallosal excitation of the homologue area to the TMS induced behavioural effects.

In conclusion, our study highlights the importance of the right SMG in phonological word decisions. This strongly motivates the investigation of phonological processing abilities in patients with right SMG damage. According to our results, we would predict that these patients have some degree of phonological processing impairment, irrespective of whether words are presented in the auditory or visual modality.

3.4 Study 3. The right posterior inferior frontal gyrus contributes to phonological word decisions in the healthy brain: evidence from dual-site TMS

This study was designed to clarify the contradictory results of right posterior inferior frontal activation during phonological word decisions in recent neuroimaging studies and investigations on patients with brain lesion. Although we did not find pIFG activation during phonological in contrast to semantic word decisions in our fMRI investigation (see study 1), other functional imaging studies have shown that the right as well as the left pIFG are activated when healthy right-handed subjects perform phonological tasks (Chee et al., 1999; Devlin et al., 2003; Poldrack et al., 1999; Shibahara, 2004; Tremblay et al., 2004). This bilateral pIFG activation contrasts with several lesion studies emphasizing the importance of the left but not right IFG for phonological processing (e.g. Dewarrat et al., 2009; Wilde, 2009; Winhuisen et al., 2007).

To address the discrepancy between functional imaging and lesion studies, the present study was designed to examine how online TMS over the left and right pIFG influences phonological word processing in healthy subjects. We used the neurodisruptive effect of TMS to distinguish between three alternative explanations for right pIFG activation with phonological processing.

One possibility is that the right pIFG contributes to the speed and efficiency of phonological decisions. Consequently, right pIFG lesions have a subtle effect that might be missed unless reaction times were measured. In this case, we would expect a significant effect of right pIFG TMS on reaction times but not error rates in the healthy brain.

An alternative hypothesis is that the right pIFG is necessary for accurate and efficient phonological decisions in the healthy brain but following right pIFG lesions, the function of the right pIFG can be supported by alternative brain regions. Consequently, right pIFG lesions may temporarily impair phonological decision performance in the acute phase after brain damage but this lesion effect will not be apparent after functional reorganisation. In this case, we would expect a significant effect of right IFG TMS on both the reaction times and accuracy of phonological decisions in the healthy brain.

Finally, a third alternative is that the right pIFG is not necessary for accurate and efficient phonological decisions but is activated in fMRI studies of the healthy brain because it is involved in task-related activation that is incidental to performance (i.e. redundant processing,

Price & Friston, 2002). In this case, neither right pIFG lesions nor right pIFG TMS should influence phonological decision performance.

Our study extends previous online TMS studies of phonological processing in three ways. First, we investigated the effect of TMS over the right pIFG. Second, we compared the effects of unilateral TMS over the right pIFG to unilateral TMS over the left pIFG and dual-site TMS over the left and right pIFG simultaneously. This manipulation allowed us to test whether impaired unilateral pIFG function was supported by the contralateral hemisphere. If so, then the effect of dual-site TMS over both the left and right pIFG should be greater than the effect of TMS over either the left or right pIFG alone (Price & Friston, 2002). Third, we compared the effect of TMS on phonological decisions to words presented in the auditory as well as visual modality, whereas previous studies investigated the effect of online TMS over the left pIFG with visually presented words only (Gough et al., 2005; Nixon et al., 2004; Romero et al., 2006). This enabled us to assess whether the expected TMS effects were dependent or independent of stimulus modality. To test the functional specificity of our effects, we also investigated how online TMS over the same pIFG sites affected semantic decisions on the same sets of stimuli. Finally, to test the regional specificity of any observed effects, we investigated how phonological decisions were affected by TMS over the aIFG. On the basis of Gough et al. (2005), we expected that phonological but not semantic judgements would be impaired with TMS applied to the pIFG but not aIFG.

The experimental design and procedures were comparable to those of study 2 except from the fact that both groups received effective TMS at a lower intensity (i.e. 90% of active motor threshold) in this study. Participants were randomly assigned to the pIFG TMS group or the aIFG TMS group. An additional control group received only sham TMS to test whether the tasks yielded comparable results with respect to reaction times and error rates without the influence of real TMS.

In this study, neuronavigated TMS was performed by using the mean MNI-coordinates for the left pIFG across four recent studies comparing visual presented words in a word comprehension task (Devlin et al., 2003; Gitelman et al., 2005; Gough et al., 2005; McDermott et al., 2003). Stereotactic coordinates for the left aIFG were obtained from study 1. For right-hemispheric TMS we used the contralateral homologue areas.

Subjects' mean reaction times (RT) were examined with a four-way repeated measures ANOVA including the factors task (phonological vs. semantic), modality (auditory vs. visual), TMS site (left, right, bilateral) and group (pIFG vs. aIFG). We again excluded the perceptual control task from analyses because preliminary investigation in the control group receiving sham TMS indicated that mean RT and error rates were significantly higher with perceptual than phonological or semantic judgements (see also study 2).

TMS over the pIFG but not aIFG increased RT for the phonological task only (significant task-by-group interaction). Accordingly, post-hoc paired comparisons indicated increased RT for the phonological compared to the semantic task in the pIFG group but not in the aIFG group. Overall, the pIFG group showed longer RT in the phonological task relative to the aIFG group. In contrast, there were no overall differences in mean RT for the semantic task between both groups. The task-specific delay of phonological decisions with TMS over the pIFG was independent of the modality. The ANOVA showed no main effect or interaction with the factor TMS site, indicating that unilateral TMS of the left and right pIFG as well as dual-site TMS of the left and right pIFG produced a similar disruption of phonological judgements.
There was also a main effect of modality due to longer RT for auditorily than visually presented words across tasks, TMS sites and groups. The RT difference between phonological and semantic judgements was greater for auditorily presented words than visually presented words. This interaction between task and modality did not interact with group or TMS site.
Overall, changes in reaction times were paralleled by increased error rates in the phonological task for TMS over the pIFG but not aIFG.

We used the same follow-up experiment as in study 2 to compare the intensity-dependence of the behavioural "lesion" effect induced by unilateral TMS over the left or right pIFG. The ANOVA again showed a main effect of intensity, indicating that RT were significantly longer with TMS at an intensity of 90% AMT compared to all other intensities. This intensity effect was comparable for TMS over the left and right pIFG. ER were not significantly different between the different conditions. Overall RT were again significantly increased for auditorily compared to visually presented words.

In this study, we showed that reaction times and error rates increased following TMS over the right pIFG as well as left pIFG. This indicates that unperturbed right pIFG activation is

necessary for accurate and efficient phonological decisions in the healthy brain. Moreover, our finding that phonological decision performance was not worse for bilateral pIFG TMS than unilateral pIFG TMS provides no evidence that the left and right pIFG can compensate for one another: if phonological decisions are possible with either the left or the right pIFG, then dual-site TMS over the left and right IFG should produce a greater "lesion" effect than TMS over the left or right pIFG alone. In contrast, our observation that the behavioural effect of TMS on phonological judgements was the same for unilateral and bilateral TMS suggests that the left and right pIFG are equally necessary for phonological decisions in the healthy brain.

Our finding that online TMS over the right pIFG selectively interfered with phonological but not semantic judgements provides the first strong evidence that the right pIFG is necessary for efficient phonological processing in healthy right-handed subjects. The disruptive effect was independent of the presentation modality (i.e. auditory or visual) and was present during unilateral as well as bilateral TMS. Therefore, this effect can not be explained by a compensatory role of the contralateral hemisphere (see Price & Friston, 2002). To the contrary, both the main experiment and the follow-up experiment manipulating TMS intensity indicated that the lesion effect of unilateral TMS over the right pIFG was comparable to the lesion effect induced by unilateral TMS over the left pIFG or bilateral TMS over the right and left pIFG. Moreover, it can not be explained in terms of a speed-accuracy trade-off because the detrimental effects of right pIFG TMS on reaction times were paralleled by an increase in error rates.

To the authors' best knowledge, no study to date has investigated the effects of TMS over the right pIFG during phonological processing although several functional imaging studies revealed bilateral activity in the pIFG when healthy right-handed subjects made phonological decisions (Chee et al., 1999; Devlin et al., 2003; Poldrack et al., 1999). Nevertheless, our results confirm several recent TMS studies demonstrating that the left pIFG is important for phonological processing of visually presented words (Gough et al., 2005; Nixon et al., 2004; Romero et al., 2006). We showed for the first time that right pIFG also contributes to phonological processing and that the effect is observed irrespective of whether the stimuli are written words or auditorily presented words. Our results thus extend previous investigations demonstrating a role of the left pIFG in phonological processing only.

We did not find a significant influence of aIFG stimulation on semantic processing as implicated by Gough et al. (2005) and Kohler et al. (2004). Since our subjects reported adverse side effects in a pilot study, we used a lower stimulation intensity than previous studies. It is thus very likely that our stimulation intensity was too low to effectively disrupt semantic processing in the aIFG. However, the low stimulation intensity was sufficient to disrupt phonological processing in the pIFG. These results can not be attributed to task difficulty since both tasks yielded comparable reaction times and error rates in the control group (sham TMS). One possible explanation is that the semantic network was able to compensate for the disruptive effect of low-intensity TMS over the left aIFG.
It is interesting to note that Kohler et al. (2004) compared the effect of TMS over the left and right aIFG and found a left lateralized effect on semantic word encoding. This contrasts with the symmetrical pIFG involvement in phonological processing in our study and suggests that phonological processing may be more bilaterally distributed in the human brain, while semantic processing is more left lateralized. This hypothesis is supported by functional activation patterns that are more left lateralized for semantic than phonological processing (Seghier et al., 2004).

Our results significantly extend current neurobiological concepts of the human language system by showing that language processing involves more than a left-hemispheric specialization. This may have implications for the interpretation of functional imaging studies showing right IFG language-related activation in aphasic patients with left-hemispheric damage (Raboyeau et al., 2008; Saur et al., 2006; Winhuisen et al., 2005; 2007). While recent studies implicated that the (temporary) recruitment of homologue areas in the right hemisphere after left-hemispheric stroke is associated with language improvement (Saur et al., 2006; Thiel et al., 2006a; Winhuisen et al., 2005), our results suggest that the involvement of right hemisphere language areas is not limited to recovery after stroke but is also essential *per se* for phonological processing in healthy subjects. Future studies are now required to systematically investigate the effect of right inferior frontal damage on the efficiency of phonological decisions in patients. According to our results, we would predict that these patients have some degree of phonological processing impairment, irrespective of whether words are presented in the auditory or visual modality.

3.5 Study 4. A frontal network for pseudoword repetition

In the dual-stream model of language processing, Hickok and Poeppel (2000; 2004; 2007) proposed that the repetition of auditorily presented pseudowords activates a network which maps auditory input onto motor-articulatory representations.
It has been argued that contrasting pseudoword with real word production isolates sublexical phonological aspects of word production without accessing semantic aspects (Graves et al., 2008) and thus allows for the identification of phonological aspects of language production.
In a recent meta-analysis, Indefrey and Levelt (2004) aimed to identify the "core" areas of language production. Among others, those regions included the bilateral (pre-) supplementary area and the left posterior inferior frontal gyrus.

The contribution of the (pre-) supplementary motor area (SMA) to language production has been described in fMRI investigations on both healthy subjects and patients with brain lesions (e.g. Alm, 2004; Burton, Noll & Small, 2001; Kotz, Schwartze & Schmidt-Kassow, 2009; Wise et al., 1991; Ziegler, Kilian & Deger, 1997). SMA activation was found for the repetition of auditorily (e.g. Papoutsi et al., 2009; Rauschecker et al., 2008) as well as visually (Fiez et al., 1999; Peeva et al., 2010) presented pseudowords or phonemes. It was suggested that the (bilateral) SMA is important for articulatory planning and initiation during (pseudo-) word production (e.g. Indefrey & Levelt, 2004; Shuster & Lemieux, 2005; Soros et al., 2006).
A variety of studies also demonstrated that the left posterior inferior frontal gyrus (pIFG) is engaged in pseudoword in contrast to word reading (Brunswick et al., 1999; Hagoort et al., 1999; Mechelli, Gorno-Tempini & Price, 2003; Paulesu et al., 2000). Other studies found activation in the left pIFG for the repetition of auditorily presented pseudowords (Rauschecker et al., 2008; Saur et al., 2008). During overt repetition, the left pIFG is proposed to be involved in different linguistic processes such as phonological aspects of (pseudo-) word production and articulatory planning (e.g. Burton et al., 2001; Fiez & Petersen, 1998).
By directly contrasting the overt repetition of auditorily presented pseudowords with real words, a recent study by Saur et al. (2008) delineated a network of areas involved in auditory-to-motor mapping. This network encompassed the left pIFG, the SMA and the premotor cortex.

Previous studies investigated phonological aspects of language production with either auditorily (e.g. Papoutsi et al., 2009; Rauschecker et al., 2008; Saur et al., 2008) or visually

presented pseudowords (Brunswick, McCrory, Price, Frith & Frith, 1999; Fiez, Balota, Raichle & Petersen, 1999; Paulesu et al., 2000; Peeva et al., 2010). So far, no study used comparisons of both auditorily and visually presented pseudowords to identify modality-independent phonological networks on the same task or same set of stimuli. Therefore, it remains unclear if the areas activated during pseudoword repetition depend on the modality used for stimulus presentation. This study was designed to address this question.

We thus used an event-related fMRI design which allowed us to compare auditorily and visually presented pseudowords and words. Based on recent findings (e.g. Saur et al., 2008) we hypothesized that the modality-independent network for pseudoword repetition would encompass the bilateral SMA and the left pIFG.
In order to make inferences about changes in functional connectivity between areas we tested for any regions showing higher coupling with the bilateral SMA and the left pIFG during pseudoword compared to word repetition. According to the results of previous studies on language production (e.g. Indefrey & Levelt, 2004; Saur et al., 2008) we expected to find increased connectivity between our two seed regions and areas in the network for motor preparation and articulation during pseudoword repetition, including the left premotor cortex.

The study used a two (task: repetition of pseudowords vs. words) by two (modality: auditory vs. visual stimuli) event-related within-subject factorial design. Subjects repeated blocks of visually or auditorily presented pseudowords or real words during fMRI.

We found increased activation for the modality-independent comparison of pseudowords relative to real words in the bilateral pre-SMA with a peak in the right hemisphere and (to a lesser degree) in the left pIFG.
Consequently, psychophysiological interactions (PPIs) were used to delineate areas showing increased task-related coupling with the right pre-SMA and the left pIFG during pseudoword in contrast to word repetition. PPI analyses model the response in one cortical area as the influence of another region (i.e. the seed area) and its interaction with an experimental treatment (the psychological variable, i.e. the repetition of pseudowords in contrast to words in our experiment) (Friston et al., 1997). These analyses revealed increased functional connectivity between both areas and the left ventral premotor cortex during the repetition of auditorily and visually presented pseudowords in contrast to words.

In this study, we demonstrate for the first time the modality-independent contribution of both the left pIFG and the right pre-SMA to the overt repetition of pseudowords in contrast to words.

Previous studies have used either visually or auditorily presented stimuli, however, the investigation of both modalities using an identical set of stimuli has not been reported to date. Our results support a variety of recent studies suggesting a role of both areas in (unimodal phonological aspects of) speech production (e.g. Ghosh, Tourville & Guenther, 2008; Indefrey & Levelt, 2004; Saur et al., 2008).

The stronger activation of both areas for pseudoword compared to word repetition is consistent with the notion of an increased processing demand for the production of unfamiliar stimuli (Mechelli et al., 2003; Papoutsi et al., 2009; Price et al., 1996; Wise, Greene, Buchel & Scott, 1999). Activation of the SMA has been attributed to the increased load associated with the production of new and unfamiliar motor plans (i.e. pseudowords consisting of less frequent syllables) in contrast to familiar or more rehearsed ones such as high-frequency pseudowords (i.e. pseudowords consisting of highly frequent syllables) (Papoutsi et al., 2009). In a study by Bohland and Guenther (2006), the pre-SMA was sensitive to sequence complexity effects during syllable repetition of visual stimuli with varying complexity. Accordingly, the right pre-SMA was also activated during the repetition of low-frequency stimuli (i.e. pseudowords) in contrast to high-frequency stimuli (i.e. real words) in our study. Our pseudowords consisted of familiar and frequent syllables merged from existing words. Therefore, the production of pseudowords can be considered as the sequencing of known motor-programs (Alario, Chainay, Lehericy & Cohen, 2006). Our results confirm and extent previous studies (Bohland & Guenther, 2006; Ghosh et al., 2008; Papoutsi et al., 2009) by showing for the first time that this effect is independent of the modality used for stimulus presentation.

Previous studies have shown that the SMA can be divided into two subregions on the basis of cytoarchitecture, connectivity, and function: the pre-SMA being located rostrally to a virtual vertical line passing through the anterior commissure (VAC line), and the SMA-proper, being located caudally to the VAC (Picard & Strick, 1996). Results of diffusion tensor imaging studies revealed different patterns of connectivity with other cortical regions between the pre-SMA and SMA-proper. While the pre-SMA is well connected with the prefrontal cortices and the anterior striatum, the SMA-proper is rather connected with the motor cortex and the posterior striatum (Johansen-Berg et al., 2004; Lehericy et al., 2004). This suggests a more

general role in planning for the pre-SMA and a stronger motor performance role for the SMA-proper.

Our connectivity analyses revealed increased functional coupling between both seed regions (i.e. the right pre-SMA and the left pIFG) and the left ventral premotor cortex (PMv). These results are consistent with a recent study by Ghosh et al. (2008) proposing a network of brain regions including the left PMv, the left pIFG and the bilateral SMA for the overt production of monosyllables. Activation of the PMv has been associated with the sequencing of complex movements, including those involved in speech (Wise et al., 1999). Disruption of white matter tracts underlying the PMv, on the other hand, is likely to interfere with the integration of sensory and motor information necessary for fluent speech production (Watkins, Smith, Davis & Howell, 2008).

In their model of language production, Indefrey and Levelt (2004) proposed that the syllabification of a stimulus is subserved by the left pIFG, which is supported by the results of Salmelin et al. (2000) and Sahin et al. (2009).
The next step in the model proposed by Indefrey and Levelt (2004) is phonetic encoding or articulatory preparation (i.e. the transformation of syllables into motor action instructions or "syllable scores") which includes activation of the right SMA and the cerebellum. The final articulation of the stimulus is associated with the PMv as well as sensorimotor areas.
The results of our functional connectivity analyses fit well with the model proposed by Indefrey and Levelt (2004). The increased functional coupling between both the right pre-SMA, the left pIFG and the left PMv support the proposed role of these areas in phonological encoding, articulatory planning and articulation.
We suggest that the repetition of pseudowords activates a frontal network encompassing the right pre-SMA, the left pIFG and the left PMv. This network is engaged in the sequencing of known motor-programs and involves the repetition of auditorily as well as visually presented pseudowords.

4 General discussion and conclusions

4.1 A bilateral network for phonological aspects of word comprehension

4.1.1 Summary of studies 1-3

The presented studies were designed to delineate brain regions engaged in efficient **phonological word processing during language comprehension and production in healthy subjects.** The results of the first three studies demonstrate the contribution of *both* hemispheres to modality-independent phonological aspects of word comprehension.

The first study used fMRI to show that the bilateral supramarginal gyri were activated during phonological in contrast to semantic aspects of single word processing. However, bilateral SMG activation during fMRI does not necessarily indicate that both hemispheres equally contribute to phonological processing. In contrast, activation of the homologue right SMG could simply reflect activation that is incidental to task performance.
The contribution of both parietal cortices to the execution of visuospatial tasks was recently investigated by Sack et al. (2005; 2007). The authors demonstrated that high-frequency TMS over the right but not left parietal cortex impaired visuospatial judgements although functional brain imaging studies had shown bilateral parietal activation during the execution of spatial cognition tasks (Sack et al., 2007).

Consequently, the second study was designed to establish the functional relevance of bilateral SMG activation patterns with online TMS. Our results indicate for the first time an equal contribution of both hemispheres to phonological processing independent of the modality used for stimulus presentation and thus question the notion of a predominantly left-hemispheric network for phonological aspects of language processing.
Although other studies also used auditory as well as visually presented words to investigate phonological aspects of word processing (e.g. Burton et al., 2003; Cohen et al., 2004) our studies were the first to systematically subtract semantic from phonological processes and thus isolate phonological aspects of word comprehension.

Study 3 used TMS to investigate whether a bilateral contribution to phonological processing also applies to the posterior inferior frontal gyrus. Although we did not find increased pIFG

activation for phonological in relation to semantic judgements in our fMRI study, this area has been repeatedly reported to serve phonological judgements (e.g. Gitelman et al., 2005; Gough et al., 2005; McDermott et al., 2003; Poldrack et al., 1999; see Costafreda et al., 2006 for a meta-analysis) and has been assigned a core role in phonological aspects of language processing (Hickok & Poeppel, 2000; 2004; 2007). While most studies focused on the contribution of the left pIFG to phonological processing, some also reported bilateral pIFG activation (Chee et al., 1999; Devlin et al., 2003; Poldrack et al., 1999; Shibahara, 2004; Tremblay et al., 2004).

Again, our results extend previous investigations by indicating that both pIFG equally contribute to phonological in contrast to semantic word processing independent of the modality used for stimulus presentation. These results further corroborate our notion of a bilateral network for phonological processing. This network encompasses the posterior inferior frontal gyri and the supramarginal gyri bilaterally. Our findings of a consistent modality-independent contribution of both areas indicate that these regions represent core areas for phonological aspects of word comprehension.

The contribution of both left inferior parietal and posterior inferior frontal activation to phonological working memory processes was also suggested by Buchsbaum et al. (2001). Based on these results, Hickok and Poeppel (2000, 2004, 2007) proposed their model of a dorsal stream mapping sound onto articulation by connecting inferior parietal with frontal areas.

A left-hemispheric phonological network connecting inferior parietal and inferior frontal regions fits well with the concept of a phonological working memory loop proposed by Vigneau et al. (2006). Phonological working memory tasks usually require the subject to remember and mentally rehearse items, for instance lists of letters, through a short delay (for a detailed review on phonological working memory studies, see Buchsbaum & D'Esposito, 2008). We used syllable counting to investigate phonological processes, a task that has been previously used to delineate areas engaged in phonological working memory (e.g. Poldrack et al., 1999). However, our results together with the results of a variety of other different studies (e.g. Buchsbaum et al., 2001; Gough et al., 2005; Jobard et al., 2003; Nixon et al., 2004) diverge from Vigneau et al. (2006) by suggesting that the posterior rather than the anterior aspect of the inferior frontal gyrus supports efficient phonological word processing.

4.1.2 A new framework for phonological aspects of word comprehension

In summary, our results extend previous concepts of phonological processing focussing on left-hemispheric areas (e.g. Hickok & Poeppel, 2000; 2004; 2007). Based on these results, it is more likely that a bilateral network serves modality-independent phonological aspects of word comprehension which connects the supramarginal gyri in the inferior parietal cortices with the posterior inferior frontal gyri bilaterally (Fig.9).

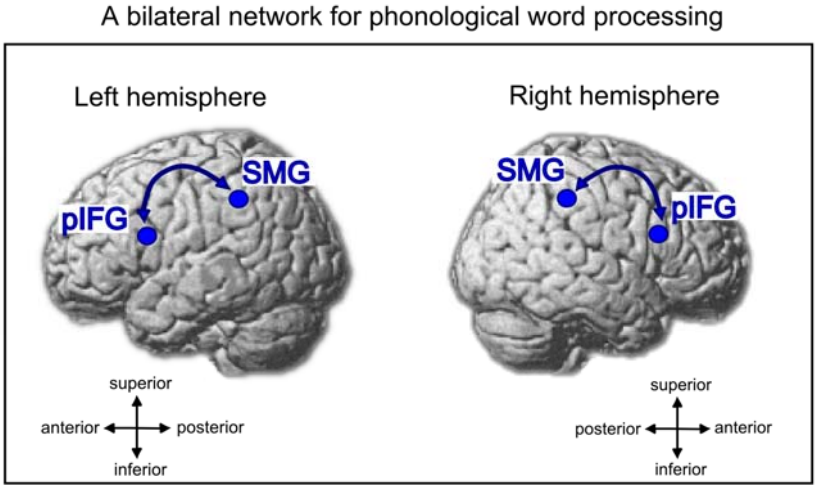

Fig.9 Phonological aspects of word comprehension. The results of our first three studies lead to the proposal of a bilateral network for phonological word processing, connecting the supramarginal gyri (SMG) in the inferior parietal cortices with the posterior inferior frontal gyri (pIFG) bilaterally.

4.1.3 Functional and regional specificity of the bilateral network

Increased activity of both the SMG and the pIFG has previously been reported for the comparison of phonological in contrast to semantic judgements during fMRI (e.g. Burton et al., 2003; Devlin et al., 2003). Consequently, our "virtual lesion" approach affected selectively phonological but not semantic processing in either the pIFG or the SMG bilaterally.

Regarding the regional specificity it should be noted that our results confirm current models suggesting a role of the posterior part of the IFG in phonological processing, as we also demonstrated that TMS over the pIFG selectively disrupted phonological processing, whereas TMS over the aIFG did not. Our results further extend current concepts of pIFG involvement in phonological processing by demonstrating that both the left and the right pIFG contribute

to efficient phonological processing and that this contribution is independent of the sensory modality used for stimulus presentation.

We used a similar approach to demonstrate the regional specificity of the SMG in phonological processing: To test the local specificity of the SMG effects, we re-examined five subjects who had participated in our second study. Those subjects performed the phonological and semantic task in both modalities again while receiving 10 Hz online rTMS over the left, right or bilateral angular gyri (G. Hartwigsen et al., unpublished data). In all other aspects, this experiment was identical to the design used in study 2. Since the angular gyrus has been associated with semantic rather than phonological processing (e.g. Demonet, Price, Wise & Frackowiak, 1994; Devlin et al., 2003; Price et al., 1997), we hypothesized that TMS over the angular gyrus would not impair phonological processing.

No significant differences between the phonological and the semantic task were found for TMS over either angular gyrus. Although these results are preliminary and restricted by the small number of subjects included, they suggest that the disruptive effect of TMS on phonological processing was specific for the SMG.

An important question is whether phonological aspects of word processing are restricted to inferior parietal and posterior inferior frontal regions.

A variety of different tasks have been used to investigate phonological aspects of word processing. These tasks include letter recognition (Jonides, Smith, Marshuetz, Koeppe & Reuter-Lorenz, 1998), syllable judgements (Devlin et al., 2003) and word rhyming (Burton et al., 2003). Although the use of different tasks and baseline conditions may result in different activation patterns (Vigneau et al., 2006), the activation of both inferior frontal and inferior parietal regions has consistently been reported using different tasks. This suggests that these areas represent core regions for phonological word processing, as proven by our results.

It remains to be determined, however, how inferior parietal and posterior inferior frontal areas interact. A promising approach to investigate the interaction between pIFG and SMG would be the use of a multifocal “online” TMS design with small TMS coils. This allows the simultaneous application of TMS over different nodes of a network and thus enables the researcher to test whether the pIFG and the SMG can compensate for each other to some degree during phonological processing. If so, then the effect of multifocal TMS over both the left (or right) pIFG and SMG should be greater than the effect of TMS over either the left or right pIFG / SMG alone.

4.2 A network for phonological aspects of word production

Study 4 revealed that the right supplementary motor area and left posterior inferior frontal gyrus were consistently activated during phonological aspects of language production (i.e. pseudoword repetition) independent of the modality used for stimulus presentation. In this fMRI study, increased functional coupling was found for both areas and the left ventral premotor cortex during pseudoword in contrast to real word repetition using psychophysiological interactions (PPIs). Thus, we suggest that these areas constitute a network of core regions for phonological aspects of language production. These findings confirm and extend the model of language production proposed by Indefrey and Levelt (2004). In their model, the left pIFG, the right SMA and the left PMv are associated with phonological encoding, articulatory planning and articulation. We show for the first time that these areas contribute to the repetition of pseudowords in contrast to words independent of the modality used for stimulus presentation. Accordingly, the results of our study lead to the proposal of a frontal network for modality-independent aspects of pseudoword repetition (Fig.10).

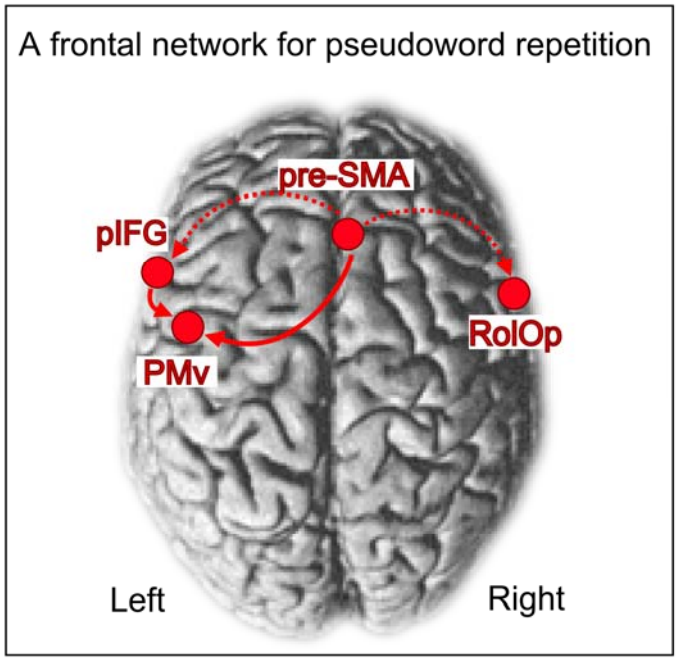

Fig.10 Core areas in the frontal network for pseudoword repetition. The results of study 4 revealed a network consisting of the right pre-supplementary motor area (pre-SMA) and the left posterior inferior frontal gyrus (pIFG), activated during the repetition of auditorily as well as visually presented pseudowords in contrast to words. Both areas showed increased functional coupling with the left ventral premotor cortex (PMv) during the repetition of auditorily as well as visually presented pseudowords as opposed to words. Additionally, connectivity was also increased between the right pre-SMA and both the right Rolandic operculum (RolOp) and the left pIFG during the repetition of auditorily presented pseudowords in contrast to words (dashed lines).

Since the days of Broca (1861), the inferior frontal gyrus has been labelled the “core area” for language production. Thus, the contribution of the left pIFG to phonological encoding, and articulatory planning during overt language production is not surprising and also fits well with more recent models (e.g. Hickok & Poeppel, 2000; 2004; 2007). Dorsal and ventral aspects of the left premotor cortex have also been assigned a role in language production although with varying locations (Demonet et al., 2005; Hickok & Poeppel, 2000; 2004; 2007; Indefrey & Levelt, 2004; Vigneau et al., 2006).

Our finding of right pre-SMA involvement in pseudoword repetition again questions the notion of a predominantly left-hemispheric network for language processing and converges with the results of Seghier et al. (2004) indicating that phonological processing may be more bilaterally distributed while semantic processing is rather left lateralized.

Additionally the right pre-SMA showed also increased functional coupling with the right Rolandic operculum and the left pIFG during the repetition of auditorily presented pseudowords in contrast to words in our study. The Rolandic operculum is associated with sensory-motor integration during language production and has been assigned to the auditory-motor network proposed by Vigneau et al. (2006). Increased connectivity between the SMA and the pIFG during phonological aspects of language processing, on the other hand, has been demonstrated in several previous studies (Bullmore et al., 2000; He et al., 2003).

The difference in the connectivity profiles between the two modalities used for stimulus presentation may indicate different processing strategies in the network for phonological aspects of language production. There is consensus that auditorily presented words are processed sequentially while visually presented words are processed in parallel fashion (Krause et al., 2006). Consequently, reaction times are usually longer for auditorily presented words (e.g. Cohen et al., 2004).

The difference in processing of both modalities may indicate that the right pre-SMA and left pIFG are activated simultaneously (i.e. in parallel) during the repetition of visually presented pseudowords. This would be in line with the results of a strong activity increase of both areas during the repetition of visually presented pseudowords in contrast to words as shown in study 4. Furthermore, the interaction between task and modality revealed a stronger activity increase in the left pIFG for visually than auditorily presented pseudowords.

The repetition of auditorily presented pseudowords, on the other hand, might require a sequential activation of both areas. This would match our results of a relatively strong increase in the pre-SMA activity and a weaker increase in pIFG activity during the repetition

of auditorily presented pseudowords. A serial activation of pre-SMA preceding the pIFG would be in line with the model of Bullmore et al. (2000) proposing an inner speech circuit or articulatory loop with the SMA being putatively responsible for endogenously directing inner speech production to left inferior frontal regions.

At first glance, the suggested serial activation of pre-SMA preceding pIFG during the repetition of auditorily presented pseudowords contradicts the model of Indefrey and Levelt (2004). Nevertheless, the authors state that the different stages in their model interact and the proposed time frames represent estimates which are variable which "cautions against a too rigid interpretation of these numbers". Finally, their meta-analysis did not include studies on pseudoword repetition. Thus, the repetition of a pseudoword may differ in some aspects from the proposed time frames of language production.

4.3 Outlook: TMS-induced reorganization in the phonological network for word production

To further clarify the effective contribution of bilateral brain areas to phonological aspects of language production, we designed another study, using continuous theta burst stimulation (cTBS) combined with fMRI to induce acute adaptive reorganization within the phonological network for pseudoword repetition (G. Hartwigsen et al., unpublished data).

cTBS is an effective TMS protocol to cause a lasting suppression of neuronal activity in the stimulated cortex beyond the time of stimulation (Huang, Edwards, Rounis, Bhatia & Rothwell, 2005). Although there is no study to date that investigated the effects of cTBS over inferior frontal regions on language processing, cTBS over premotor and motor areas can induce a suppression in cortical excitability associated with a lasting impairment in motor tasks (e.g. Cardenas-Morales, Nowak, Kammer, Wolf & Schonfeldt-Lecuona, 2010; Nowak et al., 2009).

This study extends study 4 by investigating the effects of cTBS on brain activity. In separate sessions, cTBS was either applied over the left pIFG or the left aIFG in 17 healthy subjects. In a third session, an ineffective stimulation procedure (sham cTBS) was applied. This condition served as a "baseline". The order of sessions was counterbalanced across subjects and all sessions were at least five days apart to prevent carry-over effects. After cTBS, subjects repeated visually and auditorily presented pseudowords and words during fMRI (cf. study 4).

Based on the results of recent studies in the motor system (e.g. Huang et al., 2005), we expected that cTBS over the pIFG but not aIFG would result in decreased activity during pseudoword repetition. This might lead to a lasting impairment in task performance (e.g. Cardenas-Morales et al., 2010). Alternatively, other areas of the phonological network might reveal compensatory activation increases to maintain task performance as demonstrated by previous studies using "offline" TMS before fMRI (e.g. O'Shea et al., 2007).

Preliminary results indicate that cTBS over the left pIFG decreased activity in the inferior frontal gyrus including the stimulated area for pseudowords and words of the visual and - albeit to a lesser degree - the auditory modality. In contrast, cTBS over the left aIFG decreased activity only during the repetition of visually presented real words.

There were no effects of cTBS on task performance. When comparing the repetition of pseudowords and real words after sham stimulation (ineffective stimulation), increased activity was found in the *left pIFG but not in the right pIFG* (see also study 4). Interestingly, this activation pattern was different after cTBS over the left pIFG: We found increased activity in the *right pIFG but not in the left* pIFG for the comparison between pseudowords and words across both modalities (i.e. the modality-independent conjunction; Fig.11). These activity changes were absent after cTBS over the left aIFG.

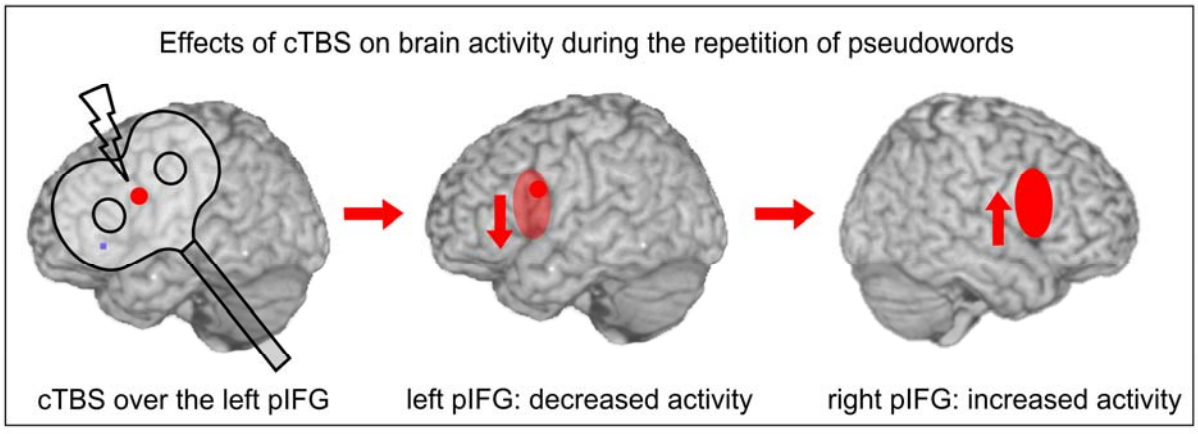

Fig.11 Effects of cTBS over the left pIFG. Preliminary results indicate that cTBS over the left pIFG decreased activity during the repetition of both visually and auditorily presented pseudowords. The modality-independent comparison of pseudowords versus real words after cTBS over the left pIFG revealed increased activity in the right pIFG. Right-hemispheric activation was absent after cTBS over aIFG or ineffective sham stimulation.

These preliminary results might indicate a compensatory upregulation of the right pIFG after left pIFG suppression which might have helped to maintain task performance.

A compensatory upregulation of the right-hemispheric homologue area would be in line with the results of O'Shea et al. (2007). The authors used fMRI in healthy subjects to probe short-

term reorganization in the right dorsal premotor cortex after TMS-induced disruption of neuronal processing in the left dorsal premotor cortex specialized for action selection. TMS specifically increased activity in the right premotor cortex and connected medial premotor areas during action selection without affecting behaviour. It was claimed that this increase in activity reflects compensatory short-term reorganization that helps to preserve behaviour after the "neuronal challenge" induced by left-hemispheric TMS.
This interpretation would also be consistent with recent lesion studies suggesting that a (temporary) recruitment of contralateral homologue areas after left-hemispheric stroke is associated with language improvement (e.g. Saur et al., 2006; Thiel et al., 2006a; Winhuisen et al., 2005).

4.4 The left pIFG - a core region for phonological aspects of language?

It is interesting to note that the left pIFG contributed to phonological aspects of both language comprehension (i.e. syllable judgements) and language production (i.e. pseudoword repetition) in our studies. This is consistent with previous studies suggesting a general role of left posterior inferior frontal areas in both processes (Heim, 2005; Sahin et al., 2009).
However, this thesis is the first systematic investigation using modality-independent comparisons of phonological tasks with semantic tasks to isolate sublexical phonological processes during language comprehension as well as production.

While our TMS investigations demonstrated bilateral pIFG involvement in phonological aspects of language comprehension, the contribution of this area to phonological aspects of language production was restricted to the left hemisphere as shown in our fourth study. We did not find any activation of the right pIFG for the repetition of pseudowords in contrast to words, even when the threshold was lowered. Neither the repetition of unimodally presented pseudowords nor the investigation of the main effects of pseudoword repetition (i.e. pseudowords compared to rest) revealed a contribution of the right-hemispheric pIFG unless the left pIFG was lesioned with continuous theta burst stimulation.
Although a left-hemispheric pIFG involvement is consistent with most of the studies found in the literature (see introduction), some studies also reported right inferior frontal activation during language production (e.g. Indefrey & Levelt, 2004; Papoutsi et al., 2009). For example, Papoutsi et al. (2009) identified a network of areas showing increased activity

during the repetition of auditorily presented low-frequency compared to high-frequency pseudowords. This network encompasses the SMA and the bilateral pIFG.

This suggests that the right pIFG may also contribute to phonological aspects of language production. It is possible that the absence of right pIFG activation for pseudoword in contrast to word repetition in our study reflects decreased task demands due to our training which reduced the novelty of the pseudowords. Thus, the effective contribution of the right pIFG to phonological aspects of language production remains to be determined. For that purpose, the use of combined fMRI and TMS is promising. One possibility is to apply TMS during overt language production to induce speech arrest (Pascual-Leone et al., 1991). However, given the variability of studies using TMS to induce speech arrest and the adverse side effects reported in previous investigations (e.g. Epstein et al., 1996; Epstein et al., 1999), it may be worthwhile to focus on the offline approach and investigate TMS-induced changes in activity during the overt repetition of pseudowords.

With regards to this issue, our preliminary investigations on the combined cTBS-fMRI data indicate that “lesioning” the left pIFG with cTBS results in compensatory activation increases in the contralateral homologue right pIFG during phonological processing warranting consistent task performance.

4.5 Implications for lesion studies

There is an ongoing debate in the lesion literature whether post-stroke activation in right-hemispheric homologue areas after left-hemispheric damage represents compensatory or maladaptive processes (Thompson & den Ouden, 2008, cf. 1.4.2). The results of our studies have several implications for such lesion studies:

First, it is important to note that right-hemispheric activation during language processing may not necessarily be a consequence of left-sided brain damage, but may reflect normal functional recruitment when task demands become more effortful (Raboyeau et al., 2008). In our first fMRI study (study 1), we found increased activity in the right posterior inferior frontal gyrus for the perceptual tasks (i.e. prosodic and graphic manipulations of the stimuli) compared to both linguistic tasks (i.e. phonological and semantic judgements). These findings indicate that over and above the activation of verbal cues during lexical retrieval, right frontal activation may indicate the processing of non-linguistic features of word stimuli.

Given the fact that we used the same manipulated stimuli in our third study comparing the effects of TMS over left and right pIFG, one might argue that our right pIFG effects might simply reflect the disruption of such non-linguistic features instead of pure phonological processing. However, two considerations render this explanation unlikely: First, a comparison of manipulated vs. non-manipulated items did not reveal any significant differences. Second, the manipulation was held constant across the phonological and semantic task.

The second implication addresses studies that show improved language recovery in aphasic patients following suppression of neuronal processing in the non-lesioned right IFG with transcranial stimulation techniques (Andoh & Martinot, 2008; Martin et al., 2009; Naeser et al., 2005a; Naeser et al., 2005b). The behavioural improvement after suppression of neuronal processing in the non-lesioned right IFG has been interpreted as a suppression of maladaptive "over-activation" in the right hemisphere which in turn may have allowed for a better modulation in the remaining left-hemispheric networks (Naeser et al., 2005a). The interpretation of a TMS-induced suppression of maladaptive "over-activation" contrasts with our observation that right-hemispheric areas contribute to efficient phonological processing in healthy subjects. It should be noted, however, that the experimental design of our study was different from those in the lesion studies cited above. Specifically, we applied TMS online (i.e. during task performance), leaving the language system no time to develop adaptive plasticity. In contrast, the studies on stroke patients cited above used a different TMS protocol, where TMS was applied offline (i.e. before the task). Furthermore, while we contrasted phonological with semantic judgements, the studies cited above used picture naming and solely targeted the anterior part of the IFG which has been associated with semantic rather than phonological processing (e.g. Devlin et al., 2003; Gitelman et al., 2005; Gough et al., 2005).

Taken together, our results motivate future investigations on the functional relevance of right-hemispheric activity over the course of recovery in patients with left-hemispheric stroke. For example, right-hemispheric areas may be more functionally relevant in the acute phase after stroke than in the chronic phase when reorganisation of the language networks has occurred (Saur et al., 2006).

The neurodisruptive effects of right-hemispheric TMS on phonological decisions in healthy subjects in our studies also call for a re-evaluation of phonological deficits in patients with right-hemispheric inferior parietal and inferior frontal lesions. Prospective longitudinal studies with

more challenging phonological tasks might demonstrate phonological impairments in the presence of acute or subacute lesions of right-hemispheric areas.

4.6 Concluding remarks

In several studies, we delineated areas that contribute to phonological aspects of language comprehension and production. The results of study 1-3 show that phonological judgements of auditorily as well as visually presented words engage a bilateral network of brain regions including the supramarginal gyri and the posterior inferior frontal gyri. Thus, these results provide the first strong evidence of a contribution of right-hemispheric regions to phonological aspects of word comprehension in healthy subjects. Further studies are required to investigate the interaction between these areas.
In study 4, it was also demonstrated that a frontal network encompassing the right pre-supplementary area, the left posterior inferior frontal gyrus and the left ventral premotor cortex are engaged in phonological aspects of language production independent of the modality used for stimulus presentation.
Taken together, these results suggest that the left posterior inferior frontal gyrus represents a “core” area engaged in modality-independent phonological aspects of both language comprehension and production.

In conclusion, the results of these studies indicate that the right hemisphere is far from being “non-linguistic”. In other words: “When it comes to language processing, two hemispheres are better than one” (Lindell, 2006).

5 Summary

The use of language is a unique ability of communication to humanity. Research aims at identifying brain regions involved in language comprehension and production since the days of Broca's and Wernicke's first post mortem studies (Broca, 1861; Wernicke, 1874). Consequently, functional-anatomic models of language comprehension and production were proposed to describe the organisation of language in the human brain. The early models of language organisation were based on behavioural deficits in patients with brain lesions (see Shalom & Poeppel, 2008 for a review).

As the results of lesion studies are often based on vague psychological constructs and may lack anatomical precision (Shallice, 1988), more recent models focus on language processing in the healthy human brain (Bookheimer 2002). These models usually take into account the results of functional imaging studies, providing insight into brain regions being activated during specific language processes.

Thus, recent models of language processing in the human brain underline that language is organized in networks with different linguistic functions being represented in separate (sub-) areas. Specifically, it has been argued that phonological aspects of language processing (i.e. the organisation of speech sounds of a language) are subserved by a dorsal stream that "maps sound onto articulation" by connecting temporo-parietal with premotor areas and inferior frontal regions. In contrast, semantic aspects (i.e. the meaning of a language) are organized in a ventral stream, connecting middle temporal areas with the ventrolateral prefrontal cortex and thus "mapping sound onto meaning" (e.g. Hickok & Poeppel, 2000; 2004; 2007).

The results of functional imaging studies have been complemented by studies applying transcranial magnetic stimulation (TMS) to test if the stimulated cortex makes a critical contribution to a specific (language) task (Devlin & Watkins, 2007).

For instance, several TMS studies demonstrated a functional subdivision of Broca's area in the left inferior frontal gyrus (IFG). According to these studies, the posterior part of the IFG is efficiently contributing to phonological aspects of single word processing while the anterior part was found to be engaged in semantic aspects of word processing (e.g. Devlin et al., 2003; Gough et al., 2005; Koehler et al., 2004; Nixon et al., 2004).

Although some functional imaging studies also found increased activation in right-hemispheric areas during language processing (e.g. Burton et al., 2003; Devlin et al., 2003; Price et al., 1997), there is general consensus about left-hemispheric dominance. Thus, most

of the systematic investigations on task-specific contributions of different brain regions have focused only on left-hemispheric areas so far.

The overall aim of this thesis was **to investigate the neural substrates of phonological aspects of language comprehension and production in the healthy human brain. Of special interest was particularly the contribution of right-hemispheric areas to these processes.**
Therefore, several studies were designed using fMRI and TMS. The use of combined fMRI and TMS gives access to non-invasive measuring of brain functions with a high spatial and temporal resolution.

Study 1 addressed the question whether phonological and semantic aspects of word comprehension engage different brain regions independent of the stimulus modality used for presentation (i.e. auditory vs. visual word presentation). While most of the previous investigations focused on the processing of visually presented words (e.g. Devlin et al., 2003; Gitelman et al., 2005; McDermott et al., 2003; Price et al., 1997; Seghier et al., 2004), the core aspects of language processing are assumed to be modality-independent (Hickok and Poeppel, 2004). Thus, this study compared phonological judgements (i.e. does a word have two or three syllables?) with semantic judgements (i.e. does a word represent a natural or man-made item?) using fMRI.
In good agreement with previous studies (e.g. Burton et al., 2003; Devlin et al., 2003; Price et al., 1997), our results suggest that phonological in contrast to semantic aspects engage posterior regions, especially the bilateral supramarginal gyri (SMG). In contrast, semantic compared to phonological aspects activated anterior regions, specifically the anterior inferior frontal gyrus (aIFG) of the left hemisphere.
These results extend previous investigations by demonstrating for the first time that these activation patterns are independent of the modality used for stimulus presentation.

To test the functional relevance of the phonological activation patterns revealed by the first experiment, study 2 applied stereotactically guided TMS over the left and right SMG. This study used a comparable experimental design as the fMRI investigation in different subjects. During the presentation of visual or auditory words, 10 Hz rTMS was applied either over the left, the right or bilateral SMG.

We hypothesized that if right supramarginal activation is redundant to phonological processing, then reaction times or error rates would only increase when online TMS was applied over the left SMG but not the right SMG. In contrast, if the right SMG also contributes to phonological decisions, then task specific reaction times or error rates should also increase with TMS over the right SMG.

If phonological decisions are possible with either the left or right SMG, the lesion effect should be greater if TMS was applied over both the left and right SMG. In contrast, if the left and right SMG are equally necessary for efficient phonological decisions, the effect of TMS should be the same irrespective of whether it was applied unilaterally or bilaterally (see Price & Friston, 2002).

The results of this study showed that TMS relative to an ineffective "sham" procedure significantly increased reaction times and error rates for the phonological but not semantic task independent of the stimulated hemisphere. Although the effects were stronger for auditorily presented words, they were also significant in the visual modality. Thus, the results indicate for the first time that efficient modality-independent phonological judgements require both the left and the right SMG in healthy subjects.

Consequently, study 3 investigated whether a bilateral contribution to phonological processing also applies to the posterior inferior frontal gyrus, an area previously associated with phonological processing (e.g. Chee et al., 1999; Devlin et al., 2003; Gitelman et al., 2005; Shibahara, 2004). The experimental design was comparable to the previous study, again using identical stimuli for both auditorily and visually presented words in different healthy subjects. Stereotactically guided TMS was applied over either the left, right or bilateral pIFG or aIFG (control area) during phonological and semantic judgements. This design allowed us to distinguish between three alternative explanations for right pIFG activation with phonological processing reported in previous fMRI studies (e.g. Chee et al., 1999; Devlin et al., 2003; Poldrack et al., 1999; Shibahara, 2004; Tremblay et al., 2004).

One possibility was that the right pIFG would contribute to the speed and efficiency of phonological decisions. Consequently, right pIFG lesions would have a subtle effect that might be missed unless reaction times were measured. In this case, we expected a significant effect of right pIFG TMS on reaction times but not error rates in the healthy brain.

Alternatively, it was possible that the right pIFG would be necessary for accurate and efficient phonological decisions in the healthy brain but following right pIFG lesions, the function of the right pIFG could be supported by alternative brain regions. Consequently, right pIFG

lesions might temporarily impair phonological decision performance in the acute phase after brain damage but this lesion effect would not be apparent after functional reorganisation. In this case, we expected a significant effect of right IFG TMS on both the reaction times and accuracy of phonological decisions in the healthy brain.
The third alternative was that the right pIFG would not be necessary for accurate and efficient phonological decisions but was activated in previous fMRI studies of the healthy brain because it was involved in task-related activation that was incidental to performance (i.e. redundant processing, Price & Friston, 2002). In this case, neither right pIFG lesions nor right pIFG TMS should influence phonological decision performance.
The results of this study again revealed that both the left and right pIFG are necessary for efficient phonological processing. Thus, TMS over the pIFG but not aIFG selectively interfered with phonological but not semantic judgements irrespective of the modality used for stimulus presentation. These results extend previous results (e.g. Gough et al., 2005; Nixon et al., 2004; Romero et al., 2006) by demonstrating for the first time that both the left and right pIFG are equally necessary for modality-independent phonological aspects of single word comprehension.

Finally, study 4 was designed to delineate brain regions engaged in phonological aspects of overt language production. This study used the comparison of auditorily as well as visually presented pseudowords (i.e. pronounceable nonwords) and real words during fMRI. Independent of the modality used for stimulus presentation, the overt repetition of pseudowords in contrast to real words revealed increased brain activity in the right pre-supplementary area (pre-SMA) and the left posterior inferior frontal gyrus (pIFG). Several psychophysiological interactions (PPIs) showed increased functional connectivity between both areas and the ventral premotor cortex (PMv) during the repetition of pseudowords in contrast to real words. Extending previous investigations on language production (e.g. Ghosh et al., 2008; Indefrey and Levelt, 2004; Saur et al., 2008) these results indicate that the right-pre-SMA, the left pIFG and the left PMv constitute a network engaged in phonological encoding, articulatory planning and articulation during the repetition of pseudowords. For the first time, our results demonstrate that this network is independent of the modality used for stimulus presentation.

The results of our studies question the notion that language processing is predominantly subserved by the left hemisphere. In contrast, our results indicate that efficient phonological

decisions in healthy subjects require both hemispheres. According to the results of study 1-3, a bilateral network for phonological processing of single words is suggested. This network encompasses the left and right supramarginal gyri and the bilateral posterior inferior frontal gyri.

The results of study 4 indicate that modality-independent phonological aspects of language production engage a network of regions previously associated with phonological encoding, articulatory planning and articulation. These regions include the right pre-supplementary motor area, the left posterior inferior frontal gyrus and the left ventral premotor cortex.

In summary, these results indicate that right-hemispheric areas play an important role in the efficient processing of phonological language aspects in the healthy human brain. These results motivate future investigations on the functional relevance of right-hemispheric activity during recovery in patients with *left-hemispheric* stroke. The results also call for a re-evaluation of phonological deficits in patients with *right-hemispheric* inferior parietal and inferior frontal lesions. Prospective longitudinal studies with more challenging phonological tasks might demonstrate phonological impairments in the presence of acute or subacute lesions of right-hemispheric areas.

6 Deutsche Zusammenfassung (summary in German)

Sprache ist die grundlegende menschliche Fähigkeit der Kommunikation. Der Gebrauch von Sprache umfasst die Assoziation von Klängen und Symbolen mit bedeutungstragenden Inhalten und ermöglicht es dem Menschen, seine Umwelt zu beschreiben und durch abstrakte Gedanken zu erfassen.

Die ersten Untersuchungen zur Repräsentation von Sprache im menschlichen Gehirn stammen aus der zweiten Hälfte des 19. Jahrhunderts. So berichtete Broca 1861 von einem Patienten, der zu Lebzeiten Probleme mit der Sprachartikulation aufgewiesen hatte. Eine post-mortem Untersuchung seines Gehirns zeigte eine Läsion im linken Gyrus frontalis inferior (IFG), der später als „Broca-Areal“ bezeichnet wurde. Aus diesem Befund schlussfolgerte Broca, dass der linke IFG für die Produktion von Sprache zuständig sei. Ergänzt wurde dieses Ergebnis durch eine post-mortem Untersuchung Wernickes (1874) an einem Patienten, der unter Einschränkungen des Sprachverständnisses gelitten hatte und dessen Gehirn eine Läsion im linken Gyrus temporalis superior („Wernicke-Areal“) aufwies. Wernicke leitete daraus ab, dass dieses Areal am Sprachverständnis beteiligt sein müsse. Diese Ergebnisse wurden 1885 von Lichtheim im sogenannten „klassischen“ Modell der Sprachorganisation zusammengefasst. Dieses erste funktionell-anatomische Modell der Sprachorganisation im menschlichen Gehirn besagte, dass das Wernicke-Areal über den Fasciculus arcuatus mit dem Broca-Areal verbunden wäre. Eine Läsion des Fasiculus arcuatus führte gemäß Lichtheim zu einer Beeinträchtigung beim Nachsprechen von gehörten Wörtern bei intaktem Sprachverständnis und intakter Sprachproduktion. Dieses klassische Modell dominierte die Sprachforschung für die nächsten 150 Jahre (Demonet et al., 2005).

Obwohl das klassische Modell lange als Grundlage für zahlreiche klinische Studien genutzt wurde, ist vielfach kritisiert worden, dass es sowohl anatomisch als auch psycholinguistisch unterspezifiziert ist und dem heutigen Kenntnisstand nicht mehr entspricht (Caplan, 2003; Demonet et al., 2005; Dronkers et al., 2004; Poeppel & Hickok, 2004; Shalom & Poeppel, 2008). Studien an Patienten mit Läsionen konnten den klassisch-modularen Ansatz nicht konsistent bestätigen, der inferior-frontale Areale mit Sprachproduktion und superior-temporale Regionen mit Sprachverständnis assoziiert.

So zeigten Patienten mit Läsionen im Broca- oder Wernicke-Areal nicht immer die prognostizierten Defizite (Dronkers et al., 2004; Schaffler et al., 1993). Umgekehrt waren Defizite auf der Verhaltensebene nicht immer mit einer Läsion im Broca- oder Wernicke-

Areal assoziiert (Otsuki et al., 1996). Die Interpretation von Läsionsstudien wird ferner dadurch erschwert, dass die beschädigten Hirnareale meist anatomisch unpräzise und die zugrunde gelegten psychologischen Konstrukte nur vage sind (siehe Shallice, 1988). Weiterhin können nach Läsionen im Rahmen von neuronalen Reorganisationsprozessen Veränderungen in der funktionellen Anatomie des Gehirns entstehen (z.B. Thiel et al., 2006).

Aufgrund der Schwierigkeiten bei der Interpretation von Läsions-Defizit-Studien basieren moderne funktionell-anatomische Modelle der Sprachrepräsentation im menschlichen Gehirn auf Studien an Gesunden. Um Reorganisationsprozesse nach Hirnschädigungen besser zu verstehen, ist ein detailliertes Wissen über die Repräsentation verschiedener Sprachkomponenten im gesunden Gehirn erforderlich. Hierbei ist ein multimodaler Ansatz hilfreich, der verschiedene Verfahren einsetzt, um die Relevanz bestimmter Hirnareale für bestimmte linguistische Komponenten der Sprache zu überprüfen. Der Einsatz moderner bildgebender Verfahren wie Positronen-Emissions-Tomographie (PET) und funktioneller Magnetresonanztomographie (fMRT) ermöglicht eine direkte Korrelation zwischen spezifischem Verhalten und Hirnaktivierung (Bookheimer, 2002). Im Gegensatz zu Läsions-Defizit-Studien, die auf die Untersuchung geschädigter Areale beschränkt sind, erlaubt der Einsatz funktioneller Bildgebungsstudien sowohl bei Patienten als auch bei Gesunden die Untersuchung von Netzwerken und Interaktionen zwischen Hirnregionen und verschiedenen (linguistischen) Funktionen (Price, 2000). Die Erkenntnisse aus funktionellen Bildgebungsstudien werden durch Untersuchungen ergänzt, in denen transkranielle Magnetstimulation (TMS) eingesetzt wird. Dieses nicht-invasive Verfahren bietet die Möglichkeit zu testen, ob ein bestimmtes Areal für die Bearbeitung einer spezifischen (Sprach-) Aufgabe relevant ist (Devlin & Watkins, 2007).

Gemäß dem derzeitigen Kenntnisstand zur Struktur von Sprachprozessen werden verschiedene linguistische Komponenten unterschieden. Dazu gehören unter anderem phonologische Prozesse, die an der Organisation der Lautstruktur einer Sprache beteiligt sind, und semantische Prozesse, die sich auf die Bedeutung von Sprachaspekten beziehen (Poldrack et al., 1999). Für die vorliegende Arbeit ist die Verarbeitung von phonologischen Sprachaspekten von besonderer Relevanz.

Basierend auf dem aktuellen Forschungsstand betonen heutige funktionell-anatomische Modelle die Organisation von unterschiedlichen Sprachaspekten in verschiedenen Netzwerken, die ein hohes kompensatorisches Potential aufweisen (Bookheimer, 2002).

So postulieren beispielsweise Hickok und Poeppel (2000; 2004; 2007), dass sich die neuronale Repräsentation von Sprache analog zum visuellen System in einen dorsalen (sensorisch-motorischen) und einen ventralen (sensorisch-konzeptuellen) Strom gliedern lässt. Der dorsale Strom verbindet temporo-parietale Areale mit prämotorischen und inferior-frontalen Regionen und ist für die Umwandlung von auditorischem Input in motorisch-artikulatorischen Output verantwortlich. Im Gegensatz dazu ermöglicht der ventrale Strom, welcher Areale im mittleren Temporallappen mit dem ventrolateralen präfrontalen Kortex verbindet, die Verarbeitung von auditorischem Input zu Inhalt. Phonologische Aspekte von Sprache sind somit im dorsalen Strom repräsentiert, während semantische Aspekte den ventralen Strom aktivieren (siehe Saur et al., 2008).

Eine Vielzahl von Studien hat bestätigt, dass verschiedene linguistische Komponenten in unterschiedlichen Netzwerken organisiert sind. So konnte mittels fMRT nachgewiesen werden, dass phonologische Aspekte des Sprachverständnisses posterior gelegene Areale im Gehirn aktivieren, während semantische Aspekte in anterioren Arealen lokalisiert wurden (Costafreda et al., 2006; Vigneau et al., 2006).

Direkte Vergleiche von phonologischen mit semantischen Entscheidungsaufgaben zeigten erhöhte Aktivierung für phonologische im Vergleich zu semantischen Entscheidungen im bilateralen Gyrus supramarginalis (SMG) (Burton et al., 2003; Devlin et al., 2003; Price et al., 1997) und im linken posterioren Gyrus frontalis inferior (pIFG) (Burton et al., 2003; Devlin et al., 2003; McDermott et al., 2003). Im Gegensatz dazu aktivierten semantische im Vergleich zu phonologischen Entscheidungen den anterioren Teil des linken IFG (Burton et al., 2003; Gitelman et al., 2005; McDermott et al., 2003; Seghier et al., 2004).

Die funktionelle Relevanz dieser Aktivierungsunterschiede für phonologische und semantische Sprachaspekte konnte mit Hilfe von TMS nachgewiesen werden (z.B. Devlin et al., 2003; Gough et al., 2005; Nixon et al., 2004; Koehler et al., 2004). So ergab beispielsweise eine Untersuchung von Gough et al. (2005) eine funktionell-anatomische „doppelte Dissoziation“ des linken IFG: TMS über dem anterioren IFG störte die Verarbeitung semantischer Aspekte der Wortverarbeitung (haben zwei Wörter dieselbe Bedeutung?), wirkte sich jedoch nicht auf eine phonologische Aufgabe aus (klingen zwei Wörter gleich?). Hingegen beeinträchtigte TMS über dem posterioren IFG nur die Verarbeitung der phonologischen, nicht aber der semantischen Aufgabe.

Einige Autoren betonen, dass es ein gemeinsames fronto-temporales Netzwerk für Sprachverständnis und Sprachproduktion gibt (Burton et al., 2000; Heim & Friederici, 2003; Heim et al., 2003).
Eine Meta-Analyse von Indefrey und Levelt (2004) zielte auf die Identifikation der „Kernareale“ für die Produktion von Sprache ab. Die Autoren beschrieben Hirnareale, die an verschiedenen Sprachproduktions-Aufgaben wie z.B. dem Wiederholen von Wörtern oder Pseudowörtern oder dem Benennen von Bildern beteiligt waren.
Diese Areale umfassten das bilaterale (prä-) supplementär-motorische Areal (SMA) und verschiedene linkshemisphärische Areale wie den posterioren IFG und den prämotorischen Kortex.

Obwohl einige fMRT-Studien erhöhte Aktivität in rechtshemisphärischen Arealen während der Verarbeitung von Sprache gezeigt haben (Burton et al., 2003; Devlin et al., 2003; Price et al., 1997), wird im Allgemeinen eine Dominanz der linken Hemisphäre für Sprache angenommen (z.B. Lindell, 2006). Dementsprechend fokussieren die meisten Studien im Sprachbereich auf die Beiträge der linken Hemisphäre.

Das Ziel der vorliegenden Dissertation war die Untersuchung **der Repräsentation phonologischer Aspekte von Sprachverständnis und Sprachproduktion im gesunden Gehirn. Insbesondere der Beitrag der rechten Hemisphäre an modalitäts-unabhängigen Aspekten der phonologischen Verarbeitung** sollte untersucht werden.
Dazu wurden verschiedene Studien durchgeführt, die eine Kombination von fMRT und TMS nutzten. Diese Kombination ermöglichte die nicht-invasive Messung von neuronalen Funktionen mit einer hohen räumlichen und zeitlichen Auflösung.

Die erste Studie beschäftigte sich mit der Fragestellung, ob phonologische und semantische Aspekte des Sprachverständnisses unabhängig von der Darbietungsmodalität der Wortstimuli (auditorisch oder visuell) separate Hirnregionen aktivieren. Die meisten bisherigen Studien beschränkten sich auf die Untersuchung visueller Wortverarbeitung (z.B. Devlin et al., 2003; Gitelman et al., 2005; McDermott et al., 2003). Der direkte modalitätsunabhängige Vergleich von phonologischen und semantischen Aspekten des Wortverständnisses wurde bisher nicht erbracht.
Unter der Annahme, dass die „Kernareale” für Sprachverständnis modalitätsunabhängig sein sollten, wurden in der ersten Studie die funktionellen Aktivierungsmuster phonologischer

Entscheidungen (hat ein Wort zwei oder drei Silben?) mit denen semantischer Entscheidungen (repräsentiert ein Wort ein natürliches oder ein vom Menschen gefertigtes Objekt?) verglichen. Dabei wurden einer Gruppe von gesunden Rechtshändern Wörter im fMRT sowohl visuell also auch auditiv dargeboten.

Im Einklang mit früheren Untersuchungen (Burton et al., 2003; Devlin et al., 2003; Price et al., 1997) weisen die Ergebnisse dieser fMRT-Studie darauf hin, dass phonologische im Vergleich zu semantischen Entscheidungen bilateral den Gyrus supramarginalis (SMG) aktivieren. Im Gegensatz dazu erbrachte der Vergleich semantischer mit phonologischen Entscheidungen den Nachweis einer Beteiligung des linken anterioren Gyrus frontalis inferior (IFG) am semantischen Sprachverständnis.

Die Ergebnisse dieser Studie zeigen zum ersten Mal, dass die Beteiligung des bilateralen SMG an phonologischen Entscheidungen und des linken aIFG an semantischen Sprachaspekten unabhängig von der Modalität der Stimuluspräsentation ist.

Die zweite Studie untersuchte die funktionelle Relevanz dieser fMRT-Aktivierungsmuster. Dazu wurden einer anderen Gruppe von gesunden Rechtshändern dieselben phonologischen und semantischen Aufgaben sowohl auditiv als auch visuell dargeboten. Während der Bearbeitung der Aufgaben wurde hochfrequente 10 Hz TMS randomisiert über dem linken, rechten oder bilateralen SMG appliziert.

Dieses Design ermöglichte die Untersuchung der Fragestellung, ob der rechte SMG essentiell an phonologischen Entscheidungen beteiligt ist. Wäre dies der Fall, müssten sich die Reaktionszeiten oder Fehlerraten in der phonologischen Aufgabe erhöhen, wenn TMS über dem rechten SMG appliziert wird. Falls die Aktivierung des rechten SMG jedoch nicht essentiell für die Durchführung phonologischer Entscheidungen ist, sollte der störende Effekt der TMS auf den linken SMG begrenzt sein.

Ferner wurde untersucht, ob der linke bzw. rechte SMG eine „Läsion“ des jeweils anderen kompensieren kann: Wenn phonologische Entscheidungen mit der Aktivierung des linken *oder* rechten SMG möglich sind, sollte der Läsionseffekt der TMS stärker sein, sofern diese bilateral appliziert wird. Falls der linke und rechte SMG jedoch *gleichermaßen* relevant für phonologische Entscheidungen sind, sollte sich der Effekt der TMS nicht ändern, wenn diese unilateral oder bilateral appliziert wird (Price & Friston, 2002).

Die Ergebnisse dieser zweiten Studie zeigen, dass TMS im Vergleich zu einer ineffektiven Scheinstimulation sowohl Reaktionszeiten als auch Fehlerraten in der phonologischen, jedoch nicht in der semantischen Aufgabe, erhöhte. Dieser Effekt war gleichermaßen für die

Stimulation des linken, rechten und beidseitigen SMG ausgeprägt. Zwar war die Verlängerung der Reaktionszeiten stärker für auditiv als visuell präsentierte Wörter, wurde aber in beiden Modalitäten signifikant. Diese Ergebnisse zeigen zum ersten Mal, dass sowohl der linke als auch der rechte SMG essentiell an effizienten phonologischen Entscheidungen beteiligt sind.

In der dritten Studie wurde untersucht, ob eine bilaterale Beteiligung an phonologischen Verarbeitungsprozessen auch für den posterioren Gyrus frontalis inferior nachzuweisen ist. Dieses Areal wurde in früheren Studien mit phonologischer Verarbeitung assoziiert. Obwohl einige fMRT Studien an Gesunden eine Aktivierung des linken und rechten pIFG fanden (z.B. Devlin et al., 2003; Poldrack et al., 1999; Shibahara, 2004), beschränkten sich die bisherigen TMS-Untersuchungen zur funktionellen Relevanz dieser Aktivierungsmuster ausschließlich auf die linke Hemisphäre (Gough et al., 2005; Nixon et al, 2004; Romero et al., 2006). Somit bleibt bisher unklar, ob der rechte pIFG essentiell an der Verarbeitung phonologischer Entscheidungen beteiligt ist.
Das experimentelle Design dieser Studie war vergleichbar mit dem der zweiten Studie (siehe oben). TMS wurde dabei über dem rechten, linken oder bilateralen pIFG appliziert, während gesunde Rechtshänder phonologische oder semantische Entscheidungsaufgaben bearbeiteten. Eine zweite Probandengruppe wurde während derselben Aufgaben über dem anterioren IFG stimuliert. Mithilfe dieses Designs konnten drei verschiedene Erklärungsansätze für rechtshemisphärische Aktivierung während phonologischer Entscheidungen überprüft werden:
Die erste Hypothese war, dass der rechte pIFG essentiell zur Geschwindigkeit und Effizienz (speed and efficiency) von phonologischen Entscheidungen beiträgt. Unter dieser Annahme könnte eine Läsion des rechten pIFG übersehen werden, sofern keine Messung der Reaktionszeiten erfolgt. Somit sollte eine Stimulation des rechten pIFG mit TMS eine signifikante Verlängerung der Reaktionszeiten, jedoch keine Beeinträchtigung der Fehlerrate in gesunden Probanden bewirken.
Eine Alternativerklärung für die Aktivierung des rechten pIFG in Studien an Gesunden besagte, dass der rechte pIFG für richtige und effiziente phonologische Entscheidungen im gesunden Hirn relevant ist, diese Funktion jedoch nach einer Läsion von anderen Hirnregionen kompensiert werden kann. Gemäß dieser Hypothese sollte sich eine Läsion des rechten pIFG kurzzeitig während der akuten Phase nach einer Hirnschädigung auf die Geschwindigkeit und Genauigkeit phonologischer Entscheidungen auswirken, sie könnte aber

aufgrund von funktioneller Reorganisation bereits in der chronischen Phase kompensiert werden. Für eine TMS-induzierte Läsion im gesunden Gehirn während der Aufgabenbearbeitung wäre somit in Analogie zur akuten Phase nach einer Hirnschädigung eine unmittelbare Auswirkung auf die Reaktionszeiten und Fehlerraten zu erwarten.
Als dritte Möglichkeit wurde in Betracht gezogen, dass der rechte pIFG nicht notwendig für die Geschwindigkeit und Genauigkeit phonologischer Entscheidungen ist. In diesem Falle wäre die rechtshemisphärische pIFG Aktivierung im fMRT zufällig gewesen und redundant für die phonologische Verarbeitung (Price & Friston, 2002).
Unter Annahme dieser Hypothese sollte sich eine TMS-induzierte Läsion des rechten pIFG weder auf die Reaktionszeiten noch auf die Fehlerraten während einer phonologischen Entscheidung auswirken.

Die Ergebnisse dieser Studie zeigen, dass sowohl der linke als auch der rechte pIFG essentiell an effizienten phonologischen Entscheidungen beteiligt sind. So zeigte sich bei Stimulation des pIFG eine Verlängerung der Reaktionszeiten und Fehlerraten für die phonologische aber nicht die semantische Aufgabe. Dieser Effekt war unabhängig davon, ob links-, rechts- oder beidseitig stimuliert wurde. Zudem war der Effekt nicht abhängig von der Darbietungsmodalität der Stimuli. TMS über dem linken, rechten oder bilateralen aIFG wirkte sich hingegen weder auf die Bearbeitung der phonologischen noch der semantischen Aufgabe aus.
Diese Ergebnisse bestätigen bisherige Studien, die die funktionelle Relevanz des linken pIFG für phonologische Aspekte des Sprachverständnisses betonen (Gough et al., 2005; Nixon et al., 2004; Romero et al., 2006). Darüber hinaus weisen die Ergebnisse dieser Studie darauf hin, dass sich die funktionelle Relevanz nicht nur auf die linke Hemisphäre beschränkt, sondern dass der linke und rechte pIFG gleichermaßen relevant zur Effizienz und Genauigkeit phonologischer Entscheidungen beitragen und dass dieser Beitrag unabhängig von der Modalität der Wortpräsentation ist.

Die vierte Studie zielte schließlich darauf ab, Hirnareale zu identifizieren, die an phonologischen Aspekten der Sprachproduktion beteiligt sind.
In dieser Studie wiederholten gesunde Rechtshänder auditiv und visuell dargebotene Pseudowörter (Phantasiewörter ohne semantischen Gehalt, z.B. „Beudo“) und Wörter. Dabei wurde ihre Hirnaktivität mittels fMRT gemessen. Der Vergleich von Pseudowörtern mit realen Wörtern wurde genutzt, um phonologische Aspekte der Sprachproduktion abzubilden

(vgl. Ghosh et al., 2008). Es zeigte sich, dass das Nachsprechen von Pseudowörtern im Vergleich mit Wörtern unabhängig von der Darbietungsmodalität eine erhöhte Aktivierung im rechten prä-supplementär-motorischen Areal (prä-SMA) und im linken posterioren Gyrus frontalis inferior (pIFG) erzeugte. Mithilfe von Konnektivitätsanalysen (Psychophysiologischen Interaktionen) konnte darüber hinaus nachgewiesen werden, dass beide Areale während des Nachsprechens von Pseudowörtern im Vergleich zu Wörtern eine stärkere funktionelle Kopplung mit dem linken ventralen prämotorischen Kortex (PMv) aufwiesen.
Diese Ergebnisse erweitern bisherige Erkenntnisse zur Sprachproduktion (z.B. Ghosh et al., 2008; Indefrey & Levelt, 2004; Saur et al., 2008), indem sie zeigen, dass das aktive Nachsprechen von Pseudowörtern unabhängig von der Darbietungsmodalität der Stimuli ein Netzwerk aus Hirnregionen aktiviert, die am phonologischen Enkodieren sowie der Planung und Initiation von artikulatorischen Prozessen beteiligt sind. Dieses Netzwerk schließt die rechte prä-SMA, den linken pIFG und den linken PMv ein.

Insgesamt deuten die Ergebnisse der vorliegenden Studien darauf hin, dass phonologische Prozesse nicht wie bisher angenommen vornehmlich in der linken Hemisphäre verarbeitet werden. Vielmehr zeigen die vorliegenden Ergebnisse, dass für effiziente phonologische Entscheidungen Areale beider Hemisphären gleichermaßen relevant sind. Basierend auf den Ergebnissen der ersten drei Studien wird ein bilaterales Netzwerk für die modalitätsunabhängige phonologische Verarbeitung von Wörtern angenommen. Dieses Netzwerk umfasst den linken und rechten Gyrus supramarginalis sowie den linken und rechten posterioren Gyrus frontalis inferior (vgl. Abbildung 9).
Die Ergebnisse der vierten Studie zeigen, dass phonologischen Aspekten der Sprachproduktion ebenfalls ein bilaterales Netzwerk zugrunde liegt. Dieses Netzwerk verbindet die rechte prä-SMA und den linken pIFG mit dem linken PMv und dient dem phonologischen Enkodieren sowie der Vorbereitung und Initiierung von artikulatorischen Prozessen der aktiven Sprachproduktion (Abbildung 10).

Zusammenfassend lässt sich feststellen, dass die Ergebnisse der vorliegenden Arbeit die bisher in der Literatur vorherrschende Dominanz der linken Hemisphäre für die Verarbeitung von Sprache in Frage stellen. Vielmehr scheinen für phonologische Aspekte der Sprachverarbeitung sowohl die linke als auch die rechte Hemisphäre eine gleichermaßen wichtige Rolle zu spielen. Der linke posteriore Gyrus frontalis inferior weist gemäß den

vorliegenden Ergebnissen eine Beteiligung sowohl an phonologischen Aspekten des Sprachverständnisses als auch der Sprachproduktion auf.
Weitere Studien werden zeigen, wie die postulierten Netzwerke interagieren und welche Auswirkungen eine vorübergehende TMS-induzierte Funktionsunterbrechung phonologischer Areale auf die Aktivierungsmuster während der Sprachproduktion hat. Hierbei wird erwartet, dass eine Funktionsunterbrechung linkshemisphärischer Areale zu einer kompensatorischen Mehraktivierung der rechten homologen Areale führt.

Abschließend bleibt anzumerken, dass die vorliegende Arbeit auf die Relevanz rechtshemisphärischer Areale für die Verarbeitung phonologischer Sprachkomponenten im gesunden Gehirn hinweist. Dieses Ergebnis motiviert eine systematische Untersuchung der funktionellen Relevanz von rechtshemisphärischen Arealen nach einer Schädigung der linken oder rechten Hemisphäre: So könnten homologe rechtshemisphärische Areale eine relevante Rolle für die Reorganisation und Erholung nach *linkshemisphärischen* Läsionen spielen. Umgekehrt könnten systematische Untersuchungen mit sensitiven Tests an Patienten mit *rechtshemisphärischen* Läsionen im Gyrus supramarginalis oder Gyrus frontalis inferior zeigen, dass diese Patienten in der akuten oder subakuten Phase nach einem Schlaganfall anders als bisher angenommen ebenfalls Defizite bei der Verarbeitung phonologischer Sprachaspekte aufweisen.

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8 Appendix

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VII **Hartwigsen, G.**, Ulmer, S. Baumgaertner, A. & Siebner, H.R.
A frontal network for pseudoword repetition. *In preparation for Cerebral Cortex.*

Appendix I

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How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition

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ABSTRACT

Transcranial magnetic stimulation (TMS) uses a magnetic field to ''carry'' a short lasting electrical current pulse into the brain where it stimulates neurones, particularly in superficial regions of cerebral cortex. TMS can interfere with cognitive functions in two ways. A high intensity TMS pulse causes a synchronised high frequency burst of discharge in a relatively large population of neurones that is terminated by a long lasting GABAergic inhibition. The combination of artificial synchronisation of activity followed by depression effectively disrupts perceptual, motor and cognitive processes in the human brain. This transient neurodisruption has been termed a ''virtual lesion''. Smaller intensities of stimulation produce less activity; in such cases, cognitive operations can probably continue but are disrupted because of the added noisy input from the TMS pulse.

It is usually argued that if a TMS pulse affects performance, then the area stimulated must provide an essential contribution to behaviour being studied. However, there is one exception to this: the pulse could be applied to an area that is not involved in the task but which has projections to the critical site. Activation of outputs from the site of stimulation could potentially disrupt processing at the distant site, interfering with behaviour without having any involvement in the task.

A final important feature of the response to TMS is ''context dependency'', which indicates that the response depends on how excitable the cortex is at the time the stimulus is applied: if many neurones are close to firing threshold then the more of them are recruited by the pulse than at rest. Many studies have noted this context-dependent modulation. However, it is often assumed that the *excitability* of an area has a simple relationship to *activity* in that area. We argue that this is not necessarily the case. Awareness of the problem may help resolve some apparent anomalies in the literature.

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1. Introduction

Transcranial magnetic stimulation (TMS) provides a method of stimulating human brain through the intact skull without producing significant discomfort (Barker et al., 1985). After its introduction in 1985, it soon became evident that TMS can be used to interfere transiently with cortical processing. For instance, TMS can suppress visual perception of briefly presented trigrams when a single TMS pulse is applied to the occipital cortex 80–100 msec after stimulus onset (Amassian et al., 1989). This type of disruptive effect of TMS on cortical function is often referred to as a ''virtual lesion'' (Pascual-Leone et al., 2000). Such effects are usually created by applying a single pulse or a short high-frequency train of stimuli to the cortical area of interest during an experimental task. The approach is now widely used in cognitive neuroscience to interfere with a wide range of brain functions, including perception, motor execution, or higher-level cognitive processes. The popularity of TMS as a means of studying perceptual and cognitive processes in the intact human brain contrasts with the limited knowledge about the mechanisms by which TMS disrupts brain function. The aim of this review is to summarize some important features of TMS and their implications for investigating brain-behaviour relations with ''neurodisruptive'' TMS. This review only deals with the acute ''online'' effects of TMS on brain function. Regarding the physiology underlying the conditioning effects evoked by repetitive TMS we refer to recent reviews of this topic (Siebner and Rothwell, 2003; Thickbroom, 2007).

2. Basic principles of TMS

The basic principles of TMS have been covered in many excellent reviews (Amassian and Maccabee, 2006; Bestmann, 2008; Pascual-Leone et al., 2000; Ziemann et al., 2008). For the present purposes three features are important when considering the ''virtual lesion'' effect. First, the electrical pulse induced in the brain is very short lasting. A typical monophasic pulse current rises to a maximum and has reversed towards zero in about 200 μs. This leads to highly synchronous activation of neurones.

Second, the stimulation is not focal. With a circular TMS coil, the maximum electric field induced in the brain lies in an annulus under the coil; to an approximation, coils wound in a figure of eight shape are equivalent to two circular coils in which the fields summate at the point of overlap. Thus they produce about twice the field under the junction region as at the edges of the wings, but even so the effective area of stimulation is still several square cm. It is impossible to give an exact answer about the volume of tissue stimulated by any TMS coil. This depends on the geometry of the coil as well as the stimulus intensity and the electrical properties of the cortex under the coil (see below). However, if focality of stimulation is the aim then it is clearly desirable to use as low a stimulus intensity as possible to prevent inadvertent activation of distant structures.

The third important feature of TMS is that the magnetic field (which induces electric current in the brain) falls off very rapidly with distance from the TMS coil. The exact relation depends on the size of the coil, but for a typical coil, the field at a distance of 4 cm may be only about 30% of that at the coil surface. This means that superficial areas of cortex are easy to stimulate, but those deep in a sulcus or far from the scalp surface such as mesial temporal or frontobasal cortex have a much higher threshold. In fact even if it is possible to activate these structures at high TMS intensities, other areas that lie superficial to the intended site will be activated even more strongly, so that any behavioural effect will be difficult to attribute to stimulation of the deep structure alone.

3. How does the electrical field induce action potentials in cortical axons?

Experiments in the motor cortex have measured the strength-duration relationship of the pulses that are needed to evoke electromyographic (EMG) activity in contralateral muscles. This relates the duration of the induced electrical current to the amplitude needed to evoke a response of a given size. The form of the curve suggests that TMS stimulates axons, and not cells because axons are most efficiently activated by a short duration pulse whereas cells require longer pulses. Exactly which axons are stimulated is not known. However, whichever they are, it is thought that excitation occurs in the grey matter of the cortex rather than in the subcortical white matter (Edgley et al., 1997) since the former is nearer the scalp surface and has a lower electrical resistance than the underlying white matter.

There is one other rule about excitation of axons that has unexpected consequences for TMS: Stimulation occurs when the spatial derivative of the electrical potential (i.e., the ''rate'' at which potential changes with distance) along the length of the axon exceeds a certain (negative) value. Effectively, stimulation is most likely to occur when there is a large change in voltage along the length of an axon. The result of this is that if an axon followed a circular course exactly under a circular TMS coil, then it would never be activated since the electrical field would be the same all along its length. The best way for it to experience a voltage gradient would be if the axon were bent out of the circle at one point. Stimulation would occur at the bend since this is the location of the maximum spatial derivative of the field.

In fact, experiments with single axons as well as theoretical calculations show that TMS is most likely to activate axons at a point where they bend out of the electric field (Maccabee et al., 1998). Since TMS coils induce electrical fields that are oriented in particular directions under the coil it is easy to see that changing the orientation of the coil is very likely to change the population of axons that are activated. This particularly applies to figure of eight coils where the electric field is aligned parallel to the junction region, and can therefore be easily rotated by rotating the coil.

The importance of the geometrical relation between the main orientation of the induced field and the neuronal structures that are to be stimulated has been demonstrated both for TMS over the hand area of the primary motor cortex ($M1_{HAND}$), and for TMS over the occipital cortex. TMS of the $M1_{HAND}$ is most effective if the induced current in the brain

runs approximately perpendicular to the central sulcus in a posterolateral to anteromedial direction (Mills et al., 1992). Similarly, the optimal current direction for stimulation of primary visual cortex to elicit a visual phosphene occurs when the coil is oriented perpendicular to the gyrus under the coil at the site of stimulation (Kammer et al., 2007). The observation that the direction of the induced tissue current contributes to the efficacy of TMS is also relevant to ''neurodisruptive'' TMS studies that target other cortical areas. For instance, the TMS-induced current orientation had a significant impact on task performance when TMS was given over the prefrontal cortex during a memory-guided saccade task, presumably because different neuronal populations were disrupted at different current orientation (Hill et al., 2000).

In addition to these macroanatomical aspects, the micro-geometry of each cortical neuronal population and the degree of axonal myelination determine the susceptibility of a given neuronal population to the induced electrical current. Interneurones with a short non-myelinated axon and a large tree arbour are less susceptible than longitudinally oriented pyramidal cells with a large-diameter myelinated axon and a dendritic tree located at the opposite site of the soma to the axon.

The bottom line is that it is still poorly understood which set of axons is initially activated by the electrical field induced by TMS. Factors such as the degree of axonal myelinisation, the cell type, and the presence of large bending axons are all known to have an important influence. At the present time it is safe to conclude that the electrical field preferentially excites the axons of a subset of neurones in the stimulated cortex.

4. Influences on activity at brain regions distant from the site of stimulation

There are two ways in which TMS at one site can influence activity at another site. First, the stimulus might directly change activity in axonal projections to other areas. This would lead to synaptic activity in the target zone and directly change patterns of activity in that structure. The second possibility is more indirect. Many cognitive operations are processed by ongoing interactions within spatially separate networks of neurones. In such a case, TMS at one node in the network can lead to changes in distant zones even if they are not directly connected to the stimulus site. This is because changing activity at any site will have knock-on effects throughout the network.

The fact that MEPs can be recorded in hand muscles after TMS of the $M1_{HAND}$ is may be the most obvious demonstration that focal excitation in the cortical target area does not remain confined to the site of stimulation. In this case, the stimulated area is at least two synapses distant from the muscle, and shows that regional excitation in the target area readily spreads within the nervous system via pre-existing neuronal connections in a network.

Within the brain, cortico–cortical interactions via directly connecting pathways have been successfully studied by stimulating two cortical motor areas with TMS (two-site TMS as opposed to single-site TMS). For instance, a TMS pulse given to one $M1_{HAND}$ can influence the excitability of $M1_{HAND}$ in the opposite hemisphere (Di Lazzaro et al., 1999; Ferbert et al., 1992). The effect may be facilitatory or inhibitory depending on the intensity of stimulation and is probably conducted via fibres in the corpus callosum since these interhemispheric interactions are absent after callosotomy. Cortico–cortical synapses are thought to be excitatory and glutamatergic, so that inhibitory effects are presumably mediated via an interneurone in the receiving cortex. The conclusion is that behavioural effects of a TMS pulse may be due not only to activation at the site of stimulation but also to direct inputs to remote areas of cortex. As at the site of stimulation, the mechanism of these remote effects depends on stimulus intensity.

At the network level, complex changes in activity patterns can be studied by analysing how TMS modulates oscillatory activity in the brain. Analysis of event-related electroencephalographic (EEG) activity shows that a single pulse of TMS induces a characteristic negative deflection at 45 msec (N45) and a transient oscillation in the beta frequency-range (15–30 Hz) close to the stimulation site (Paus et al., 2001; Van Der Werf and Paus, 2006). It has been proposed that these oscillations reflect TMS-induced resetting of natural brain oscillators by the TMS pulse. Event-related coherence analysis revealed that single-pulse TMS enhanced coherence in the alpha band between both hemispheres within the first 500 msec after the pulse which was also interpreted in the context of resetting (Fuggetta et al., 2005). These studies raise the interesting possibility that some of the neurodisruptive effects of TMS may be related to the resetting of ongoing inter-regional network activity.

5. Interference with function

There are two main ways in which TMS could interfere with function: it could prevent activity by silencing neurones (the ''virtual lesion'') or it could add extra ''noisy'' activity to ongoing processing. In practice it seems likely to be a combination of each, with the balance depending on the intensity of stimulation.

Physiological studies have shown that a single TMS pulse to the $M1_{HAND}$ area that is suprathreshold for evoking a muscle contraction on the opposite side of the body produces a complex pattern of activity in the cortex. The initial effect is the induction of synchronised high frequency discharges in pyramidal output neurones at frequencies of around 600 Hz. These last for up to about 10 msec and are followed by a long lasting GABAergic inhibition.

The evidence for the former comes from recordings from epidural stimulating/recording electrodes that have been implanted in the spinal epidural space of patients for the treatment of pain and other conditions (Di Lazzaro et al., 2004). They show that a suprathreshold TMS pulse produces a series of 4 or more descending volleys of activity, each separated from the next by about 1.5 msec (i.e., about 600 Hz). These are thought to be analogous to the D and I waves seen in recordings of corticospinal activity in animals after direct electrical stimulation of the exposed cortex (Amassian and Cracco, 1987). The initial D wave, which is seen only at high

intensities, is the result of activation of corticospinal axons in the subcortical white matter, whilst the lower threshold I waves that follow are the result of repetitive excitatory synaptic inputs to the same neurones.

Evidence for emergence of a large GABAergic IPSP comes from examining the effects if TMS pulses are applied while the subject is maintaining a background contraction of the target muscle. In this case, the MEP is followed by a period of silence in ongoing activity that lasts 100 msec or more (the cortical silent period, CSP). The later part of this from about 50 to 75 msec onwards represents suppression of motor cortical output. The duration of the CSP increases with the intensity of stimulation and can reach several hundreds of milliseconds (Haug et al., 1992; Inghilleri et al., 1993). The duration of the CSP can be markedly prolonged by intrathecal application of a $GABA_B$-agonist, suggesting that the CSP is mediated by the induction of $GABA_B$-mediated long-lasting inhibitory postsynaptic potentials (IPSPs) (Siebner et al., 1998).

This combination of artificial neural synchronisation plus a long lasting IPSP is the main evidence for the ''virtual lesion'' effect. Together they prevent the continuation of any ongoing neural activity that might have been of behavioural relevance. However, the depth of inhibition and the extent of synchronisation depends on the intensity of the TMS pulse. Thus, intensities that are at threshold for producing a MEP induce only 2–3 discharges in the initial burst, and the silent period is absent or very short. Intensities that are below threshold for generating any MEP can generate activity in the cortex, but this is primarily inhibitory. In the motor area it can be seen either as a small and short lasting suppression of ongoing EMG activity, or (more clearly) as suppression of a subsequent MEP evoked by a suprathreshold pulse (Kujirai et al., 1993).

Such small changes in activity may be insufficient to prevent ongoing processing and are better thought of as added ''noise'' rather than a ''lesion''. The result of adding such noise could reduce task performance or increase decision times because neural activity would have to be sampled for longer in order for optimal discrimination of signal and noise. However, addition of noise can also have the opposite effects. The phenomenon of stochastic resonance depends upon addition of an appropriate amount of noise bringing a subthreshold input signal to threshold: in this case, noise enhances processing.

In practical terms it can be difficult in any one situation to disentangle whether the effect of a TMS pulse is equivalent to a ''virtual lesion'' or to addition of ''noise''. However, a recent experiment in the visual system addressed this quite successfully (Harris et al., 2008). Subjects had to discriminate briefly presented contrast gratings to which various amounts of visual noise could be added. In addition they could also receive a TMS pulse 100 msec after the presentation of the grating. Addition of either a TMS pulse or visual noise increased subjects' detection threshold. However, if both were applied in the same trial, the effect of TMS and visual noise were not additive, they were multiplicative. The implication was that the TMS pulse was not adding ''noise'' to the system; the results were best interpreted as a loss of signal effect caused by TMS.

6. State dependency of TMS in the motor cortex

MEP measurements initially highlighted another fundamental feature of TMS by showing that the state of the stimulated cortex has a marked influence on the effect of TMS. Voluntary pre-contraction of the target muscle is an impressive example how strongly a change in functional state can impact on the brain response that can be elicited with TMS: a magnetic stimulus that is just suprathreshold for evoking a motor response will induce a considerably larger motor response in the target muscle if the subject performs a slight voluntary pre-contraction. It is important to note that these relationships occur because the responses that are measured require activation of synaptic connections. Thus, the number of axons that are stimulated by the TMS pulse probably changes very little with changes in activity. However, spread of excitation along synaptic connections is highly state dependent.

The state of the cortex not only determines the overall neuronal response of the stimulated cortex but also shapes the responsiveness of distinct subpopulations of cortical neurones. When participants prepare to grasp different objects, transcranial excitability of cortico–cortical inputs to the corticospinal output neurones that project from $M1_{HAND}$ to the muscles that will be used for the grasp was specifically enhanced for at least 600 msec before the grasping movement (Cattaneo et al., 2005). There is also evidence that the excitability of cortical motor representations that do not subserve a specific movement are actively inhibited during movement execution and thus, become less responsive to TMS (Sohn and Hallett, 2004; Stinear and Byblow, 2003). Context-dependent changes in the excitability of distinct motor representations within the $M1_{HAND}$ have been demonstrated in many TMS studies on motor control, including passive movements (Lewis et al., 2001), action observation (Gangitano et al., 2001; Strafella and Paus, 2000), and motor imagery (Stinear and Byblow, 2003, 2004).

It is tempting to conclude that the relative level of activity in distinct neural populations within the stimulated region determines the responsiveness of these populations to TMS. Thus, it is often asserted if neuronal populations in the $M1_{HAND}$ are active in a motor task then they will be more readily activated to produce a larger motor response to TMS. Conversely, those sets of neurones that are inactive during a task or even inhibited, will be less excitable and show a context dependent reduction in MEP amplitude. However, careful examination of the examples above shows that it is clearly incorrect to equate *activity* in a population with *excitability* to TMS. For example, in the experiments of Cattaneo et al. (2005) on grasping, TMS responses are facilitated in muscles that are about to be used in a forthcoming grasp, but at the time of the stimulus, those neurones are not actually actively discharging.

Physiological studies show that as a rough rule, neurones are most excitable when their membrane potential is just below threshold but not discharging. Conversely, if they discharge at high rates then the excitability declines. However, the exact relationships depend on a variety of factors including amplitude of the input versus ongoing noise

as well as changes in membrane resistance as well as membrane potential.

A model of the responsiveness of a single spinal motoneurone explored by Matthews (1999) illustrates how complex the relation can be (Fig. 1a). The simulation shows that a given excitatory input to a motoneurone produces a steeply rising increase in response probability when at rest (MN silent), whereas if the motoneurone is already discharging at say 10 Hz, then small inputs have a greater probability of producing firing than at rest whereas large inputs are less effective than at rest. In TMS terms the input is equivalent to the synaptic input evoked by the axons that had been activated by the stimulus (which as noted above we can assume to be constant since axonal threshold is not much affected by the mean level of ongoing activity). The output is cell discharge which can potentially cause the "virtual lesion" or added "noise" effect. The graph implies that if all other factors are controlled, the effect of small TMS pulses might be facilitated if the cortex is active, whereas the response to a higher intensity pulse might be suppressed relative to rest.

The size of the input in relation to ongoing synaptic activity is also important (see Fig. 1b). Thus for any level of activity in the cortex, the synaptic input could be relatively constant (i.e., low noise) or it could fluctuate a great deal (high noise). The motoneurone model shows that the probability that a given input (i.e., a TMS pulse) will activate neurones is much reduced during periods of high noise (twofold synaptic noise). Given that BOLD contrast imaging is very sensitive to levels of synaptic activity this would lead to the paradoxical conclusion that areas appearing to have a highly active BOLD response during a particular task might actually be less responsive to TMS inputs. The conclusion is that although state-dependency of TMS responses clearly occurs, the interpretation of the effects and generation of rules about what might happen in other conditions is very difficult.

7. State dependency of TMS effects in the visual cortex

The state dependency of TMS-induced functional effects has also been demonstrated in the visual cortex by measuring the threshold for inducing illusory visual percepts (phosphenes) with occipital TMS (Bestmann et al., 2007a; Romei et al., 2008; Silvanto et al., 2007). The moment to moment expression of alpha activity in the occipital EEG positively correlated with the phosphene threshold (Romei et al., 2008). It is tempting to say that alpha power indicates that the occipital cortex is in an idling state, and therefore that this state is less excitable by TMS. Although correct, this is no more than a restatement of the results and not a causal explanation. In fact, rather than being idle, the presence of high levels of alpha indicate that quite a lot of synaptic activity is going on. The important thing is that compared with periods of low alpha, the activity is more synchronised when alpha levels are high. So why are phosphenes more difficult to evoke during periods of high alpha activity? One possibility is that during periods of high alpha, the TMS pulse can only activate neurones on one (depolarised) half of each cycle, whereas there would be a much higher probability of activation if there were smaller swings in synaptic potential. However, this is speculation; the model above warns us that intuition is not to be relied on in such conditions. For example, a completely different explanation could be that the actual response to TMS is the same in all states, but that perceptual discrimination is more difficult during periods of synchronised (high alpha) activity.

In another study, colour adaptation was used as an experimental manipulation to induce an imbalance in the activity of distinct neuronal populations within the same visual areas (Silvanto et al., 2007). In a first experiment, subjects adapted to a uniformly coloured stimulus which produced a visual afterimage of the complementary colours in the same spatial arrangement as the adapting stimulus.

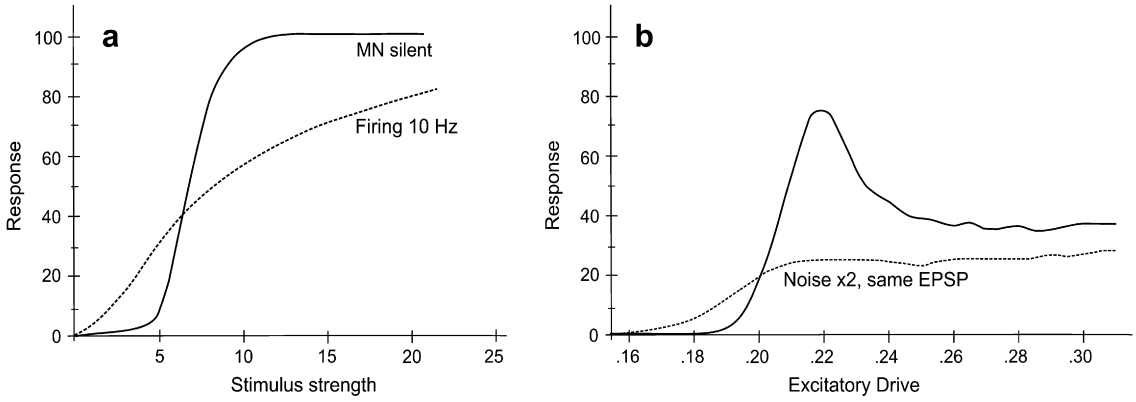

Fig. 1 – Model of the responsiveness of a single spinal motoneurone to a synaptic input. In panel a, the abscissa shows the conductance change of a stimulus with increased excitatory conductance. The ordinate gives the response of the unit; it shows the number of extra spikes, above the resting level, produced by the stimulus and is expressed as the percentage probability of the unit responding to the stimulus (i.e., the increase in its 'firing index'). MN = motoneurone. Panel b depicts the variation of the response size depending on a twofold change in synaptic noise. The abscissa plots the background excitatory conductance. The occurrence of a maximum depends upon the size of the stimulus relative to the noise rather than upon its absolute magnitude [adapted from Matthews (1999)]. Reproduced with permission of Blackwell Publishing Ltd.

During this state of imbalance with increased activity of neuronal representations that are the colour of the afterimage and reduced activity of neuronal representations of the colour of the adapting stimulus, single-pulse TMS was applied at 110% of individual phosphene threshold. In this state of functional imbalance, TMS-induced phosphenes, which are usually colourless, assumed the colour to which subjects were adapted "as if a region of the visual afterimage had been replaced with the colour of the adapting stimulus" (Silvanto et al., 2007). Similar results were obtained in a task in which participants had to detect the colour of briefly presented gratings that were either congruent with the adapting stimulus (i.e., same colour and orientation), incongruent (i.e., opposite colour and orientation) or partly congruent (shared either colour or orientation) after adapting to a conjunction of orientation and colour. Three pulses of TMS were given to the visual cortex 0, 50, and 100 msec after target onset. In the control condition, visual adaptation enhanced the detection of stimuli incongruent with the adapting stimulus and depressed detection of fully congruent stimuli. Application of TMS cancelled the adaptation-induced difference in detection performance between the fully incongruent stimuli and fully congruent stimuli.

Based on these results it was argued that the neuro-disruptive effects of TMS have a relatively greater impact on less active neurones, akin to microstimulation of the less active neural populations (Silvanto et al., 2007). At first sight this might seem a little counterintuitive if we go back to the original assumption that *activity* equals *excitability*. In this case, the less active, adapted neurones should be less excitable. However, as we can see from the model above this is not necessarily the case.

To understand this it is important to go back to the experiment. When subjects stare at, say, a red pattern, the red photoreceptors of the retina become fatigued and less sensitive to red light. Thus, when subjects then look at a white background, the red receptors are less active than the blue and green ones and the subject sees cyan where s/he had previously seen red. Presumably at the cortex, this means that neurones responsive to red inputs will receive less than normal red input, and hence they discharge fewer impulses in comparison with the blue and green sensitive neurones. In this state, it is possible that they are more readily activated by a TMS pulse than the more rapidly discharging blue and green neurones. Thus, in the first experiment with phosphenes, the percept evoked will be "redder" than usual.

It is more difficult to analyse what may have happened in the second experiment. Although there may have been some adaptation of retinal red receptors, the fact that the effect was selective for both orientation and colour of the grating suggests that it involves cortical rather than retinal adaptation. Without any TMS, prolonged viewing of a red, 45 ° angle grating might cause adaptation of a set of colour/orientation selective neurones in visual cortex. This would reduce subsequent detection of a grating with the same orientation and colour. If there existed some antagonistic interaction between orientation/colour selective neurones then we might also expect the observed increase in detection of gratings of the opposite orientation and complementary colour.

The authors speculate that adaptation to a 45 °/red grating increases the sensitivity of the orientation/colour neurones in the cortex to TMS. Thus in trials where TMS is given, the 45 °/red neurones are activated more than other orientation/colour neurones. This brings their sensitivity to visual inputs back to baseline, and detection of 45 °/red grating is increased. It would also provide a competing activity that would make detection of the incongruent colour/orientation similar to that seen at baseline. As we have seen in the model motoneurone it is certainly possible that reducing the activity of a neurone can increase the chance that it will discharge in response to a TMS pulse. This extra activity could then add on to the activity evoked by a 45 °/red grating and increase the chances of detection; it might also interfere with detection of gratings of opposite orientation and colour.

However, as always with TMS experiments, there is an opposite explanation. An important feature of both experiments was that TMS was given during an illusory visual percept (the presence of a coloured afterimage). In this state, the functional effect of TMS could be primarily inhibitory. If so, TMS should induce a stronger suppression of activity in the more active neuronal presentations coding the colour of the afterimage and spare the inactive neuronal presentations coding the colour of the adapting stimulus. This might flip the functional imbalance in neuronal activity between the complementary neuronal representations and induce an illusory percept of the adapting stimulus (experiment1) and cancel the adaptation-induced difference in detection performance (experiment 2). This scenario is not far-fetched as extracellular single-unit recordings in cat visual cortex revealed distinct episodes during which spontaneous and visually evoked activity were enhanced and suppressed by a single biphasic TMS pulse (Moliadze et al., 2003). Critically, strong biphasic stimuli exceeding 50% of maximal stimulator output led to an early suppression of neuronal activity during the first 100–200 msec, followed by stronger (rebound) facilitation, showing that under some conditions, inhibitory effects may prevail after TMS of the occipital cortex.

8. State dependency and spread of excitation to connected brain regions

The notion of state dependency not only applies to the regional neuronal response to TMS at the site of stimulation but can readily be extended to the transsynaptic spread of excitation to connected brain areas. The cortico–cortical interactions that can be probed with bifocal TMS of two connected areas show dynamic changes during an experimental task (Koch et al., 2006, 2007; Murase et al., 2004). For instance, the ipsilateral facilitatory interaction between right posterior parietal cortex and $M1_{HAND}$ was only present at two specific time points (50 and 125 msec after an auditory cue) during the reaction time of a reach task and only when a leftward reach was planned, showing that the parieto-motor connectivity is enhanced during early stages of planning a reach in the contralateral direction (Koch et al., 2008).

The state dependency of TMS-induced spread of excitation to connected cortical areas has been further corroborated in studies that combined TMS with functional brain mapping.

A combined TMS-EEG study showed a break-down of the TMS-induced spread of activation to connected cortical areas during slow-wave sleep relative to wakefulness (Massimini et al., 2005). A recent study interleaved TMS with functional magnetic resonance imaging to show that TMS to left PMd influenced activity in contralateral right PMd and $M1_{HAND}$ in a state-dependent fashion (Bestmann et al., 2007b). Compared to low-intensity TMS, high-intensity TMS led to activity increases in contralateral right PMd and M1 during a left-hand gripping task. In contrast, high-intensity TMS decreased activity in these areas relative to the low-intensity TMS condition when subjects performed no grip. There was also stronger interhemispheric coupling between left and right PMd, when high-intensity TMS was applied to left PMd during left-hand grip.

The state-dependent changes of TMS-induced effects on functional connectivity between the stimulated and remote areas parallel those on regional activity in the stimulated cortex showing a stronger impact of TMS on active cortico–cortical connections. This implies that neuronal excitation spreads more efficiently throughout a neuronal network if the connections are in an activated state, presumably producing a stronger disruptive effect on the functional interplay between the stimulated area and connected brain regions.

9. A neurophysiological framework of TMS-induced neurodisruption

A TMS pulse to the cortex produces a synchronous burst of activity in a proportion of available neurones. This is followed by a longer lasting IPSP, which together with the burst will interfere with any processing that the cortex was doing at the time of the stimulus (''virtual lesion''). The size of the neural population that is affected will depend on the stimulus intensity and the intrinsic excitability of the neurones.

A TMS pulse of constant size does not always have the same effect. The response changes according to the state of the cortex when the stimulus is applied (state dependency). This is because the state affects the distribution of excitability in the population of neurones. It is important to remember that the cortical state is unlikely to alter the number of axons that are activated by the TMS pulse. Rather it affects the transmission of impulses across synapses innervated by these axons. We wish to stress that it is very difficult if not impossible to produce a simple set of rules that will explain how the effect of TMS depends on state. This is because there is no simple relationship between the *excitability* of a region and the *activity* in that region. Thus, interpretation of state dependent effects is always speculative.

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Appendix II

Combining transcranial magnetic stimulation with (f)MRI

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Abstract

In this chapter, we review how transcranial magnetic stimulation (TMS) can be beneficially combined with (clinical) fMRI. (i) When TMS is given during a fMRI session (online approach), fMRI can be used to test the immediate influences of TMS on brain activity and behaviour. An interesting approach is to give TMS while subjects are performing a particular task during fMRI. This allows to map how the TMS effects on neuronal activity undergo context-specific changes depending on the task. TMS and fMRI can also be separated in time (offline approach). (ii) A conditioning session of repetitive TMS (rTMS) can be applied outside the MRI scanner to induce an acute reorganization in functional brain networks which can be subsequently mapped with fMRI. (iii) Alternatively, fMRI can be performed first to localize brain areas that are involved in a given task. Based on the spatial information offered by fMRI, focal TMS can then be applied in a consecutive session outside the MR sanner to precisely target a specific area during the task. If TMS impairs task performance it can be inferred that the stimulated cortex makes a critical contribution to the task.

1 Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive and painless tool for electrical stimulation of human cortex (Barker et al. 1985). TMS depolarises cortical neurons which can evoke measurable electrophysiological and behavioural effects. TMS is usually applied to one cortical area, but can also be given to two or more areas (i.e., multi-site TMS). Single or paired stimuli, and short stimulus trains (i.e. high-frequency bursts) provide a means of transiently disrupting ongoing neuronal processing in the stimulated cortex. Repetitive TMS (rTMS) refers to the application of prolonged trains of stimuli which are either given continuously as long trains at a constant rate (continuous rTMS) or intermittently as repetitive bursts (i.e. intermittent or burst-like rTMS). rTMS can modify the excitability of the cerebral cortex at the stimulated site and also at remote connected brain regions beyond the time of stimulation. Its neuromodulatory effects make rTMS a valuable tool to study functional plasticity of neuronal networks and may be used therapeutically in patients with neurological and psychiatric disorders.

1.1 How does TMS excite cortical neurons?

TMS causes inductive (electro-magneto-electric) stimulation of neuronal axons. A brief, high-current pulse is produced in a stimulating coil. The time-varying electrical field produces a time-varying magnetic field with lines of flux oriented perpendicularly to the plane of the coil. The pulsed magnetic field is not attenuated by the scull and induces an electric field in the superficial brain tissue (i.e. cortex) which runs parallel to the plane of the coil but has a direction that is opposite to the electric field in the coil. Hence, the pulsed magnetic field is only used as a means to generate an electric field in the brain that is suprathreshold for exciting cortical axons.

How does the time-varying electrical field induced in the cortex excite neurons? The electrical field induced in the neuronal tissue drives transmembraneous ionic currents. The most relevant parameter is the rate of change of electric field along the nerve. Depending on the gradient and the orientation of the electric field gradient relative to the course of the axon, the pulsed electrical field may generate an outward current and local depolarization at distinct sites of neuronal axons. If the outward current causes sufficient membrane depolarization, this will trigger an action potential. This action potential propagates along the axon and may cause a transsynaptic excitation of postsynaptic neurons. Crucial for an effi-

cient depolarisation of an axon is the spatial gradient of the induced electric field in relation to the orientation of the axon. At the cellular level, the events that lead to neuronal excitation are still poorly understood. For instance the relevance of cellular and gyral shapes, grey matter boundaries, local variations in tissue conductivity and the role of background neuronal activity for neuronal stimulation are largely unknown.

The majority of studies have investigated the physiological mechanisms of TMS in the human primary motor cortex (M1) because its effects can be quantified by recording the TMS evoked motor potential (MEP). For other brain regions, such direct quantification is difficult to obtain. Therefore, researchers have used neuroimaging techniques such as positron emission tomography (PET), electroencephalography (EEG), or functional magnetic resonance imaging (fMRI) to map TMS-evoked changes in regional neuronal activity throughout the brain (Bestmann et al. 2003b; Ilmoniemi et al. 1997; Lee et al. 2003; Massimini et al. 2005; Siebner et al. 2003). These studies revealed that the TMS-induced changes in regional neuronal activity are not restricted to the stimulated cortex but give rise to functional changes in connected cortical areas, including subcortical brain regions (Bestmann et al. 2003b; Lee et al. 2003; Siebner et al. 2003).

Regarding fMRI, a critical question is whether the blood oxygen level dependend (BOLD) signal really captures the TMS induced changes in regional neuronal activity. Allen et al. (2007) combined optical imaging with electrophysiological recordings of neuronal activity in cat visual cortex to show that TMS-induced changes in neural activity are readily reflected by cerebral hemodynamics. Further, the quantitative coupling between TMS-evoked neural activity and cerebral hemodynamics was present over a range of stimulation parameters. These results demonstrate the usefulness of combined TMS-fMRI studies in humans showing that TMS-induced neural changes are “faithfully reflected in hemodynamic signals” (Allen et al. 2007).

1.2 Some physical aspects of transcranial magnetic stimulation

The induced magnetic and electric field decreases rapidly with increasing distance from the coil. The maximal depth of penetration depends on the shape and size of the coil, the employed stimulation intensity and the responsiveness of the targeted tissue. The decrease with distance is more rapid for small coils than for large ones. The coil should be placed tangentially on the skin to minimize the coil-cortex distance. Commercially used coils reach a penetration depth of approximately 2-6 cm. This implies that only cortical neuronal tissue is within the range of TMS while deep cerebral grey matter nuclei cannot be stimulated directly with TMS.

In general, TMS does not produce a focal stimulation of neuronal tissue at a small predictable site. The geometry of the coil is an important factor in determining the magnitude and spatial extent of cortical stimulation. The two most commonly used coil shapes are circular (i.e. referred to as round coil) and figure-of-eight (referred to as figure-of-eight shaped coil or butterfly coil). The circular coil induces a concentric circular electric field. If the coil is placed with its entire surface tangentially to the skin, neuronal structures in the tissue underlying the circular coil will be activated. It should be noted that neuronal stimulation is minimal in the brain tissue underlying the center of the coil when the flat surface of the circular coil is placed on the scalp tangentially to the skin (Weyh and Siebner 2007). The other coil design has a figure-of-eight configuration. Figure-of-eight coils consist of two circular coils placed side by side and are wired such that the current from the stimulator passes in opposite directions in each. This produces a relatively clear defined maximum of the induced current where the two coils approach each other (i.e. in the geometrical center of the coil). With a spatial resolution of approximately 1-1.5 cm, the figure-of-eight coil is substantially more focal than the circular coil. This explains why the figure-of-eight coil is preferred to the round coil when TMS is used to map cortical functions (Walsh and Rushworth 1999). It needs to be born in mind that commercially available stimulation devices may differ in terms of coil design. This may alter the characteristics of neuronal stimulation, including the heating properties during

rTMS and the hardware design (Lang et al. 2006; Weyh et al. 2005).

1.3 Clinical and neuroscientific applications of TMS

TMS can be used in several ways to study human brain function. Single-pulse or paired-pulse TMS can be applied to probe the excitability of intracortical inhibitory and facilitatory circuits in the motor and visual cortex. Since the action potentials induced by TMS spread along pre-existing axonal connections, TMS induced neuronal excitation is not limited to the stimulated cortex but leads to a transsynaptic spread of excitation to interconnected cortical areas. This renders TMS a very powerful means of studying functional and effective connectivity in the intact human brain (Kobayashi and Pascual-Leone 2003). For instance, TMS has been extensively used to probe cortico-cortical and cortico-spinal connectivity in the motor system. In clinical neurology, TMS is commonly used as routine evaluation of the excitability and conductivity of corticospinal pathways.

TMS can induce a transient dysfunction in the stimulated cortex (i.e. a "virtual lesion"). When being applied in its "virtual lesion" mode during an experimental task, TMS may produce measurable changes in task performance. These changes in behaviour can be used to make inferences about the importance of the stimulated brain area for a specific cognitive, sensory or motor function (Walsh and Cowey 2000; Walsh and Rushworth 1999). Various rTMS protocols are being increasingly used by clinicians and neuroscientists to induce lasting changes in the status of the human brain (Siebner and Rothwell 2003). Conventional rTMS protocols consist of a continuous series of pulses with constant repetition rates. In the "continuous mode" of rTMS, stimulation rates of around 1 Hz are referred to as *low-frequency rTMS*, and stimulation rates between 5-50 Hz as *high-frequency rTMS*. Most studies regarding the motor cortex suggest inhibitory effects of low-frequency rTMS and facilitatory effects of high-frequency rTMS (Berardelli et al. 1998; Chen et al. 1997a; Pascual-Leone et al. 1998). Recent protocols use more complex temporal stimulation patterns such as double-pulse rTMS (Thickbroom et al. 2006), quadro-pulse rTMS (Hamada et al. 2007), or theta burst stimulation (TBS) which gives short, high-frequent *bursts* of pulses every 0.2 s (Huang et al. 2005). Ongoing research addresses the question whether the neuromodulatory effects of these rTMS protocols may have a therapeutic application in neurological and psychiatric disorders (Wassermann and Lisanby 2001).

TMS can be applied while subjects perform an experimental task (*online TMS*) or shortly before they perform the task (*offline TMS*). Offline TMS usually involves a rTMS protocol that induces a lasting alteration of cortical excitability, while online TMS may consist of single pulses or short high-frequency trains that are given at distinct time-points during task performance. Both approaches allow the testing of the functional relevance of the targeted brain area by measuring the acute (*online TMS*) or conditioning (*offline TMS*) effects of TMS on electrophysiological measures (e.g., the MEP amplitude), behavioural measures (e.g., response latencies or error rate) or more directly on regional brain activity using brain mapping techniques such as EEG, PET, or fMRI.

1.4 Adverse effects and safety precautions

TMS has the capability of producing adverse effects, especially if rTMS is used. These side effects are extensively discussed in a recent review (Wassermann 2008). The most relevant adverse effect is the induction of epileptic seizures. Since rTMS induces stronger and more persistent effects on cortical excitability and function than single-pulse TMS, it bears a higher risk of provoking epileptic seizures even in healthy individuals. Therefore, safety guidelines were established which specify the maximal number of pulses per session, stimulus intensity and frequency that are considered to be safe in terms of seizure induction (Chen et al. 1997b; Wassermann 1998). Since the introduction of the safety guidelines, only a few cases of accidental seizures with TMS have been reported worldwide, and none of the individuals who had experienced rTMS-induced seizures has suffered lasting physical sequelae.

The rapid discharge through the coil produces a characteristic clicking sound in the frequency range of 2-7 kHz. The click is caused by mechanical deformation of the coil

during the strong magnetic pulses. Peak sound pressure has been reported to be 120-130 dB at a distance of 10 cm from the coil (Starck et al. 1996). Sound levels will be higher when TMS is given inside the MRI bore because of the additional magnetic field generated by the MR scanner. Therefore, individuals who receive rTMS or are examined in the MR scanner should always wear ear plugs (cf. section 3.2.1).

2 Placement of the coil over the cortical target area

Accurate placement of the TMS coil over the cortex area that is to be stimulated with TMS is crucial. The motor response that is evoked by TMS can be used to localize the primary motor cortex. A similar approach can be chosen for TMS of the visual cortex by positioning the coil at the site where TMS most reliably elicits a phosphene. In both instances, TMS produces an overt response which can be used to functionally determine the appropriate site of stimulation. For most remaining cortical areas, no such responses can be elicited and other strategies have to be used to accurately place the coil over the cortical target.

Some researchers use the optimal site to stimulate the primary motor cortex as “anchor point” for stimulation of pericentral cortical areas such as premotor or somatosensory areas (Gerschlager et al. 2001; Koch et al. 2006; Lee and van Donkelaar 2006). However, this method is not sufficiently accurate for targeting more distant areas such as the dorsolateral prefrontal cortex (Bohning et al. 2003b).

The International 10-20 system for the placement of EEG electrodes (Jasper 1958) is often used for positioning of the TMS coil. The 10-20 system offers a grid of electrode sites located on the scalp that is derived from standard cranial landmarks, i.e. the inion, nasion, or preauricular points. This method assumes a consistent correlation between scalp locations and underlying brain structures across subjects. Greater accuracy can be obtained by acquiring structural MR images of the brain together with capsules containing a high-contrast marker attached to the head (Terao et al. 1998). The placement of the coil can then be referenced to the position of the marker.

Neuronavigated TMS guided by frameless stereotaxy represents the method of choice as it allows both, exact placement and monitoring of the coil throughout the TMS experiment (Herwig et al. 2003a; Neggers et al. 2004; Denslow et al. 2005a; Schonfeldt-Lecuona et al. 2005; Sack et al. 2006). Optical (infrared based) and acoustic (ultrasound based) devices are available for neuronavigation. These systems use passive (reflecting) or active (emitting) markers which are attached to the subject´s head and to the TMS coil (Ettinger et al. 1998). Sparing et al. (2008) compared different methods for the placement of the TMS coil over the primary motor cortex in terms of accuracy. The least accurate results were obtained when the 10-20 EEG system or function-guided procedures were used, although there was a great variation among different electrode positions as some can be located more reliably than others. In that study, fMRI guided neuronavigated stimulation yielded the highest spatial accuracy in the range of a few millimetres. Other studies have confirmed these results (Denslow et al. 2005a; Herwig et al. 2003b; Schonfeldt-Lecuona et al. 2005).

Neuronavigation requires a T1-weighted, high-resolution image of the subject´s brain. The anatomical images have to be transferred into three-dimensional space. Optionally, individual fMRI activation maps can be overlaid on the structural images. Pre-defined anatomical landmarks are marked on the individual structural MRI with special neuronavigation software. Usually, the nasion, the nibs of the tragus of both ears, and the internal angle of the eyes are used. A headband is then strapped around the subject´s head. A tracker with at least 3 passive spheres or ultrasound reflecting transmitters is firmly attached to the headband, indicating the position of the subject´s head. Another tracker is fixed onto the TMS coil. These dynamic reference systems provide online information about the location of the head and the coil in space. A camera system detects the position of the dynamic reference systems and displays this information on a computer screen using navigation software for visual localization of the coil (see Fig.1).

The subject´s head and their structural MR scans are coregistered by touching the predefined landmarks on the subject´s face using a pointer equipped with trackers. An accurate coregistration procedure is crucial to exact placement of the coil. The position of the coil is visualized in realtime on a computer screen relative to the individual three-dimensional

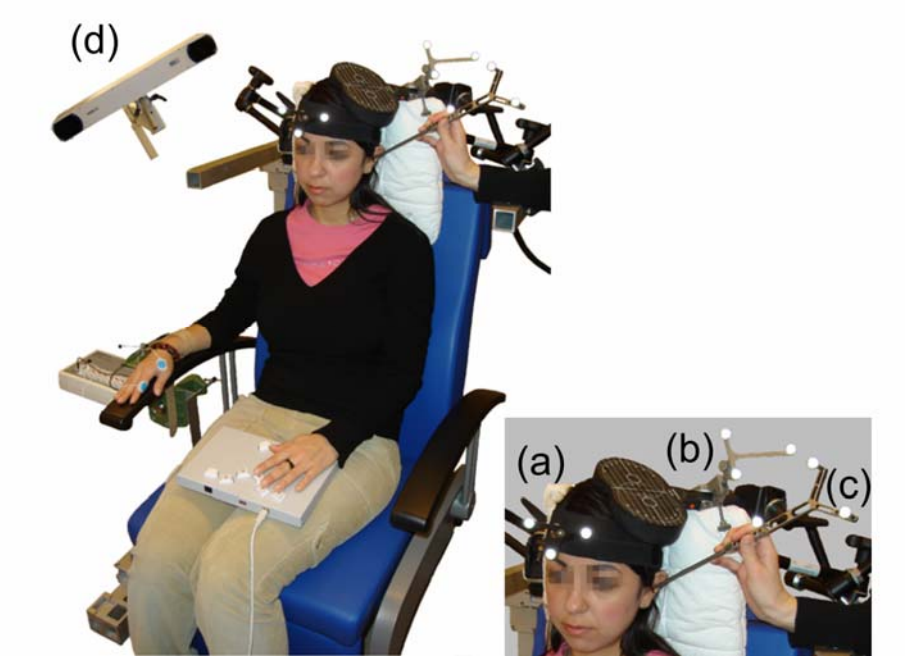

Fig.1 Neuronavigated TMS guided by frameless stereotaxy. A tracker with 3 passive spheres is attached to the headband of the subject (a), to the TMS coil (b), and fixed on a pointer (c). These dynamic reference systems provide online information about the location of the head and the coil in space. A camera system (d) detects the position of the dynamic reference systems and displays this information on a computer screen using navigation software for visual localization of the coil.

anatomy of the brain. The exact position of the cortical target area can be defined either anatomically based on the gyral anatomy or functionally on the basis of activation maps that have been obtained with fMRI. In addition to the individual activation map, one can also use the stereotactic coordinates of a peak activation that has been identified in a group of subjects. In this instance, the coordinates from standardized space (MNI, Talairach) have to be transformed to the subject's "native" space.

3 Combinations of fMRI with TMS

3.1 Why combine TMS with fMRI?

fMRI provides a sensitive means of identifying brain regions where regional neuronal activity correlates with behaviour. Due to its correlative nature, fMRI based activation maps cannot establish whether such activation makes a relevant contribution to the behaviour. By temporarily disrupting ongoing neural activity, transcranial magnetic stimulation (TMS) permits to make causal inferences regarding the contribution of the stimulated cortex to a specific brain function. Since single-pulse TMS offers a high temporal resolution it can also be used to identify the period during which the stimulated area makes a critical contribution to the experimental task. Thus, combined TMS and fMRI gives access to noninvasive measuring of stimulation effects on the brain with a high spatial (fMRI: spatial resolution in the millimeter range) and temporal (single-pulse TMS: temporal resolution in the order of milliseconds) resolution.

The temporal relationship between TMS and fMRI defines which question can be addressed using a combined TMS-fMRI approach. TMS can be given in the MR scanner during fMRI data acquisition (online approach) to investigate the immediate effects of TMS on brain activity and behaviour. Alternatively, TMS and fMRI may be separated in space and time (off-

line approach). In this case, TMS is given outside the MRI suite before or after fMRI (see Fig.2).

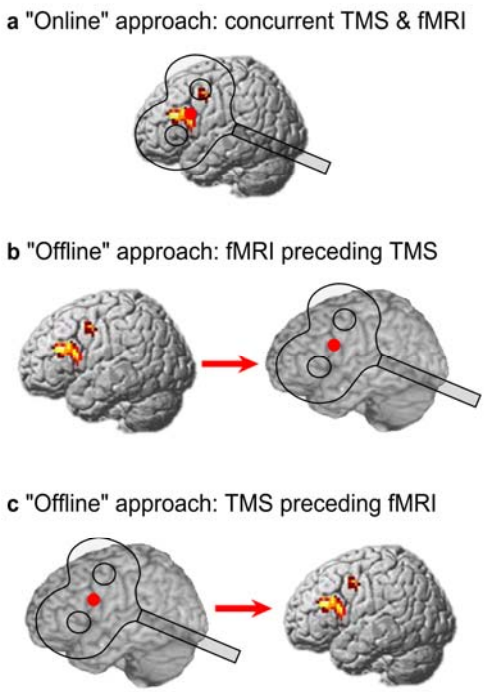

Fig.2. Relative timing of TMS and fMRI determines the application of combined TMS-fMRI. TMS and fMRI can be performed interleaved, (i.e. "online" approach) to investigate immediate effects of TMS on brain functions (a). In the "offline" approach, fMRI precedes or follows TMS. fMRI preceding TMS is usually used to identify appropriate sites for focal TMS (b), while TMS preceding fMRI can be used to probe the lasting effects of TMS conditioning on brain functions (c).

3.2 TMS in the MR scanner during fMRI (online TMS-fMRI approach)

TMS during fMRI (interleaved TMS-fMRI) enables the researcher to probe the immediate impact of TMS on regional neuronal activity across the whole brain. By applying TMS during different functional states of the brain, the online TMS-fMRI approach can explore how the TMS influences on neuronal activity in the stimulated and distant areas vary with task demands.

3.2.1 Methodological issues

Although the prerequisites to apply TMS during fMRI were already introduced by Bohning et al. (1997; 1998; 1999) approximately 10 years ago, interleaved TMS-fMRI failed to become a routine procedure yet. At present, most of the studies that used interleaved TMS-fMRI were carried out by three research groups in Charleston (North Carolina, USA), Göttingen (Germany), and London (UK) (for details, see Table 1). A simple implementation of TMS in the MRI environment is precluded by problems originating from the application of magnetic pulses in the static magnetic field of the MR scanner and in the presence of magnetic field gradients required for image acquisition (Baudewig et al. 2001). Therefore, non-ferromagnetic coils have to be used which are mechanically strengthened to prevent coils from breaking during fMRI. Subjects have to wear ear plugs and headphones because mechanical interactions between the TMS evoked local magnetic field and the static magnetic field of the MR scanner result in a louder click when the coil is discharged inside the scanner. The presence of the MR-compatible TMS coil may cause geometric image distortions (Baudewig et al. 2000; Bestmann et al. 2003a). These can be reduced by a shorter read-out time of echo-planar imaging (EPI) sequences, the use of stronger imaging gradients and parallel imaging.

The ferromagnetic stimulation device must be placed at sufficient distance from the magnetic field of the MR scanner, outside the scanner room or in a radiofrequency-shielded cabinet inside the scanner room. This requires a longer cable to connect the coil with the stimulator.

MR-compatible TMS coil holders help to ensure accurate placement of the coil inside the scanner. Yet spatial limitations imposed by the MR head coil may restrict the access to some cortical areas, especially in the basal frontal and temporal lobe. TMS also evokes twitches of cranial muscles, somatosensory and auditory stimulation which may cause discomfort, movement artefacts and contribute to functional brain activation. Non-specific auditory and somatosensory stimulation as well as the unpleasantness of TMS complicate the interpretation of TMS-induced brain activation by causing BOLD signal changes in subcortical and cortical areas involved in sensory or affective processing (Bestmann et al. 2005). It is therefore advisable to include a control condition which matches the auditory and somato-

sensory stimulation but does not cause transcranial cortical stimulation. Alternatively, the same TMS protocol might be applied to a control area in a separate fMRI session.

Dynamic artifacts pose a major problem to concurrent TMS during fMRI. Radiofrequency (RF) noise can markedly reduce the signal-to-noise ratio of MR images. TMS stimulators may themselves produce RF noise, and the antenna-like properties of the TMS coil cable can additionally guide RF noise into the scanner which can be reduced by customized RF filters. Leakage-currents that originate from the high-voltage capacitors of the TMS stimulator may induce additional image distortions and artifacts. Of note, these leakage-currents change with the intensity of TMS, and can give rise to intensity-dependent BOLD signal changes. Remote-controlled high-voltage relay-diode systems reduce leakage-currents flowing between the stimulator and the TMS coil and can thus be used to resolve this problem (Bestmann et al. 2007).

The strong magnetic pulses induced by TMS can severely distort MR images depending on TMS coil orientation, TMS pulse intensity, and MR magnetic field strength (Bestmann et al. 2003a; Shastri et al. 1999). Therefore, a direct interference between TMS pulse and EPI excitation pulses should be avoided, and images being perturbed by TMS pulses must be replaced (Bestmann et al. 2008). A feasible solution to this problem is to introduce a sufficiently long temporal gap between TMS pulses and subsequent MR image acquisition (for more technical details see Baudewig and Bestmann 2007; Bestmann et al. 2008).

3.2.2 Applications of interleaved TMS-fMRI

Several researchers applied TMS over the motor cortex during rest and showed that TMS induced acute changes in BOLD signal is a dose-dependent fashion (Bohning et al. 1998; 1999; 2000b; Baudewig et al. 2001; Bestmann et al. 2003a; 2004). A single TMS pulse evoked regional increases in BOLD signal which were similar to those evoked by volitionally movements (Bohning et al. 2000b). Such BOLD signal increases were only observed at suprathreshold intensities which evoked a muscle twitch in the contralateral hand. Hence, it remains unclear whether the observed activation was directly induced by cortical stimulation or resulted from somatosensory feedback activation caused by the TMS-induced movement. However, Bestmann et al. (2005) applied short trains of 3 Hz rTMS over the left premotor cortex which produced an increase in BOLD signal in the stimulated cortex and connected areas. Since the premotor TMS train did not produce overt muscle movements, it was concluded that these BOLD signal changes resulted from cortical stimulation rather than from somatosensory feedback activation.

Interleaved TMS-fMRI studies revealed that TMS can evoke changes in neural activity in connected cortical and subcortical areas (Bohning et al. 1998; 1999; 2000a; Baudewig et al. 2001; Bestmann et al. 2004, 2005; Ruff et al. 2008). These distant BOLD signal changes can occur even in the absence of consistent signal changes in the area that was directly targeted by TMS (Bestmann et al. 2004). This suggests that transsynaptic spread of excitation from the stimulated to connected brain areas makes a major contribution to neuronal stimulation that is induced by TMS in the human brain.

Interleaved TMS-fMRI opens up the possibility to examine how TMS interacts with intrinsic task-related activation and how these TMS-induced changes in task-related activity relate to changes in behaviour. In a recent study, parietal rTMS was performed during fMRI to map TMS-induced changes in task-related brain activity that underly the TMS-induced impairment of visuospatial judgements (Ruff et al. 2008). Concurrent TMS-fMRI was employed to investigate the influences of a short high-frequency rTMS train over the right frontal eye field or intraparietal sulcus on the BOLD response in occipital activity to visual stimulation. The authors showed that TMS induced changes in occipital activity critically depend on the actual state of the visual system at the time of TMS. Increased activity over visual area V5 / MT+ was only found if moving stimuli were concurrently presented. Conversely, visual areas V1-V4 were specifically activated during the absence of input.

So far, very few interleaved TMS-fMRI studies have been carried out in patients. In a case study, Bestmann et al. (2006) investigated TMS induced activity changes in distinct cortical areas of an amputee. At an intermediate stimulus intensity, TMS over the motor hand representation contralateral to amputation elicited a phantom sensation of a movement in half of the trials without producing overt acti-

Tab.1. Studies using interleaved TMS-fMRI in healthy volunteers

Target area	Task	TMS protocol (frequency; %MT; total no. of pulses per train /session)	Reference
Left M1	Rest	0.83 Hz; 110; 20/session	Bohning et al. 1998
Left M1	Rest	1 Hz; 80 /110; 18/session	Bohning et al. 1999
Left M1	Rest / finger movements	1 Hz; 110; 21/train	Bohning et al. 2000a
Left M1	Rest	SP; 120; 15/session	Bohning et al. 2000b
Left M1 Left PMd	Rest/ finger movements	10 Hz; 110; 10/train 10 Hz; 90 /110; 10/train	Baudewig et al. 2001
Left PFC	Rest	1 Hz; 80 /100/120; 21/train	Nahas et al. 2001
Left M1 / S1	Rest	4 Hz; 90 /110 /110 AMT; 40/train	Bestmann et al. 2003b
Left M1	Rest	1 Hz; 110; *not reported*	Bohning et al. 2003a
Left M1	Rest	1 Hz; 120; 1,2,4,8,16,24/train	Bohning et al. 2003c
Left M1	Rest	4 Hz; 150; 4/train	Kemna and Gembris 2003
Left M1	Rest	1 Hz; 110; 21/train	McConnell et al. 2003
Left M1	Rest	3.1 Hz; 90/110 AMT; 30/session	Bestmann et al. 2004
Left M1 / S1	Rest / finger movements	1 Hz; 110; 21/train	Denslow et al. 2004
Left PFC	Rest	1 Hz; 100; 21/session	Li et al. 2004a*
Left M1 Left PFC	Rest	1 Hz; 110/120; *not reported*	Li et al. 2004b
Left PMd	Rest / finger movements	3 Hz; 90/110 AMT; *not reported*	Bestmann et al. 2005
Left M1	Rest / finger movements	1 Hz; 110; 21/train	Denslow et al. 2005a
Left M1	Rest	1 Hz; 110; 21/train	Denslow et al. 2005b
Left M1	Rest	SP; ~90;98/102;110 SoM; 20; 40/session	Bestmann et al. 2006**
Right FEF	Rest / visual judgement	9 Hz; 40/55/70/85 TOP; 10 Hz; 65 TOP; 5/train	Ruff et al. 2006
Left PMd	Isometric left hand grips	11 Hz; 70/110; 5/train	Bestmann et al. 2007
Left / right SPL	Visuospatial tasks	13.3 Hz; 100 TOP; 5/train	Sack et al. 2007
Right IPS / FEF	Visual task (moving stimuli)	9 Hz; 40/55/70/85 TOP; 5/train	Ruff et al. 2008

AMT= active motor threshold; FEF= frontal eye field; IPS= intraparietal sulcus; M1= primary motor cortex; PFC= prefrontal cortex; PMd= dorsal premotor cortex; RMT= resting motor threshold; SoM= Sense of movement; SP= single pulse; TOP= total output; *Depressive patients; **Amputee patient

vity in remaining muscles. The authors compared event-related BOLD signal changes in trials with versus without a phantom sensation of movement. Because the settings of TMS were identical, this comparison subtracted out any non-specific TMS effects on regional neuronal activity. The sensation of a phantom movement was associated with increased activity in primary motor cortex, dorsal premotor cortex, anterior intraparietal sulcus, and caudal supplementary motor area. Based on these results, it was argued that activity in these frontoparietal areas represents the neuronal correlate of the phantom sense of movement (see Fig.3 for details). Concurrent TMS-fMRI may also be of value to study how "therapeutic" rTMS protocols acutely change neuronal activity in functional brain networks. For instance, fMRI has been used to probe the immediate effects of continuous 1 Hz TMS at 100% MT over the left dorsolateral prefrontal cortex in 14 patients with major depression (Li et al. 2004a).

3.3 Offline combination of TMS and fMRI

3.3.1 TMS following fMRI

There is consensus that fMRI can reliably identify brain regions in which increases in BOLD signal are correlated with the performance of an experimental task. Yet the correlational nature of fMRI provides no information about the functional contribution of any activated brain region to the task. This question can be addressed using TMS. TMS can be applied over the area of interest to disrupt neuronal processing while participants perform the same experimental task. If the TMS-induced local perturbation affects task performance, this is taken as evidence that the stimulated cortical area is functionally relevant.

An elegant illustration of this approach was provided by Cohen and colleagues in a TMS study on blind subjects (Cohen et al. 1997). Previous neuroimaging studies had shown that Braille reading consistently activated visual cortical areas in blind subjects but not in those with sight. To investigate the significance of task-related activation in the occipital cortex, short trains of 10 Hz rTMS were given to several brain regions time-locked to Braille reading. Occipital rTMS induced errors and distorted the tactile perceptions of congenitally blind subjects but had no effects on tactile performance in normal-sighted. This finding proved that the occipital visual cortex makes a relevant contribution to the processing of tactile input in blind subjects.

Functional MRI can be used to functionally localize the optimal site for TMS. In a study by Neggers and colleagues (2007), participants first performed a saccade task during fMRI. In each subject, the individual peak activation in the precentral sulcus was identified and superimposed on the structural image of the subject's brain. Then they used frameless stereotaxy to place the coil over the fMRI defined FEF. This fMRI guided stereotactic approach is likely to be more precise than relying on structural anatomical landmarks because it takes into account the inter-individual variability of the functional representation of the FEF in the precentral cortex. An alternative strategy uses the results of a previous fMRI study that has used the same or a similar experimental task. The sterotactic coordinates of task-related peak activation in the area of interest define the site of stimulation. The individual site of stimulation is determined by using the inverse of the normalisation trans-

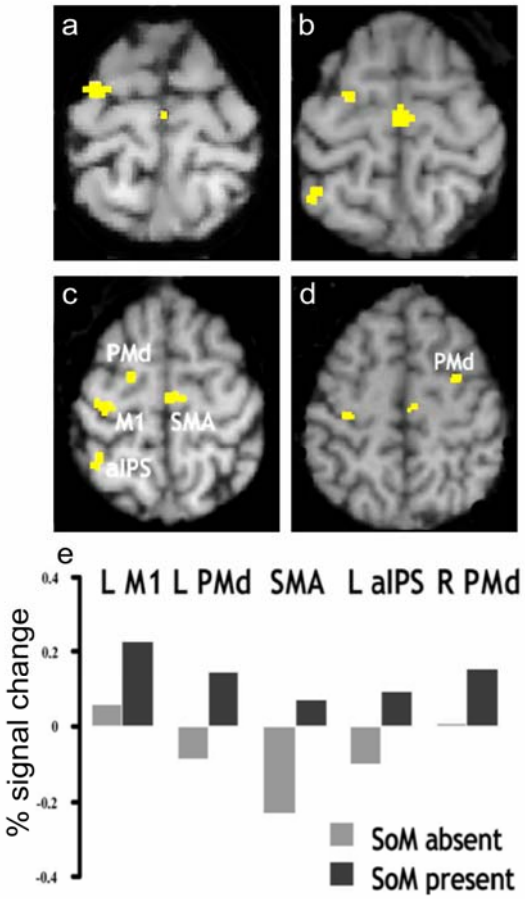

Fig.3. Activity changes for the comparison of trials with vs. without SoM reported, at intermediate TMS intensities (SPM (T) thresholded at T $\geq$3). When a conscious phantom SoM was perceived, activity increases were observed in several motor-related regions, including the left (stimulated) M1, left and right PMd, left anterior intraparietal sulcus (aIPS), and caudal SMA. Note that the intermediate stimulation intensities applied were held constant in this contrast, and were below threshold for evoking peripheral muscle responses. The results are displayed on the patient´s anatomical T1-weighted MRI: (a) transverse section, z=72; (b) z=67; (c) z=62; (d) z=57; (e) fMRI percent signal change with repect to the session mean in peaks from these five motor-related regions (left M1, left and right PMd, SMA, left aIPS). *Reprinted from Neuropsychologia, 44 (14), Bestmann et al., Cortical correlates of TMS-induced phantom hand movements revealed with concurrent TMS-fMRI, pp. 2959-71, 2006, with permission from Elsevier.*

formation and transforming the coordinates from standard to "individual" space. Considering the high inter-individual variability of the therapeutic effects of rTMS in psychiatric and neurological disorders (e.g., Gross et al. 2007; Lefaucheur et al. 2007; Ridding and Rothwell 2007), the use of fMRI-guided TMS which takes into account the functional neuroanatomy of each individual may also increase the efficacy of rTMS as a therapeutic tool.

3.3.2 fMRI following TMS

Another way to combine rTMS and fMRI is to apply rTMS before fMRI. Here rTMS is used to induce an acute reorganization in the human brain (Siebner and Rothwell 2003). After rTMS, fMRI is performed to map the lasting functional impact of rTMS on task-related neuronal activity at a system level (O'Shea et al. 2007; Rounis et al. 2007). Performing fMRI after rTMS outside the scanner does not require specific methodological precautions because rTMS and fMRI are separated in space and time. This *condition-and-map approach* can be used to study the changeability of functional brain networks. Preferably, fMRI should start as quickly as possible after rTMS to capture transient effects of rTMS (Baudewig and Bestmann 2007). The conditioning effects of rTMS on regional neuronal activity can be detected by comparing task-related activation before and after rTMS. It is important to control for unspecific changes in task related activity that are simply due to the repetition of the experimental task in the MR scanner. This can be achieved by introducing a second session during which sham rTMS is given to the cortical target area. Sham rTMS should match real rTMS in terms of auditory and somatosensory stimulation but without inducing transcranial stimulation of the cortex. Alternatively, the same effective rTMS protocol might be applied to a second (control) area. A change in the pattern of activation after rTMS but not after control rTMS indicates a true reorganization in response to rTMS conditioning. The task specificity of functional reorganization can be shown by having participants perform a control task during the same fMRI session. The condition-and-map approach has mostly been applied to study functional plasticity in healthy volunteers (see Table 2).

For example, a recent study investigated the modulation and reorganization of networks associated with sensory perception and motor performance after sub-threshold high-frequency (10 Hz, 90% resting motor threshold) rTMS of the right primary motor hand area (Yoo et al. 2008). Using a sham-controlled within-subject design, BOLD signal change during a sequential finger motor task and noxious tactile stimulation of the left hand were assessed before and after real and sham rTMS. Compared to sham rTMS, real rTMS led to increased activation in the motor network which was associated with enhanced motor performance. On the other hand, real rTMS caused deactivation in the sensory network which correlated with an increase in tactile sensory threshold. Another study used fMRI in healthy right handers to probe short-term reorganization in right PMd after 1Hz rTMS induced a lasting disruption of neuronal processing in the dominant left PMd specialized for action selection (O'Shea et al. 2007). 1 Hz rTMS specifically increased activity in right PMd and connected medial premotor areas during action selection without affecting behaviour. Based on additional experiments it was claimed that this increase in activity reflects compensatory short-term reorganization that helps to preserve behaviour after the "neuronal challenge" induced by rTMS.

To date patients have been rarely studied with the offline combination of rTMS and fMRI (Fitzgerald et al. 2007; Cardoso et al. 2008; Nowak et al. 2008). However, a large number of condition-and-map study studies used offline rTMS followed by positron emission tomography (PET) in patients with neurological and psychiatric disorders such as tinnitus (Richter et al. 2006; Smith et al. 2007), depression (Speer et al. 2000; Peschina et al. 2001; Kuroda et al. 2006), schizophrenia (Langguth et al. 2006), dystonia (Siebner et al. 2003) or Parkinson´s disease (Strafella et al. 2005). These studies have shown that the condition-and-map approach is important to advance our understanding of the therapeutic effects of rTMS as well as the underlying pathological brain mechanisms and should encourage investigators to perform fMRI after rTMS in patients.

Tab.2. Studies performing fMRI after a conditioning session of rTMS

Target area	Task during fMRI	TMS protocol (frequency; %RMT; total no. of pulses per session)	Reference
Left S1	Rest	5 Hz; 90; 2500	Tegenthoff et al. 2005
Left IFG	Semantic object classification	10 Hz; 110; 300	Wig et al. 2005
Left S1	Tactile frequency discrimination	5 Hz; 90; 1250	Pleger et al. 2006
Right vs. Left DLPFC	Cued choice reaction	5 Hz; 90 AMT; 1800	Rounis et al. 2006
Left PFC	Face-name memory	5 Hz; 80; 500	Sole-Padulles et al. 2006*
Right PFC	Tower of London	1 Hz; 110; 720 vs. 10 Hz; 100; 1500	Fitzgerald et al. 2007**
Left PMd, Left SM	Action selection	1 Hz; 90 AMT; 900	O'Shea et al. 2007
Left DLPFC	Emotional stimuli	5 Hz; 120; 3750	Cardoso et al. 2008***
Right FEF	Saccade-fixation	30 Hz TBS; 80; 600	Hubl et al. 2008
Contrales. M1	Hand grip movements	1 Hz; 100; 600	Nowak et al. 2008****
Right M1	Sequential finger motor task, noxious tactile stimuli	10 Hz; 90; 1000	Yoo et al. 2008

AMT = active motor threshold; DLPFC = dorsolateral prefrontal cortex; FEF = frontal eye field;IFG = inferior frontal gyrus; M1= primary motor cortex; PFC = prefrontal cortex; PMd = dorsal premotor cortex; RMT = resting motor threshold; S1 = primary somatosensory cortex; SM = sensori-motor cortex; TBS = theta burst stimulation; *elderly subjects with memory complaints; **patients with treatment-resistant depression; ***depressive patients with Parkinson's disease; ****stroke patients

4 Conclusion

TMS can be used concurrently with fMRI (online approach) or it can be given before or after fMRI (offline approach). While online TMS during fMRI is technical demanding and requires specific safety precautions, the offline TMS before or after fMRI approach outside the MR scanner can be easily performed. The relative timing between TMS and fMRI defines the scientific and clinical questions that can be tackled with the combined TMS-fMRI approach. This approach provides unique opportunities to explore dynamic aspects of functional neuronal networks in space and time and how these functional interactions are affected by disease. It also bears a great potential for studying the physiological impact of TMS on the human brain. This knowledge will be crucial to increased efficacy of TMS as a therapeutic tool.

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Appendix III

Preoperative functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS)

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Abstract

Neurosurgical resection of brain lesions aims to maximize excision while minimizing the risk of permanent injury to the surrounding intact brain tissue and resulting neurological deficits. While direct electrical cortical stimulation at the time of surgery allows the precise identification of essential cortex, it cannot provide information preoperatively for surgical planning.

Brain imaging techniques such as functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) and transcranial magnetic stimulation (TMS) are increasingly being used to localize functionally critical cortical areas before brain surgery. The use of multimodal preoperative information improves the accuracy of preoperative planning and facilitates decision-making regarding the extent and exact location of surgical resections.

This manuscript reviews how fMRI and TMS can be used in presurgical settings to map motor as well as higher cognitive functions (i.e. language). Pre-operative fMRI can be used to identify the brain regions that are activated during specific sensorimotor or language tasks. TMS is able to disrupt neuronal processing in the targeted brain area which in turn may affect task performance, if the stimulated cortex makes a critical contribution to the brain functions subserving the task. While the relationship between task and functional activation as revealed by fMRI is correlative in nature, the neurodisruptive effect of TMS reflects a causal effect on brain activity.

The use of preoperative fMRI is well established although the number of studies on presurgical language fMRI is still limited. In contrast, the reliability and accuracy of preoperative TMS remains to be determined.

Blood Oxygen Level Dependent functional Magnetic Resonance Imaging (BOLD fMRI)

BOLD fMRI measures specific functions of the human brain noninvasively without the use of ionizing radiation. Brain functions are measured indirectly, but with high spatial resolution via local hemodynamic changes in "functional areas", i.e., in regions of the human brain which control important functions such as voluntary movements, sensitivity, speech, or memory. To this end, the corresponding neurofunctional systems must receive targeted stimulation, which is usually done using specific stimulation schedules (i.e. paradigms). Stimulation leads to increased synaptic activity in the functional area with increasing energy and oxygen consumption of the activated neurons, which is not only met but overcompensated by local hemodynamic changes: regional cerebral blood volume (rCBV), blood flow (rCBF), and blood oxygen content are rising. In blood oxygenation level-dependent (BOLD) fMRI, the blood itself serves as an intrinsic contrast agent rendering the intravenous administration of paramagnetic contrast agents or radioactive substances unnecessary [1, 2]. The different magnetic properties of oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) are exploited to produce image contrast: Paramagnetic deoxy-Hb disturbs the local magnetic field resulting in a signal drop on susceptibility-weighted (T2*) MR sequences, while oxy-Hb is magnetically "neutral" (diamagnetic). A few seconds after stimulus onset, the over-proportional "washout" of oxygen-starved blood by oxygen-rich blood leads to a reduction in relative deoxy-Hb concentration with increasing local field homogeneity in the functional area corresponding to an increase in BOLD signal. By statistical correlation of the measured BOLD signal time course to the hemodynamic response function (hrf), those areas of the brain can be identified that exhibit task-synchronic hemodynamic changes [3]. These changes follow neuronal activation with a time lag of several seconds. Even if the physiology of the underlying neurovascular coupling is not yet conclusively understood, there is very good agreement between the localization of the BOLD signal and the actual site of neuronal activation [4]. BOLD measurements are generally carried out with ultrafast single-shot echo planar imaging (EPI) sequences in gradient echo (GE) or spin echo (SE) technique. GE sequences achieve higher BOLD signals of primarily venous origin, while SE sequences better reflect the capillary bed of the parenchyma. The temporal resolution using paradigms in block design or parametric design corresponds to the length of the blocks (typically >15 s). With event-related measurements, a temporal resolution of less than 100 ms may be achieved [5]. The temporal resolution capability of fMRI is thus lower compared to electrophysiological measures such as electroencephalography (EEG) or magnetoencephalography (MEG). However, the outlay on techni-

cal methods is lower and functional localization is more precise due to the direct relation of the fMR images to the surface anatomy. Complex mathematical modelling as in electromagnetic source localization for EEG or MEG is not necessary [6]. The BOLD signal intensity and the achievable spatial resolution change with the main magnetic field strengths. MR-scanners with field strengths below 1.0 Tesla (T) are not suitable for BOLD imaging. 1.5-T machines equipped with powerful gradients permit reliable measurements of cortical activations, while high-field MR-imagers with 3.0 T (or more) also permit robust functional imaging of subcortical structures. Because of the low signal-to-noise ratio (SNR) many similar stimulations must be carried out during fMRI to obtain enough BOLD signal. This also makes statistical post processing of fMRI data necessary, typically carried out after the fMRI measurements with commercial or freely available software, most programs not being licensed for medical applications [7]. Today, most manufacturers offer programs for "online" processing of fMRI data on their latest generation scanners [8]. The functionality of the different programs varies markedly; however, the selection of suitable programs is usually made depending on individual criteria. In principle, any evaluation software should offer at least image alignment with correction for movement, possibilities for temporal and spatial smoothing of the data, several statistical test procedures to calculate functional activations and options for spatial normalization. The tools for overlaying functional and morphological images and data export (e.g., neuronavigation) are also crucial for clinical applications. Compared to positron emission tomography (PET) and single-photon emission computed tomography (SPECT), fMRI is noninvasive, repeatable, does not involve exposure to radiation, and there is wide availability of equipment for clinical investigations. We refer the reader to the extensive specialist literature for a wider presentation of the physiological substrates and technical methods of fMRI [9].

Preoperative fMRI

Neurosurgical procedures in or next to functionally relevant brain structures invariably carry the risk of surgery-induced post-operative neurological deficits. Although undoubtedly all brain areas are in some way of functional importance, in clinical practice the term of "functionally relevant" or "eloquent" brain region refers to brain structures where damage can result in severe neurological symptoms and consequently in a significant reduction of the patient's life quality. Resection of so called "rolandic" or "central" brain tumors, for example, can lead to injury of the primary

motor and somatosensory cortices and therefore cause permanent movement and sensibility impairments. Patients with frontal or temporal lesions of the left hemisphere are particularly prone to suffer from post-operative motor or sensory language deficits, while mesiotemporal interventions can entrain memory dysfunction. Therefore, the indication of neurosurgery has to be interpreted with special caution in such patients and other, less invasive therapeutic options have to be taken into consideration. Alternative therapeutic options include radiotherapy or neuroradiological intervention. This holds true especially for patients where curative treatment is not possible. With regards to this issue, the preservation of brain function and the reduction of morbidity associated with treatment are crucial. Prudent individual choice of optimal surgical access and resection borders for each patient can be of utmost importance to avoid damage to functionally relevant brain structures. Similar to brain tumor surgery, epilepsy surgery aims at complete removal of epileptogenic zones with minimized damage to eloquent brain areas. Thus, depending on the location of the pathology, the determination of hemispheric dominance and precise spatial relationship between brain tumor/epileptogenic zone and functionally relevant brain area can be mandatory for the selection of appropriate therapeutic strategies and for the planning and implementation of function-preserving neurosurgical interventions. This information should be available before treatment, to substantiate therapeutic decision making and patient information, to reduce neurosurgical morbidity and to shorten post-operative hospitalization. Accordingly, functional neuroimaging not only offers a variety of novel options for clinical diagnostics and research, but also opens up a new diagnostic field of neuroradiology, with a shift from strictly morphological imaging to measurement and visualization of brain function [10].

Preoperative fMRI of motor and language function is in clinical use for more than 15 years now and represents the best established and best validated clinical application of BOLD-fMRI [11, 12]. Standardization of the imaging protocols (mainly a set of clinically tested and validated paradigms) and of data processing and data evaluation routines is indispensable for the diagnostic use of preoperative fMRI [10]. Moreover, a profound knowledge of structural neuroanatomy [13, 14] and of the different physiological activation patterns for the applied paradigms (reference data) including typical variations (e.g. effects of handedness, multilinguality, age, gender, etc.) is warranted to achieve correct functional diagnoses [15-19].

Preoperative fMRI of motor and somatosensory function

The indication for preoperative fMRI in patients with rolandic brain tumors results mainly from the limitations of structural neuroimaging, providing only a single, well defined structural landmark in the intact brain, namely the hand-knob of the precentral gyrus, which represents the anatomical substrate of the motor hand area (M1) [20]. Here, fMRI adds substantial diagnostic information: at least six different functional landmarks enable to localize the different representations of the human body (head / face, upper and lower extremities) within the precentral gyrus (primary motor cortex, M1) and postcentral gyrus (primary somatosensory cortex, S1) in relation to the tumor even if morphological landmarks are no longer identifiable due to mass effect and / or infiltration. In most preoperative cases, self-paced voluntary movements performed contralateral to the brain tumor will suffice to map M1 [21]. The scanning time per paradigm is usually 140 seconds. In patients with severe tumor related contralateral paresis, preoperative fMRI can be applied successfully when using dedicated fMRI protocols [22]. A simple block-designed paradigm consisting of complex finger movements of the unimpaired hand ipsilateral to the tumor alternating with a true rest condition activates the whole cortical motor network in both hemispheres robustly, providing premotor activation (PM) also on the tumor side as a functional landmark for the precentral sulcus at the junction with the superior frontal sulcus / the ventral bank of the precentral gyrus, respectively. Using this paradigm ipsilateral co-activation of the M1 hand representation can be observed [23]. In order to map the rolandic region completely in patients with high grade tumor associated hemiparesis, an additional somatosensory stimulation is recommended as a helpful adjunct to localize different body representations of the postcentral gyrus [24, 25].

A large number of validation studies reported highly concordant data of presurgical fMRI and intraoperative cortical stimulation (ICS) serving as reference procedure or “gold standard” in patients with lesions around the central sulcus. Concordance rates of fMRI and ICS data range between 83% in 33 patients [26] to 92% in 60 patients [27]. Task sensitivity for the identification of the sensorimotor region estimated in large groups of tumor patients was 85% in 103 patients [28] or 97% in 125 patients [29], respectively. Lee et al. [30] used preoperative fMRI to map sensorimotor function in 32 tumor patients. According to the authors, the results were useful to determine feasibility of surgical resection in 55%, to aid in surgical planning in 22% and to select patients for invasive surgical functional mapping in 78%. Overall, fMRI was an important factor in one or more

of these surgical decision making categories in 89% of all examined tumor patients. A similar range was documented by Ternovoi et al. [31], who found that presurgical fMRI results had an influence on therapeutic tactics in 69% of 16 tumor patients. Some investigators attempted to establish a functional risk predictor for postoperative clinical outcome. Haberg et al. [32] examined 25 patients with primary brain tumors near sensorimotor regions. In 80% of the patients, successful fMRI measurements were obtained, and 75% of these results were used in preoperative planning. The risk of postoperative loss of function was significantly lower when the distance between tumor periphery and BOLD activation was 10 mm or more. Similarly, Krishnan et al. [33] evaluated BOLD activation in 54 patients and found a lesion-to-activation distance of less than 5 mm and incomplete resection to be predictors for new postoperative neurological deficits. Thus, the authors recommended cortical stimulation within a distance of 10 mm. However, the availabel data to quantify a safe distance between functional activation and resection borders with respect to surgically induced neurological deficits is still very limited and does not justify any general conclusion or recommendation.

Besides cortical motor areas, the efferent pathways must be kept intact during surgery on rolandic brain tumors to preserve motor function. This is also true for surgery on tumors in critical spatial relationship to cortical language areas regarding important connecting fiber bundles. Hence, the combination of fMRI with DTI-tractography of the corticospinal tract (pyramidal tract) and of the arcuate fascicle is highly recommended to complete the preoperative neuroradiological diagnostic workup, especially when used for functional neuronavigation [10, 34-36]. In this context, it should be noted that multimodal integration with other MR-imaging modalities is also very helpful. A multimodal approach includes classical perfusion-weighted imaging (PWI) using contrast bolus tracking or contrast free arterial spin labeling techniques (ASL) to better assess tumor perfusion and vascularity as well as MR-spectroscopy in single voxel or chemical shift imaging (CSI) techniques to incorporate information on pathological metabolic changes in brain tumors.

Fig. 1

Preoperative fMRI of language

The indication for preoperative fMRI of language function is far more independent from anatomical information as there are no reliable morphological landmarks available for any cortical language center. Aphasic symptoms are most relevant in this context and justify fMRI examinations, regardless of whether the tumor is in the left or right hemisphere. In tumor related aphasia, the pathology has obviously affected cerebral language networks. In patients without language deficit, however, neuroanatomy comes into play [14]. Here, it is necessary to exclude that the tumor has affected structures belonging to the classical model of language, i.e. Broca's expressive language area of the left inferior frontal gyrus (B), Wernicke's receptive language area of the left superior temporal gyrus (W) and the arcuate fascicle (AF) connecting both. Surgical damage to those structures will result in severe and persisting language deficit and should be avoided. This holds also true for Geschwind's language area (G) of the adjacent left supramarginal gyrus (SMG), for the angular gyrus (AG) - being also important for mathematical operations - and for Dronker's area (D), the language area of the left anterior insula (AI). Left-handedness, ambidexterity and multilinguality represent relative indications of preoperative language fMRI for both, language lateralization and localization of the essential cortical language centers. As in other cognitive tasks, sufficient cooperation of the patient is crucial to achieve robust language related BOLD activation. Therefore, an intensive individual training of each patient prior to preoperative fMRI examination is of utmost importance for diagnostic success, ideally conducted in combination with an assessment and documentation of linguistic and neuropsychological deficits. A large body of data has been published on different language paradigms, most of them being designed for highly elaborated research in the neurosciences. A review of this extensive work is beyond the scope of this review, we thus refer the reader to current textbooks and review articles [37-39]. The approach of preoperative language fMRI focuses on a robust and reproducible localization of B and W and on reliable language lateralization. To this end, a set of various paradigms is usually applied, covering different linguistic aspects [40]. Comparable localization should be available from different paradigms to achieve reproducibility as a very important prerequisite for the diagnostic use of preoperative language fMRI [41, 42]. Language lateralization is highly variable when using fMRI, between paradigms, between measurements and between patients. Language lateralization also changes with the "cerebral workload" associated with a language paradigm, roughly following the principle: the higher the workload, the stronger the activation of the dominant hemisphere [43].

Despite these limitations, language lateralization using fMRI is clinically feasible, when lateralization results of multiple paradigms point towards the same direction [29, 42, 44, 45]. Besides reliable localization of important cortical language areas, preoperative language fMRI enables to reduce the number of invasive diagnostic measures prior to treatment (intraarterial barbiturate injection, aka Wada test) and to better stratify patients for intraoperative cortical mapping and awake craniotomies [27, 46-49].

Numerous studies used fMRI to identify language hemispheric dominance reliably [16, 19, 47]. However, the areas identified in different studies of language processing have varied markedly, likely relating to the use of different linguistic tasks or different imaging and post-processing techniques, among other factors. Language is a complex process which involves specialized sensory systems for speech, text, and object recognition, access to whole-word information, access to word meaning, processing of syntax and multiple mechanisms for written and spoken language production. Hence, the activation pattern is crucially dependent on the chosen fMRI task design. There is no single fMRI paradigm that identifies „language cortex“.

In a review by Baxendale [50], 70 patients were found in the literature having undergone both fMRI language studies and Wada testing serving as reference procedure to determine language dominance. With the exception of one study [51], which showed a comparatively low concordance of only 75% with a verbal fluency task used as fMRI paradigm, all other studies report impressive concordance rates between the two techniques despite the use of different language tasks and Wada test protocols. A study by Binder and colleagues [47] correlated the results of Wada test and fMRI assessment of language laterality, using a laterality index for the Wada test (a continuous variable) and a laterality index from fMRI calculated as an asymmetry in the voxels activated in each hemisphere by a semantic decision task. The correlation was extremely strong ($r=0.96$, $p<0.0001$) and all 22 subjects were classified to the same laterality by the two tests. Concordance at or near 100% was also found in other studies that have employed categorical analyses to classify language representation [52, 53].

In addition to information on lateralization, fMRI has the potential to provide detailed maps of the intrahemispheric localization of critical language areas as revealed by comparison of fMRI activation and ICS. A recent study by Rutten et al. [42] compared the results of fMRI quantitatively with intraoperative electrocortical stimulation mapping in thirteen patients. In eight pa-

tients, critical language areas were detected by electrocortical stimulation, and in seven out of eight patients, sensitivity of fMRI was 100% (i.e. fMRI correctly detected all critical language areas with high spatial accuracy). This indicates that such areas could be safely resected without the need for intraoperative electrocortical stimulation. A combination of three different fMRI language tasks (verb generation, picture naming, and sentence processing) was needed to ensure this high sensitivity, as no single task was sufficient for this purpose. On the other hand, on average only 51% of fMRI activations were confirmed by electrocortical stimulation, resulting in a low specificity of fMRI. Both sensitivity and specificity are strongly dependent on the statistical threshold applied in fMRI data evaluation. This study illustrates some of the current problems of basing clinical decisions (e.g. surgical strategies) on fMRI activation maps. Different language-related paradigms activate a different set of brain regions and a combination of different tasks is necessary to achieve high sensitivity in identifying critical areas [44].

Finally, some of the most prominent limitations and pitfalls of preoperative fMRI will be addressed shortly. Further reading on these topics is highly recommended before using fMRI as a diagnostic tool. Given appropriate imaging protocols, standardized data processing and evaluation routines and a correct diagnostic interpretation of the fMRI findings based on different sets of reference data for the applied paradigms, some important factors should be considered that may influence preoperative fMRI. Patient cooperation is of utmost importance for diagnostic success in clinical fMRI. A proper control of task performance and a sufficient training of the patients prior to fMRI is indispensable. Movement artefacts may alter the BOLD responses leading to non-physiological signals and wrong localizations [54, 55]. Consequently, it is crucial to apply robust movement correction during data processing and to individually check both the raw data and the processed data for artefacts. Data showing strong movement artefacts should be omitted and cannot be used for clinical purposes. In case of very high BOLD signals, a vascular (venous) origin should be considered. It is recommended to analyze the BOLD signal time course of the cluster carefully and compare it with the reference data. A visual comparison with contrast filled sulcal vessels may also be helpful [56]. The BOLD response may be compromised by the tumor or arteriovenous malformation both affecting the hemodynamic response through compression, hypervascularization or steal phenomena. Drugs may also exhibit hemodynamic effects. A BOLD compromise should be considered in case of no or mild clinical deficits and a weak or missing BOLD response [57]. Finally, inaccuracies from overlay procedures and referencing in navigation systems affect functional localizations. Last but not least,

preoperatively acquired data do not reflect the intraoperative situation after opening the dura and removal of tissue (brain shift) [10].

In conclusion, fMRI is feasible for clinical routine neuroimaging and provides important diagnostic information noninvasively being otherwise unavailable. Preoperative fMRI is valid and reasonably accurate to localize the different representations of the human body in the primary motor and somatosensory cortex prior to brain tumor surgery, which in general holds also true for language localization and lateralization. Yet the number of studies on presurgical language fMRI is still limited, and the results are more heterogeneous. Here, fMRI has at least some potential to help reducing the number of invasive diagnostic measures needed. If, and to what extent, intraoperative electrocorticography or Wada test can be replaced, remains to be determined.

Transcranial magnetic stimulation (TMS)

TMS is a non-invasive and painless technique for electrical stimulation of human cortex through the intact skull [58]. By depolarizing cortical neurons and triggering action potentials, TMS can evoke measurable electrophysiological and behavioural effects and allows for the modulation of neural processes in high temporal and spatial resolution. TMS is used in cognitive neuroscience to assess causality of structure-function relationships as revealed by functional neuroimaging [59, 60]. In the clinical setting, TMS has also a potential as a diagnostic tool [61] or as a therapy for neuropsychiatric disorders such as depression [62, 63]. Recent studies used TMS for preoperative planning and decision making in epileptic surgery candidates [64, 65] or tumor patients [66-68]. Single stimuli and short stimulus trains of TMS provide a means of transiently disrupting ongoing neuronal processing in the stimulated cortex. Repetitive TMS (rTMS) can modify neuronal excitability in the directly stimulated cortex beyond the time of stimulation. Since TMS induced neural excitation spreads along pre-existing neuronal pathways, “focal” TMS may also induce longer lasting neuromodulatory effects in remote cortical and subcortical brain regions which are connected with the stimulated cortical area.

Some physical aspects of TMS

The basic mechanisms of TMS have been covered in recent reviews [69-72]. TMS causes inductive (electro-magneto-electric) stimulation of neuronal axons. A brief, high-current pulse is produced in a stimulating coil. The time-varying electrical field produces a time-varying magnetic field with lines of flux oriented perpendicularly to the plane of the coil. The pulsed magnetic field is not attenuated by the scull and induces an electric field in the superficial brain tissue which runs parallel to the plane of the coil but has a direction that is opposite to the electric field in the coil. Hence, the pulsed magnetic field is only used as a means to generate an electric field in the brain that is suprathreshold for exciting cortical axons. The electrical pulse induced in the brain is very short lasting. A typical monophasic pulse current rises to a maximum and has reversed towards zero in about 200 μs. This leads to highly synchronous activation of neurons [72].

The electrical field induced in the neuronal tissue drives transmembraneous ionic currents. The most relevant parameter is the rate of change of electric field along the nerve. Depending on the gradient and the orientation of the electric field gradient relative to the course of the axon, the pulsed electrical field may generate an outward current and local depolarization at distinct sites of neuronal axons. If the outward current causes sufficient membrane depolarization, this will trigger an action potential. This action potential propagates along the axon and may cause a transsynaptic excitation of postsynaptic neurons. Crucial for an efficient depolarisation of an axon is the spatial gradient of the induced electric field in relation to the orientation of the axon. At the cellular level, the events that lead to neuronal excitation are still poorly understood. For instance the relevance of cellular and gyral shapes, grey matter boundaries, local variations in tissue conductivity and the role of background neuronal activity for neuronal stimulation are largely unknown [72].

The majority of studies have investigated the physiological mechanisms of TMS in the healthy human primary motor cortex (M1) because its effects can be quantified by recording the TMS evoked motor potential (MEP). For other brain regions, such direct quantification is difficult to obtain. Therefore, researchers have used neuroimaging techniques such as fMRI to map TMS-evoked changes in regional neuronal activity throughout the brain [73-75]. These studies revealed that the TMS-induced changes in regional neuronal activity are not restricted to the stimulated cortex but give rise to functional changes in connected cortical areas, including subcortical brain regions [73, 74, 76].

The TMS-induced magnetic and electric field decreases rapidly with increasing distance from the coil. The maximal depth of penetration depends on the shape and size of the coil, the employed stimulation intensity and the responsiveness of the targeted tissue. Commercially used coils reach a penetration depth of approximately 2-6 cm and the field at a distance of 4 cm may be only about 30% of that at the coil surface [77]. To minimize the coil-to-cortex distance, the coil should be placed tangentially on the skin. This implies that only cortical neuronal tissue is within the range of TMS while deep cerebral grey matter nuclei cannot be stimulated directly with TMS.
In general, TMS does not produce a focal stimulation of neuronal tissue at a small predictable site. The geometry of the coil is an important factor for determining the magnitude and spatial extent of cortical stimulation. Usually, figure-of-eight shaped coils are used for cortical mapping [78]. These coils offer a spatial resolution of approximately 1-2 cm.

It needs to be born in mind that TMS may produce adverse effects, especially if rTMS is used. These side effects are extensively discussed in a recent consensus paper on safety issues of TMS [79]. The most relevant adverse effect is the induction of epileptic seizures. Therefore, safety guidelines were established which specify the maximal number of pulses per session, stimulus intensity and frequency that are considered to be safe in terms of seizure induction [80, 81]. Since the introduction of the safety guidelines, only a few individuals experienced rTMS-induced seizures worldwide and none of them suffered lasting physical sequelae. Previous studies used TMS in candidates for epilepsy surgery without reporting any adverse effects [64, 65, 82].
The high magnetic fields that are used during TMS exclude subjects or patients with cardiac pacemakers and metal implants from TMS investigations. Since the rapid discharge through the coil produces a characteristic clicking sound, individuals who receive TMS should always wear ear plugs.

Neuronavigated TMS

Accurate placement of the TMS coil over the cortical target area is crucial. The motor response that is evoked by TMS can be used to localize the primary motor cortex. For most cortical areas, no overt responses for the determination of the appropriate stimulation site can be elicited and other strategies have to be used to accurately place the coil over the cortical target. Neuronavigated TMS guided by frameless stereotaxy represents the method of choice as it allows

exact placement and monitoring of the coil throughout the TMS experiment with a spatial accuracy in the range of a few millimetres [83-85]. Optical (infrared based) and acoustic (ultrasound based) devices are available for neuronavigation. These systems use passive (reflecting) or active (emitting) markers which are attached to the subject's head and to the TMS coil [86].

Neuronavigation requires a T1-weighted, high-resolution image of the subject's brain. The anatomical images have to be transferred into three-dimensional space. Optionally, individual fMRI activation maps can be overlaid on the structural images. Pre-defined anatomical landmarks are marked on the individual structural MRI with special neuronavigation software.

The subject's head and the structural MR scans are coregistered by touching the pre-defined landmarks on the subject's face using a pointer equipped with trackers. An accurate coregistration procedure is crucial to the exact placement of the coil. Localization errors result primarily from inaccuracies in the identification and matching of the fiducial markers on the MRI and the subject's head. The position of the coil is visualized in realtime on a computer screen relative to the individual three-dimensional anatomy of the brain. The exact position of the cortical target area can be defined either anatomically based on the gyral anatomy or functionally on the basis of activation maps that have been obtained with fMRI. In addition to the individual activation map, one can also use the stereotactic coordinates of a peak activation that has been identified in a group of subjects. Figure 2 gives a detailed description of neuronavigated TMS guided by frameless stereotaxy.

Fig.2

Preoperative TMS of motor function

Mapping the motor cortex with TMS is based on the relationship between the averaged amplitude of the MEP and the density of cortical motoneurons in the stimulated area [87, 88]. It can be used to investigate reorganizational changes in the motor cortex, such as a shift in the position of a map or a change in other map parameters under certain conditions [89].

TMS mapping of the motor cortex at the hemispherical surface (e.g., motor hand area or motor face area) is usually performed with the coil placed tangentially on the scalp with the handle pointing backward and perpendicular to the central sulcus. Stimuli are applied at various scalp

sites using a latitude/longitude based coordinate system referenced to the vertex [90], and the amplitude of MEPs evoked in contralateral muscles is measured. Multiple stimuli are applied to each stimulation site to prevent amplitude variability due to cortical fluctuations in excitability. With this method, a map of sites on the scalp can be obtained from which responses for the muscles of interest can be recorded. The two most important measures that can be derived from such maps are the "centre of gravity" (i.e. an amplitude-weighted centre of the map) and the "hot spot" (the point of maximum response) [91]. MEP amplitude can fluctuate significantly, even under carefully controlled conditions. Therefore, a major factor likely to influence the reliability of TMS maps is the reliability of the estimate of MEP amplitude at each scalp site [92]. Increasing the simulation intensity will result in a higher degree of stimulus spread and the consecutive activation of more cortical motoneurons. Since the cortical stimulus spread at higher intensities elicits MEPs even from less than optimal stimulation sites, mapping experiments should be performed with stimulation intensities 10% above the resting motor threshold of the small hand muscles to ensure stimulation focality [93]. By moving the coil in small increments over the scalp while observing and interpolating the amplitude changes in the MEP, a mapping accuracy of 0.5 cm can be obtained [68, 94, 95]. The representation of individual hand muscles in the primary motor cortex can be mapped reliably and reproducibly with TMS [92, 96, 97] and the expected somatotopy of different muscle groups along the mediolateral axis has been demonstrated within the individual [98]. The use of stereotactically guided TMS can increase the accuracy of TMS mapping and provides a means for showing the functional localization of different muscles over the cortical convexity [67, 94]. TMS mapping of the motor cortex has been used in normal subjects as well as patients with amputations and brain tumors in order to assess the cortical representation of muscles of the upper and lower extremity and the face [87, 88, 99, 100]. TMS has also been used to investigate reorganization and functional plasticity in the motor cortex after experimental deafferentiation [101], and in patients after central and peripheral lesions [102]. Kamida et al. [65] suggested that TMS is useful to assess motor function in the affected hemisphere of hemiplegic patients with intractable epilepsy.

A high spatial localization accuracy for TMS based mapping of the primary motor cortex has been confirmed by correlation studies combining TMS and PET [103, 104] and TMS and fMRI [105-111]. However, few studies compared the results of preoperative TMS with intraoperative cortical stimulation and those studies are limited by the small number of patients included. Krings et al. [68] compared TMS based motor maps for individual hand and arm muscles with the results obtained from direct electrical cortical stimulation (DECS) in two tumor patients. In their study,

all MEPs were within 1 cm of the electrode locations producing movements. MEPs larger than 75% of the maximum MEP for a given muscle mapped to within 5 mm of the cortical motor area determined by DECS with a probability of 75%. MEPs smaller than 50% of the maximum never mapped closer than 5 mm to their respective cortical area.

In another recent study, Vitikainen et al. [64] used stereotactically guided TMS, magnetoencephalography (MEG) and DECS in two epilepsy surgery candidates. TMS was applied over the primary motor cortex to map the cortical representation areas of selected upper and lower extremity muscles. MEG was used to determine the location of the primary somatosensory cortex. In that study, TMS and MEG provided accurate functional maps. Representation areas defined by TMS were in line with the equivalent current dipole (ECD) sources of the somatosensory evoked fields (SEFs), adding reliability to the preoperative localization of the primary motor cortex (Fig.3).

Fig.3

Preoperative TMS of language

While the use of TMS to investigate cognitive processing is established in healthy subjects (see for review [112, 113]), few studies used TMS for preoperative mapping of higher cognitive functions. Pascual-Leone et al. [114] were the first who used TMS in a preoperative setting to induce speech-arrest in six presurgical epilepsy patients. The authors tested whether TMS could be used as a non-invasive alternative to the Wada test [46]. Short trains of repetitive TMS at rates of 8, 16 or 25 Hz were applied over different scalp positions around the perisylvian cortex defined by the international 10-20 electrode system in both hemispheres. rTMS over the left but not right inferior frontal cortex (i.e. Broca's area) produced a reproducible speech arrest 4-6 s after stimulation when subjects counted aloud. Wada test revealed left hemispheric language dominance in these patients, suggesting that the rTMS induced speech arrest offered a non-invasive alternative for the determination of language dominance. Other studies, however, failed to replicate these promising results: Jennum et al. [115] reported that 30 Hz rTMS induced complete speech arrest in 14 of 21 preoperative patients. In the remaining seven patients, there was only a slowing of speech or partial speech arrest in some of the test procedures. Michelucci et al. [116] also called into question the reliability of rTMS for the determination of language

dominance. In their study, rTMS only induced speech arrest in 7 of 14 epilepsy patients. A systematic investigation of stimulation intensity and rate in healthy subjects by Epstein et al. [117] may explain the inter-study variability. Although higher stimulation rates induced stronger effects of speech arrest, lower rates of 4-8 Hz were more reliable. Since higher frequencies produced prominent facial and laryngeal muscle contractions and discomfort, speech arrest was more difficult to determine. In another study with healthy subjects, Epstein et al. [118] demonstrated that low frequency 4 Hz rTMS also interfered with reading and spontaneous speech. When comparing the reliability of 4 Hz rTMS with the Wada test in 16 preoperative epilepsy patients, rTMS indicated left hemispheric language dominance for 12 patients and right hemispheric dominance for the remaining 4 while Wada test showed left dominance for all patients. Thus, rTMS overestimated right hemispheric involvement in 4 patients although there was a significant moderate correlation between Wada test and rTMS. Further, results from Wada test were a better predictor of postoperative language impairment. These results call into question the reliability of rTMS for the preoperative determination of language dominance. However, when comparing Wada test and TMS, one should bear in mind that the Wada test affects the functions over a large region in one hemisphere for several minutes while TMS disruption is far more focal and transient. Studies in healthy subjects have suggested that different sites within Broca's area can be targeted with rTMS to induce speech arrest and that more anterior sites may correspond more closely with results from Wada test [119, 120].

Other studies confirmed that the TMS-induced effects are to subtle to be used for preoperative evaluation of higher cognitive functions [82]. To date, TMS can not be regarded as non-invasive alternative for the preoperative determination of language dominance.

Comparing preoperative TMS and fMRI

The preoperative use of fMRI is well established [121]. However, since fMRI does not allow for a reliable detection of the extent of the motor representation in the brain, neuronavigated TMS mapping may add a new dimension to preoperative planning [64]. Krings et al. [122] found a high correlation between the areas of hemodynamic change revealed by fMRI and the localization of cortical motoneurons defined by TMS. The cortical loci corresponding to peak MEP amplitude and peak fMRI activation corresponded closely in three normal subjects and two patients with mass lesions near the central sulcus. In that study, no MEPs were found for TMS

sites further than 2 cm from the cortical surface projection of the fMRI activation. Both techniques demonstrated interhemispheric asymmetries resulting in larger activation maps in the dominant hemisphere. However, TMS maps showed a more widespread activation than fMRI maps due to the relatively large area of the electric field induced by TMS. Here, highly focal "minicoils" may substantially increase the spatial resolution of TMS mapping of corticomotor representations.

In another study by Krings et al. [110], preoperative TMS motor mapping was compared with the results from fMRI in ten patients with mass lesions near the central sulcus. The primary motor cortex was localized by voluntary finger movements during fMRI and with stereotactically guided TMS mapping. Both methods revealed corresponding results: The distance between fMRI peak activation and the cortical site of maximal MEPs ranged between 0 and 1.2 cm. According to the authors, stereotactically guided TMS provides a reliable alternative for the preoperative localization of motor-related areas and may complement fMRI. Since TMS can provide accurate functional maps of cortical motor representation even in patients with local cerebral abnormalities, it may be especially useful for the investigation of patients in whom motor cortex localization by means of fMRI is not possible [68]. Further, TMS is easily applied, does not suffer from motion artefacts and does not rely on elaborate post-processing methods [67].

In conclusion, the reliability and accuracy of preoperative TMS remains to be determined, although some studies indicate that TMS may be a useful tool for the preoperative mapping of motor as well as higher cognitive functions. Given the complementary information that is provided by the various brain mapping techniques, we argue that the integration of different non-invasive imaging methods such as fMRI and TMS or EEG / MEG and TMS will be most useful in the context of preoperative planning. The combination of fMRI and TMS gives access to non-invasive measuring of stimulation effects on the brain with a high spatial (fMRI: spatial resolution in the millimeter range) and temporal (single-pulse TMS: temporal resolution in the order of milliseconds) resolution.

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Figure legends

Figure 1. Preoperative fMRI and DTI in a patient with a left glioblastoma in critical distance to Wernicke's language area and the rolandic region. Left: Somatotopic mapping of the primary motor cortex, pyamidal tract. Right: Functional localization of Wernicke's area, Broca's area, arcuate fascicle, tumor segmented in pink. Top: Transverse crossectional images. Down: 3D surface views.

Figure 2. Neuronavigated TMS guided by frameless stereotaxy [TMS-Navigator, Localite, Sankt Augustin, Germany]. A tracker with 3 passive spheres is attached to the headband of the subject (a), on the TMS coil (b), and (c) fixed on a pointer. These dynamic reference systems provide online information about the location of the head and the coil in space. (d) A camera system detects the position of the dynamic reference systems and displays this information on a computer screen using navigation software for visual localization of the coil. *Adapted from Hartwigsen et al., 2009; reprinted with kind permission of Springer; Germany.*

Figure 3. Results from the mapping experiment for one patient. (A) Results from TMS, the dots represent the stimulation sites. For hand and palm area, red indicates MEPs from biceps brachii (BB) and extensor digitorum communis (EDC), orange from BB, green from abductor digiti minimi (ADM) and abductor pollicis brevis (APB), and yellow only from APB, responses from the leg area are represented with turquoise (rectus femoris) and from foot area (tibialis anterior and abductor hallucis) with light orange [figure from eXimia NBS]. 3-D MRI reconstructions in lateral (B) and cross sectional view (C). MEG ictal and somatosensory evoked field (SEF) equivalent current dipole (ECD)-source areas (purple = epileptic; green = right median and tibial nerve representation area) and TMS representation areas (all areas marked with turquoise) are shown on top of the DECS-grid and strips (yellow, numbered). The lesion area is depicted in red. Responses to DECS are shown with coloured circles. Sensory responses from the right hand and lower arm (G20–G9 and G12–G9) as well as from the right leg and foot (G4–G9 and G5–G9) are color coded with green in panel B. Sensory responses from the right shoulder are represented with yellow. Motor responses from the arm and hand are coded with turquoise circles in panel B and from leg and foot in panel C. Habitual seizures elicited by stimulation are coded with purple. Circles with several colours represent several types of responses provoked by DECS. Electrode

locations included in the resection are encircled by a purple line. Double asterisks (**) mark the central sulcus at both ends, also depicted in panel A. (D) A photograph after the resection showing the removed area anterior to the cortical vein, marked with an encirceled white asterisk, also in (B). Ant.=anterior; Post.=posterior direction. *Adapted from Vitikainen et al., 2009; reprinted with kind permission of Neuroimage.*

Fig.1

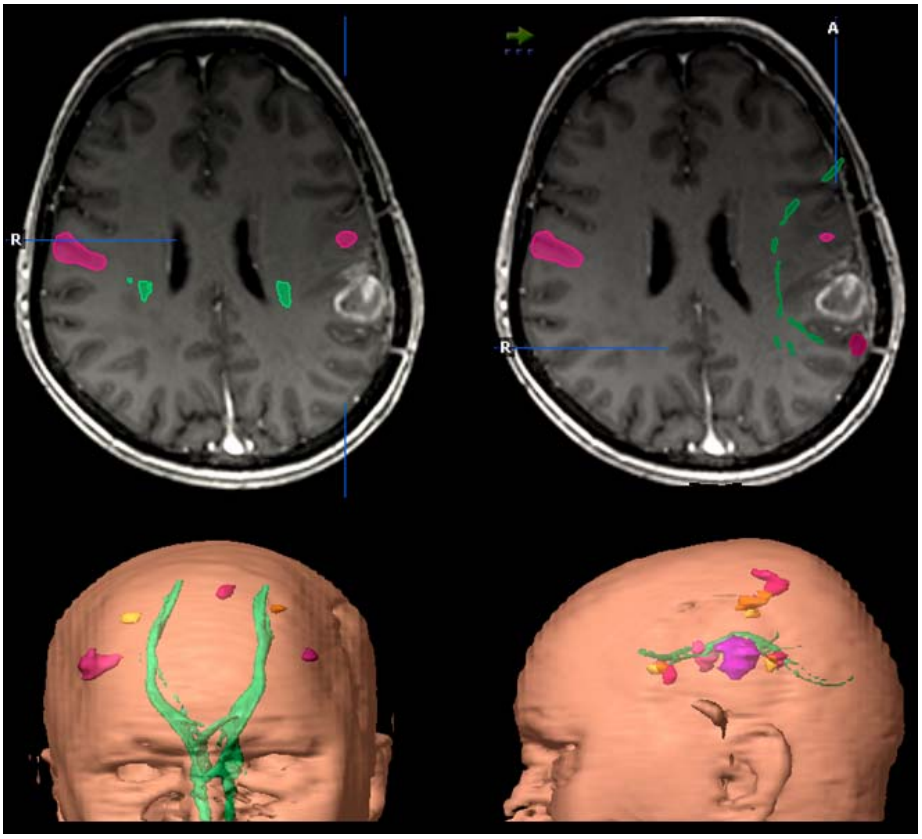
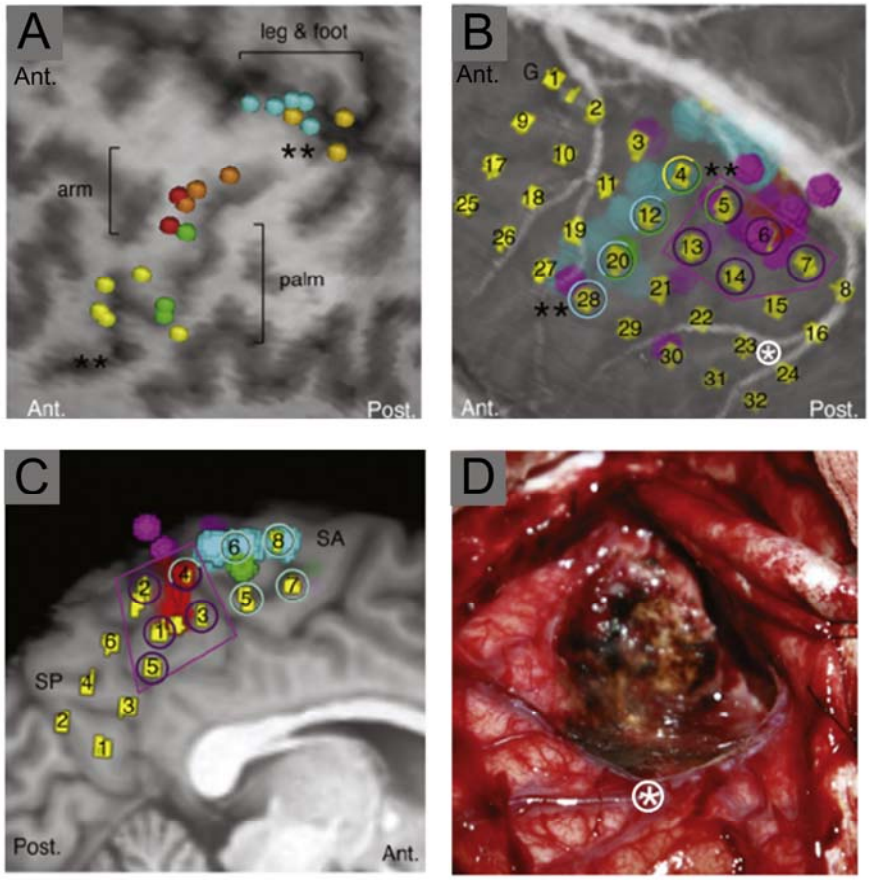


Fig.2

Fig.3


A
leg & foot
Ant.
arm
palm
Ant.
Post.
B
Ant.
G
Ant.
Post.
C
SA
SP
Post.
Ant.
D

Appendix IV

Modality-independent semantic, phonologic and perceptual word processing in the human brain

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Short title: Linguistic and perceptual word processing

Key words: Functional laterality, functional imaging, language, nonlinguistic

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Abstract

Recent functional imaging studies on language processing have shown that separate brain networks are involved when healthy subjects judge semantic or phonologic aspects of words. However, most of the studies focussed on unimodal processing of either visual or auditory word stimuli. We used event-related fMRI to identify modality-independent correlates of semantic and phonologic word processing. Relative to phonologic decisions (number of syllables), we expected that semantic decisions (natural versus man-made items) would result in more anterior activation of left inferior frontal gyrus (IFG) both in the visual and auditory modality. Conversely, phonologic judgements should activate more posterior aspects of the IFG, and the bilateral supramarginal gyrus (SMG) of the inferior parietal cortices. Participants also performed a non-linguistic perceptual judgement related to vocal pitch or font size on the same set of word stimuli used for the linguistic tasks to identify brain regions involved in the processing of non-linguistic properties of word stimuli. Regardless of modality, semantic compared to phonologic decisions activated anterior IFG (aIFG), while phonologic compared to semantic judgements led to a bilateral activation of SMG. Modality-independent processing of non-linguistic perceptual features activated right inferior frontal areas. Our results demonstrate for the first time that modality-independent semantic, phonologic, and non-linguistic word processing rely partly on discrete circuits, each of which may depend on separate neural subsystems. The increased activation of right inferior frontal areas during language tasks in aphasic patients with left-hemispheric stroke might at least partially reflect stronger processing of non-linguistic perceptual aspects of language related stimuli.

Introduction

Recent functional imaging studies have demonstrated that semantic and phonologic aspects of word comprehension engage distinct networks in the healthy human brain, with semantic aspects resulting in more anterior and more left lateralized activation compared to phonologic judgements (for meta-analyses, see Costafreda et al. 2006; Vigneau et al. 2006). Consequently, functional-anatomic models of language processing propose neuroanatomically segregated routes for semantic and phonologic word processing (Hickok and Poeppel 2000; 2004; 2007).

Direct comparisons of semantic with phonologic word judgement tasks revealed increased activation in the anterior part of the inferior frontal gyrus (aIFG) both for auditory and visual stimuli (e.g. Burton et al. 2003; Gitelman et al. 2005; McDermott et al. 2003; Seghier et al. 2004). In contrast, phonologic compared with semantic word processing resulted in relatively stronger activation in the supramarginal gyri (SMG) of the inferior parietal cortices bilaterally (Burton et al. 2003; Devlin et al. 2003; Price et al. 1997) and in left posterior inferior frontal gyrus (pIFG) (Burton et al. 2003; Devlin et al. 2003; McDermott et al. 2003).

Most of the above cited studies presented stimuli only visually (e.g., Devlin et al. 2003; Gitelman et al. 2005; McDermott et al. 2003; Price et al. 1997; Seghier et al. 2004). Only one study presented auditory stimuli (Burton et al. 2003). Other studies have examined either phonologic (e.g. Burton et al. 2003; Cohen et al. 2004) or semantic word processing (e.g. Chee et al. 1999; Marinkovic et al. 2003) in both the auditory and the visual modalities, but none of these studies directly compared semantic and phonologic processing within the same subjects. Therefore, it remains to be determined which regions in the brain specifically contribute to phonologic or semantic word processing in a modality-independent fashion. Using a task in which participants had to make semantic as well as phonologic decisions on

the same set of heard or written words, this neuroimaging study was designed to delineate areas in the human language system subserving modality-independent processing of word semantics and word phonology.

Our experimental design built upon an experimental task used by Devlin et al. (2003) who contrasted semantic with phonologic judgements using the same set of words. Different from Devlin et al. (2003), however, stimuli were presented not only in the visual but also in the auditory modality. We reasoned that the core aspects of word processing should be modality-independent. Therefore, we expected to find activation in the left aIFG for modality-independent semantic word processing in comparison to phonologic word processing. In contrast, phonologic relative to semantic processing should activate more posterior regions, including the left pIFG and the bilateral SMG.

We designed our experimental task to address a second issue which has received little attention. In addition to a semantic and phonologic task, we included a perceptual control task to capture neuronal activity patterns involved in the processing of perceptual, non-linguistic features that are inherent in auditorily and visually presented word stimuli. Depending on the exact nature of these (e.g. prosodic or graphic) features, functional activation patterns may extend to areas beyond left perisylvian language regions, for example in right inferior frontal or extrastriate regions (Demonet et al. 2005). The influence of such stimulus-inherent, non-linguistic perceptual stimulus characteristics on the resulting activation pattern might be particularly relevant when using fMRI to draw conclusions about potential reorganisation processes in the language system after left-hemispheric brain damage.

Materials and Methods

Subjects

Fourteen right-handed German native speakers with no history of neurological disorder or head injury (7 females, 27-61 years old, mean age 41.9; 7 males, 31-69 years old, mean age 49.1) participated. Right-handedness was tested with the 10-item version of the Edinburgh Handedness Inventory (Oldfield 1971). All subjects gave written informed consent prior to the investigation and were paid for participation. The study was performed according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital Hamburg-Eppendorf.

Experimental design

The study used a two (modality: spoken vs. written words) by three (task: semantic, phonologic, nonlinguistic) event-related within-subject factorial design (see Figure 1). Word stimuli were divided into two sets (Set A, Set B). Stimuli in Set A were matched to those in Set B with respect to word frequency, number of letters, and imageability, and contained an equal number of manmade vs. natural and two- vs. three-syllable words. For the first half of the subjects, Set A was presented auditorily and Set B was presented visually. After half of the subjects had been tested, Set A was switched with Set B such that Set A was now visually presented, while Set B was presented in the auditory modality. Thus, all of the 112 stimuli were presented in both modalities, in order to minimize stimulus-induced differences in the planned comparisons between modalities.

Experimental stimuli were divided into six runs with 56 stimuli each (Figure 1A,B). Each subject received three ‘auditory’ and three ‘visual’ runs, while the order of modality of each run was pseudorandomly rearranged for each subjects. Three of the six runs presented the

same 56 auditory stimuli, while subjects performed a different task in each run (semantic, phonologic, nonlinguistic, respectively). In the same manner, three of the six runs presented the other 56 stimuli visually three times while subjects performed a different task in each run. Within any given run, the task remained the same. Each word only appeared once within a run. Within runs, stimuli were arranged into seven 'miniblocks'. To increase design efficiency, miniblocks were separated by 6 periods of 20 seconds of silence during which the screen remained dark and no stimuli were presented. Each miniblock contained eight stimuli (four three-syllable and four two-syllable words for which the semantic, phonologic and nonlinguistic characteristics had been completely crossed) which were separated by a randomly assigned stimulus onset asynchrony of between 2.5 and 3.5 seconds. Each miniblock was preceded by a spoken or written instruction, according to the modality of the run. Subjects initiated the presentation of the stimuli in the miniblock by button press. The order of miniblocks within each run and the order of stimuli within miniblocks were pseudorandomly assigned for each subject. Each run took about 4.5 to 5 minutes to complete.

Figure 1 about here

Before scanning, the experiment was explained and subjects had a training session outside the scanner during which subjects practiced all of the tasks with at least ten practice trials per task. Different practice items were used to explain the three different tasks per modality, in order to focus subjects' attention on the task and, as much as possible, guard for potential "spill-over" and recognition effects resulting from using the same stimuli repeatedly across the three runs per modality.

Tasks

Subjects performed three different tasks in the visual and the auditory modality (Figure 1A). In the phonologic task, subjects categorized the words as having two or three syllables. The semantic task consisted of deciding whether a word represented a natural or man-made item. Two perceptual tasks were included as nonlinguistic tasks. In the perceptual auditory task, subjects decided whether or not there had been a decrease in vocal pitch towards the end of the word. In the perceptual visual control task, subjects decided whether or not font size had decreased towards the end of the word. Subjects were instructed to respond as quickly and as accurately as possible by pressing one of two buttons on a response box with their left middle and index finger, respectively.

Stimulus construction

Stimulus construction was adapted from Devlin et al. (2003) such that the stimulus material was held constant while the task was varied. In addition, in order to allow perceptual judgements about inherent surface features of the auditory and visual word stimuli we applied two specially piloted perceptual auditory and visual manipulations as described below. Importantly, non-linguistic perceptual word features had to be unobtrusive enough to allow for a relatively unimpeded processing of semantic and phonologic stimulus characteristics.

In sum, 112 highly frequent two- and three-syllable German nouns representing concrete natural and man-made items were chosen as stimuli. In piloting, about 300 highly frequent, unambiguous nouns from the CELEX lexical database for German (Centre for Lexical Information, Max Planck Institute for Psycholinguistics, The Netherlands) were selected. No compound nouns, hypernyms or foreign words were included. Thirty German native speakers (15 females, age 24-47, mean age 29.0) independently categorized each item as either man-

made or natural, rated each item's imageability on a 4-point scale, ranging from 1 (concrete) to 4 (abstract), and provided the number of syllables for each item. Only those words which (i) at least 29 out of 30 pilot subjects correctly classified as being either man-made or natural, (ii) received an average imageability rating of < 1.6, and (iii) reached $> 90\%$ agreement (i.e., agreement among at least 27 of 30 pilot subjects on the intended syllable count were included). Since more two-syllable than three-syllable words passed the above validation criteria, we were able to select the two-syllable nouns that most closely matched the three-syllable words in terms of imageability ratings and number of letters. In total, 56 three-syllable nouns and 56 two-syllable nouns were selected.

Auditory versions of the words were recorded by an experienced female speaker and had an average duration of 0.74 s / 0.85 s (two-syllable words in Set A / Set B) and 0.87 s / 0.86 s (three-syllable words in Set A / Set B). Half of the auditory stimuli were manipulated using the sound editing program Adobe Audition 2.0. (www.adobe.com/products/audition) such that there was an audible yet unobtrusive decline (13 halftones) in vocal pitch towards the end of the word. In analogy to the auditory condition, the font size of the letters was manipulated for half of the visual stimuli such that it changed linearly from an initial 70 pt to a final 50 pt font size (Type Albany AMT) across the length of the word, to result in a noticeable yet unobtrusive change in the visual appearance of the word (Figure 1C). Both manipulations were piloted prior to implementation to ensure that the nonlinguistic manipulations were perceptually noticeable within the timing constraints of the experiment without impeding performance on the linguistic tasks.

Stimulus presentation and response collection

Auditory stimuli were presented via MR-compatible headphones (MR Confon, Magdeburg, Germany). Sound volume was individually adjusted for each subject. Visual stimuli appeared in light gray on a dark screen. Visual stimulus duration was set to the mean duration of the auditory word stimuli, which changed slightly when the auditory and visual stimulus lists were switched. Stimuli were projected centrally via LCD projector onto a screen placed behind the head coil. Subjects viewed the screen via a mirror on top of the head coil (10 x 15° field of view). Subjects responded by button press, using the index and middle finger of their left hand (see Fig.1A). Presentation of stimuli and task sequence, and collection of motor responses were controlled by the software `Presentation´ (Version 11.0, Neurobehavioral Systems, www.neurobehavioralsystems.com). The start of each session was announced by brief auditory or visual instructions. Throughout scanning subjects kept their eyes open.

Magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) was performed on a 3T Siemens TRIO system (Siemens, Erlangen, Germany). A total of about 200 fMRI volumes per run with 38 contiguous axial slices covering the whole brain (3mm thickness, no gap) was acquired using a gradient echo-planar (EPI) T2*-sensitive sequence (TR 2.52 s, TE 30 ms, flip angle 90°, matrix 64 x 64 pixel). The first three volumes were discarded to allow for T1 equilibration effects. Following the acquisition of the functional images, a high-resolution (1x1x1 voxel size) structural MR image was acquired for each participant using a standard three-dimensional T1-weighted MPRAGE sequence.

Statistical analysis of behavioural data

To analyze reaction times (RT), we performed a two-way repeated measures ANOVA (SPSS software, version 13, Chicago, Illinois, USA), using the within subjects factors 'task' (three levels: semantic vs. phonology vs. nonlinguistic) and 'modality' (two levels: auditory vs. visual). For all conditions, sphericity could be assumed. Conditional on a significant F-value we performed post-hoc paired t-tests to characterize the differences among experimental conditions that resulted in significant main effects or interactions in the ANOVA. Only trials with correct responses were included in RT analyses. Error trials were analysed separately. As Kolmogorov-Smirnov tests indicated that error rates were not normally distributed, Bonferroni corrected nonparametric Wilcoxon signed-rank tests were used.

Statistical analyses of the imaging data

Task related changes in the blood oxygen level dependent (BOLD) signal were analysed using Statistical Parametric Mapping (SPM5; Wellcome Department of Imaging Neuroscience, www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 7.1 [The Mathworks Inc., Natick, MA, USA], (Friston et al. 1995a; Worsley and Friston 1995). For preprocessing, a novel normalization routine as implemented in SPM5 was used, combining segmentation and coregistration of the individual T1-weighted image, bias correction, and spatial normalization (Crinion et al. 2007). First, all functional EPI image slices were corrected for different acquisition times of signals by shifting the signal measured in each slice relative to the acquisition of the middle slice. Next, all volumes were spatially realigned to the first volume in order to correct for motion artefacts. The individual T1-weighted image was then segmented using the standard tissue probability maps provided in SPM5, and coregistered to the mean functional EPI image. The information resulting from a second segmentation of the

coregistered T1-image was then used to normalize all of the functional EPI images. All normalised images were then smoothed using an isotropic 10-mm Gaussian kernel to account for inter-subject differences.

Statistical analyses of the functional images were performed in two steps. At the first level, the six different runs (semantic, phonologic, and nonlinguistic processing in the auditory and visual modality, respectively) were modelled as six separate conditions, each consisting of at least two regressors. One regressor modelled onset and actual duration of the instruction events. The second regressor modelled the onset of the correctly judged word items within each run. When subjects had made one or more errors in any given run, the onsets of the erroneously judged word events were modelled as a separate regressor of no interest. All of the onsets in each regressor were convolved with a canonical hemodynamic response function as implemented in SPM5. Voxel-wise regression coefficients for all conditions were estimated using the least squares method within SPM5, and statistical parametric maps of the t statistic (SPM{t}) were generated from each condition. At this step we computed the contrast of each of the conditions against rest, resulting in at least 12 (and up to 18, if subjects had made one or more errors in each of the runs) separate contrast images for each subject.

Our research questions were addressed in several second-level analyses treating participants as random effect. The contrast images based on the regressors of the correctly judged word items were used for the second level analyses. To examine effects of modality and task, the six contrast images for each subject which represented the (correctly judged) events in each of the six conditions of interest, compared with rest, were entered into a within-subject ANOVA model, using the 'flexible factorial design' option in SPM 5 including a correction for non-sphericity. This ANOVA model was used to perform several

conjunction analyses under the conjunction null hypothesis (Nichols et al. 2005), as described below. The conservative 'conjunction null' test is a valid test for a logical AND of effects; that is, it tests whether there is an effect at a predetermined level of significance in both factors (Nichols et al. 2005).

Conjunction analysis was employed to identify increases in regional activity which were specifically related to semantic and phonologic word processing of both auditory and visual word stimuli. The first set of conjunctions focused on the 'pure' effects of semantic and phonologic processing by identifying conjointly activated regions in the auditory and visual semantic condition (and, respectively, in the auditory and visual phonologic condition) using the respective main effects. Next, we performed two conjunctions across modalities of the differential contrasts of the semantic compared to the phonologic condition (and vice versa) to identify modality-independent activation associated preferentially with semantic and with phonologic processing, respectively. We also computed differential contrasts for the unimodal comparisons of semantic and phonologic decisions. Finally, we tested for areas showing increased activity with non-linguistic perceptual processing relative to linguistic (i.e., semantic and phonologic) processing, both across and within modalities. To ensure that the obtained activations did not result from deactivation in the respective comparison condition, we inclusively masked all differential contrasts with the contrast of the respective condition of interest compared to rest (following Cohen et al. 2004).

For conjunction analyses based on main effects, we applied a level of significance of $p < 0.05$ (corrected), while conjunctions of task-specific activation were thresholded at $p < 0.01$ (uncorrected). Because we had anatomically restricted a-priori hypotheses regarding the differential activation in the IFG and SMG with respect to semantic versus phonologic judgements, we applied a small volume correction (SVC) when testing for differential effects

directly contrasting semantic with phonologic processing (and vice versa). For each SVC we defined a spherical region-of-interest (ROI) with a diameter of 16 mm. The center of the ROI was determined based on activation peaks reported in previous neuroimaging studies that contrasted phonologic and semantic processing. The reported activation peaks were transformed into MNI stereotactic space where appropriate and then averaged, first within and then across studies. Using this procedure, we derived the center of the SVC for preferential semantic processing in the left IFG (x=-45 y=25 z=9; MNI) including the data reported in three previous neuroimaging studies (Gitelman et al. 2005; McDermott et al. 2003; Seghier et al. 2004). Analogously, the centers of a small volume correction for preferential phonologic processing (x=-47 y=-46 z=43; x=47 y=-48 z=43; MNI) were derived by averaging the activation peaks in the supramarginal gyri of the left and right hemispheres as reported in four neuroimaging studies (Burton et al. 2003; Devlin et al. 2003; McDermott et al. 2003; Price et al. 1997). SVC used a significance level of $p < 0.05$ after correction for multiple comparisons within the ROI. Correction for multiple comparisons was performed using the family-wise error method as implemented in SPM. The SPM anatomy toolbox (Version 1.3b) was used for anatomical localization of activation peaks which are reported as Talairach coordinates in standardized MNI space (Eickhoff et al. 2005). For the behavioural data, the level of significance was set to $p < 0.05$.

Results

Behavioral data

Overall, subjects were highly accurate when performing the tasks (mean accuracy 97.2%, range: 95% - 100%). Most of the errors were made in the vocal pitch decision (mean error rate: 6.8%), followed by the syllable decision for written words (mean error rate: 3.3%) and the font size decision (mean error rate: 3.2%; Figure 2A). Error rates for the other tasks were negligible. Wilcoxon tests showed a significant difference in error rates between the perceptual and both of the two linguistic tasks in the auditory modality ($Z=3.07$; $p= 0.0001$; $Z=3.19$; $p=0.0001$; for the auditory perceptual compared to the auditory semantic and phonologic tasks, respectively). In the visual modality, error rates were higher for the perceptual relative to the semantic task ($Z=2.16$; $p=0.034$) and for the phonologic relative to the semantic task ($Z=2.38$; $p=0.018$), but neither of these comparisons survived Bonferroni correction ($p=0.006$). Subjects made significantly more errors in the visual compared to the auditory phonologic task ($Z=2.72$; $p=0.004$). A trend towards an increased error rate was also found for the auditory perceptual relative to the visual perceptual task ($Z=2.45$; $p=0.012$), but this difference did not survive Bonferroni correction.

Individual mean reaction times across tasks ranged from 842 ms to 1438 ms (mean 968 ms; SD 174.83 ms). Overall, subjects responded faster to the visual than to the auditory stimuli. Mean reaction times for the three auditory tasks were 1069 ms, 1158 ms, and 1108 ms for the semantic, phonologic, and vocal pitch tasks, respectively. Respective mean reaction times for the three visual tasks were 853 ms, 889 ms, and 733 ms, respectively (Figure 2B). A repeated measures ANOVA showed a main effect of modality ($F_{1,13} = 192.9$, $p < 0.0001$; visual presentation resulted in shorter reaction times than auditory presentation) and a task by modality interaction ($F_{2,26} =5.21$, $p=0.013$; Fig. 2B). This interaction was caused by task

related differences in reaction time within the visual modality. Participants responded significantly faster in the font size task than in either the semantic (t_{13}=4.67, p=0.0001) or the phonologic task (t_{13}=2.99, p= 0.01). The difference between the visual semantic and the visual phonologic task was not significant, however (p=0.42). No significant differences in reaction time were present among the three tasks in the auditory modality (all p>0.10).

Post hoc t-tests also confirmed that subjects were significantly faster in the visual than the auditory modality in all tasks with the strongest effect for the nonlinguistic task (t_{13}= 7.50; t_{13}= 5.74; t_{13}=13.61; all $p < 0.0001$, for the semantic, phonologic and nonlinguistic task, respectively).

There was a speed-accuracy trade-off only for the phonologic task: when subjects had to make syllable decisions to written words, they responded significantly faster than when words were presented auditorily; however, subjects' error rates also increased significantly in the visual compared to the auditory phonologic task.

Imaging data

Modality independent main effects of task

For all three tasks, conjunction analyses of the main effects across modalities showed activation in core areas related to the button presses, including the anterolateral cerebellum, primary motor cortex, and anterior cingulate cortex. For semantic decisions, additional activations were present in left middle temporal cortex and in the fusiform gyri bilaterally as well as in left inferior parietal cortex. Further, there was a widespread area of activation in inferior and posterior middle frontal gyrus predominantly in the left hemisphere which extended into anterior aspects of the left inferior frontal gyrus (Figure 3A, Figure 4). For

phonologic decisions, activation in the inferior and middle frontal gyri bilaterally was located more posteriorly, while there was widespread left and to a smaller extent right parietal activation (Figure 3B, Figure 4). For perceptual decisions, task related increases in BOLD signal across modalities were located in the left posterior frontal and parietal cortex. Compared to the activation patterns associated with linguistic judgements, the perceptual decisions led to pronounced activation in right frontal areas (Figure 3C).

Semantic versus phonologic processing

Independent of the modality of stimulus presentation, semantic decisions resulted in stronger activation of the pars triangularis in the left inferior frontal gyrus as compared to phonologic decisions ($p=0.013$; T-value=3.55, corrected for multiple comparisons in the left aIFG ROI; Table 1 and Figure 5A). Within the auditory modality, semantic compared to phonologic processing resulted in an increase of activation in left hemispheric areas, with preferential activation in the left fusiform gyrus (Table 2 and Figure 5B). The same comparison computed for the visual modality showed a bilateral distribution of activation increases in several areas, including the supplementary motor area, middle frontal areas, and cerebellum bilaterally as well as in left anterior inferior frontal gyrus (Table 2 and Figure 5C).

Compared to semantic decisions, phonologic decisions resulted in increased activation in the dorsal supramarginal gyrus of the inferior parietal cortices bilaterally with visual and auditory word stimuli ($p=0.046$; T-value=3.01, corrected for multiple comparisons in the left SMG ROI; Table 1 and Figure 6A). Within the right SMG ROI, activation was found when the diameter was extended by 4 mm to 20 mm ($p=0.062$; T=3.08, corrected for multiple comparisons). With the given constraint on cluster extent (> 10 contiguous voxels), no activation was found in the pIFG. When this constraint was dropped, a small modality-

independent activation cluster (4 contiguous voxels) emerged in precentral gyrus adjacent to ventral premotor cortex (BA 44/6, x=-45 y=-6 z=45). Within the auditory modality, phonologic relative to semantic processing resulted in activation increases predominantly in right postcentral gyrus. In addition, there were bilateral increases in inferior parietal areas (Table 2 and Figure 6B). The same comparison computed for the visual modality showed bilateral increases in activation in parietal and occipital areas, with maximal changes in activation in right superior occipital cortex (Table 2 and Figure 6C).

There was no significant interaction between task and modality, computed across the whole brain, even at the liberal threshold of $p < 0.01$ (uncorrected).

Non-linguistic versus linguistic processing

Finally, non-linguistic perceptual decisions were contrasted with the two linguistic decisions. A modality-independent conjunction across auditory and visual perceptual decisions relative to linguistic decisions revealed a maximal change of activation in pars opercularis of the right inferior frontal gyrus (Table 3 and Figure 7A).

Auditory perceptual decisions on changes in vocal pitch resulted in a clear cluster of activation in pars triangularis of the right inferior frontal gyrus (Table 3 and Figure 7B). Compared to linguistic decisions, visual perceptual decisions related to a change in font size resulted in a right-lateralized large cluster of activation in temporo-occipital cortex with a peak in the right posterior inferior temporal gyrus (Table 3 and Figure 7C).

Discussion

In the present study we mapped task-related BOLD signal changes while healthy subjects made semantic, phonologic, or perceptual decisions on an identical set of auditory and visual word stimuli. This enabled us to identify cortical areas which showed a task-specific modality-independent increase in regional activity with phonologic, semantic or perceptual processing. Our findings are consistent with the proposal of an anterior - posterior gradient for semantic and phonologic processes, respectively. Modality-independent semantic computations preferentially engaged left anterior inferior frontal gyrus, while phonologic computations, independent of modality, were preferentially processed bilaterally in posterior areas, specifically the supramarginal gyri.

We show for the first time that the anterior aspect of the left inferior frontal gyrus (i.e., pars triangularis of the frontal operculum) has a modality-independent capability for semantic processing with a strong left-lateralization. This finding substantiates the central role of the left aIFG as core region for semantic processing and is in good agreement with a recent fMRI study showing activation of the left aIFG during semantic processing of both words and pictures (Mechelli et al. 2007). Our results suggest that the left aIFG subserves the modality-independent convergence of semantic information that is fed into the aIFG through separate visual and auditory word processing pathways via the "ventral language processing stream" (see Hickok and Poeppel 2000; 2004; 2007). This hypothesis is corroborated by an MEG study on semantic "size" judgements based on concrete, auditorily or visually presented words (Marinkovic et al. 2003). Anatomically constrained analysis of MEG activity revealed a temporospatial flow of activity which originates in the primary sensory areas, increasingly converges along middle and superior temporal areas in the left hemisphere, and is finally

elaborated in inferior prefrontal areas primarily in the left hemisphere. Likewise, anatomical connectivity patterns assign the left pars triangularis of the frontal operculum a central role in semantic processing. Recent evidence from a study combining fMRI with diffusion tensor imaging (DTI)-based tractography suggests that this region forms the anterior component of a ventral pathway which connects posterior temporal with inferior frontal language areas via the extreme capsule and is implicated in higher-level language comprehension (Saur et al. 2008).

The supramarginal gyrus was activated bilaterally during phonologic decisions relative to semantic decisions. This finding adds to existing evidence of supramarginal gyrus involvement in phonologic processes based on visual stimuli (Devlin et al. 2003; McDermott et al. 2003; Price et al. 1997). Here we found a task-specific activation of the bilateral supramarginal gyrus for phonologic decisions on visually and auditorily presented words. The observation that the functional involvement of the supramarginal gyrus in phonologic judgements extends beyond the constraints of a given modality leads us to propose that the supramarginal gyrus forms a modality-independent core area for phonologic processing. This is well in line with several studies reporting supramarginal gyrus activation bilaterally during phonologic word processing of either visual (Burton et al. 2003; Devlin et al. 2003; Price et al. 1997) our auditory stimuli (Burton et al. 2003).

For instance, bilateral parietal involvement in phonologic processing of auditory input has been suggested in previous neuroimaging studies using an auditory rhyme identification task (Burton et al. 2003) or similarity judgements on auditorily presented nonwords (Strand et al. 2008). In the study by Strand et al. (2008), parietal activation was observed not during the periods of stimulus encoding or maintenance, but during the periods of comparison and

decision, a computation which may be argued to be rather similar to a syllable judgement to auditorily presented words. The modality-independent phonologic activation of the supramarginal gyrus strongly suggests that phonologic processing preferentially engages dorsal stream components within the human language system as recently proposed by Hickok and Poeppel (2000; 2004), and that this engagement applies to auditory as well as visual stimuli. In contrast to unilateral left-hemispheric activation of aIFG during semantic word processing, the SMG showed a bilateral increase in activity with phonologic word processing. This finding corresponds well with a recent study suggesting that functional activation patterns are more left lateralized for semantic than phonologic processing (Seghier et al. 2004).

Instead of the predicted activation in pIFG, we found a small cluster of activation in left precentral gyrus bordering ventral premotor cortex. One potential explanation for this finding is that semantic as well as phonologic decisions activated the posterior inferior frontal gyrus (as suggested by Figure 4) due to automatic processing of task-irrelevant information (Gough et al. 2005). For example, even if a task requires only phonologic information (and thus engages the posterior inferior frontal gyrus), skilled readers may automatically access semantic information as well (engaging the anterior inferior frontal gyrus), although it is not required to perform the task (MacLeod 1991; Price et al. 1996; Van Orden et al. 1988). Our finding of left precentral activation is in accord with prior studies suggesting that left precentral (i.e., BA 6) and parietal (i.e. BA 40) activation reflects unique preferential engagement for phonologic compared to semantic processing (Gold et al. 2005). It also matches prior reports of left posterior inferior frontal activation extending into left precentral gyrus (Devlin et al. 2003; McDermott et al. 2003). Left precentral activation during phonologic processing as required by syllable decision has been linked to subvocal

articulation (Price et al. 1997). In the present study, such strategies may have contributed to phonologic processing both in the auditory as well as in the visual modality.

Apart from identifying core areas for modality-independent semantic and phonologic processing, our results reveal notable differences in activation patterns and behavioural strategies depending on the given modality in which stimuli are presented. This is evident when considering the speed-accuracy trade-off for the phonologic task in the auditory and visual domain. Subjects were significantly faster in their syllable judgement when stimuli were presented visually than when they were presented auditorily. However, the speed of visual judgements improved at the expense of an increase in error rate. This suggests that subjects may have occasionally guessed the number of syllables based on the length of the visually presented word. This 'strategy' is bound to fail for words such as 'olive' which (in German) has only five letters but three syllables. Our finding of increased activation in superior occipital areas during syllable (relative to semantic) judgements to written words may provide additional support for the proposal that subjects used a surface-level criterion to perform the syllable judgement in the visual modality. In contrast, when syllable judgements had to be performed to auditorily presented words, subjects were slower (but also more accurate) than when words were presented visually. In terms of the underlying mechanisms, an increase in right inferior postcentral gyrus and the supramarginal gyri bilaterally in the phonologic (relative to the semantic) judgement for auditorily presented words suggests that this task required subjects to attend closely to the auditorily presented information (Sabri et al. 2008).

Finally, right inferior frontal areas showed a modality-independent increase in activity related to the processing of non-linguistic perceptual features of auditory and visual word stimuli. In

accord with our finding, right inferior frontal areas were found to be involved in vocal pitch processing. According to Zatorre and colleagues (1992), the perceptual analysis of linguistic stimuli takes place in the left temporal lobe. However, any additional task-related requirement (such as attending to and making a judgement about changes in vocal pitch) may involve neural systems that are different from those involved in auditory perceptual analysis per se. Zatorre et al. (1992) suggested that right prefrontal cortex may be part of a distributed network involved in maintenance of pitch information in auditory working memory. This interpretation fits well with the demands of our experimental task (maintaining pitch information over and above the duration of a word), and matches later reports of pitch and auditory working memory (e.g. Wilson et al. 2009; Zatorre et al. 1994). The present study significantly extends previous work by showing that the right inferior frontal cortex is sensitive to stimulus aspects beyond the auditory modality (i.e., changes in the visual surface structure of written stimuli). Our findings highlight the need to take into account the perceptual characteristics of language related stimuli when interpreting activation in the right-hemispheric Broca homologue as being linguistic in nature. Post-stroke activation in right inferior frontal cortex has been previously linked to compensatory or even maladaptive processing (for a review, see Thompson and den Ouden 2008). However, right hemispheric activation during language processing may not be a necessary consequence of left-sided brain damage, but may reflect normal functional recruitment when task demands become more effortful (Raboyeau et al. 2008). Our findings indicate that over and above the activation of verbal cues during lexical retrieval, right frontal activation may indicate the incidental processing of non-linguistic features of word stimuli.

In summary, the present study confirms and extends previous studies (e.g. Devlin et al. 2003; Gitelman et al. 2005; Gough et al. 2005; Jescheniak et al. 2002; McDermott et al. 2003) showing that semantic, phonologic, and nonlinguistic word processing rely partly on discrete circuits, each of which may depend on separate neural subsystems. A better understanding of the functional anatomy supporting these linguistic components will greatly assist in planning targeted neuromodulatory intervention, in order to identify and, in the case of patients with language disorders following stroke, possibly ameliorate the function of critical convergence zones for semantic and phonologic processing in the language network.

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Figure legends

Fig 1.

A. Experimental design. The experiment consisted of three auditory and three visual runs. The order of runs was counterbalanced across subjects. B. Example of a run. Each miniblock was preceded by the same brief instruction. In total, there were 3 runs for each modality, such that each stimulus was repeated 3 times, once per task per modality. Within miniblocks, stimuli were pseudorandomized such that there were no more than 3 repetitions of stimuli with the same feature (e.g., manmade). Original stimuli were in German. C. Examples of manipulated and non-manipulated stimuli. In the visual perceptual task, font size decreased across the length of the word. In the auditory perceptual task, vocal pitch was decreased 13 halftones towards the end of the word.

Fig 2.

Average error rates (A) and reaction times (B) for 14 subjects. Error bars represent onefold standard error from the mean (SEM). *p<0.05; two-tailed; (*) did not survive the Bonferroni correction (p>0.006); ms= milliseconds; sem= semantic; phon=phonologic; perc=perceptual task.

Fig. 3.

A. Conjunction of the main effects of the two semantic runs (auditory, visual). B. Conjunction of the main effects of the two phonologic runs (auditory, visual). C. Conjunction of the main effects of the two perceptual runs (auditory, visual). All conjunctions, $p < 0.05$ FWE-corrected.

Fig 4.

This figure combines the data used for Figure 3 A and B into a single image in order to depict overall multimodal linguistic effects (overlapping areas, marked in purple) as well as 'pure', modality-independent effects of semantic (red) and phonologic (blue) processing. Note that modality-independent semantic processing uniquely activates anterior inferior left frontal regions, while modality-independent phonologic processing results in unique activation predominantly in parietal areas bilaterally. The large overlapping activation in the right hemisphere reflects sensorimotor activation due to button press.

Fig 5.

Direct comparison of the semantic with the phonologic tasks (all figures thresholded at $p < 0.01$ uncorrected, using an extent threshold of > 10 voxels). A. Conjunction across auditory and visual modalities of the differential contrasts of the semantic compared to the phonologic condition, in order to identify modality-independent activation associated preferentially with semantic processing. Conjunction inclusively masked with the respective main effects at $p < 0.05$ (uncorrected). B. Differential contrast of the semantic compared to the phonologic task in the auditory modality. C. Differential contrast of the semantic compared to the phonologic task in the visual modality.

Fig 6.

Direct comparison of the phonologic with the semantic tasks (all figures thresholded at $p < 0.01$ uncorrected, using an extent threshold of > 10 voxels). A. Conjunction across auditory and visual modalities of the differential contrasts of the phonologic compared to the semantic

condition, in order to identify modality-independent activation associated preferentially with phonologic processing. Conjunction inclusively masked with the respective main effects at $p < 0.05$ (uncorrected). B. Differential contrast of the phonologic compared to the semantic task in the auditory modality. C. Differential contrast of the phonologic compared to the semantic task in the visual modality.

Fig 7.

Activation in the non-linguistic perceptual compared to the linguistic tasks (considered together). All figures thresholded at $p < 0.01$ uncorrected, using an extent threshold of > 10 voxels). A. Conjunction across auditory and visual modalities of the differential contrasts of the perceptual compared to the linguistic conditions, in order to identify modality-independent activation associated preferentially with perceptual processing. Conjunction inclusively masked with the respective main effects at $p < 0.05$ (uncorrected). B. Vocal pitch decision > auditory semantic/phonologic decision, C. Font size decision > semantic/phonologic decision.

Table 1. Modality-independent effects of semantic versus phonologic word processing

Region	Cluster extent	MNI coordinates x	y	z	T-value	Z-score
semantic > phonologic processing						
L inferior frontal gyrus (pars triangularis)	30	-45	27	12	3.55	3.38
phonologic > semantic processing						
R supramarginal gyrus	16	45	-39	45	3.08	2.97
L supramarginal gyrus	37	-45	-39	45	3.01	2.91

Conjunction analyses of the contrasts semantic > phonologic and phonologic > semantic decision based on auditorily and visually presented words ($p < 0.01$, uncorrected; cluster extent > 10 contiguous voxels. Contrasts masked inclusively by main effects of auditory and visual semantic (and phonologic, respectively) processing at $p < 0.05$ (uncorrected).

Table 2. Unimodal effects of semantic versus phonologic word processing

Region	Cluster extent	MNI coordinates x	y	z	T-value	Z-score
auditory semantic > auditory phonologic processing						
L fusiform gyrus	45	-27	-33	-21	5.04	4.61
L middle temporal gyrus	10	-60	-15	-24	3.90	3.69
L superior frontal gyrus	26	-18	60	15	3.89	3.67
visual semantic > visual phonologic processing						
L supplementary motor area	84	-6	21	57	4.69	4.34
R cerebellum	43	15	-81	-33	4.21	3.94
L middle frontal gyrus	55	-30	9	63	4.15	3.89
L inferior frontal gyrus (pars triangularis)	34	-45	27	9	4.08	3.83
R superior frontal gyrus	30	33	51	9	4.04	3.81
L inferior frontal gyrus (pars orbitalis)	16	-30	30	-12	3.93	3.71
L cerebellum	22	-12	-84	-30	3.78	3.58
R middle frontal gyrus	56	39	24	33	3.72	3.53
L middle temporal gyrus	14	-51	-30	-6	3.56	3.39
auditory phonologic > auditory semantic processing						
R postcentral gyrus	26	66	-6	15	4.60	4.27
R supramarginal gyrus	16	51	-39	45	3.85	3.64
L inferior parietal lobe	49	-48	-42	39	3.81	3.60
visual phonologic > visual semantic processing						
R sup occipital gyrus	59	27	-66	42	4.95	4.55
L sup occipital gyrus	32	-21	-66	36	4.41	4.11
L intraparietal sulcus	12	-36	-42	33	3.95	3.72
L postcentral gyrus	11	-42	-36	48	3.68	3.50

Differential contrasts comparing phonologic and semantic processing within each modality ($p < 0.001$, uncorrected; cluster extent > 10 contiguous voxels). Contrasts were masked inclusively by respective main effects of the condition of interest at $p = 0.05$ (uncorrected).

Table 3. Effects of nonlinguistic perceptual compared to linguistic word processing

Region	Cluster extent	MNI coordinates X	y	z	T-value	Z-score
Vocal pitch decision > auditory linguistic decision (semantic and phonologic)						
$p < 0.05_{FWE}$, contrast masked inclusively by main effect of vocal pitch decision at p = 0.05. Cluster extent > 10 contiguous voxels.						
L cerebellum	14	-15	-72	-36	6.17	5.45
R inferior frontal gyrus (peak in pars triangularis)	11	48	18	21	5.85	5.22
Font size decision > visual linguistic decision (semantic and phonologic)						
$p < 0.05_{FWE}$, contrast masked inclusively by main effect of font size decision at p = 0.05. Cluster extent > 10 contiguous voxels.						
R inferior temporal gyrus	63	48	-60	-6	6.50	5.69
Perceptual > linguistic decision (both modality-independent)						
Conjunction of the two analyses above, applying p < 0.01 (uncorrected) and a cluster extent threshold of > 10 voxels. Contrasts masked inclusively by main effects of auditory and visual perceptual processing at p = 0.05 (uncorrected).						
R inferior frontal gyrus (pars opercularis)	108	48	12	24	4.11	3.86
L cerebellum	148	-15	-66	-39	3.57	3.40
R inferior parietal lobule	24	42	-42	36	3.05	2.94
R precentral gyrus	14	42	6	51	2.71	2.63

FWE = family-wise error correction

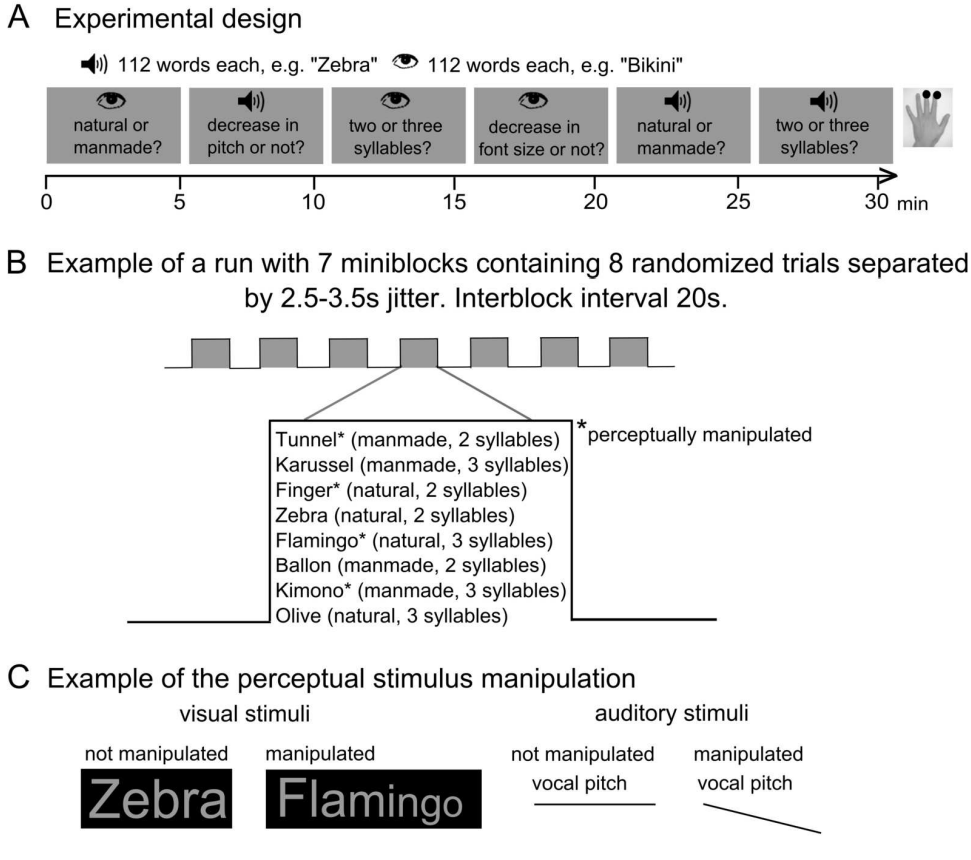

Figure 1
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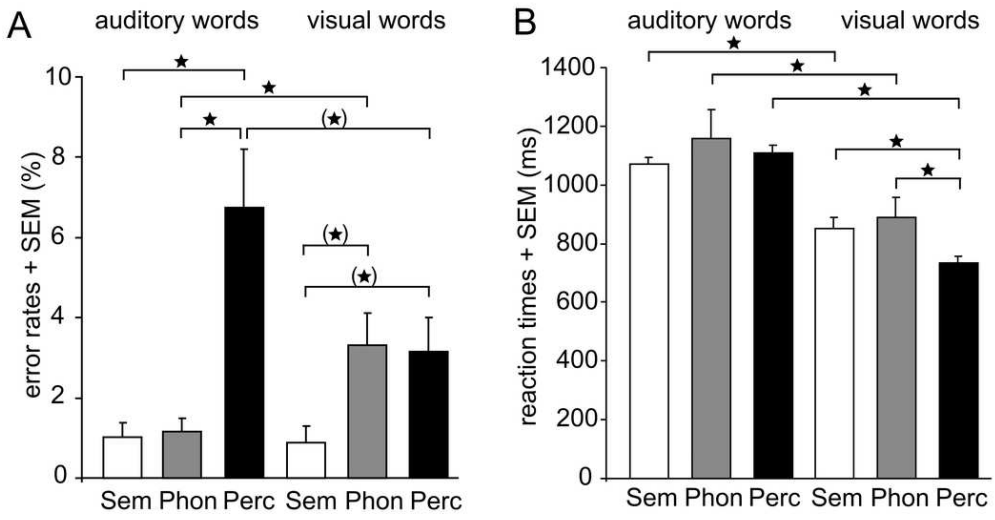

Figure 2
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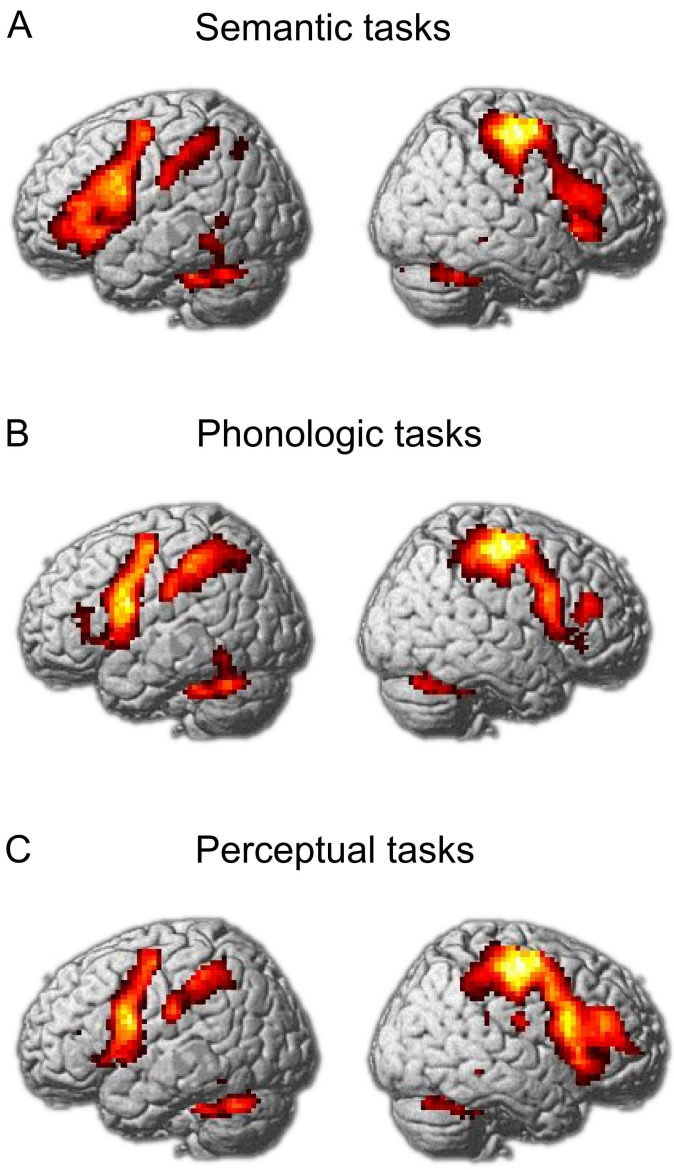

Figure 3
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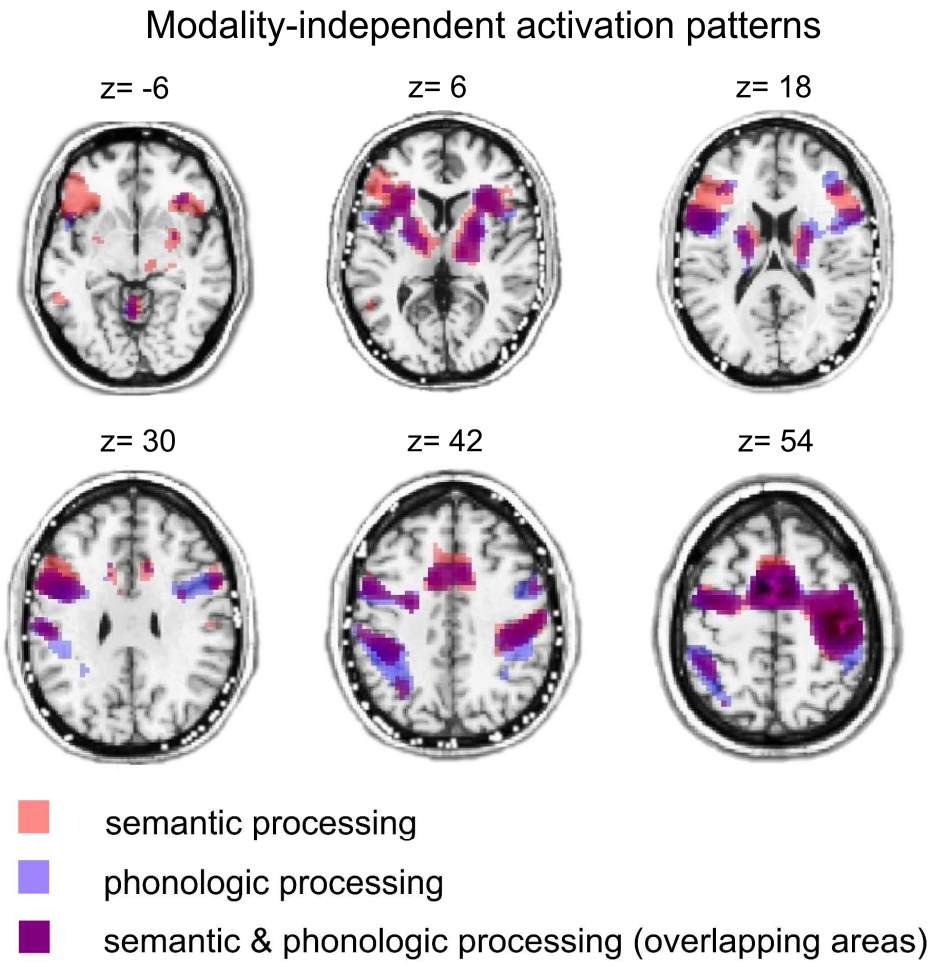

Figure 4
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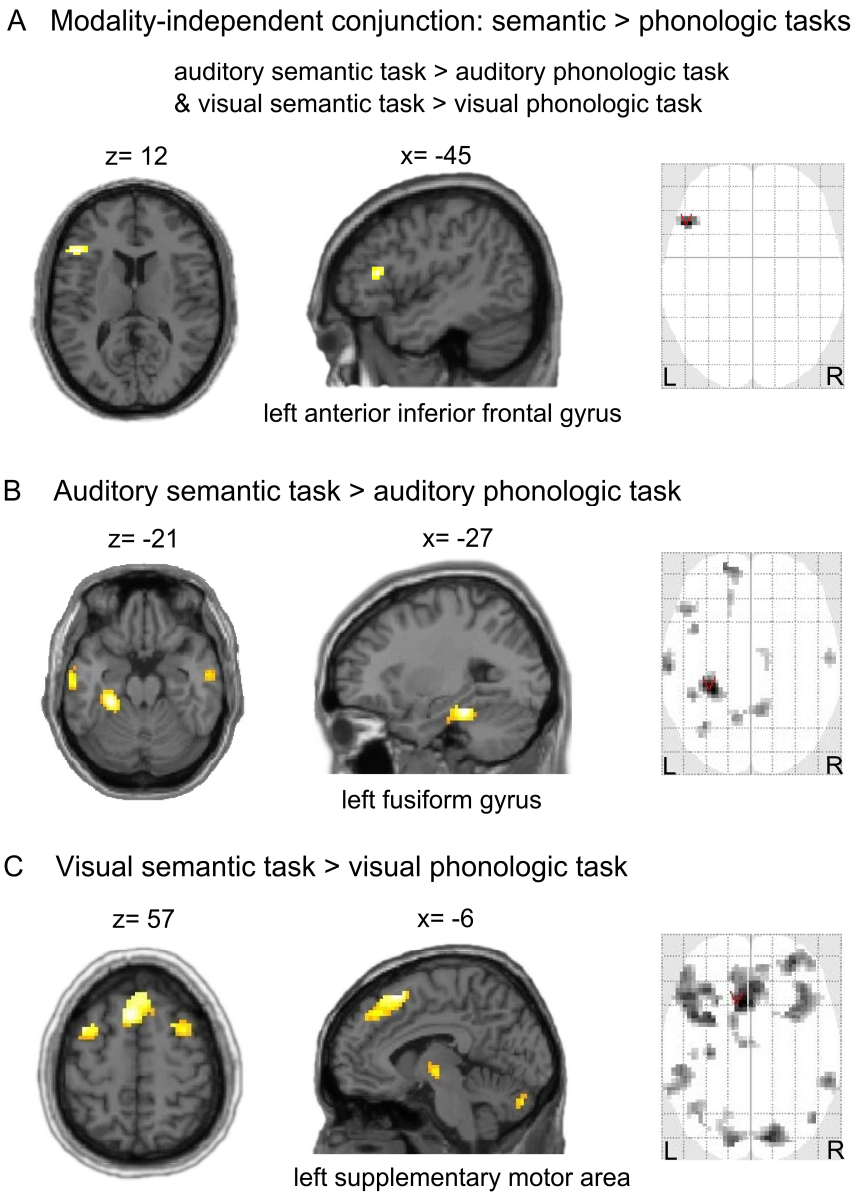

Figure 5
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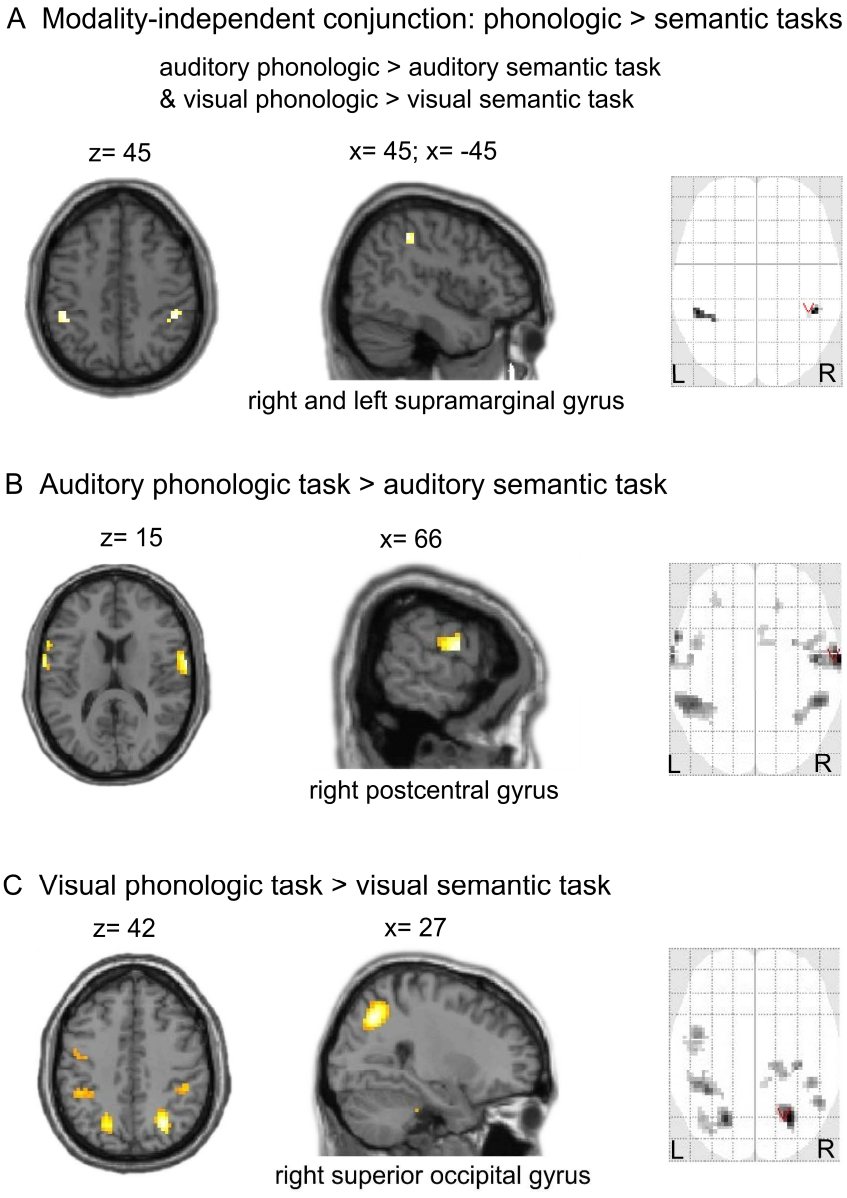

Figure 6
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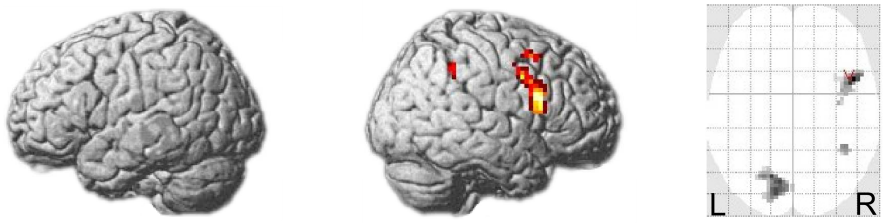
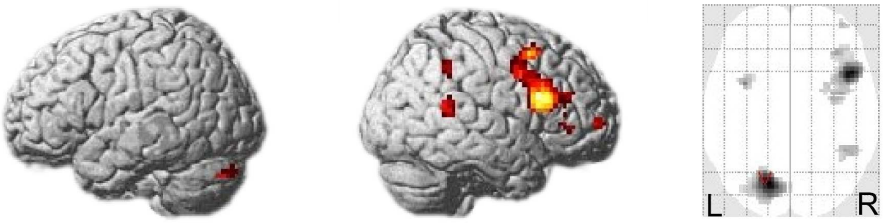
A Modality-independent conjunction: perceptual > linguistic tasks

auditory perceptual > auditory linguistic tasks
& visual perceptual > visual linguistic tasks



B Auditory perceptual > auditory linguistic tasks



C Visual perceptual > visual linguistic tasks

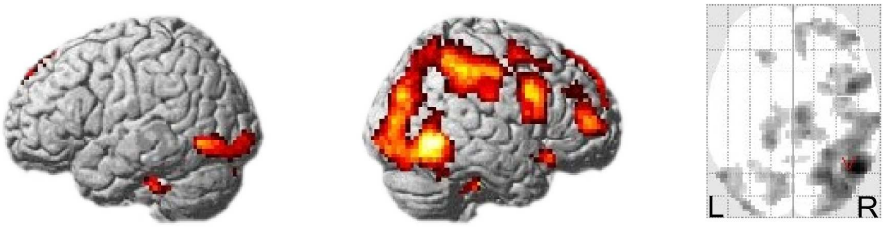


Figure 7
165x192mm (600 x 600 DPI)

Appendix V

Phonological decisions require both the left and right supramarginal gyri.
A dual-site transcranial magnetic stimulation study

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Abstract

Recent functional imaging studies demonstrated that both the left and right supramarginal gyri (SMG) are activated when healthy right-handed subjects make phonological decisions. However, lesion studies found that difficulties with phonological processing arise after left rather than right hemisphere damage. Here, we used a novel dual-site transcranial magnetic stimulation (TMS) approach to test whether the SMG in the right hemisphere contributes to modality-independent (i.e. auditory and visual) phonological decisions. To test task specificity, we compared the effect of real or sham TMS during phonological, semantic and perceptual decisions. To test laterality and anatomical specificity, we compared the effect of TMS over the left, right or bilateral SMG and angular gyri. The accuracy and reaction times of phonological decisions were selectively disrupted relative to semantic and perceptual decisions when real TMS was applied over the left SMG, the right SMG or bilateral SMG. These effects were not observed for TMS over the angular gyri. A follow-up experiment indicated that the threshold-intensity for inducing a disruptive effect on phonological decisions was identical for unilateral TMS over the right or left SMG. Together, these findings provide converging evidence that the right SMG contributes to accurate and efficient phonological decisions in the healthy brain with no evidence that the left and right SMG can compensate for one another during TMS. Our findings motivate detailed studies of phonological processing in patients with acute or long-term damage of the right SMG.

\body Introduction

Many previous functional imaging studies have shown that the left and right supramarginal gyri (SMG) are activated when right-handed participants make decisions about the sounds of words (i.e. their phonology) compared to decisions about their meanings (i.e. their semantics). This effect has been replicated in both the visual or auditory modalities (1-6). However, the functional significance of right SMG activation is unclear because lesion studies have reported phonological difficulties following left rather than right temporo-parietal lesions (7-17). Consequently, anatomical models of phonological processing have included left but not right parietal cortex (18-20).

The present study was designed to address the discrepancy between functional imaging and lesion studies. More specifically, we examined how "online" TMS (i.e. TMS during a task) over the left and right SMG influences phonological word processing in healthy subjects. We thus used the neurodisruptive effect of TMS to distinguish between three alternative hypotheses to explain right SMG activation with phonological processing.

Hypothesis 1. Right SMG only contributes to the speed but not the accuracy of phonological decisions. Consequently, right SMG lesions have a subtle effect on phonological processing that might be missed unless reaction times were measured. In this case, we expect a selective effect of right SMG TMS on reaction times in the healthy brain without affecting error rates.

Hypothesis 2. Right SMG is necessary for accurate and efficient phonological decisions in the healthy brain but following right SMG lesions, the function of right SMG can be supported by alternative brain regions. Consequently, right SMG lesions may temporarily impair phonological decision performance in the acute phase after brain damage but this lesion effect will not be apparent after functional reorganisation. In this case, we expect a significant effect of right SMG TMS on both the reaction times and accuracy of phonological decisions in the healthy brain.

Hypothesis 3. Right SMG is not necessary for accurate and efficient phonological decisions but is activated in fMRI studies of the healthy brain because it is involved in task-related activation that is incidental to performance (i.e. redundant processing, (21)). In this case, neither right SMG lesions nor right SMG TMS will influence phonological decision performance.

There are three novel features of our study relative to previous online TMS studies of phonological processing (22, 23). First, we investigated the effect of TMS to the right SMG. Second, we compared unilateral TMS over the right SMG to unilateral TMS to the left SMG and dual-site TMS over left and right SMG simultaneously. This manipulation allowed us to test whether impaired unilateral SMG function was supported by the contralateral hemisphere. If so, then the effect of dual-site TMS to both the left and right SMG should be greater than the effect of TMS to either the left or right SMG alone (21). Third, we compared the effect of TMS on phonological decisions to words presented in the auditory as well as visual modality, whereas previous studies investigated the effect of online TMS to left SMG with visually presented words only (22, 23). This enabled us to assess whether the expected TMS effects were dependent or independent of stimulus modality. To test the functional and anatomical specificity of our effects, we also investigated how online TMS affected semantic or perceptual decisions on the same sets of stimuli; and whether the effect of TMS on phonological decisions was greater when TMS was over the SMG than over a neighbouring parietal area in the angular gyrus (ANG).

Results

Reaction times

The effect of real versus sham TMS over left, right and bilateral SMG

Subjects' mean reaction times (RTs; supporting Table 1) were analyzed with a four-way repeated measures ANOVA. The four factors were: group (14 subjects with real TMS vs. 14 subjects with sham TMS), task (phonological, semantic, perceptual), modality (auditory vs. visual) and TMS laterality (left, right, bilateral). Table 1 displays the results from the ANOVA.

A main effect of group showed increased RTs for real TMS relative to sham TMS ($F_{1,25}$=4.27; p= 0.049). However, this group effect interacted with task ($F_{2,50}$=5.82; p=0.005; Fig.2). Across modalities and laterality sites, the disruptive effect of real TMS on RTs was greater on phonological compared to semantic (t_{27}=5.89; p=0.0001; post-hoc paired t-test) or perceptual decisions (t_{27}=5.45; p=0.0001; post-hoc paired t-test). There were no significant differences in the effect of real versus sham TMS on the perceptual and semantic tasks, and no task effects in the sham TMS group (all p>0.12). Further post hoc t-tests confirmed that real TMS compared to sham TMS increased RTs in the phonological task (t_{27}=2.12; p=0.039) but not in the semantic (p=0.75) or perceptual (p=0.42) tasks. The task-specific delay of phonological decisions with TMS over SMG was independent of TMS laterality as there was no task-by-group-by-laterality interaction (p=0.35). Effects that did not interact with TMS group (i.e. real vs. sham TMS) can be found in the supporting information.

The effect of real TMS over SMG versus angular gyrus (ANG)

A four-way repeated measures ANOVA (subset of 10 subjects only) investigated the effect of real TMS on region (SMG vs. ANG), task (phonological, semantic, perceptual), TMS laterality (left, right, bilateral), and modality (auditory, visual). The results demonstrated that the task-specific effect of TMS over the SMG (i.e. delayed responses for phonological relative to semantic

or perceptual decisions) was not observed when TMS was applied over ANG ($p>0.41$ for all two-way comparisons). This was confirmed by a two-way interaction between region (SMG versus ANG) and task ($F_{2,18}=8.37$; $p=0.003$; Fig.3) which arose because the effect of region (slower RTs when TMS was over SMG than ANG) was greater during the phonological than semantic ($t_{19}=5.02$; $p=0.0001$) or perceptual ($t_{19}=4.43$; $p=0.0001$) tasks. Furthermore, post-hoc tests confirmed significant longer RTs for TMS over SMG than ANG with the phonological task ($t_{19}=5.65$; $p=0.001$) but not for the semantic task ($p=0.30$) or the perceptual task ($p=0.12$). These effects did not interact with modality ($p=0.43$) or TMS laterality ($p=0.51$).

Error rates

The effect of real versus sham TMS over left, right and bilateral SMG

There were no significant differences between the three TMS laterality sites (i.e. left, right or bilateral TMS) in any of the tasks (all $p>0.32$; see supporting Table 1). Consequently, ER were pooled across the factor TMS laterality to reduce the number of necessary comparisons.

In both the auditory (Fig.4A) and visual modalities (Fig.4B), ER were higher for phonological than semantic decisions during real TMS ($Z=2.73$; $p=0.004$ in the auditory modality; and $Z=2.67$; $p=0.004$ in the visual modality) but not during sham TMS ($p=0.39$ in the auditory modality and 0.23 in the visual modality). The task effect for real versus sham TMS was significant for phonological decisions in the auditory modality ($Z=2.72$; $p=0.006$) but not the visual modality; ($p=0.11$) and not during semantic decisions in either the auditory ($p=0.14$) or visual ($p=0.45$) modalities. There were no significant differences between phonological and perceptual errors in the real TMS group ($p=0.30$ in the auditory modality and $p=0.18$ in the visual modality), however, the sham group showed decreased error rates for phonological compared with perceptual decisions ($Z=3.05$; $p=0.001$ in the auditory modality; $Z=3.18$; $p=0.001$ in the visual

modality). This is likely to be the consequence of a speed-accuracy trade-off in this subject group.

For both real and sham TMS, errors were higher during the perceptual than semantic task in both the auditory and visual modalities ($Z=2.72$; $p=0.004$ for the real TMS group in the auditory modality; $Z=3.23$; $p=0.001$ for the real TMS group in the visual modality; $Z=3.04$; $p=0.001$ for sham TMS in the auditory modality; and $Z=3.18$; $p=0.001$ for sham TMS in the visual modality).

The effect of real TMS over SMG versus angular gyrus

With only 10 subjects, we did not find significant differences in ER for TMS over SMG versus ANG that survived a Bonferroni-Holm correction for multiple comparisons ($p<0.004$). However, there were trends towards increased ER for phonological relative to semantic decisions with TMS to SMG but not ANG (Fig.5).

The effect of TMS intensity over left versus right SMG

The above results indicated comparable effects for unilateral TMS over left and right SMG during phonological decisions. In a follow-up experiment, we compared the intensity-dependence of the behavioral "lesion" effect induced by unilateral TMS to the left or right SMG. We thus wanted to investigate whether the TMS-intensity-effect-size curves for left versus right SMG were different. More specifically, this experiment enabled us to test if left SMG TMS disrupted phonological processing at lower intensities than right SMG TMS.

We re-examined all subjects from the real TMS group (n=14) and applied real TMS to left or right SMG at four different stimulation intensities (55, 60, 75 and 90% of individual resting motor threshold [RMT]). Subjects performed two sessions of the phonological task again while receiving TMS over left (session one) or right SMG (session two). Both sessions consisted of four blocks of different TMS intensities. Each block included 30 trials of the phonological task

and was separated by 5 minutes rest to prevent carry-over effects. TMS was applied at different intensities (55, 60, 75 and 90% RMT). The order of sessions was counterbalanced across subjects. In all other aspects, the follow-up experiment was identical to the main experiment.

Repeated measures ANOVA revealed a main effect of intensity ($F_{3,39}$=15.34; p=0.0001; Fig.6A,B). Post hoc t-tests showed that only the highest intensity (90% of RMT) increased mean RT of phonological judgments (t_{13}=5.38; p=0.0001; t_{13}=4.03; p=0.0001; t_{13}=5.24; p=0.0001; for 90 vs. 55, 60 and 75%; respectively). This intensity effect was comparable for left and right SMG TMS (p=0.88). ER were not significantly different between the different tasks (all p>0.25; Fig.6C,D) but mean RTs were longer in the auditory than visual conditions ($F_{1,13}$=72.31; p=0.0001).

Unpleasantness scores

Real TMS was significantly more unpleasant than sham TMS (p=0.001 in all conditions). In the real TMS group, bilateral stimulation was significantly more unpleasant than left or right TMS, (all p<0.05) with no significant difference in the pre-experimental and post-experimental experience (all p>0.32). Please refer to the supporting information for more details.

Discussion

We used a novel dual-site TMS approach to compare the disruptive effects of high-frequency TMS over the left, right and bilateral supramarginal gyri during phonological word decisions. This allowed us to test three different explanations for why previous fMRI studies have shown bilateral SMG activation during phonological decision tasks in healthy subjects while lesion studies emphasize the importance of left but not right hemisphere damage in aphasia. Our finding that reaction times and error rates increased following TMS to right SMG as well as left SMG indicates that unperturbed right SMG activation is necessary for accurate and efficient

phonological decisions in the healthy brain. Moreover, our finding that phonological decision performance was not worse for bilateral SMG TMS than unilateral SMG TMS provides no evidence that the left and right SMG can acutely compensate for one another: If phonological decisions are possible with either the left or the right SMG, then dual-site TMS over the left and right SMG should produce a greater "lesion" effect than TMS over left or right SMG alone (21). To the contrary, both the main experiment and the follow-up experiment manipulating TMS intensity indicated that the lesion effect of unilateral TMS to the right SMG was comparable to the lesion effect induced by unilateral TMS to the left SMG or bilateral TMS to the right and left SMG. Further, the disruptive effect was independent of the modality used for stimulus presentation (i.e. auditory or visual). Moreover, the TMS-induced lesion effect was both functionally and anatomically specific: We found a selective impairment in modality-independent phonological decisions but not semantic nor perceptual decisions when TMS was given over the supramarginal gyri and these effects were not observed when TMS targeted the angular gyri.

When interpreting TMS-induced behavioural effects one should bear in mind that TMS causes a synchronised discharge in a relatively large population of neurones that is terminated by a long lasting GABAergic inhibition (24). On one hand, TMS suppresses ongoing processing by silencing neurones. On the other hand TMS adds extra ‘‘noisy’’ activity to ongoing processing (24). Both mechanisms adversely affect the ongoing neuronal activity in the stimulated area for a limited period of time. At a behavioural level, the neurodisruptive effects of TMS may increase reaction times or error rates (25). In previous online TMS studies of language, TMS usually affected either reaction times or error rates (1, 26, 27). In our experiments, TMS increased both RTs and errors during phonological decisions, providing evidence for a strong "virtual lesion" effect independent of the laterality of the TMS stimulation. The concurrent increase in RTs and errors also excludes a non-specific speed-accuracy trade-off during phonological decisions.

The critical contribution of the left SMG to phonological decisions has been demonstrated previously in TMS studies of healthy volunteers: In Romero et al. (23), 5 Hz TMS to left SMG significantly disrupted judgements on visually presented words in different tasks, providing evidence for the involvement of the left SMG in short term retention of verbal material as well as phonological judgements (23). Our findings confirm and extend those of Romero et al. (23) by showing that the right SMG also contributes to phonological processing; and that both SMG are important for phonological decisions on auditorily as well as visually presented words. To the authors' best knowledge there is no study to date that systematically examined the role of the left and right SMG in language processing.

Our results seem to be in discordance with the existing literature on phonological processing in patients with focal brain lesions. Damage to the right hemisphere is not typically associated with deficits in phonological processing (16), although there is a lack of studies directly comparing phonological deficits after left versus right supramarginal lesions. While recent studies indicate that the (temporary) recruitment of homologue areas in the right hemisphere after left-hemisphere stroke may be adaptive, longer term language improvement is associated with left-hemisphere language function (9, 28, 29). For example, Winhuisen et al. (30) argue that restoration of the left-hemisphere network seems to be more effective for recovery after stroke, but in some cases, right-hemisphere areas are integrated successfully. Our TMS results contribute by showing that the involvement of right-hemisphere language areas is not limited to recovery after stroke but is also essential for phonological processing in healthy subjects.

The discrepancy between our study and previous patient data may be due to differences in the time scale of functional reorganization. In our study, TMS was applied online during task performance, leaving the language system no time to develop adaptive plasticity. This may be different in patients with chronic structural lesions where massive reshaping of the language

network occurs during recovery (28). The neurodisruptive effects of TMS over right SMG on phonological decisions in healthy subjects call for a re-evaluation of phonological deficits in patients with right-hemispheric inferior parietal lesions. As emphasized by Seghier et al. (31), further investigation of aphasic patients with right-hemisphere lesions is necessary to fully understand the causal basis of aphasia. Prospective longitudinal studies might demonstrate that the right SMG may be more functionally relevant in the acute phase after stroke than in the chronic phase when reorganisation of the language networks has occurred (28).

Alternatively, unilateral TMS of right SMG might have produced its detrimental effect on phonological processing not by disrupting neuronal processing in the stimulated SMG but by activating transcallosal inputs from the right to the left SMG (24). These transcallosal inputs might have activated inhibitory circuits or added "noisy" activity in the left SMG and thereby interfered with phonological processing in the left SMG. This interpretation would be in line with previous studies demonstrating significant acute remote effects of TMS in contralateral homotopic areas (32-34). For example, it has been shown that TMS over the motor cortex can change the metabolic rate in contralateral motor areas and may lead to behavioural or functional effects ipsilateral to the side of stimulation (35, 36).

Although we can not discard the "transcallosal" hypothesis, several considerations render this explanation of our findings unlikely. Neurophysiological studies of the primary motor cortex showed that TMS of the ipsilateral motor hand area has much stronger excitatory and longer lasting inhibitory effects on regional excitability as opposed to the transcallosally induced effects induced by TMS of the contralateral motor hand area (37). The threshold for inducing transcallosal inhibitory effects is also considerably higher than for inducing intracortical inhibition with the coil placed over the motor cortex (38, 39). Therefore, the effect size of a lesion effect should be stronger and the threshold for inducing a lesion effect should be lower with

ipsilateral than contralateral TMS using the same stimulation intensity. This was not the case in the present study. The threshold as well as the magnitude of the disruptive effect on phonological decisions was comparable with TMS to both hemispheres. Furthermore, there is little evidence from previous studies that transcallosal excitation spread to the homologue parietal area makes a substantial contribution to the behavioural effects obtained with TMS. Indeed, many studies found a specific deterioration in task performance with unilateral TMS over one hemisphere but not over the homologue area in the other hemisphere (40-42). The fact that most previous studies revealed a clear asymmetric sensitivity of the right and left parietal cortex to TMS lesioning argues against a significant contribution of transcallosal excitation of the homologue area to the TMS induced behavioural effects.

In conclusion, our study highlights the importance of the right dorsal SMG in phonological decisions. This strongly motivates the investigation of phonological processing abilities in patients with acute right SMG damage. According to our results, we would predict that these patients have some degree of phonological processing impairment, irrespective of whether words are presented in the auditory or visual modality.

Materials and Methods

Subjects

For examining the effect of real versus sham TMS, 28 right-handed native German speakers with no history of neurological disorders or head injury were randomly assigned to the real TMS group (n=14, 8 females, 20-28 years old, mean age 24) or the sham TMS group (n=14, 8 females, 22-32 years old, mean age 25). All subjects were right-handed (laterality index >95%) according to the German version of the Edinburgh Handedness Inventory (43). All subjects were naive to TMS. Written informed consent was obtained before the experiment. The study was performed according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee

of the Medical Faculty of the University of Kiel. For comparing the effect of real TMS over SMG versus ANG**,** 10 subjects from the real TMS group (6 females, 21-27 years old, mean age 23) were re-examined after six months to minimize repetition and familiarity effects.

Experimental design

The main experiment compared the effect of real versus sham TMS over left, right and bilateral SMG. It entailed a 2x3x3x2 factorial design with two groups (real TMS group vs. sham TMS group), three different tasks (phonological, semantic and perceptual), three different TMS laterality sites (left, right, and bilateral stimulation over the SMG) in two modalities (auditory and visual). An identical set of 120 stimuli (see supporting information for more details) were presented in each of the three tasks in both the auditory and visual modalities. This resulted in six repetitions of the same words with the effect of repetition controlled across tasks. In order to keep the repetition of identical stimuli per subject at a minimum (i.e. six) we decided against the inclusion of real vs. sham TMS as within subject factor and thus included the sham TMS group. The factorial design enabled us to test for task, laterality and group specific modality-independent effects while controlling for stimulus and repetition effects.

For comparing the effect of real TMS over SMG versus ANG, 10 of the subjects in the real TMS group participated in exactly the same experiment with the exception that TMS was over left ANG only, right ANG only or bilateral ANG. To avoid repetition and familiarity with the stimulus sets, the effect of ANG TMS was conducted six months after the effect of SMG TMS.

Tasks

Subjects performed three different types of tasks making judgments on the same set of visual or auditory stimuli. In the phonological task, subjects categorized the items as having two or three syllables. The semantic task consisted of deciding whether a word represented a natural or

manmade item. A perceptual control task was also included as a baseline. In the perceptual auditory task, subjects decided whether or not there had been a decrease in pitch towards the end of the word. In the perceptual visual control task, subjects decided whether or not font size had decreased towards the end of the word. Tasks were blocked to ensure a constant cognitive set. Subjects were instructed to respond as quickly and as accurately as possible by pressing a button on a response pad with their left middle or index finger (Fig.1).

Procedure

After a training session (supporting information), the two TMS coils were positioned over the left and right SMG (Fig.1A) and remained fixed during the experiments. Neuronavigated TMS was used to guide the placement of the coil over SMG and to monitor the correct coil position throughout the experiment. Subjects received three test bursts of 10 Hz TMS over left, right and bilateral SMG each and judged them on a 4-point scale (1=neutral, 4=highly unpleasant).

The experiment consisted of an auditory and a visual run for each subject (Fig.1B). During each run the three blocked tasks were presented. The order of runs and blocks was counterbalanced across subjects. Each task started with a verbal or written instruction of the task and consisted of 120 trials for each condition, with a trial-duration of three seconds (Fig.1C). Presentation of visual words was matched to the mean duration of the auditory stimuli (range= 0.74-0.87 s) and followed by a fixation cross to complete the three second trial. During the auditory run, the fixation cross stayed on the screen for the whole experiment. Having completed all 6 conditions, subjects again rated the unpleasantness of the TMS sites. The sham TMS group underwent exactly the same experimental procedure. Stimulus presentation and response recording was obtained using E-PRIME software (Psychology Software Tools Inc., Pittsburgh, PA, USA; version 1.1).

Transcranial magnetic stimulation

Neuronavigated TMS was performed by using the mean *Montreal Neurological Institute* (MNI*)* coordinates for left SMG across previous studies comparing visually presented words in a word comprehension task (x,y,z= -45, -39, 45 mm; (1, 3, 4) see Fig.1A).

The stereotactic coordinates for left ANG (x, y, z= -42, -66, 28; MNI) were obtained from the comparison of the semantic to the phonological task in Devlin et al. (1). For TMS of right SMG and right ANG, we used the homologue coordinates in the right hemisphere (i.e. x, y, z= 45, -39, 45 mm; x, y, z= 42, -66, 28 mm; MNI; respectively). The individual stimulation sites were then determined by calculating the inverse of the normalisation transformation and transforming the coordinates from standard to "individual" space for each subject.

Stimulation intensity was set to 90% of individual resting motor threshold (RMT) of the left primary motor hand area and was corrected for the difference in the scalp-cortex distance between the motor cortex and the SMG using a simple linear correction ((44); see supporting information for further details). During each experimental trial, a four-pulse train of biphasic pulses was applied at a rate of 10 Hz over left, right or bilateral SMG 100 ms after word onset (Fig.1C). Trials with left, right and bilateral TMS (40 each) were pseudorandomly intermingled. The overall application of TMS was well within safety limits (45).

Data Analysis

For the effect of real versus sham TMS over the left, right and bilateral SMG, reaction times (RTs) were examined with a four-way repeated measures ANOVA. The 2x3x3x2 ANOVA model included a between-subjects factor group (real TMS vs. sham TMS) and the within-subject factors task (phonological, semantic, perceptual), TMS laterality (left, right or bilateral) and modality (auditory vs. visual).

For the effect of real TMS over SMG versus ANG, reaction times (RTs) were examined with a four-way repeated measures ANOVA. The 2x3x3x2 ANOVA model included the four within-subject factors region (SMG versus ANG), task (phonological, semantic, perceptual), TMS laterality (left, right or bilateral) and modality (auditory vs. visual).

ANOVAs only included trials with correct responses. The Greenhouse-Geisser method was used to correct for non-sphericity when appropriate. Conditional on significant F-values, post hoc paired t-tests were used to further characterize differences among conditions within groups. Between group differences were examined using independent samples t-tests. An α-level of 0.05 was considered significant for all comparisons, and all reported p-values are two-tailed.

We used Bonferroni-Holm corrected non-parametric Wilcoxon signed-rank tests and Mann-Whitney U tests for statistical analyses of error rates since Kolmogorov-Smirnov tests had indicated that these data were not normally-distributed, precluding the use of an ANOVA. All statistical analyses were performed with SPSS software (version 13, Chicago, Illinois, USA).

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Figure Legends

Figure 1

Experimental design. A. Stimulation sites over the left, right and bilateral SMG. MNI-coordinates were obtained from our recent fMRI data. ant=anterior, post=posterior, l=left, r=right. B. Auditory and visual run of the three blocked tasks. C. Single trial: Each trial had a duration of 3000 milliseconds. A 4-pulse train of 10 Hz online TMS was applied 100 milliseconds after word onset over left, right or bilateral SMG. Subjects responded with their left index or middle finger. ms=milliseconds; min=minutes.

Figure 2

Mean reaction times (RTs) for the effect of real versus sham TMS over left, right and bilateral SMG. For illustrating purposes, responses for auditorily and visually presented stimuli are displayed in different panels. All panels depict the significant two-way interaction between the factors task and group. Note that the three different TMS laterality sites (left, right, bilateral) are displayed separately for illustrating purposes in panel A and B although the interaction was pooled across the factors TMS laterality site and modality. Error bars represent onefold standard error from the mean (SEM); *$p<0.05$; two-tailed; ms=milliseconds.

Figure 3

Mean reaction times (RTs) for the effect of real TMS over SMG versus ANG. The significant two-way interaction between the factors region and task is shown in both panels. For illustrating purposes, responses for auditorily and visually presented stimuli are displayed in different panels although the interaction was pooled across modality. *$p<0.05$ two-tailed; ANG= angular gyrus; SMG= supramarginal gyrus.

Figure 4

Mean error rates (ER) for the effect of real versus sham TMS over left, right and bilateral SMG. ER are pooled across the factor TMS laterality as there were no differences between left, right and bilateral TMS. Error bars represent onefold standard error from the mean (SEM); *$p<0.05$; two-tailed.

Figure 5

Mean error rates (ER) for the effect of real TMS over SMG versus ANG. ER are pooled across the factor stimulation site as there were no differences between left, right and bilateral TMS. Error bars represent onefold standard error from the mean (SEM); (*): does not survive the Bonferroni-Holm correction ($p>0.004$); ((*)) $p<0.10$. ANG= angular gyrus; SMG= supramarginal gyrus.

Figure 6

Mean reaction times (RTs; panel A,B) and error rates (ER; panel C,D) for the phonological task in the follow-up experiment (TMS at different intensities over the left and right SMG). In panel A and B, the main effect of intensity on RTs is displayed. The two different TMS laterality sites (left and right SMG) and the two modalities (auditory and visual) are displayed here separately for illustrating purposes although the main effect was pooled across the factors TMS laterality and modality. Error bars represent onefold standard error from the mean (SEM); *$p<0.05$; two-tailed; RMT= resting motor threshold.

Tab. 1 Results from the ANOVA comparing the effect of real vs. sham TMS over left, right and bilateral SMG

Effect	F	df	p
Main effect			
task	16.39	1.34,33.41	0.0001
TMS laterality	5.74	2,50	0.006
modality	586.97	1,25	0.0001
group	4.27	1,25	0.049
Interaction			
task x group	5.82	2,50	0.005
task x modality	13.17	1.54,38.52	0.0001

df= degrees of freedom; a p-value <0.05 was considered significant

Figure 1

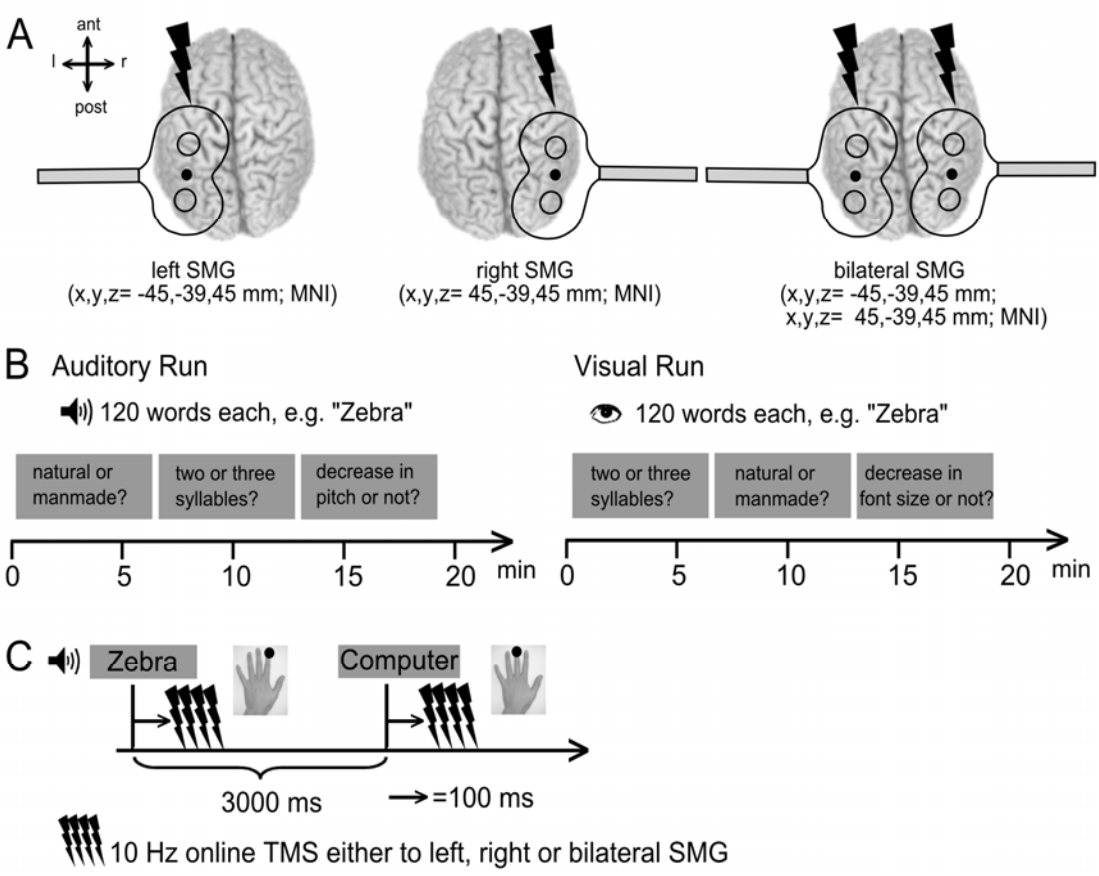

A
ant
l
r
post
left SMG
(x,y,z= -45,-39,45 mm; MNI)
right SMG
(x,y,z= 45,-39,45 mm; MNI)
bilateral SMG
(x,y,z= -45,-39,45 mm;
x,y,z= 45,-39,45 mm; MNI)
B
Auditory Run
120 words each, e.g. "Zebra"
natural or manmade?
two or three syllables?
decrease in pitch or not?
0
5
10
15
20
min
Visual Run
120 words each, e.g. "Zebra"
two or three syllables?
natural or manmade?
decrease in font size or not?
0
5
10
15
20
min
C
Zebra
Computer
3000 ms
=100 ms
10 Hz online TMS either to left, right or bilateral SMG

Figure 2

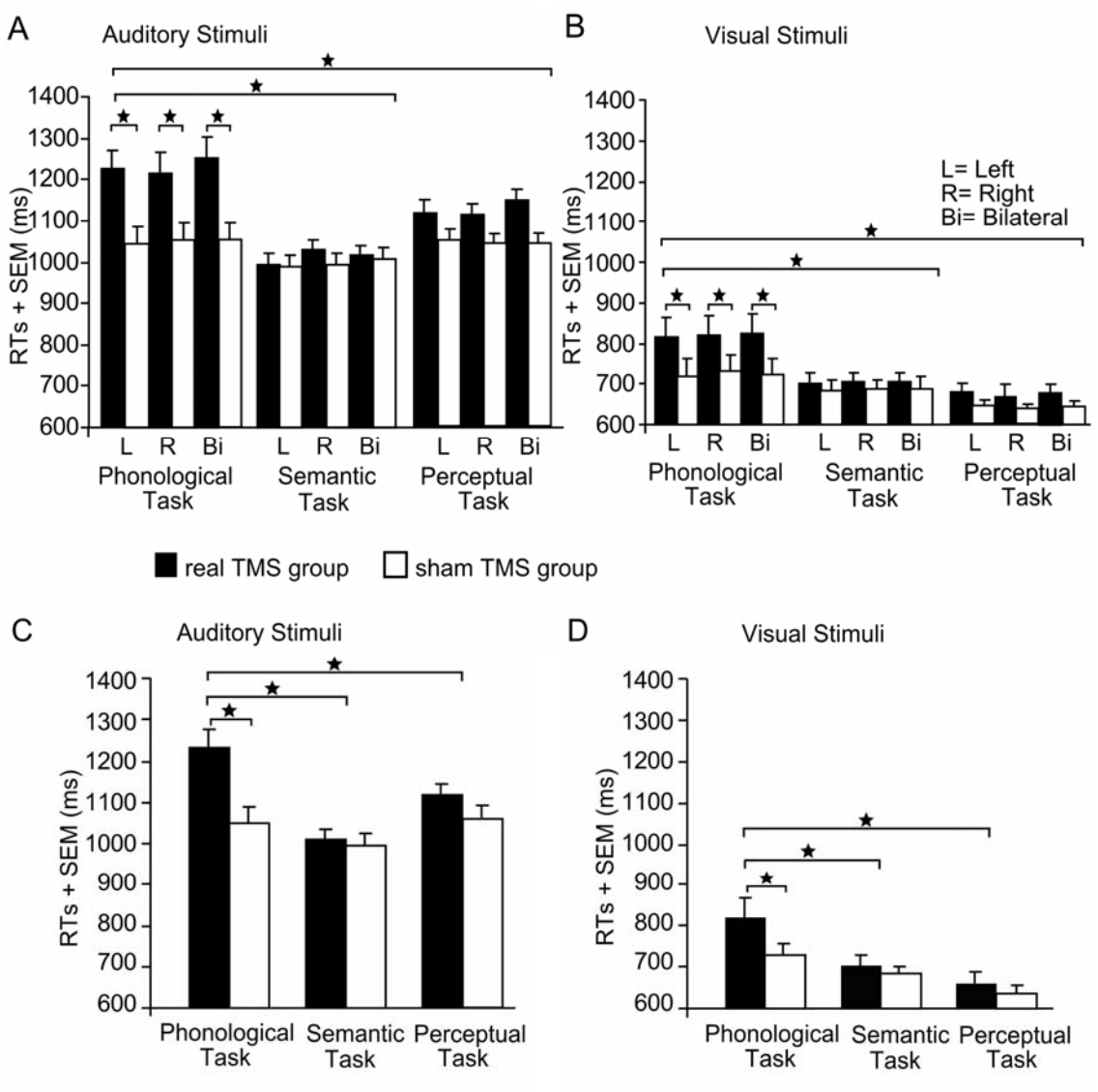

A
Auditory Stimuli
B
Visual Stimuli
RTs + SEM (ms)
1400
1300
1200
1100
1000
900
800
700
600
L R Bi L R Bi L R Bi
Phonological Task
Semantic Task
Perceptual Task
L= Left
R= Right
Bi= Bilateral
real TMS group
sham TMS group
C
Auditory Stimuli
D
Visual Stimuli
Phonological Task
Semantic Task
Perceptual Task

Figure 3

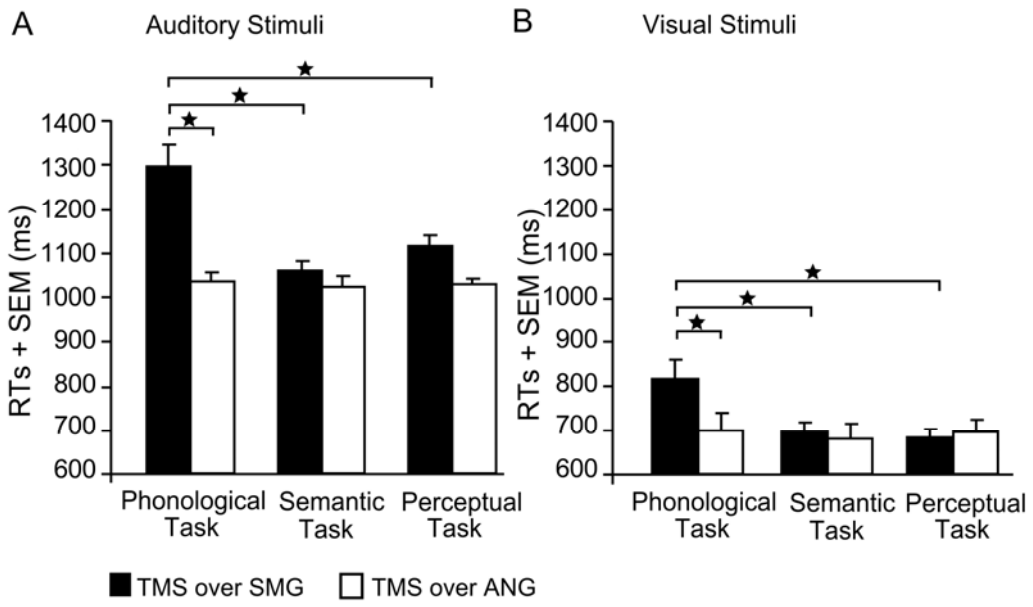

A
Auditory Stimuli
B
Visual Stimuli
RTs + SEM (ms)
1400
1300
1200
1100
1000
900
800
700
600
Phonological Task
Semantic Task
Perceptual Task
TMS over SMG
TMS over ANG

Figure 4

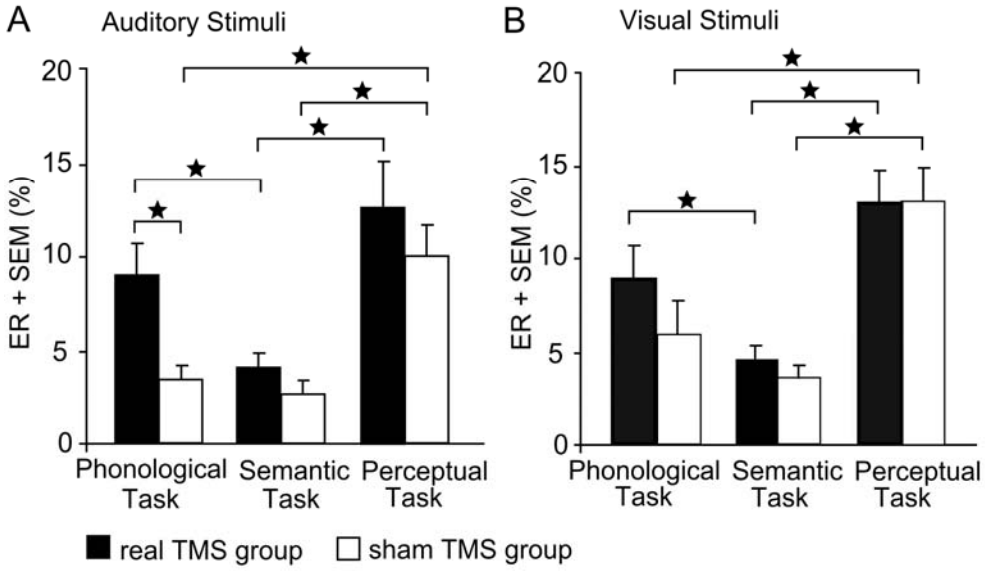

A
Auditory Stimuli
B
Visual Stimuli
ER + SEM (%)
20
15
10
5
0
Phonological Task
Semantic Task
Perceptual Task
real TMS group
sham TMS group

Figure 5

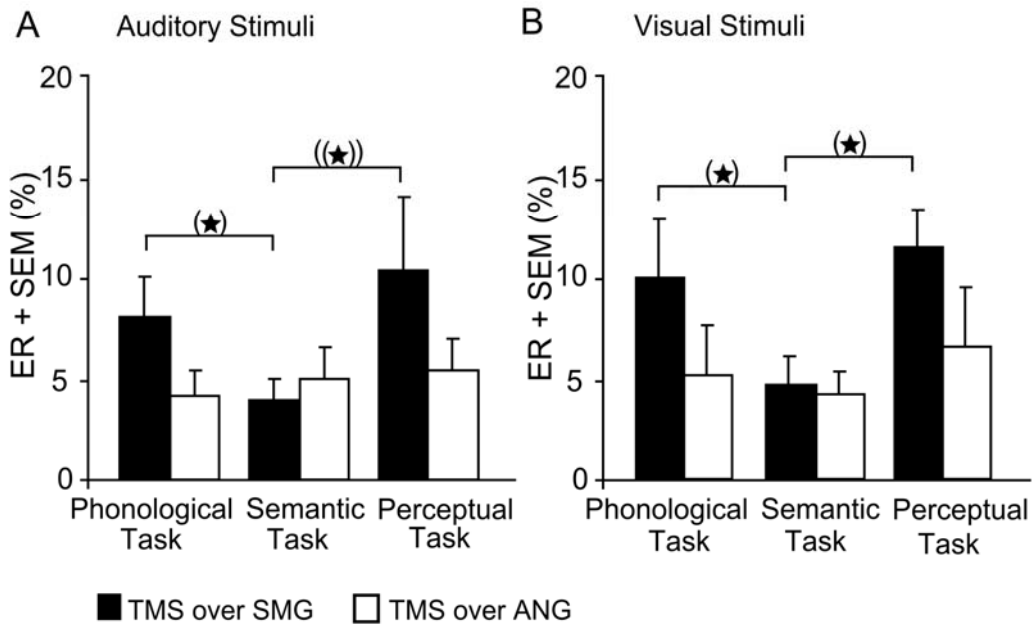
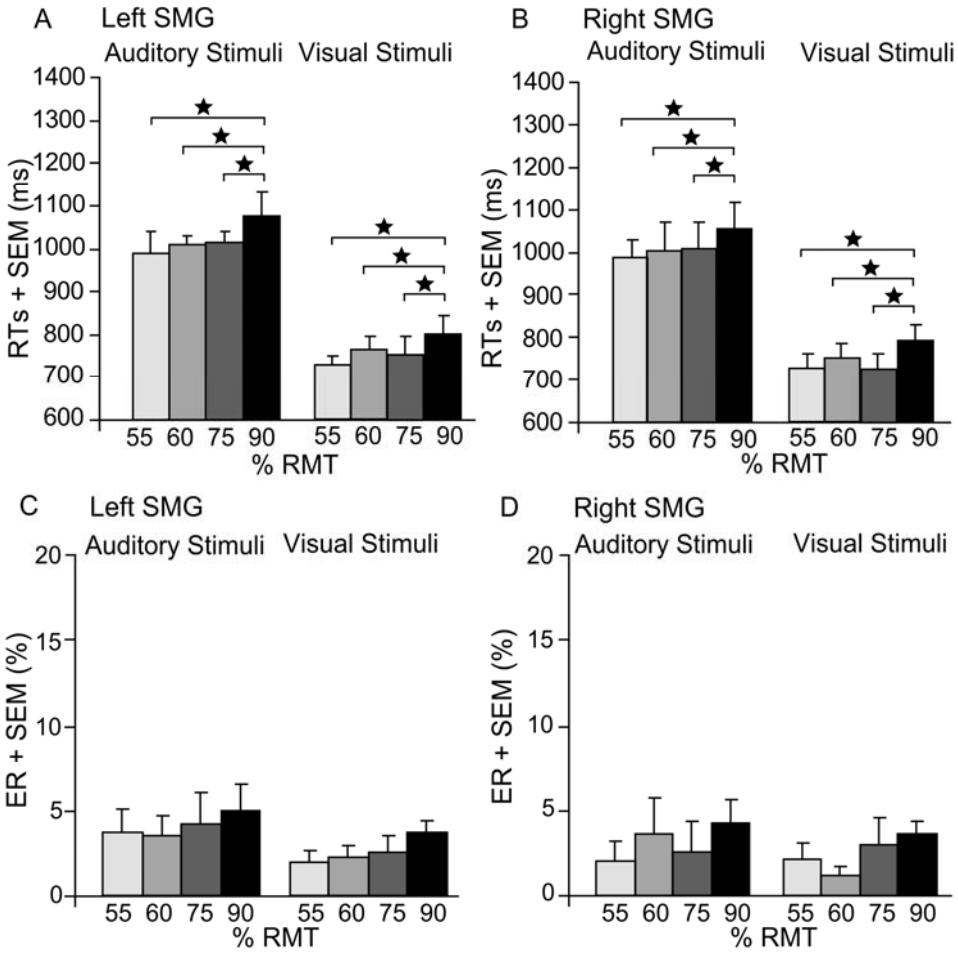

A
Auditory Stimuli
B
Visual Stimuli
ER + SEM (%)
20
15
10
5
0
(★)
((★))
Phonological Task
Semantic Task
Perceptual Task
TMS over SMG
TMS over ANG

Figure 6


A
Left SMG
Auditory Stimuli
Visual Stimuli
RTs + SEM (ms)
1400
1300
1200
1100
1000
900
800
700
600
55 60 75 90
55 60 75 90
% RMT
B
Right SMG
Auditory Stimuli
Visual Stimuli
RTs + SEM (ms)
55 60 75 90
55 60 75 90
% RMT
C
Left SMG
Auditory Stimuli
Visual Stimuli
ER + SEM (%)
20
15
10
5
0
55 60 75 90
55 60 75 90
% RMT
D
Right SMG
Auditory Stimuli
Visual Stimuli
ER + SEM (%)
55 60 75 90
55 60 75 90
% RMT

Supporting Tab.1 RTs and ER for the different tasks in the real TMS group and the sham TMS group

Task / TMS	Auditory RTs(ms)±SEM	ER(%)±SEM	Visual Stimuli RTs(ms)±SEM	ER(%)±SEM
Group receiving real TMS (n=14)				
Phonological				
Left	1223 ± 48.07	0.10 ± 0.02	814 ± 49.00	0.11 ± 0.02
Right	1216 ± 49.93	0.09 ± 0.03	820 ± 49.24	0.08 ± 0.02
Bilateral	1252 ± 48.62	0.11 ± 0.02	826 ± 44.30	0.09 ± 0.02
Semantic				
Left	991 ± 27.41	0.03 ± 0.01	699 ± 26.52	0.04 ± 0.01
Right	1026 ± 25.56	0.03 ± 0.01	704 ± 27.75	0.05 ± 0.02
Bilateral	1014 ± 23.00	0.03 ± 0.01	705 ± 22.48	0.05 ± 0.01
Perceptual				
Left	1113 ± 27.00	0.14 ± 0.03	673 ± 20.99	0.14 ± 0.02
Right	1105 ± 24.69	0.14 ± 0.04	662 ± 25.01	0.12 ± 0.03
Bilateral	1142 ± 25.95	0.14 ± 0.03	674 ± 22.65	0.13 ± 0.03
Group receiving sham TMS (n=14)				
Phonological				
Left	1042 ± 41.05	0.03 ± 0.01	719 ± 29.12	0.06 ± 0.02
Right	1051 ± 42.99	0.02 ± 0.01	730 ± 32.14	0.08 ± 0.02
Bilateral	1053 ± 42.31	0.04 ± 0.01	721 ± 32.44	0.06 ± 0.02
Semantic				
Left	990 ± 26.30	0.02 ± 0.01	684 ± 17.59	0.03 ± 0.01
Right	992 ± 25.97	0.03 ± 0.01	689 ± 19.64	0.04 ± 0.01
Bilateral	1006 ± 30.29	0.02 ± 0.01	686 ± 17.91	0.04 ± 0.01
Perceptual				
Left	1060 ± 25.15	0.09 ± 0.02	645 ± 14.48	0.12 ± 0.02
Right	1052 ± 23.48	0.11 ± 0.02	637 ± 13.61	0.12 ± 0.02
Bilateral	1053 ± 25.40	0.10 ± 0.03	645 ± 14.32	0.14 ± 0.02

ER= Error rates in % of trials; RTs= Reaction times in ms; SEM= standard error of the mean

Supplementary information

Results

Reaction times

Effects that did not interact with TMS group as revealed by the ANOVA comparing the effect of real versus sham TMS were as follows: There was a main effect of TMS laterality ($F_{2,50}$=5.74; p=0.006) because RTs were slower when real or sham TMS was bilateral compared to left only (t_{27}=3.35; p=0.001) or right only (t_{27}=2.34; p=0.021) but this did not interact with task or group (all p>0.45). There was also a main effect of stimulus modality ($F_{1,25}$=586.97; p=0.0001) because RTs were slower in the auditory than visual conditions, and a main effect of task ($F_{1.34,33.41}$=16.39; p=0.0001) because RTs were slower for phonological compared with semantic (t_{27}=5.70; p=0.0001) or perceptual (t_{27}=4.34; p=0.0001) decisions. The effect of phonological relative to semantic decisions was highly significant in both the auditory (t_{27}=4.56; p=0.0001) and visual (t_{27}=3.54; p=0.001) modalites but an interaction between task and modality ($F_{1.54,38.52}$=13.17; p= 0.0001) arose because the difference between phonological and perceptual decisions was greater in the visual modality (t_{27}=4.91; p=0.0001) than the auditory modality (p=0.093). In the visual modality, RTs were faster to perceptual than semantic decisions (t_{27}=3.07; p=0.005) but in the auditory modality, RTs were faster to semantic than perceptual decisions (t_{27}=4.87; p=0.0001). Across modalities, these effects resulted in a trend for longer RT in the perceptual relative to the semantic task (p=0.09).

Unpleasantness scores

In all conditions, real TMS was significantly more unpleasant than sham TMS (TMS of left SMG: $Z=3.86$, $p=0.001$; TMS of right SMG: $Z=3.87$, $p=0.001$; TMS over bilateral SMG: $Z=5.43$, $p=0.001$; pooled over pre- and post-experimental ratings). In the real TMS group, bilateral stimulation was significantly more unpleasant than left or right TMS, both pre-experimentally ($Z=2.65$; $p=0.016$ compared to left and $Z=2.33$; $p=0.031$ compared to right) and post-experimentally ($Z=2.45$; $p=0.031$ compared to left and $Z=2.31$; $p=0.035$ compared to right) with no significant difference in the pre-experimental and post-experimental experience (all $p>0.32$). All subjects in the sham TMS group rated the three different sham TMS conditions as neutral (1).

Material and Methods

Stimuli

We used 120 German words for stimulus presentation. Only highly frequent, unambiguous nouns from the CELEX lexical database for German (Centre for Lexical Information, Max Planck Institute for Psycholinguistics, The Netherlands) were selected. All words represented natural or manmade items (50% each).

Thirty German native speakers (15 females, age 24-47, mean age 29.0) independently categorized each item as either manmade or natural, rated each item's imageability on a four-point scale, ranging from 1 (concrete) to 4 (abstract), and provided the number of syllables for each item. These subjects were not included in the present study.

Only those words which (i) at least 29 out of 30 pilot subjects correctly classified as being either manmade or natural, (ii) received an average imageability rating of < 1.6, and (iii) reached > 90% agreement on the intended syllable count were included. Since more two-syllable than three-syllable words passed the above validation criteria, we were able to select the two-syllable nouns that most closely matched the three-syllable words in terms of their imageability ratings and number of letters (to the degree possible). In total, 60 two-syllable nouns and 60 three-syllable nouns were selected. All words represented natural or manmade items (50% each).

Half of the auditory stimuli were manipulated using the sound program Adobe Audition 2.0 (www.adobe.com/products/audition) such that there was an audible yet unobtrusive decline (13 halftones) in vocal pitch towards the end of the word. In analogy to the auditory condition, the font size was manipulated for half of the visual stimuli such that it changed from an initial 86 pt in 1 pt steps across the length of the word, to result in a noticeable yet unobtrusive change in the visual appearance of the word. Auditory versions of the words were recorded by a professional female speaker and had an average duration of 0.74 s (range: 0.52-1.02 s, two-syllable words) or 0.87 s (range: 0.66-1.12 s, three-syllable words), respectively.

Procedure

To allow for neuronavigated TMS, all subjects underwent MR imaging using an MPRage sequence in sagittal orientation (slice thickness 1 mm; in plane resolution 1 x 1 mm; TE / TR = 3.78 / 8.25 ms). After stereotactic coregistration and determination of the individual motor threshold with TMS over the left motor cortex, the experiment was explained and subjects performed a training session with three trials per task. None of the stimuli used in that session were repeated in the main experiment. During the practice session, sound volume was individually adjusted for each subject (with a range of 100 to 105.8 decibel [dB(A)]). Auditory stimuli were presented via in-ear headphones equipped with earplugs to shield the subject from the TMS induced noise. For further shielding, a foam cushion was fixed around the subject´s head above the ears during the whole procedure. During volume adjustment, TMS coils were charged closely above the subject´s head to induce noise that was comparable to the experimental session. Visual stimuli were presented in the center of a computer monitor in front of the subject (19" flat-screen monitor, resolution: 1280 x 1024 pixels, distance from the subject: 70 cm). The font size for presentation was set to an initial 86 pt.

Transcranial magnetic stimulation

A recently developed algorithm (http://r-forge.r-project.org/projects/rniftilib/) calculated the shortest distance from the target coordinate in the brain to the surface for each subject. The TMS coils were placed over these "entry-coordinates" on the surface of the head.

Stimulation intensity was corrected for the difference in the scalp-cortex distance between the motor cortex and the SMG. Therefore, the location of the motor cortex (M1) was determined by using the same algorithms as described above. The average MNI coordinates for the M1 were taken from a recent meta-analysis (49). For the distance correction, we adapted the following formula recommended by Stokes et al. (47):

$$AdjMT\% = MT + 3\,(D_{SMG} - D_{M1})$$

where AdjMT% corresponds to the adjusted motor threshold in percentage stimulator output, MT is the unadjusted MT in percentage stimulator output, D_{SMG} is the distance between scalp and target in the left or right SMG and D_{M1} corresponds to the distance between scalp and target in the motor cortex. The difference in the distance between the two sites is multiplied by 3 to account for the spatial gradient relating MT to distance (47). Since this correction would have resulted in very high and thus unpleasant stimulation intensities for most of the subjects, we used 90% instead of 100% of MT for the correction, corresponding to our TMS protocol (90% RMT). Corrected mean stimulation intensity was 44.5 $\pm$ 5.83% total stimulator output; adjusted RMTs for the left and right SMG were not significantly different.

The RMT was defined as the lowest stimulus intensity that elicited at least five visible twitches in 10 consecutive stimuli given over the motor hot spot. Figure-of-eight shaped coils (double 90 mm; coil type Q.C., Mag and More GmbH, Munich, Germany) and P-Stim 160 stimulators (Mag and More GmbH, Munich, Germany) were used in all TMS conditions. The coils were positioned with the handle pointing lateral and perpendicular to the midline over the left and right SMG, with the second phase of the biphasic pulse inducing a lateral to medial current flow (46).

We used frameless stereotaxy (TMS-Navigator, Localite, Sankt Augustin, Germany) based on the coregistered individual T1-weighted MR image to navigate the TMS coils and maintain their exact location and orientation throughout the experimental sessions.

In the sham TMS group, an additional coil was placed in an angle of 90º over each coil. Stimulation intensity of these coils was set 15% higher to create a comparable acoustic stimulus without stimulating the brain. Trials with sham stimulation over the left, right or bilateral SMG (40 each) were pseudorandomly intermingled.

Appendix VI

The right posterior inferior frontal gyrus contributes to phonological word decisions in the healthy brain: evidence from dual-site TMS.

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Running Head: Phonological processing in the inferior frontal gyrus
Keywords: language, human brain, hemisphere, transcranial magnetic stimulation, compensation, functional magnetic resonance imaging

Number of text pages: 20 Figures: 4 (+ 1 supplementary) Tables: 1
Word count manuscript: Abstract: 256 words; Discussion: 2020 words

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Abstract

There is consensus that the left hemisphere plays a dominant role in language processing, but functional imaging studies have shown that the right as well as the left posterior inferior frontal gyri (pIFG) are activated when healthy right-handed individuals make phonological word decisions. Here we used online transcranial magnetic stimulation (TMS) to examine the functional relevance of the right pIFG for auditory and visual phonological decisions. Healthy right-handed individuals made phonological or semantic word judgements on the same set of auditorily and visually presented words while they received stereotactically guided TMS over the left, right or bilateral pIFG (n= 14) or the anterior left, right or bilateral IFG (n= 14). TMS started 100 ms after word onset and consisted of four stimuli given at a rate of 10 Hz and intensity of 90 % of active motor threshold. Compared to TMS of aIFG, TMS of pIFG impaired reaction times and accuracy of phonological but not semantic decisions for visually and auditorily presented words. TMS over left, right or bilateral pIFG disrupted phonological processing to a similar degree. In a follow-up experiment, the intensity threshold for delaying phonological judgements was identical for unilateral TMS of left and right pIFG. These findings indicate that an intact function of right pIFG is necessary for accurate and efficient phonological decisions in the healthy brain with no evidence that the left and right pIFG can compensate for one another during online TMS. Our findings motivate detailed studies of phonological processing in patients with acute and chronic damage of the right pIFG.

Introduction

Functional imaging studies have shown that right as well as left posterior inferior frontal gyri (pIFG) are activated when healthy right-handed subjects perform phonological tasks (Chee et al., 1999; Devlin, Matthews and Rushworth, 2003; Poldrack et al., 1999; Shibahara, 2004; Tremblay, Monetta and Joanette, 2004). This bilateral pIFG activation pattern is surprising given that lesion studies emphasize that phonological processing is more impaired after left than right inferior frontal damage (e.g. Dewarrat et al., 2009; Wilde, 2009; Winhuisen et al., 2007) and theoretical models of language focus on the importance of the left rather than right hemisphere (e.g. Shalom and Poeppel, 2008). Transcranial magnetic stimulation (TMS) studies of phonological processing in healthy right-handed subjects have also focused on the functional relevance of left but not right pIFG (e.g. Gough, Nobre and Devlin, 2005; Nixon et al., 2004; Romero, Walsh and Papagno, 2006). These studies demonstrated that left pIFG is more involved in phonological than semantic judgements on written words but they did not investigate the role of pIFG in the right hemisphere. To address the discrepancy between functional imaging and lesion studies, the present study was designed to examine how "online" TMS (i.e. TMS during a task) over the left and right pIFG influences phonological word processing in healthy subjects. We used the neurodisruptive effect of TMS to distinguish between three alternative explanations for right pIFG activation with phonologic processing.

Hypothesis 1: Right pIFG contributes to the speed and efficiency of phonological decisions. Consequently, right pIFG lesions have a subtle effect that might be missed unless reaction times were measured. In this case, we expect a significant effect of right pIFG TMS on reaction times but not error rates in the healthy brain.

Hypothesis 2: Right pIFG is necessary for accurate and efficient phonological decisions in the healthy brain but following right pIFG lesions, the function of right pIFG can be supported by

alternative brain regions. Consequently, right pIFG lesions may temporarily impair phonological decision performance in the acute phase after brain damage but this lesion effect will not be apparent after functional reorganisation. In this case, we expect a significant effect of right IFG TMS on both the reaction times and accuracy of phonological decisions in the healthy brain.

Hypothesis 3: Right pIFG is not necessary for accurate and efficient phonological decisions but is activated in fMRI studies of the healthy brain because it is involved in task-related activation that is incidental to performance (i.e. redundant processing, Price and Friston, 2002). In this case, neither right pIFG lesions nor right pIFG TMS will influence phonological decision performance.

Our study extends previous online TMS studies of phonological processing in three ways. First, we investigated the effect of TMS to the right pIFG. Second, we compared unilateral TMS over the right pIFG to unilateral TMS to the left pIFG and dual-site TMS over left and right pIFG simultaneously. This manipulation allowed us to test whether impaired unilateral pIFG function was supported by the contralateral hemisphere. If so, then the effect of dual-site TMS to both the left and right pIFG should be greater than the effect of TMS to either the left or right pIFG alone (Price and Friston, 2002). Third, we compared the effect of TMS on phonological decisions to words presented in the auditory as well as visual modality, whereas previous studies investigated the effect of online TMS to left pIFG with visually presented words only (Gough, Nobre and Devlin, 2005; Nixon et al., 2004; Romero, Walsh and Papagno, 2006). This enabled us to assess whether the expected TMS effects were dependent or independent of stimulus modality.

To test the functional specificity of our effects, we also investigated how online TMS to the same pIFG sites affected semantic decisions on the same sets of stimuli. Finally, to test the regional specificity of any observed effects, we investigated how phonological decisions were affected by TMS over anterior inferior frontal gyri (aIFG). Functional imaging studies have demonstrated a functional-anatomic subdivision within the IFG with more anterior regions being preferentially

engaged in semantic processing and more posterior regions in phonological processing (e.g. Burton, 2001; Fiez, 1997; Gold et al., 2005; Poldrack et al., 1999; Wise, 2003). On the basis of a recent TMS study by Gough, Nobre and Devlin (2005), we expected that phonological but not semantic judgements would be impaired with TMS applied to the pIFG but not aIFG.

Materials and Methods

Subjects

28 right-handed native German speakers with no history of neurological disorders or head injury were randomly assigned to the pIFG TMS group (n=14, 8 females, 20-28 years old, mean age 24.01 $\pm$ 2.38) or the aIFG TMS group (n=14, 7 females, 20-30 years old, mean age 23.85 $\pm$ 2.53). We also included a control group of another 7 healthy subjects (3 females, 21-27 years old, mean age 24.03 $\pm$ 2.32) receiving only sham TMS. Written informed consent was obtained before the experiment. Handedness was tested with the German version of the Edinburgh Handedness Inventory Oldfield, 1971. All subjects had normal or corrected-to-normal visual acuity and were naive to TMS. The study was performed according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Medical Faculty of the Christian-Albrechts-University of Kiel.

Experimental design

The experiment had a 2x2x3x2 design with two different tasks (phonological and semantic) in two modalities (auditory and visual) and three TMS sites (left, right, and bilateral stimulation) for two groups receiving TMS either over the pIFG or aIFG, respectively (Fig.1A,B). An identical set of 120 stimuli was presented in each of the two tasks in both the auditory and visual modalities. This resulted in four repetitions of the same words with the effect of repetition

controlled across tasks. In order to keep the repetition of identical stimuli per subject at a minimum (i.e. four) we decided against treating the pIFG vs. aIFG TMS conditions as within subject factor and thus included two different groups. The factorial design enabled us to test for task, site and group specific modality-independent effects while controlling for stimulus and repetition effects. The control group received only sham TMS to test whether the different tasks yielded comparable results with respect to reaction times (RT) and error rates (ER) without the influences of real TMS (supplementary data). In all other aspects the experimental design for the control group was comparable to the main experiment.

Tasks

Subjects performed two different tasks in the visual and the auditory modality on the same stimuli in both tasks. In the phonological task, subjects categorized the items as having two or three syllables. The semantic task consisted of deciding whether a word represented a natural or manmade item. Tasks were blocked to ensure a constant cognitive set. Subjects were instructed to respond as quickly and as accurately as possible by pressing a button on a response pad with their left middle or index finger (Fig.1D).

Stimuli

60 two-syllable and 60 three-syllable German words were used for stimulus presentation. Only highly frequent, unambiguous nouns from the CELEX lexical database for German (Centre for Lexical Information, Max Planck Institute for Psycholinguistics, The Netherlands) were selected. No compound nouns, hypernyms or foreign words were included. Thirty German native speakers (15 females, age 24-47, mean age 29.0) independently categorized each item as either manmade or natural, rated each item's imageability on a four-point scale, ranging from 1 (concrete) to 4

(abstract), and provided the number of syllables for each item. These subjects were not included in the present study.

Words were only included if (i) at least 29 out of 30 pilot subjects correctly classified them as being either manmade or natural, (ii) they received an average imageability rating of < 1.6, and (iii) they reached > 90% agreement on the intended syllable count. Since more two-syllable than three-syllable words passed the above validation criteria, we were able to select the two-syllable nouns that most closely matched the three-syllable words in terms of their imageability ratings and number of letters (to the degree possible). In total, 60 two-syllable nouns and 60 three-syllable nouns were selected. All words represented natural or manmade items (50% each).

Auditory versions of the words were recorded by a professional female speaker and had an average duration of 0.74 s (range: 0.52-1.02 s, two-syllable words) and 0.87 s (range: 0.66-1.12 s, three-syllable words), respectively.

Procedure

As a prerequisite for neuronavigated TMS, all subjects underwent MR imaging using a MPRage sequence in sagittal orientation (slice thickness 1 mm; in plane resolution 1 x 1 mm; TE / TR = 3.78 / 8.25 ms). After stereotactic coregistration and determination of the individual motor threshold with transcranial magnetic stimulation (see below), the experiment was explained and subjects performed a training session with three trials per task. None of the stimuli used in that session were repeated in the main experiment. During the practice session, sound volume was individually adjusted for each subject (with a range of 99 to 105 decibel [dB(A)]). Auditory stimuli were presented via in-ear headphones equipped with earplugs to shield the subject from the TMS induced noise. For further shielding, a foam cushion was fixed around the subject´s head above the ears during the whole procedure. During volume adjustment, TMS coils were charged closely above the subject´s head to induce noise that was comparable to the experimental

session. Visual stimuli were presented in the center of a computer monitor in front of the subject (19" flat-screen monitor, resolution: 1280 x 1024 pixels, distance from the subject: 70 cm). The font size for presentation was set to an initial 86 pt.

After the training session, the two TMS coils were stereotactically positioned over the left and right pIFG or aIFG (Fig.1A,B) and remained fixed during the experiments. Subjects received three test bursts of 10 Hz TMS over left, right and bilateral pIFG or aIFG and judged them on a 4-point scale either as "neutral" (1), "moderate unpleasant" (2), "unpleasant" (3) or "highly unpleasant" (4). The unpleasantness scores were implemented to assess whether TMS was comparable for all stimulation sites (i.e. left, right and bilateral aIFG or pIFG).

The experiment consisted of an auditory and a visual run for each subject (Fig.1C). The order of runs was counterbalanced across subjects. During each run the two blocked tasks were randomly presented and each task started with a verbal or written instruction of the task and consisted of 120 trials for each condition, with a trial-duration of three seconds (Fig.1D). Presentation of visual words was matched to the mean duration of the auditory stimuli (range= 0.74-0.87 s) and followed by a fixation cross to complete the three second trial. During the auditory run, the fixation cross stayed on the screen for the whole experiment. Having completed all four conditions, subjects again rated the unpleasantness of the three TMS sites.

The control group underwent exactly the same experimental procedure including MR scan, stereotactically guided coil positioning and unpleasantness ratings. For each experimental condition, mean reaction times (RT) and error rates (ER) were calculated. Stimulus presentation and response recording was obtained using E-PRIME software (Psychology Software Tools Inc., Pittsburgh, PA, USA; version 1.1).

Transcranial magnetic stimulation

We used neuronavigated TMS (TMS-Navigator, Localite, Sankt Augustin, Germany) based on the coregistered individual T1-weighted MR image to navigate the TMS coils and maintain their exact location and orientation throughout the experimental sessions. Neuronavigated TMS was performed by using the mean MNI-coordinates for left pIFG across four recent studies comparing visual presented words in a word comprehension task (-47 6 21; Devlin, Matthews and Rushworth, 2003; Gitelman et al., 2005; Gough, Nobre and Devlin, 2005; McDermott et al., 2003 see Fig.1A). Stereotactic coordinates for left aIFG (x,y,z= -45, 27, 12 mm) were obtained from group activation data from a previous fMRI study which used the same experimental paradigm in an independent sample of subjects (A. Baumgaertner, G. Hartwigsen, and H.S. Siebner, unpublished data). Thus, we used the modality-independent comparison between the semantic and phonological task in our previous fMRI study (Fig.1B). For right hemisphere TMS we used the contralateral homologue areas. Using these stereotactic coordinates, the individual stimulation sites were determined by calculating the inverse of the normalisation transformation and transforming the coordinates from standard to "individual" space for each subject. A recently developed algorithm (http://r-forge.r-project.org/projects/rniftilib/) calculated the shortest distance from the target coordinate in the brain to the surface for each subject. The TMS coils were placed over these "entry-coordinates" on the surface of the head.

The coils were placed tangentially on the head with the handle pointing at 45º to the sagittal plane, with the second phase of the biphasic pulse inducing a posterior to anterior current flow (Fig.1A,B). Stimulation intensity was set to 90% of individual active motor threshold (AMT). AMT was defined as the lowest stimulus intensity producing an MEP of approximately 150–200 µV in the tonically active first dorsal interosseus muscle (20% of maximum contraction). Mean stimulation intensities were 28.07 $\pm$ 5.64% and 8.96 $\pm$ 3.19 total stimulator output for pIFG and aIFG, respectively. Figure-of-eight shaped coils (double 90 mm; coil type Q.C., Mag and

More GmbH, Munich, Germany) and P-Stim 160 stimulators (Mag and More GmbH, Munich, Germany) were used in all TMS conditions.

During each experimental trial, a four-pulse train of stereotactically guided 10 Hz TMS was applied over left, right or bilateral pIFG or aIFG 100 ms after word onset (Fig.1D).

Trials with left, right and bilateral TMS (40 each) were pseudorandomly intermingled. The overall application of TMS was well within safety limits (Wassermann, 1998). In the control group receiving sham TMS, an additional coil was placed in an angle of 90º over each coil. Stimulation intensity of these coils was set 15% higher to create a comparable acoustic stimulus without stimulating the brain. Trials with left, right and bilateral sham TMS (40 each) were pseudorandomly intermingled.

Data Analysis

Reaction times for trials with correct responses were examined with a four-way repeated measures ANOVA. The 2x2x3x2 ANOVA model included the within-subject factors task (phonological vs. semantic), modality (auditory vs. visual stimulus presentation) and TMS site (left, right, or bilateral) and a between-subjects factor group (TMS over pIFG vs. TMS over aIFG).

The Greenhouse-Geisser correction was used to correct for non-sphericity when appropriate. Conditional on significant F-values, post hoc paired t-tests were used to further characterize differences among conditions within groups. Between group differences were examined using independent samples t-tests, an α-level of 0.05 was considered significant for all comparisons. All reported p-values are two-tailed.

Results from the control group (sham TMS) were analysed separately to test whether the different tasks yielded comparable results with respect to reaction times (RT) and error rates (ER) without

the influences of real TMS. RT for trials with correct responses were examined using a three-way repeated measures ANOVA with the factors task (phonological, semantic), modality (auditory vs. visual) and TMS site (left, right or bilateral sham stimulation).

We used Bonferroni-Holm corrected non-parametric Wilcoxon signed-rank tests and Mann-Whitney U tests for statistical analyses of error rates since Kolmogorov-Smirnov tests had indicated that these data were not normally-distributed, precluding the use of an ANOVA.
For the comparisons on ER within the control group, no Bonferroni-Holm correction was applied since we wanted to test the null-hypothesis (e.g. no significant differences between the tasks). Unpleasantness ratings were also analysed with nonparametric Wilcoxon signed-rank tests and Mann-Whitney U tests without Bonferroni-Holm correction since the null-hypothesis (no significant differences between the three stimulation sites) should be maintained. All statistical analyses were performed with SPSS software (version 13, Chicago, Illinois, USA).

Results

Reaction Times

Subjects' mean reaction times (RT) were examined with a four-way repeated measures ANOVA. The ANOVA model included the factors: task (phonological vs. semantic), modality (auditory vs. visual), TMS site (left, right, bilateral) and group (pIFG vs. aIFG). Table 1 lists mean RT and ER for the phonological and semantic task in the pIFG and aIFG groups.

Overall, RT were longer when subjects made phonological compared to semantic judgements. This was indicated by a main effect of task pooled over the factors TMS site (left, right or bilateral), modality (auditory and visual) and group (pIFG and aIFG) ($F_{1,26}$=12.94; p=0.001).

There was also a main effect of modality due to longer RT for auditorily than visually presented words across tasks, TMS sites and groups ($F_{1,26}$=199.76; p=0.0001).

Repeated-measures ANOVA revealed that TMS over pIFG but not aIFG increased RT for the phonological task only (significant task-by-group interaction: $F_{1,26}$=13.77; p=0.001; Fig.2).

Accordingly, post-hoc paired comparisons indicated increased RT for the phonological compared to the semantic task in the pIFG group (t_{27}=4.82; p<0.001; post-hoc t-test) but not in the aIFG group (p=0.89). Overall, the pIFG group showed longer RT in the phonological task relative to the aIFG group (t_{27} =2.02; p=0.048; between-group comparison). In contrast, there were no overall differences in mean RT for the semantic task between both groups (p=0.88). The task-specific delay of phonological decisions with TMS to pIFG was independent of the modality as there was no task-by-group-by-modality interaction. The ANOVA showed no main effect or interaction with the factor TMS site, indicating that unilateral TMS of left and right pIFG as well as dual-site TMS of right and left pIFG produced a similar disruption of phonological judgements.

We also found an interaction between task and modality ($F_{1,26}$=9.38; p=0.005) pooled across the factors group and TMS site. This interaction indicated that the RT difference between phonological and semantic judgements was greater for auditorily presented words (t_{27}=3.51; p=0.002; post-hoc t-test) than visually presented words (n.s.; p=0.16).

Error Rates

Relative to TMS over aIFG, TMS over pIFG resulted in an increase in error rates (ER) when participants made phonological judgements (Fig.3). The effects that were still significant after Bonferroni-Holm correction for multiple comparisons were as follows: In the auditory modality, phonological errors increased relative to semantic errors when TMS was applied to right pIFG

(Z=2.89; p=0.009). There was also a trend for increased error rates for phonological compared to semantic errors in the auditory modality with TMS of left pIFG (Z=1.80; p=0.075; Fig.3A).

In the visual modality, Wilcoxon signed-rank tests revealed significant increases in phonological errors relative to semantic errors when TMS was given to the left pIFG (Z=2.52; p=0.012) or right pIFG (Z=3.05; p=0.001). A similar trend towards a selective increase in phonological errors was present in the visual modality when TMS was applied to both the left and right pIFG (Z=1.97; p=0.052; Fig.3B). Neither TMS of pIFG or aIFG caused a significant increase in ER for semantic decisions.

Mann-Whitney U tests showed differences in ER between the pIFG and aIFG group: Left pIFG TMS was associated with an increase in ER for the auditory phonological task relative to left aIFG (Z=3.18; p=0.001). Right pIFG TMS compared with right aIFG TMS also significantly increased phonological errors in the auditory modality (Z=2.88; p=0.0091). Increased phonological error rates were also present with auditory stimuli when TMS was applied to bilateral pIFG relative to bilateral aIFG (Z=2.05; p=0.042) and with visual stimuli when TMS was given to right pIFG (Z=2.02; p=0.044), however, these comparisons did not survive the Bonferroni-Holm correction. There were no significant differences in semantic errors between the groups (i.e. pIFG and aIFG group) in either modality (Fig.3).

Follow-up experiment

Our main experiment indicated comparable effects for unilateral TMS over left and right pIFG on phonological processing. In a follow-up experiment, we compared the intensity-dependence of the behavioral "lesion" effect induced by unilateral TMS to the left or right pIFG. We thus wanted to investigate whether the relationship between TMS-intensity and behavioural perturbation for left versus right pIFG were different by constructing intensity-effect-size curves.

More specifically, this experiment enabled us to test if left pIFG TMS disrupted phonological processing at lower intensities than right pIFG TMS.

To this end, 7 subjects (5 females, mean age 22.75 $\pm$ 2.54) from both experimental groups (i.e. pIFG vs. aIFG) performed two sessions of the phonological task again while receiving TMS over left (session one) or right pIFG (session two). TMS was applied at four different stimulation intensities with increasing intensity (55, 60, 75 and 90% individual AMT). Both sessions consisted of four blocks of different TMS intensities. Each block included 30 trials of the phonological task and was separated by 5 minutes rest to prevent carry-over effects. The order of sessions was counterbalanced across subjects. In all other aspects, this experiment was identical to the main experiment. Overall RT were again significantly increased for auditorily compared to visually presented words ($F_{1,6}$=122.93; p<0.0001). A main effect of intensity ($F_{3,18}$=3.80; p=0.029; Fig.4A,B) showed that RT were significantly longer with TMS at an intensity of 90% AMT compared to all other intensities (t_6=2.44; p=0.02; t_6=2.95; p=0.006; t_6=2.16; p=0.04 for 90 vs. 55, 60 and 75%; respectively). This intensity effect was comparable for left and right pIFG TMS (p=0.74). ER were not significantly different between the different conditions (all p>0.13; Fig.4C,D).

Unpleasantness scores

All subjects in the control group rated the three different sham TMS conditions as neutral (1). In the pIFG group, pre-experimental (mean: 1.29, 1.29, 1.36; standard deviation: 0.91, 0.63, 0.66 for left, right and bilateral stimulation, respectively) and post-experimental ratings (mean: 1.21, 1.43, 1.79; standard deviation: 0.58, 0.76, 0.97) were not significantly different. There were also no significant differences between pre-experimental (mean: 1.43, 1.43, 1.71; standard deviation: 0.51, 0.65, 0.61) and post-experimental ratings (mean: 1.71, 1.36, 1.86; standard deviation: 0.91, 0.63, 0.66) in the aIFG group nor between the two groups (i.e. pIFG vs. aIFG).

Discussion

Using a perturb-and-measure approach, we compared the disruptive effects of high-frequency TMS over the left, right and bilateral posterior and anterior inferior frontal gyri during phonological and semantic word decisions. This allowed us to test three different explanations for why fMRI studies show bilateral pIFG activation during phonological decision tasks but lesion studies emphasize the importance of left but not right hemisphere damage in aphasia (see Introduction for details). Our finding that reaction times and error rates increased following TMS to right pIFG as well as left pIFG indicates that unperturbed right pIFG activation is necessary for accurate and efficient phonological decisions in the healthy brain. Moreover, our finding that phonological decision performance was not worse for bilateral pIFG TMS than unilateral pIFG TMS provides no evidence that the left and right pIFG can compensate for one another: If phonological decisions are possible with either the left or the right pIFG, then dual-site TMS over the left and right IFG should produce a greater "lesion" effect than TMS over left or right pIFG alone. In contrast, our observation that the behavioural effect of TMS on phonological judgements was the same for unilateral and bilateral TMS suggests that the left and right pIFG are equally necessary for phonological decisions in the healthy brain.

Our finding that online TMS over the right pIFG selectively interfered with phonological but not semantic judgements provides the first strong evidence that right pIFG is necessary for efficient phonological processing in healthy right-handed subjects. The disruptive effect was independent of the presentation modality (i.e. auditory or visual) and was present during unilateral as well as bilateral TMS. Therefore, it can not be explained in terms of the contralateral hemisphere playing a compensatory role (see Price and Friston, 2002). To the contrary, both the main experiment and the follow-up experiment manipulating TMS intensity indicated that the lesion effect of unilateral TMS to the right pIFG was comparable to the lesion effect induced by unilateral TMS to the left pIFG or bilateral TMS to the right and left pIFG. Moreover, it can not be explained in terms of a

speed-accuracy trade-off because the detrimental effects of right pIFG TMS on reaction times were paralleled by an increase in error rates. Although the TMS-induced change in behavioural measures was stronger for reaction times than error rates, TMS over pIFG but not aIFG increased error rates, especially when given over the right hemisphere. We thus conclude that the right pIFG is necessary for efficient *and* accurate phonological decisions in the healthy brain.

To the authors' knowledge, no study to date has investigated the effects of TMS to right pIFG during phonological processing although several functional imaging studies revealed bilateral activity in the pIFG when healthy right-handed subjects made phonological decisions (Chee et al., 1999; Devlin, Matthews and Rushworth, 2003; Poldrack et al., 1999). Nevertheless, our results confirm several recent TMS studies demonstrating that the left pIFG is important for phonological processing of visually presented words (Gough, Nobre and Devlin, 2005; Nixon et al., 2004; Romero, Walsh and Papagno, 2006). For example, Gough et al. (2005) applied 10 Hz online TMS to either left pIFG or aIFG while right-handed healthy subjects had to decide whether or not two visually presented words sounded the same (phonological task) or meant the same (semantic task). Their results revealed a double dissociation within the left IFG with TMS over left pIFG selectively increasing reaction times for the phonological but not the semantic task and vice versa for left aIFG stimulation. Our results extent these findings by showing that the right pIFG also contributes to phonological processing and that the effect is observed irrespective of whether the stimuli are written words or auditory words.

The finding by Gough et al. (2005) that TMS over aIFG impaired semantic decisions more than phonological decisions contrasts with that of Kohler et al. (2004) who found that high-frequency online TMS to the left but not right aIFG enhanced the accuracy of semantic word encoding in comparison to TMS over parietal sites. The authors concluded that TMS to left aIFG might have

triggered a more extensive processing of the stimulated items underlining the important role of the left aIFG in episodic memory function.

We did not find a significant influence of aIFG stimulation on semantic processing as implicated by Gough et al. (2005) and Kohler et al. (2004). This is striking since we used a comparable TMS protocol to the Gough et al. study (10 Hz TMS starting 100 ms after word onset). However, in these previous studies, stimulation intensity ranged from 100-110% resting motor threshold or 60% total stimulator output compared to 90% active motor threshold (approximately corresponding to 29% total stimulator output) in the present study. We refrained from using higher stimulation intensity because subjects reported substantial discomfort and muscle contractions at stimulus intensities above 100% active motor threshold in a pilot study, especially when TMS was given over the aIFG. It is thus very likely that our stimulation intensity was too low to effectively disrupt semantic processing in the aIFG. However, the low stimulation intensity was sufficient to disrupt phonological processing in the pIFG. These results can not be attributed to task difficulty since both tasks yielded comparable RT and ER in the control group (sham TMS). One possible explanation is that the semantic network was able to compensate for the disruptive effect of low-intensity TMS over left aIFG.

An alternative interpretation of our results is that TMS over unilateral right pIFG affected phonological processing in the left pIFG by activating transcallosal inputs from the right to the left pIFG (see Siebner et al., 2009; Thiel et al., 2006b). This interpretation would be in line with previous TMS studies demonstrating acute remote effects of TMS in contralateral homotopic areas (Baumer et al., 2006; Bestmann et al., 2005; Bestmann et al., 2008; Irlbacher et al., 2006; Thiel et al., 2006b). For example, it has been shown that TMS over the motor cortex can change the metabolic rate in the contralateral motor areas and may lead to behavioural or functional effects ipsilateral to the side of stimulation (Paus et al., 1998; Siebner et al., 2000; Strafella and

Paus, 2001). However, several considerations render this explanation unlikely. Neurophysiological studies of the primary motor cortex showed that TMS over the ipsilateral motor hand area has much stronger excitatory and longer lasting inhibitory effects on regional excitability as opposed to the transcallosally induced effects induced by TMS over the contralateral motor hand area (Kobayashi and Pascual-Leone, 2003). The threshold for inducing transcallosal inhibitory effects is also considerably higher than for inducing intracortical inhibition with the coil placed over the motor cortex (Ferbert et al., 1992; Kujirai et al., 1993). Hence, the effect size of a lesion effect should be stronger and the threshold for inducing a lesion effect should be lower with ipsilateral than contralateral TMS using the same stimulation intensity. This was not the case in the present study. The threshold as well as the magnitude of the disruptive effect on phonological decisions was comparable with TMS to both hemispheres as supported by our follow up experiment.

Our results significantly extend current neurobiological concepts of the human language system by showing that language processing involves more than a left-hemisphere specialization. This may have implications for the interpretation of functional imaging studies showing right IFG language-related activation in aphasic patients with left-hemisphere damage (Raboyeau et al., 2008; Saur et al., 2006; Winhuisen et al., 2005; Winhuisen et al., 2007). While recent studies indicate that the (temporary) recruitment of homologue areas in the right hemisphere after left-hemisphere stroke may be adaptive, longer term language improvement is associated with left-hemisphere language function (Saur et al., 2006; Thiel et al., 2006a; Winhuisen et al., 2005). For example, Winhuisen et al (2007) argue that restoration of the left-hemisphere network seems to be more effective for recovery after stroke, but in some cases, right-hemisphere areas are integrated successfully. Likewise, Dewarrat et al. (2009) showed that word comprehension and repetition were impaired after right-hemisphere damage but less frequently than after left-hemisphere damage. Our TMS results contribute by showing that the involvement of right-

hemisphere language areas is not limited to recovery after stroke but is also essential for phonological processing in healthy subjects.

In contrast to the evidence showing that the right frontal cortex contributes to phonological processing, other studies have shown improved language recovery in aphasic patients following suppression of neuronal processing in the non-lesioned right IFG with transcranial stimulation techniques (Andoh and Martinot, 2008; Martin et al., 2009; Naeser et al., 2005a; Naeser et al., 2005b): The behavioral improvement after suppression of neuronal processing in the non-lesioned right IFG has been interpreted as a suppression of maladaptive "over-activation" in the right hemisphere which in turn may have allowed for a better modulation in the remaining left-hemisphere networks (Naeser et al., 2005a). It should be noted, however, that the experimental design of this study was different from ours. Specifically, we applied TMS online (i.e. during task performance), leaving the language system no time to develop adaptive plasticity. In contrast, the above cited studies of stroke patients used a different TMS protocol, where TMS was applied offline (i.e. before the task). Further, while we contrasted phonological with semantic judgements, the above cited studies used picture naming and solely targeted the anterior part of the IFG which is associated with semantic rather than phonological processing (e.g. Devlin, Matthews and Rushworth, 2003; Fiez, 1997; Gitelman et al., 2005; Gough, Nobre and Devlin, 2005; Poldrack et al., 1999). Together, the current set of results motivates future investigation of the functional relevance of the right pIFG over the course of recovery from left-hemisphere stroke. For example, the right pIFG may be more functionally relevant in the acute phase after stroke than in the chronic phase when reorganisation of the language networks has occurred (Saur et al., 2006).

In a recent study, Raboyeau et al. (2008) investigated the involvement of the right inferior frontal cortex in recovery after left-hemisphere stroke. Using positron emission tomography (PET), the authors found increased activation of the right inferior frontal gyrus in both aphasic patients and healthy subjects during word retrieval following difficult re-learning. Based on this finding, it was concluded that right inferior frontal activations were not a mere consequence of left-hemisphere lesions as they existed in patients as well as healthy subjects who had to work out the phonetic / phonologic forms of once learned but forgotten foreign words. Accordingly, right inferior frontal activation was related to lexical retrieval following re-learning. In their study, right IFG activity increased with performance improvement in aphasic patients. Although this seems to contradict studies suggesting that right-hemisphere activation in chronic aphasics could be deleterious for language recovery when left frontal gyrus is not totally damaged (e.g. Buckner et al., 1996; Naeser et al., 2005b; Rosen et al., 2000), Raboyeau et al. (2008) argue that most studies only investigated chronic word retrieval deficit processing which is different to the dynamic lexical learning processes examined in their study. Our results are in good agreement with the findings by Raboyeau et al. (2008) since we also show the contribution of a right inferior frontal region to phonological processing in healthy subjects. Although our syllable judgements are less difficult than the task used by Raboyeau et al. (2008), both require phonological working memory processes. As emphasized by Seghier et al. (2001), further investigations on aphasic patients with right-hemisphere lesions are necessary to understand the large literature on aphasic patients with left-hemisphere damage.

In conclusion, our findings extend current concepts by showing that both, the right and left pIFG, are critical nodes within the neural network implicated in phonological processing. Our study highlights the importance of the right posterior inferior frontal gyrus during phonological

decisions in healthy right-handed subjects independent of the modality that the words are presented in. Future studies are now required to systematically investigate the effect of right inferior frontal damage on the efficiency of phonological decisions in patients. According to our results, we would predict that these patients have some degree of phonological processing impairment, irrespective of whether words are presented in the auditory or visual modality.

Acknowledgments

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Table 1. Reaction times and error rates for the different tasks in both groups

	Auditory word stimuli		**Visual word stimuli**	
	RT±SEM(ms)	ER±SEM(%)	RT±SEM(ms)	ER±SEM(%)
Group receiving TMS over the pIFG (n=14)				
Task: Phonological word judgement				
TMS to left pIFG	1157±57.51	0.12±0.04	792±53.03	0.09±0.02
TMS to right pIFG	1166±56.78	0.12±0.04	792±58.98	0.10±0.02
Bilateral TMS of pIFG	1176±59.07	0.12±0.04	802±57.34	0.07±0.02
Task: Semantic word judgement				
TMS to left pIFG	978±41.25	0.08±0.03	712±38.62	0.03±0.01
TMS to right pIFG	977±33.78	0.06±0.03	714±32.50	0.04±0.01
Bilateral TMS of pIFG	970±39.26	0.07±0.04	723±33.15	0.03±0.01
Group receiving TMS over the aIFG (n=14)				
Task: Phonological word judgement				
TMS to left aIFG	1031±37.13	0.02±0.01	676±15.78	0.07±0.02
TMS to right aIFG	1029±45.17	0.02±0.01	665±18.22	0.06±0.02
Bilateral TMS of aIFG	1029±43.54	0.04±0.01	688±21.70	0.05±0.02
Task: Semantic word judgement				
TMS to left aIFG	1013±28.30	0.04±0.01	687±10.72	0.06±0.03
TMS to right aIFG	1016±28.97	0.06±0.02	690±13.12	0.05±0.02
Bilateral TMS of aIFG	1017±32.82	0.04±0.01	710±15.44	0.05±0.02

ER= Error rates; RT= Reaction times; SEM= standard error of the mean (in milliseconds or percent of all trials)

Figure Legends

Figure 1

Experimental design. A,B. Stimulation sites over the left, right and bilateral pIFG and aIFG; respectively. Mean MNI-coordinates were obtained from previous studies (Devlin, Matthews and Rushworth, 2003; Gitelman et al., 2005; Gough, Nobre and Devlin, 2005; McDermott et al., 2003). ant=anterior, post=posterior, l=left, r=right. C. Auditory and visual run of the two blocked tasks. D. Single trial: Each trial had a duration of 3000 milliseconds. A 4-pulse train of 10 Hz online TMS was applied 100 milliseconds after word onset over left, right or bilateral aIFG or pIFG. Subjects responded with their left index or middle finger. ms=milliseconds; min=minutes.

Figure 2

Mean reaction times (RT) for the phonological and semantic task in the aIFG and pIFG group. For illustrating purposes, responses for auditorily and visually presented stimuli are displayed in different panels. The significant two-way interaction between task and group is displayed in all panels. Note that the three different TMS sites (left, right, bilateral) are shown separately in panel A and B for illustrating purposes although the two-way interaction was pooled across the factors TMS site and modality. Error bars represent onefold standard error from the mean (SEM); *$p<0.05$; two-tailed; ms=milliseconds.

Figure 3

Mean error rates (ER) for the phonological and semantic task in the aIFG and pIFG group. Error bars represent onefold standard error from the mean (SEM); *$p<0.05$; two-tailed; (*) did not survive the Bonferroni-Holm correction; ((*)) $p<0.10$ (trend).

Figure 4

Mean reaction times (RT; panel A,B) and error rates (ER; panel C,D) for the phonological task in the follow up experiment (TMS at different intensities over the left and right pIFG). In panel A and B, the main effect of intensity on RT is displayed. Note that the two different TMS sites (left and right pIFG) and the two modalities (auditory and visual) are displayed here separately for illustrating purposes although the main effect was pooled across the factor TMS site and modality. For ER, no significant differences were found between the different conditions. Error bars represent onefold standard error from the mean (SEM); *$p<0.05$; two-tailed; AMT= active motor threshold.

Supplementary Data

Task performance without TMS

The results from the control group (n=7 receiving only sham TMS) were analyzed to test whether the two different tasks yielded comparable results with respect to reaction times (RT) and error rates (ER) without the influence of real TMS. Analyses on RT and ER in the control group revealed no significant differences between the phonological and semantic task (see suppl. Fig.1). Repeated measures ANOVA on RT showed significantly prolonged RT for auditorily than visually presented words ($F_{1,6}$=116.26; p=0.0001).

There were no significant differences in ER between the different (sham) TMS sites or the two modalities.

Supplementary Fig.1

Mean reaction times (RT) are and error rates (ER) for the two different tasks in the sham TMS group. In panel A and B, RT are displayed. ER are shown in Panel C and D. For illustrating purposes, responses for auditorily and visually presented words and the different sham TMS sites (left, right, bilateral) are displayed in different panels. Neither RT nor ER were significantly different between the phonological and the semantic task. Error bars represent onefold standard error from the mean (SEM); ms=milliseconds.

Figure 1

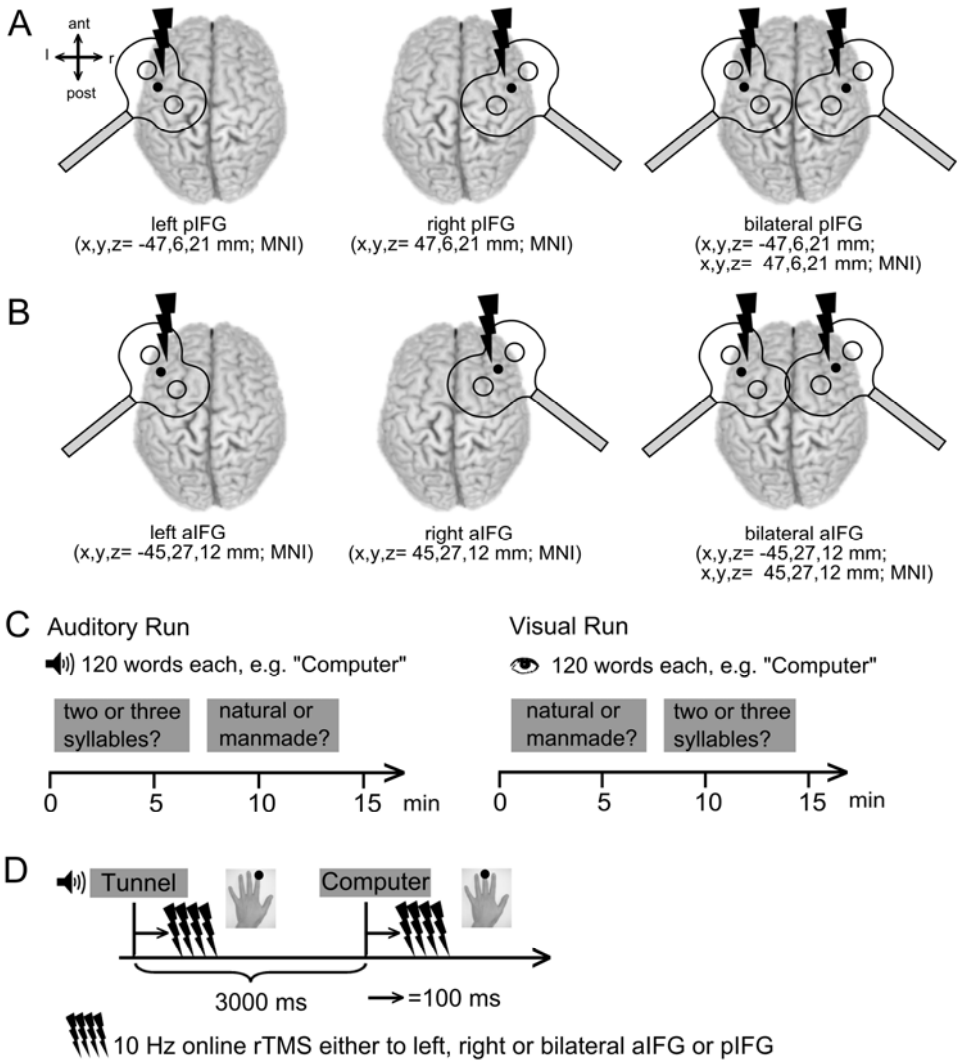

A
ant
l
r
post
left pIFG
(x,y,z= -47,6,21 mm; MNI)
right pIFG
(x,y,z= 47,6,21 mm; MNI)
bilateral pIFG
(x,y,z= -47,6,21 mm;
x,y,z= 47,6,21 mm; MNI)
B
left aIFG
(x,y,z= -45,27,12 mm; MNI)
right aIFG
(x,y,z= 45,27,12 mm; MNI)
bilateral aIFG
(x,y,z= -45,27,12 mm;
x,y,z= 45,27,12 mm; MNI)
C
Auditory Run
120 words each, e.g. "Computer"
two or three syllables?
natural or manmade?
0
5
10
15
min
Visual Run
120 words each, e.g. "Computer"
natural or manmade?
two or three syllables?
0
5
10
15
min
D
Tunnel
Computer
3000 ms
=100 ms
10 Hz online rTMS either to left, right or bilateral aIFG or pIFG

Figure 2

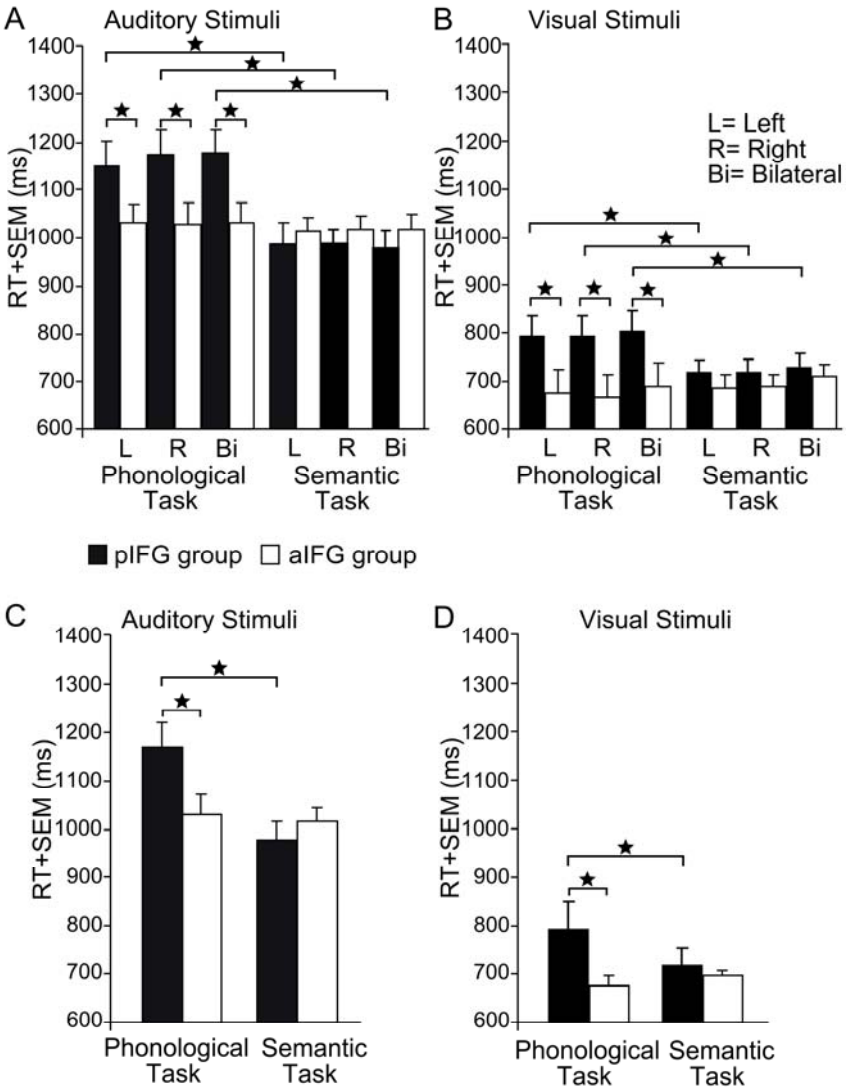

A
Auditory Stimuli
B
Visual Stimuli
RT+SEM (ms)
1400
1300
1200
1100
1000
900
800
700
600
L R Bi L R Bi
Phonological Task
Semantic Task
L= Left
R= Right
Bi= Bilateral
pIFG group
aIFG group
C
Auditory Stimuli
D
Visual Stimuli
Phonological Task
Semantic Task

Figure 3

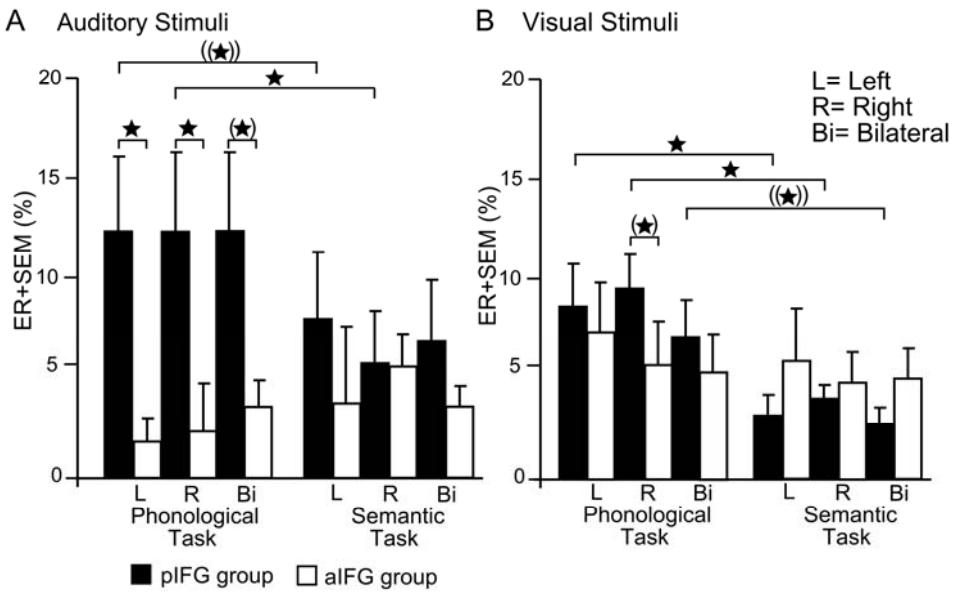
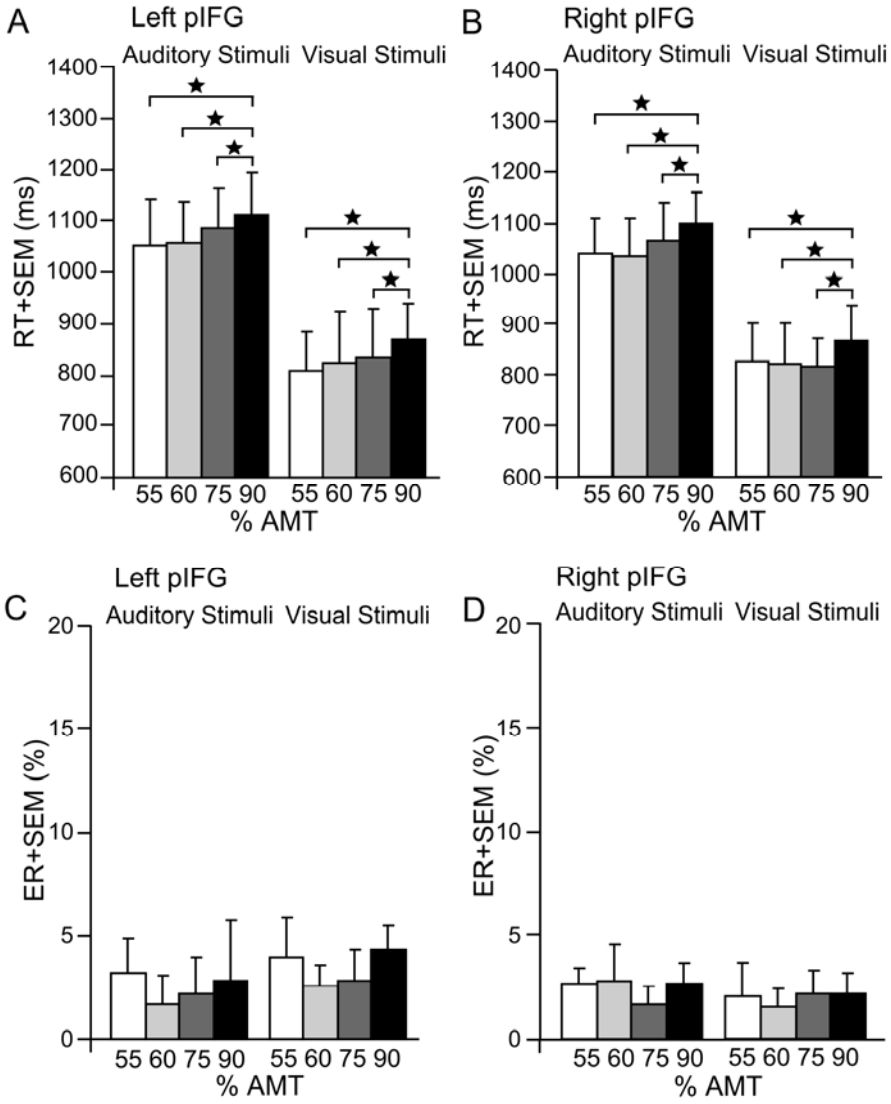
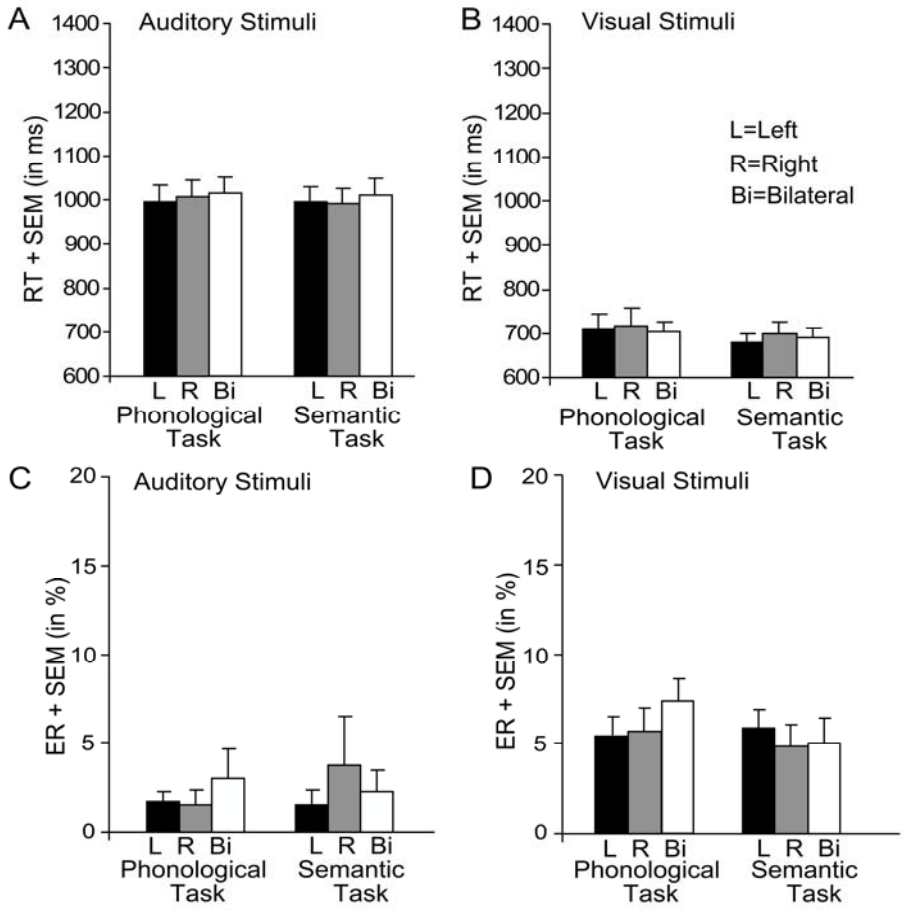

A Auditory Stimuli
B Visual Stimuli
L= Left
R= Right
Bi= Bilateral
ER+SEM (%)
20
15
10
5
0
L R Bi L R Bi
Phonological Task
Semantic Task
pIFG group
aIFG group

Figure 4


A
Left pIFG
Auditory Stimuli Visual Stimuli
RT+SEM (ms)
1400
1300
1200
1100
1000
900
800
700
600
55 60 75 90 55 60 75 90
% AMT
B
Right pIFG
Auditory Stimuli Visual Stimuli
RT+SEM (ms)
55 60 75 90 55 60 75 90
% AMT
C
Left pIFG
Auditory Stimuli Visual Stimuli
ER+SEM (%)
20
15
10
5
0
55 60 75 90 55 60 75 90
% AMT
D
Right pIFG
Auditory Stimuli Visual Stimuli
ER+SEM (%)
55 60 75 90 55 60 75 90
% AMT

Supplementary Figure 1



Appendix VII

A frontal network for pseudoword repetition

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Key words: functional magnetic resonance imaging, word, phonology, psychophysiological interaction, language production

Number of text pages: 21 Figures: 6 Tables: 2

Word count manuscript: Abstract: 237 words Introduction: 697 words Discussion: 2202 words

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Abstract

Previous functional imaging studies have demonstrated activation of the bilateral (pre-) supplementary motor area (SMA) and pars opercularis (POp) of the left inferior frontal gyrus during the repetition of auditorily or visually presented pseudowords. However, most of the studies focused on the unimodal processing of either visual or auditory stimuli. Here, we investigated the modality-independent contribution of the bilateral pre-SMA and left POp to the overt repetition of pseudowords using event-related functional magnetic resonance imaging (fMRI). We expected that overt pseudoword repetition of auditorily as well as visually presented stimuli would activate a network of brain regions involved in articulatory planning and articulation. The comparison of overt pseudoword with word repetition revealed a modality-independent contribution of both the right pre-SMA and left POp to language production. During pseudoword in contrast to word repetition, both areas showed increased functional coupling with the left ventral premotor cortex (PMv) as revealed by several connectivity analyses (i.e. psychophysiological interactions). Our results demonstrate for the first time the modality-independent contribution of both the right pre-SMA and left POp to the overt repetition of pseudowords. The increased functional coupling between both areas and the left PMv supports the notion that these areas represent core regions for phonological encoding, articulatory planning and articulation of pseudoword repetition. Accordingly, we suggest a frontal network engaged in the repetition of auditorily as well as visually presented pseudowords, encompassing the right pre-SMA, left POp and the left PMv.

Introduction

Recent functional-anatomic models of language processing proposed that the repetition of (auditorily) presented pseudowords (i.e. pronounceable nonwords) activates a left hemispheric network which maps auditory input onto motor-articulatory representations (e.g. Hickok and Poeppel, 2000, 2004, 2007). Contrasting pseudoword with real word production isolates sublexical phonological aspects without accessing semantics (Graves et al., 2008) and thus allows for the identification of phonological aspects of language production.

A meta-analysis by Indefrey and Levelt (2004) aimed to identify the "core" areas of language production. Those regions included the bilateral (pre-) supplementary area, the left posterior inferior frontal gyrus, the left insula, the left precentral cortex and additional temporal and subcortical areas.

The contribution of the (pre-) supplementary motor area (SMA) to language production has been described in fMRI investigations on both healthy subjects and patients with lesions (e.g. Alm, 2004; Burton et al., 2001; Kotz et al., 2009; Petersen et al., 1988; Wise et al., 1991; Ziegler et al., 1997). SMA activation was found for the repetition of auditorily (e.g. Papoutsi et al., 2009; Rauschecker et al., 2008) as well as visually (Fiez et al., 1999; Peeva et al., 2009) presented pseudowords or phonemes. It was suggested that the (bilateral) SMA is important for articulatory planning and initiation during (pseudo-) word production (e.g. Indefrey and Levelt, 2004; Shuster and Lemieux, 2005; Soros et al., 2006).

A variety of studies also demonstrated that pars opercularis (POp) of the left inferior frontal gyrus is engaged in pseudoword in contrast to word reading (Brunswick et al., 1999; Fiebach et al., 2002; Hagoort et al., 1999; Mechelli et al., 2003; Paulesu et al., 2000). Some studies found activation in left POp during the overt or covert repetition of auditorily presented pseudowords (Rauschecker et al., 2008; Saur et al., 2008). During overt repetition, left POp is

involved in different linguistic processes such as phonological aspects of (pseudo-) word production and articulatory planning (e.g. Burton et al., 2001; Fiez and Petersen, 1998).
By directly contrasting the overt repetition of auditorily presented pseudowords with real words, a recent study by Saur et al. (2008) delineated a network of areas involved in auditory-to-motor mapping. This left-hemispheric network encompassed POp, the SMA and the premotor cortex.

However, none of the above cited studies used comparisons of auditorily as well as visually presented pseudowords and words to identify modality-independent networks on the same set of stimuli or the same task. Therefore, it remains unclear if the areas activated during pseudoword repetition depend on the modality used for stimulus presentation.
While some studies used covert language production paradigms as a substitute to overt language paradigms (e.g. Lurito et al., 2000; Rauschecker et al., 2008; Wildgruber et al., 2001) to avoid motion induced artefacts from overt articulation, these results may not be comparable to those of studies using overt articulation. It has been argued that the overt versus covert repetition of pseudowords may not reveal the same patterns of BOLD responses in the core language areas (Shuster and Lemieux, 2005). For instance, left inferior frontal activation is not typically observed in silent reading (Salmelin, 2007).

Here we aimed to delineate modality-independent areas for overt pseudoword compared to word repetition. We thus used an event-related fMRI design which allowed us to compare the effects of auditorily and visually presented pseudowords and words. Based on previous studies (e.g. Ghosh et al., 2008; Indefrey and Levelt, 2004; Saur et al., 2008) we hypothesized that the modality-independent network would encompass the bilateral SMA and left POp.

In order to make inferences about changes in functional coupling between areas we tested for any regions showing higher coupling with the bilateral SMA or left POp during pseudoword compared to word repetition. We thus computed several psychophysiological interactions (Friston et al., 1997; Gitelman et al., 2003; Lee et al., 2003). Thereby we aimed to delineate areas showing task-related activity increases with activity in the SMA or POp during pseudoword in contrast to word repetition. According to the results of previous studies on language production (e.g. Indefrey and Levelt, 2004) we expected to find increased connectivity between our two seed regions and areas in the network for motor preparation and articulation during pseudoword repetition, including the left premotor cortex.

Methods and Materials

Participants

17 right-handed native German speakers (10 females age 21-30 years, mean 23.8 $\pm$ 2.2) with no history of neurological disorders or head injury participated in the experiment. Written informed consent was obtained before the experiment. Handedness was tested with the German version of the Edinburgh Handedness Inventory (Oldfield, 1971). All subjects had normal or corrected-to-normal visual acuity. The study was performed according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Medical Faculty of the University of Kiel.

Experimental design & tasks

The study used a two (task: repetition of pseudowords vs. words) by two (modality: auditory vs. visual stimuli) event-related within-subject factorial design (Fig.1). This resulted in four event types: auditory words (AW), visual words (VW) auditory pseudowords (APW) and

visual pseudowords (VPW). The same 60 stimuli (30 pseudowords and words each) were presented auditorily and visually, in order to minimize stimulus-induced differences in the planned comparisons between modalities (Devlin et al., 2003).

Experimental stimuli were divided into two runs with ten blocks each (Fig.1A), resulting in five blocks for each of the four conditions. Each run started and ended with a rest block. Block duration was set to 36 s and blocks were separated by 16 s rest leading to a total duration of approximately 9 minutes per run. Stimulus type (i.e. pseudowords or words) and modality (i.e. auditory or visual stimulus presentation) were held constant during each block. Each block contained six pseudowords or words which were separated by a randomly assigned stimulus onset asynchrony of between 4 and 8 s. After stimulus presentation a fixation cross appeared which remained on the screen during the whole block for auditory stimulus presentation. The duration of stimulus presentation for visually presented words and pseudowords was matched to the mean duration of auditory stimuli (see stimuli).

During rest blocks, a fixation cross was presented. At the end of each rest period, a visual cue indicated the following block. Cues consisted of a symbol of either an eye or a loudspeaker in a red or blue box. Blue boxes indicated that the next block would contain pseudowords; red boxes indicated real word presentation. The onset of the cue was jittered such that it appeared 9.5-12.5 s after block onset and remained on the screen for 2.5s. The order of runs, blocks and trials was randomized across subjects.

Before scanning, subjects had a training session outside the scanner during which both tasks were practiced and all experimental stimuli were presented to reduce the novelty of the pseudoword relative to the word stimuli. The experiment started with a written instruction to repeat the written or spoken stimulus as soon as it was finished (auditory stimuli) or vanished from the screen (visual stimuli). Before scanning, subjects were trained to move their head as

little as possible when repeating the stimuli and the head was fixated in the head coil using foam cushions.

After scanning, subjects quickly indicated on a questionnaire which of the pseudowords used in the experiment had been familiar to them or had reminded them of an existing word. This allowed us to model the pseudowords associated with existing words as a separate regressor and thus assured that the pseudowords included did not have any associated meaning.

Stimuli

30 two-syllable German nouns representing concrete items were used for stimulus presentation. Only highly frequent, unambiguous nouns from the CELEX lexical database for German (Centre for Lexical Information, Max Planck Institute for Psycholinguistics, The Netherlands) were selected. No compound nouns, hypernyms or foreign words were included. Auditory versions of the words were recorded by a professional female speaker and had an average duration of 0.85 s. Pseudowords were constructed by dividing the syllables of the real words and rearranging them to meaningless nonwords that were matched for bigram frequency and stimulus duration according to Dollaghan and Campbell (1998).

Stimulus presentation and response collection

Auditory stimuli were presented, recorded and processed via MR-compatible dual channel headphones and OPTI MRI software 2.0 (MR Confon, Magdeburg, Germany). Sound volume was individually adjusted for each subject. The headphones allowed the subjects to hear their own voice during language production. Visual stimuli appeared in black on a grey screen on a head-mounted display. Visual stimulus duration was adjusted to the mean duration of the auditory word stimuli. Presentation of stimuli and task sequence were controlled using E-PRIME (Psychology Software Tools Inc., Pittsburgh, PA, USA; version 1.1) implemented in

IFIS-SA system software (http://www.invivocorp.com/fmri/ifis.php; version 1.1). Throughout scanning subjects kept their eyes open.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) was performed on a Philips 3-Tesla scanner (Philips, Best, The Netherlands) to acquire both *T*1-weighted anatomical images (MPRage sequence in sagittal orientation; slice thickness 1 mm; in plane resolution 1 x 1 mm; TR / TE = 8.25 /3.78 ms) and *T*2*-weighted MRI transverse echo-planar images (EPI) (TR / TE = 2500 / 35 ms, flip angle 90°, matrix: 64 x 64, voxel size: 3.38 x 3.38 x 3 mm) with blood oxygenation level dependent (BOLD) contrast. A total of 214 volumes consisting of 38 slices were acquired continuously during each run.

Statistical analyses

fMRI data

Task related changes in the BOLD signal were analysed using Statistical Parametric Mapping (SPM5, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab 7.7 (The Mathworks Inc., Natick, MA, USA) (Friston, Ashburner et al., 1995; Worsley and Friston, 1995). During preprocessing, all functional EPI images were corrected for different acquisition times of signals by shifting the signal measured in each slice relative to the acquisition of the middle slice. All volumes were then realigned and unwarped to account for motion-induced artefacts (Andersson et al., 2001). The individual T1-weighted image was segmented using the standard tissue probability maps provided in SPM5 with a medium bias regularisation, and coregistered to the mean functional EPI image (Crinion 2007). The resulting segmentation information was used for a second segmentation of the individual T1 image without any bias regularisation. Afterwards, the resulting image

was normalized and re-sampled to 1x1x1 mm voxels. The functional EPI images were then normalised to this T1 image and re-sampled to 3 x 3 x 3 mm voxels. Finally, all normalised images were smoothed with an isotropic 8 mm full-width half-maximum Gaussian kernel to account for inter-subject anatomical differences and allow valid statistical inference according to Gaussian random field theory (Friston, Holmes et al., 1995).

Statistical analyses of the functional images were performed in two steps. At the first level, the two runs were modelled separately each consisting of at least five regressors including the four different experimental conditions (i.e. AW, VW, APW and VPW) and a regressor modelling the onset of the instruction events. A regressor for uncorrectly repeated stimuli was included if appropriate. Pseudowords judged as real words were also modelled as a different regressor. All of the onsets in each regressor were convolved with a canonical hemodynamic response function as implemented in SPM5. To assure that the regressors were sampled in the middle point, microtime resolution was specified equal to the number of slices (i.e. 38) and microtime onset was specified equal to the reference slice (i.e. 19). Voxel-wise regression coefficients for all conditions were estimated using the least squares method within SPM5, and statistical parametric maps of the t statistic (SPM{t}) were generated from each condition. At this step we computed the contrast of each of the conditions against rest, resulting in four separate contrast images for each subject.

The data for the second stage of analysis comprised pooled parameter estimates for each of these contrasts across all subjects and both runs in a random effects analysis using a flexible factorial within-subject ANOVA design including a correction for non-sphericity. The specification of task (pseudoword vs. word repetition) and modality (auditory vs. visual stimulus presentation) resulted in a 2x2 condition matrix for each subject. Within the ANOVA model, the main effect of subject and the interaction between task and modality were specified. T-contrasts were computed for the main effect of each condition, the

differential effects of task and modality and the interaction between task and modality. To delineate task-related increases in brain activity during the repetition of pseudowords and words, we computed modality-independent conjunction analyses of all trials compared to rest for both conditions, respectively, using the conservative conjunction-null-conjunction (Nichols et al., 2005). A conservative conjunction was also computed to test for the modality-independent effect of the differential contrasts 'pseudoword vs. word repetition' across auditory and visual stimuli.

The height threshold for the resulting SPM{t}s was set at $p< 0.001$ uncorrected for multiple comparisons across whole brain and the cluster extent was set to 10 voxels. To ensure that the obtained activations did not result from deactivation in the respective comparison condition, we inclusively masked all differential contrasts with the appropriate main effect (following Cohen et al., 2004). Our a-priori regions of interest (ROI) were left POp and the bilateral pre-SMA because previous studies have shown that these areas are critically involved in overt pseudoword in contrast to word repetition (e.g. Ghosh et al., 2008; Indefrey and Levelt, 2004; Saur et al., 2008).

ROIs were defined as spheres of 12 and 15 mm radius, respectively, centered on (i) left POp (x= -45, y= 9, z= 24) and (ii) the left pre-SMA (x= -6, y= 6, z= 57) as described by Saur et al. (2008). Within these ROIs, a small volume correction was applied using the family-wise error correction (FWE) and a $p< 0.05$.

Psychophysiological interactions (PPIs)

In order to make inferences about changes in 'functional coupling' between areas, we tested for any regions showing higher coupling with the peak activation in the unimodal comparisons of pseudowords relative to words as revealed by our second level analyses.

To do so, we used the well-established 'psychophysiological interaction' or PPI approach, a data-driven analysis that makes minimal assumptions (Friston et al., 1997; Lee et al., 2003). We thus computed four PPI analyses, one for each region of interest in each modality (i.e. auditory vs. visual stimulus presentation) for pseudowords in contrast to words (i.e. pseudowords > words). The PPI analyses were first carried out at the single subject level. First, we created masks for the bilateral SMA and left POp with the aid of the Anatomy toolbox (version 1.6. Eickhoff et al., 2005) and the WFU PickAtlas Tool (version 2.4.; Wake Forest University of School of Medicine). We then identified the peak voxel in each subject for the contrasts 'APW>AW' and 'VPW>VW' at a liberal threshold of $p< 0.01$ uncorrected within the corresponding masks of the bilateral SMA and left POp. Subject specific ROIs within the corresponding mask were created for each run, and the first eigenvariate of the fMRI signal during the trials of interest was extracted.

We then tested whether regional co-variation of task-related signal between the area of peak activation in the group and other brain regions was modulated by the task (i.e. pseudoword vs. word repetition). The data for the second stage of the PPI analyses comprised the pooled parameter estimates for each single subject PPI from both runs. Contrast images for each subject were entered into a one sample t-test.

Our a-priori region of interest was the left premotor cortex (PM; x= -48, y= 0, z= 36) as described by Saur et al. (2008). A ROI comprising of a 12 mm sphere was centered on these MNI coordinates. The height threshold for the resulting SPM{t}s was set at $p< 0.001$ uncorrected for multiple comparisons across whole brain. Only clusters with a size > 4 contiguous voxels are reported. A small volume correction was applied within the ROI of our a-priori region using the family-wise error correction (FWE) and a $p< 0.05$.

Anatomical identification was carefully performed by superimposing the maxima of activation foci both on the mean normalized structural images of the group and of the individual T1 of each subject. The SPM anatomy toolbox (version 1.6; Eickhoff et al., 2005) and the WFU PickAtlas Tool (version 2.4. Wake Forest University of School of Medicine) were used for anatomical localization of activation peaks which are reported as Tailairach coordinates in standardized MNI space.

Results

Behavioural data

A two-way repeated-measures ANOVA on reaction times using the factors task (pseudoword vs. word repetition) and modality (auditory vs. visual stimulus presentation) revealed no significant main effects or interactions between the different conditions (all $p > 0.25$). Mean reaction times were 920 ms and 895 ms (range: 889 - 952 ms; 887 - 902 ms), for auditorily and visually presented pseudowords, respectively, and 897 ms and 887ms (range: 882 - 901; 878 - 891) for auditorily and visually presented words, respectively. Subjects were overall very accurate and errors or omissions were negligible (< 0.02% per subject).

Imaging data

Despite the use of overt stimulus repetition during fMRI, head motion was negligible and could be corrected for.

Main effects of task

The repetition of both pseudowords and words engaged a widespread bilateral network of pre- and postcentral regions previously associated with language production (e.g. Bohland and

Guenther, 2006; Indefrey and Levelt, 2004; Peeva et al., 2009; Price, 2000) including our regions of interest in the premotor cortex, the bilateral supplementary motor area, and inferior frontal gyrus (Fig.2). The maximum of peak activation was found in the left postcentral gyrus for both pseudoword and word repetition. While pseudowords and words activated the same regions, the network for pseudoword repetition was more widespread.

Brain regions involved in pseudoword compared to word repetition

The unimodal comparison of pseudoword vs. word repetition on auditorily presented stimuli revealed strong activation in the bilateral SMA with a peak in the right pre-SMA ($p= 0.038$ corrected for multiple comparisons in the SMA ROI; Fig.3A; Tab.1). Lowering the threshold to $p< 0.01$ uncorrected revealed additional activation in the left pallidum and a strong trend for activation in left POp of the inferior frontal gyrus ($p= 0.051$ corrected for multiple comparisons in the POp ROI). In contrast, repetition of visually presented pseudowords relative to words activated a large network of areas associated with phonological processing (Fig.3B; Tab.1), with a peak in POp of the left inferior frontal gyrus ($p= 0.002$ corrected for multiple comparisons in the POp ROI) and in the right pre-SMA ($p= 0.005$ corrected for multiple comparisons in the SMA ROI). Strong activation was also found in pars triangularis of the right hemisphere, in the left and right inferior parietal cortices, the left insula and the right cuneus.

Finally, the modality-independent conjunction of areas involved in both auditory and visual pseudoword repetition relative to word repetition revealed a peak in the right pre-SMA ($p= 0.039$ corrected for multiple comparisons in the SMA ROI; Fig.3C; Tab.1). Reducing the threshold to $p< 0.01$ uncorrected revealed additional activation in the left pallidum and a strong trend for activation in left POp ($p= 0.052$ corrected for multiple comparisons in the POp ROI).

We found a significant interaction between task and modality: Visually presented pseudowords resulted in relatively stronger activation of pars triangularis in the right hemisphere (x= 51, y=27, z= 24; T= 3.96; p< 0.001) and pars opercularis (POp) in the left hemisphere (x= -54, y= 12, z=21; T= 3.73; p< 0.001).

The comparison of brain regions more activated for words in contrast to pseudowords did not reveal any significant activation clusters.

Investigations on functional connectivity

Several PPI analyses were used to delineate areas showing increased task-related coupling with the right pre-SMA and left POp during pseudoword in contrast to word repetition.

Areas showing increased functional coupling with the right pre-SMA

The seed area in the right pre-SMA for the first PPI analysis was derived from the second-level comparison of auditorily presented pseudowords > auditorily presented words. Increased functional coupling was found between the right pre-SMA and the right Rolandic operculum (Fig.4A; Tab.2). The right pre-SMA showed also increased functional coupling with left POp during the repetition of auditorily presented pseudowords compared to words. Reducing the threshold to p< 0.01 uncorrected revealed a strong activation trend of the left premotor cortex (p= 0.051 corrected for multiple comparisons in the left PM ROI; Tab.2).

For the next PPI, the unimodal peak from the comparison visual pseudowords > visual words in the right pre-SMA was used. The right pre-SMA showed increased connectivity during the repetition of visually presented pseudowords relative to words with the left premotor cortex (p= 0.007 corrected for multiple comparisons in the left PM ROI; Fig. 4B; Tab.2).

Areas showing increased functional coupling with left POp

The seed area from the comparison of auditory pseudowords > auditory words in left POp showed increased functional coupling for the repetition of auditorily presented pseudowords relative to words with the left premotor cortex (p= 0.049 corrected for multiple comparisons in the left PM ROI; Fig.5A; Tab.2). Increased functional connectivity was also found between left POp (i.e. the seed area from the comparison of visually presented pseudowords > visually presented words) and the left premotor cortex (p= 0.01 corrected for multiple comparisons in the left PM ROI; Fig.5B; Tab.2).

Discussion

To investigate cortical networks required for language production, the use of overt articulation tasks is mandatory. Previous studies have used either visually or auditorily presented stimuli, however, the investigation of both modalities using an identical set of stimuli has not been reported to date. In this study, we demonstrate for the first time the modality-independent contribution of both left POp and the right pre-SMA to the overt repetition of pseudowords in contrast to words.

Both areas were consistently activated for unimodal and modality-independent comparisons of pseudowords vs. words. These results support a variety of previous studies suggesting a role of both areas in (unimodal phonological aspects of) language production (e.g. Ghosh et al., 2008; Indefrey and Levelt, 2004).

The stronger activation of both areas for pseudoword relative to word repetition is consistent with the notion of an increased processing demand for the production of unfamiliar stimuli (Mechelli et al., 2003; Papoutsi et al., 2009; Price et al., 1996; Wise et al., 1999). In a recent study, Papoutsi et al. (2009) identified a network of areas showing increased activity during the repetition of auditorily presented low-frequency compared to high-frequency pseudowords. This network encompassed the bilateral pre-SMA with a left-hemispheric peak and bilateral POp. The authors attributed the increased activity in the pre-SMA to the increased load associated with the production of new and unfamiliar motor plans (i.e. low-frequency pseudowords) in contrast to familiar or more rehearsed ones (i.e. high-frequency pseudowords). Pre-SMA activation for an increased sequencing load during the overt production of bisyllables compared with monosyllables has also been demonstrated by Ghosh et al. (2008). In a study by Bohland and Guenther (2006), the pre-SMA was sensitive to sequence complexity effects during syllable repetition of visual stimuli with varying complexity. Accordingly, the right pre-SMA was also activated during the repetition of low-

frequency stimuli (i.e. pseudowords) in contrast to high-frequency stimuli (i.e. real words) in our study. Our pseudowords consisted of familiar and frequent syllables merged from existing words. Therefore, the production of pseudowords can be considered as the sequencing of known motor-programs (Alario et al., 2006).

It has been argued that POp is specialized for the regulation of sequential activity in several different effector domains beyond those involved in language processing (e.g. Fuster, 1995; Lieberman, 1991; Passingham, 1981). Moreover, POp is particularly responsive to the perception and reproduction of rapid temporal patterns (Fiez et al., 1995; Platel et al., 1997; Schubotz et al., 2000). According to Schubotz and von Cramon (2001), this suggests that POp is the anatomical correlate for linguistic and timing functions, which is well supported by the results of Tallal et al. (1993) proposing that rapid temporal integration is the core function of linguistic processing.

Our results confirm and extent previous studies (e.g. Bohland and Guenther, 2006; Ghosh et al., 2008; Papoutsi et al., 2009) by showing that the activation of the right pre-SMA and left POp during the repetition of pseudowords is independent of the modality used for stimulus presentation.

Unimodal vs. modality-independent differences in pseudoword compared to word repetition

Since the core aspects of pseudoword repetition should be modality-independent, we expected to find the same regions independent of the modality used for stimulus presentation. In fact, both the right pre-SMA and left POp were activated during the repetition of auditorily as well as visually presented pseudowords in contrast to words.

The consistent activation of the right pre-SMA for both modalities corresponds with the results of Alario et al. (2006). In that study, the bilateral pre-SMA was activated during the conjunction of pseudoword reading and repetition relative to rest. However, the authors did

not find significant activation increases for the modality-independent comparison of pseudoword relative to word repetition.

Although phonological processing is supposed to play a role in both spoken and written language, it is not yet clear to what extent phonological processes used in speech, such as segmentation, rely on the same neural substrate as those in print, such as orthographic-to-phonological conversion (Burton et al., 2001). As outlined in the introduction, only few studies (e.g. Alario et al., 2006) used overt repetition tasks of auditorily and visually presented pseudowords relative to words within the same subjects to date and none of them reported areas consistently activated for both modalities.

With our data, visually presented pseudowords activated a widespread network of areas with a peak in left POp being relatively stronger for visually than for auditorily presented pseudowords as supported by a significant interaction between task and modality. The strong activation for visually presented pseudowords presumably resulted from the fact that visually presented stimuli have to be transformed to auditory output. Since the present experiment was not designed to separate aspects of pseudoword perception from that of production, it is likely that the increased activation during visually presented stimuli resulted from orthographic-to-phonological conversion processes from word to sound (Burton, 2001; Fiez and Petersen, 1998).

The role of the pre-SMA in language production

With our data, we found increased activity for pseudoword relative to word repetition in the right pre-SMA. Previous studies have shown that the SMA can be divided into two subregions on the basis of cytoarchitecture, connectivity, and function: the pre-SMA being located rostrally to a virtual vertical line passing through the anterior commissure (VCA line), and the SMA-proper, being located caudally to the VCA (Picard and Strick, 1996). Results

from diffusion tensor imaging studies revealed different patterns of connectivity with other cortical regions between the pre-SMA and SMA-proper (Johansen-Berg et al., 2004; Lehericy et al., 2004): While the pre-SMA is well connected with the prefrontal cortices and the anterior striatum, the SMA-proper is rather connected with the motor cortex and the posterior striatum. This suggests a more general role in planning for the pre-SMA and a stronger motor performance role for the SMA-proper. Other studies using fMRI support this proposal of the SMA-proper being more related to the initiation or execution of speech production than to planning (Alario et al., 2006; Bohland and Guenther, 2006). Shima and Tanji (2000) showed that the pre-SMA contains cells that code for an entire sequence to be produced. If the separation of syllabic frames and phonemic content is realized in the brain, then a possible role for the pre-SMA is to represent syllable or word-sized frames and to coordinate serial position or timing signals with the motor apparatus via the SMA-proper (Bohland and Guenther, 2006).

Increased functional connectivity

Our connectivity analyses revealed increased functional coupling between both the right pre-SMA and left POp and the left premotor cortex. These results are consistent with a recent study by Ghosh et al. (2008) proposing a network of brain regions including left ventral premotor cortex, left posterior inferior frontal gyrus and bilateral supplementary motor area for the overt production of monosyllables. According to the meta-analysis by Mayka et al. (2006), the activation peaks within the premotor cortex in our study were located in the ventral aspect of the premotor cortex (PMv). Activation of the PMv is associated with the sequencing of complex movements, including those involved in speech (Wise et al., 1999). Disruption of white matter tracts underlying the PMv, on the other hand, is likely to interfere with the integration of sensory and motor information necessary for fluent speech production

(Watkins et al., 2008). Klein et al. (2006) demonstrated increased PMv activity during pseudoword repetition of increased length and increased articulatory complexity. Accordingly, the authors suggested a role of this region in the complex motor control needed for the production of novel sequences.

The results of Peeva et al. (2009) indicate that the SMA is involved in phoneme-level processing of pseudowords while the PMv is engaged in processing at the syllable level. The authors speculate that their results can be interpreted in terms of the gestural view of speech production (Browman and Goldstein, 1989) with the SMA representation corresponding to phoneme-specific articulatory gestures and the PMv being involved in the generation of the gestural score that specifies the timing and overlap of these individual gestures.

Accordingly, Indefrey and Levelt (2004) proposed a model describing the different components involved in language production. The model assumes that all production tasks involve the phonological encoding or syllabification of the stimulus (i.e. the incremental clustering of the word's segments in syllabic patterns). Syllabification is conceived of as operating on an abstract segmental representation, whereas in the subsequent stages of phonetic encoding and articulation, motor representations are built up and executed. The syllabification of a stimulus is subserved by the left posterior inferior frontal gyrus (i.e. left POp). This is supported by the results of Salmelin et al. (2000) who used magnetoencephalography (MEG) to define the spatiotemporal activation patterns in overt reading. Their results show that an early articulatory based phonological encoding of single words takes place in the left inferior frontal cortex.

The next step in the model proposed by Indefrey and Levelt (2004) is phonetic encoding or articulatory preparation (i.e. the transformation of syllables into motor action instruction or "syllable scores") which includes activation of the right SMA and the cerebellum. The final

articulation of the stimulus is associated with the ventral premotor cortex as well as sensorimotor areas. The results of Salmelin et al. (2000) also suggest that bilateral motor and premotor areas and the SMA are activated during the motor preparation for oral output and actual vocalization.

A frontal network for pseudoword repetition

The results from our functional connectivity analyses fit well with the model proposed by Indefrey and Levelt (2004). The increased functional coupling between both the right pre-SMA and left POp and the PMv support the proposed role of these areas in phonological encoding, articulatory planning and articulation. Accordingly, we suggest that the repetition of pseudowords activates a frontal network encompassing the right pre-SMA, left POp and the left PMv. This network is engaged in the sequencing of known motor-programs and involves the repetition of auditorily as well as visually presented pseudowords (Fig.6).

Additionally, the right pre-SMA showed also increased functional coupling with the right Rolandic operculum and left POp during the repetition of auditorily presented pseudowords in contrast to words in our study. The Rolandic operculum has previously been associated with sensory-motor integration during language production (see Vigneau et al., 2006 for a meta-analysis). Increased connectivity between the SMA and POp during phonological aspects of language processing, on the other hand, has been demonstrated in several previous studies (Bullmore et al., 2000; He et al., 2003). Bullmore et al. (2000) proposed an inner speech circuit or articulatory loop which assumes strong connections between the SMA and POp being responsible for subvocal planning and articulation. These results also converge with the findings of Xiang et al. (2009). The authors demonstrated increased functional connectivity between left POp and a right pre-SMA region (x=6, y=15, z=52) close to the peak activation of our study during resting state fMRI.

The difference in the connectivity profiles between the two modalities used for stimulus presentation may indicate different processing strategies in the network for phonological aspects of language production. There is consensus that auditorily presented words are processed sequentially while visually presented words are processed in parallel fashion (Krause et al., 2006).

The difference in processing of both modalities may indicate that the right pre-SMA and left POp are activated simultaneously (i.e. in parallel) during the repetition of visually presented pseudowords. This would be in line with the results of a strong activity increase of both areas during the repetition of visually presented pseudowords in contrast to words as shown in the unimodal comparison. Furthermore, the interaction between task and modality revealed a stronger activity increase in left POp for visually than auditorily presented pseudowords.

The repetition of auditorily presented pseudowords, on the other hand, might require a sequential activation of both areas. This would match our results of a relatively strong increase in the pre-SMA activity and a weaker increase in POp activity during the repetition of auditorily presented pseudowords. A serial activation of pre-SMA preceding POp would be in line with the model of Bullmore et al. (2000) proposing an inner speech circuit or articulatory loop with the SMA being putatively responsible for endogenously directing inner speech production to left inferior frontal regions.

At first glance, the suggested serial activation of pre-SMA preceding POp during the repetition of auditorily presented pseudowords contradicts the model of Indefrey and Levelt (2004). Nevertheless, the authors state that the different stages in their model interact and the proposed time frames represent estimates which are variable which “cautions against a too rigid interpretation of these numbers”. Finally, their meta-analysis did not include studies on pseudoword repetition. Thus, the repetition of a pseudoword may differ in some aspects from the proposed time frames of language production.

Conclusions

Our results indicate for the first time that both the right pre-SMA and left POp are involved in the articulatory planning of overt pseudoword in contrast to word repetition independent of the modality used for stimulus presentation. The increased functional coupling between both areas and the left ventral premotor cortex supports the notion that these areas represent core regions for phonological encoding, articulatory planning and articulation of pseudoword in contrast to word repetition. Accordingly, we suggest a frontal network engaged in the repetition of pseudowords, encompassing the right pre-SMA, left POp and the left PMv.

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Table 1. Unimodal and modality-independent effects of pseudoword vs. word repetition

Region	Side	MNI coordinates in mm			T	Z
		x	y	z		
Unimodal comparison: auditory pseudowords > auditory words						
Pre-supplementary motor area	R	6	18	48	**4.24**	**3.89**
Pallidum	L	-15	0	-3	3.25*	3.08*
Inferior frontal gyrus (pars opercularis)	L	-51	6	12	**2.80***	**2.69***
Unimodal comparison visual pseudowords > visual words						
Inferior frontal gyrus (pars opercularis)	L	-51	9	18	**4.71**	**4.25**
Pre-supplementary motor area	R	6	18	54	**4.61**	**4.17**
Inferior frontal gyrus (pars triangularis)	R	48	27	27	4.43	4.04
Inferior parietal lobe	L	-45	-39	45	4.13	3.80
Insula	L	-30	24	3	4.02	3.71
Inferior parietal lobe	R	42	-51	48	3.77	3.51
Cuneus	R	12	-72	39	3.64	3.41
Inferior parietal lobe	L	-27	-66	42	3.60	3.37
Inferior frontal gyrus (pars triangularis)	L	-45	18	0	3.56	3.34
Modality-independent conjunction: Auditory pseudowords > auditory words & visual pseudowords > visual words						
Pre-supplementary motor area	R	6	18	54	**3.92**	**3.36**
Pallidum	L	-15	0	-3	3.17*	3.00*
Inferior frontal gyrus (pars opercularis)	L	-51	6	12	**2.78***	**2.67***

Differential contrasts thresholded at p< 0.001 uncorrected for the whole brain. Cluster level > 10 contiguous voxels. Contrasts were inclusively masked by respective main effects of the condition of interest at p= 0.05 uncorrected. In bold: a small volume correction (p < 0.05, FWE-corrected) was applied to our a-priori regions of interest. *significant at p< 0.01, uncorrected; *in bold: small-volume correction: p= 0.051.

Table 2. Results from the PPI analyses of auditory and visual pseudoword vs. word repetition

Region	Side	MNI coordinates in mm			T	Z
		x	y	z		
Seed area: right pre-SMA **auditory pseudowords > auditory words (x= 6, y= 18, z= 48)**						
Rolandic operculum	R	57	6	3	3.86	3.47
Inferior frontal gyrus (pars opercularis)	L	-45	15	3	3.75	3.39
ventral premotor cortex	L	-48	-6	39	**2.67***	**2.52***
Seed area: right pre-SMA **visual pseudowords > visual words (x= 6, y= 18, z= 54)**						
ventral premotor cortex	L	-48	0	39	**4.42**	**3.88**
Seed area: left POp **auditory pseudowords > auditory words (x= -51, y= 6, z= 12)**						
Ventral premotor cortex	L	-54	3	33	**3.34**	**3.07**
Seed area: left POp **visual pseudowords > visual words (x= -51, y= 9, z= 18)**						
Ventral premotor cortex	L	-48	0	33	**4.19**	**3.71**

Results from the different PPI-analyses, thresholded at p< 0.001 uncorrected for the whole brain. In bold: a small volume correction (p< 0.05, FWE-corrected) was applied to our a-priori region of interest. *****significant at p= 0.01, uncorrected; small-volume correction: p= 0.051.

Figure legends

Figure 1

Experimental design. A. Example of a run. The experiment consisted of two runs with five blocks of pseudowords and words each. The order of runs was randomized across subjects. At the end of each rest block, a visual cue indicated whether the next block would consist of auditorily or visually presented pseudowords or words, respectively. The onset of the cue was jittered such that it appeared 9.5-12.5 s after the rest block had started.

B. Example of a visual block of pseudowords. Each block consisted of six pseudowords (or words). C. Example of an auditory block of words. Original stimuli were in German.

Figure 2

A. Modality-independent conjunction of the main effects of pseudoword repetition ($p < 0.05$ FWE-corrected). B. Modality-independent conjunction of the main effects of word repetition ($p < 0.05$ FWE-corrected).

Figure 3

Differential effects of pseudoword > word repetition. A. Comparison of auditorily presented pseudowords > words. B. Comparison of visually presented pseudowords > words. C. A Conjunction across auditory and visual modalities of the differential contrasts of pseudoword > word repetition was used to identify modality-independent activation associated preferentially with pseudoword processing.

For illustrating purposes, all comparisons were thresholded at $p < 0.01$ uncorrected and the extent threshold was set to 10 voxels. Parameter estimates (arbitrary units) of the peak voxels +/- 90 % confidence intervals were plotted with the aid of the rfxplot toolbox

(http://rfxplot.sourceforge.net/; see Glascher, 2009). AW= auditorily presented words, VW= visually presented words, APW= auditorily presented pseudowords, VPW= visually presented pseudowords. Spatial references are given in MNI space.

Figure 4

Areas showing increased functional connectivity with the right pre-supplementary area (pre-SMA). A. Results from the psychophysiological interaction (PPI) using the peak activation from the differential comparison of auditorily presented pseudowords and words in the right pre-SMA as seed region. B. Results from the PPI using the peak activation from the differential comparison of visually presented pseudowords and words in the right pre-SMA as seed region. For illustrating purposes, all comparisons were thresholded at $p < 0.01$ uncorrected. Spatial references are given in MNI space.

Figure 5

Areas showing increased functional connectivity with left pars opercularis (POp). A. Results from the psychophysiological interaction (PPI) using the peak activation from the differential comparison of auditorily presented pseudowords and words in left POp as seed region. B. Results from the PPI using the peak activation from the differential comparison of visually presented pseudowords and words in left POp as seed region. For illustrating purposes, all comparisons were thresholded at $p < 0.01$ uncorrected. Spatial references are given in MNI space.

Figure 6

Connectivity in the proposed frontal network for the repetition of pseudowords for auditorily (left) and visually presented stimuli (right). Pre-SMA: pre-supplementary area; POp: pars opercularis; PMv: ventral premotor cortex; RolOp: Rolandic operculum.

Figure 1

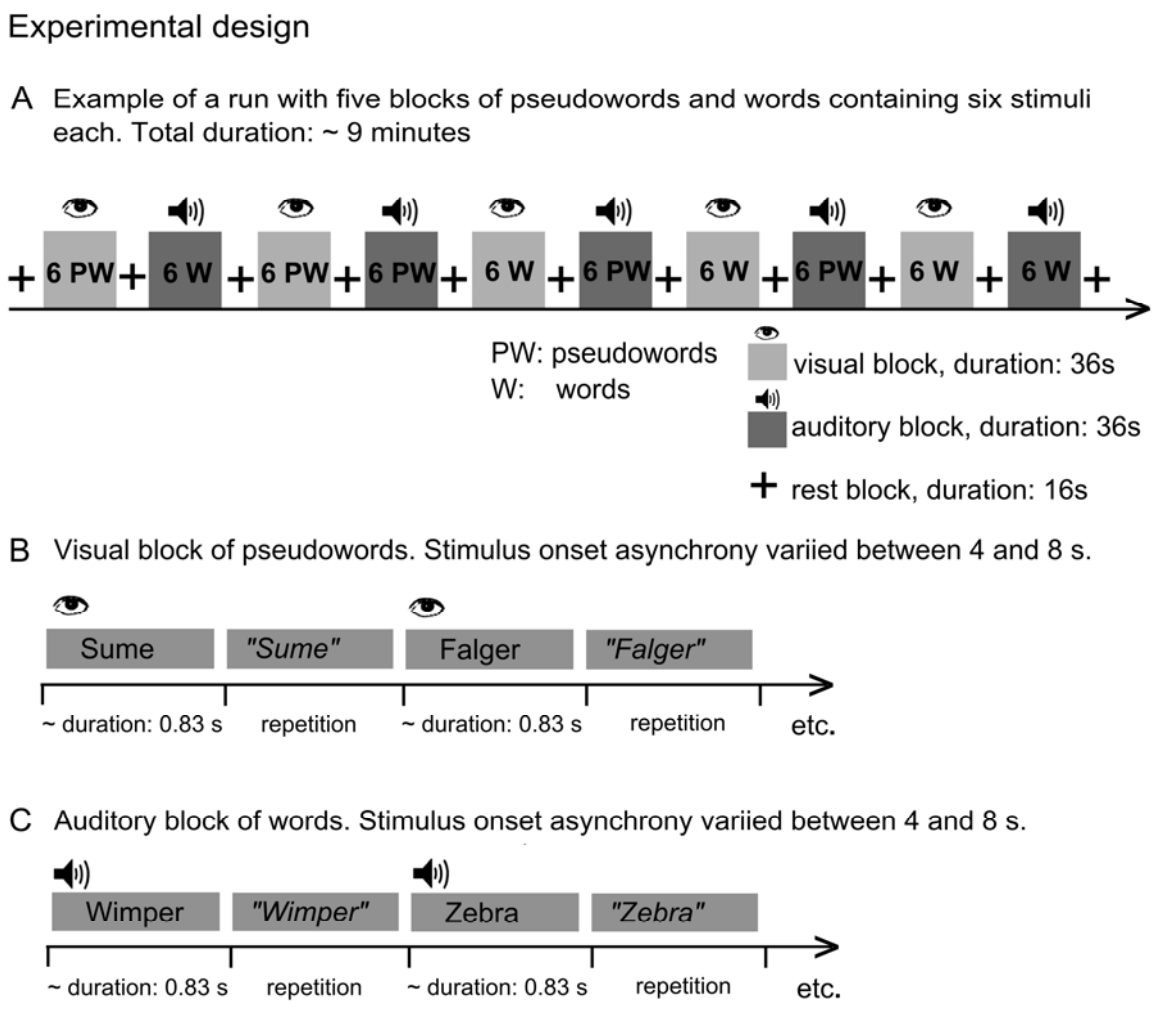


Figure 2

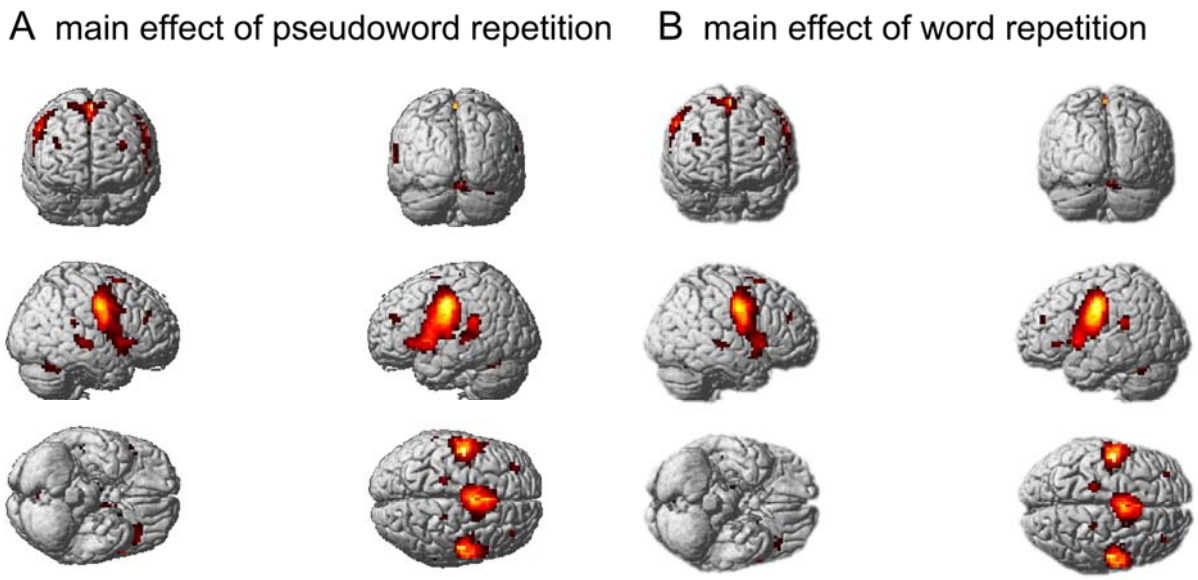

A main effect of pseudoword repetition
B main effect of word repetition

Figure 3

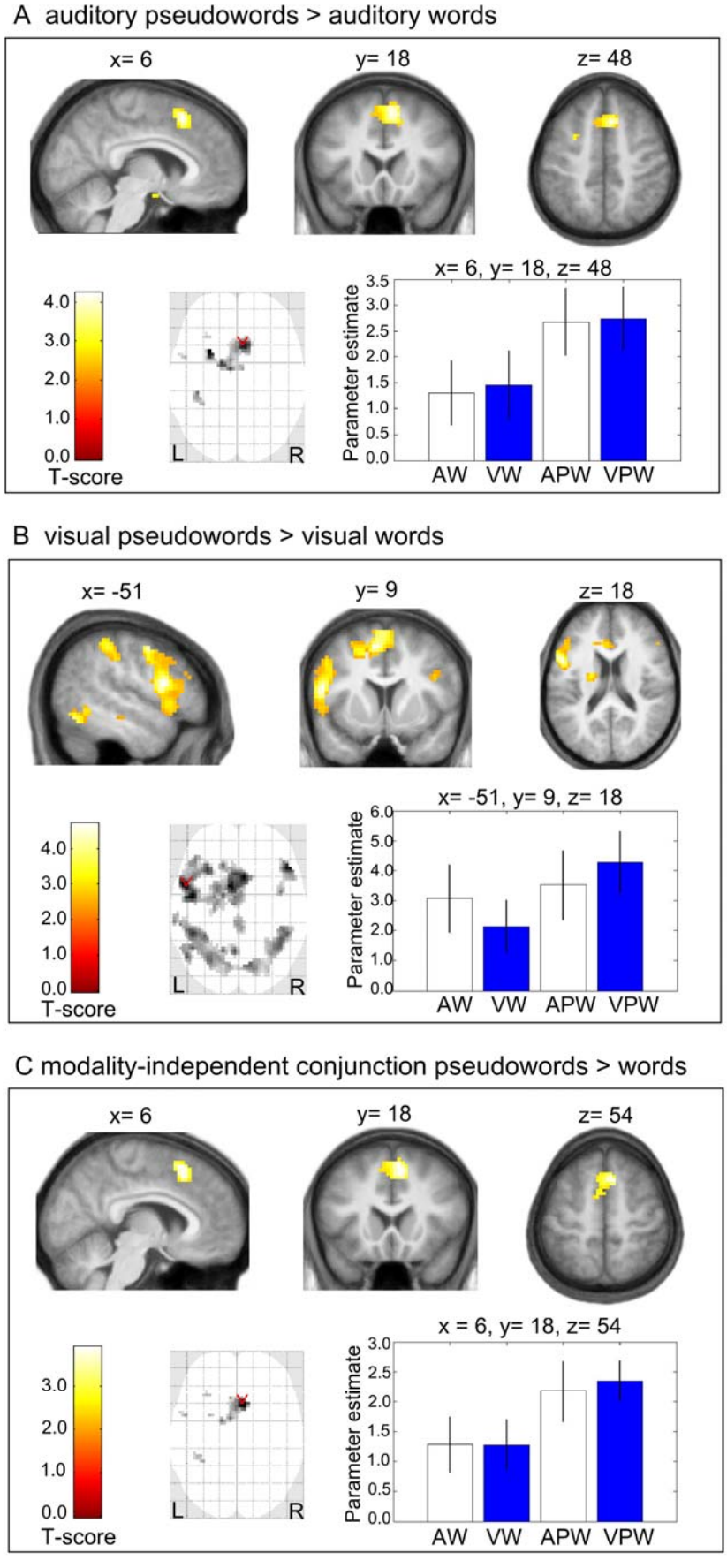

A auditory pseudowords > auditory words
x= 6
y= 18
z= 48
x= 6, y= 18, z= 48
Parameter estimate
AW VW APW VPW
T-score
L R
B visual pseudowords > visual words
x= -51
y= 9
z= 18
x= -51, y= 9, z= 18
Parameter estimate
AW VW APW VPW
T-score
L R
C modality-independent conjunction pseudowords > words
x= 6
y= 18
z= 54
x = 6, y= 18, z= 54
Parameter estimate
AW VW APW VPW
T-score
L R

Figure 4

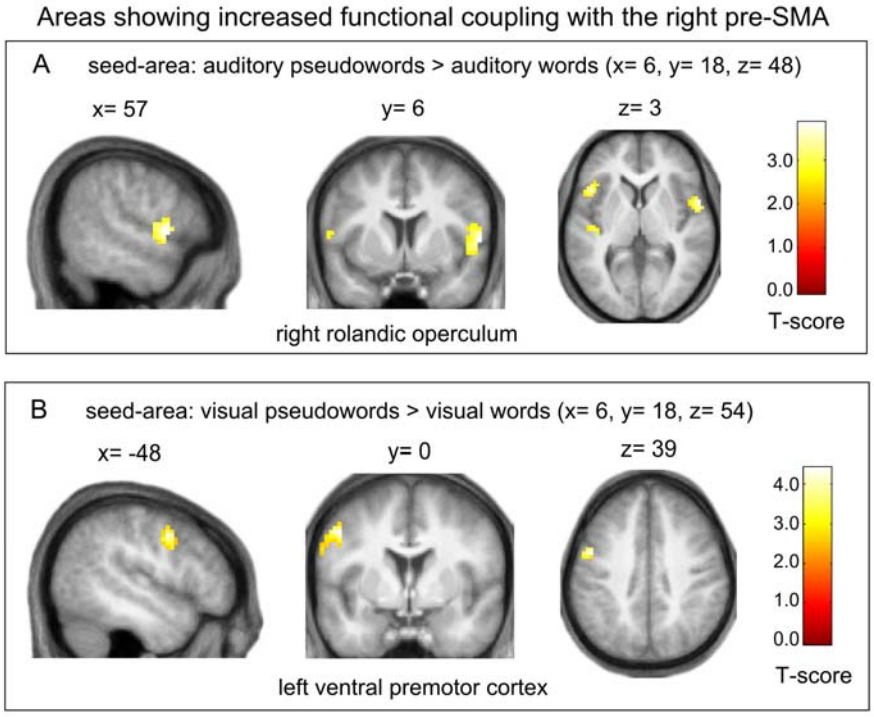

Areas showing increased functional coupling with the right pre-SMA
A
seed-area: auditory pseudowords > auditory words (x= 6, y= 18, z= 48)
x= 57
y= 6
z= 3
3.0
2.0
1.0
0.0
T-score
right rolandic operculum
B
seed-area: visual pseudowords > visual words (x= 6, y= 18, z= 54)
x= -48
y= 0
z= 39
4.0
3.0
2.0
1.0
0.0
T-score
left ventral premotor cortex

Figure 5

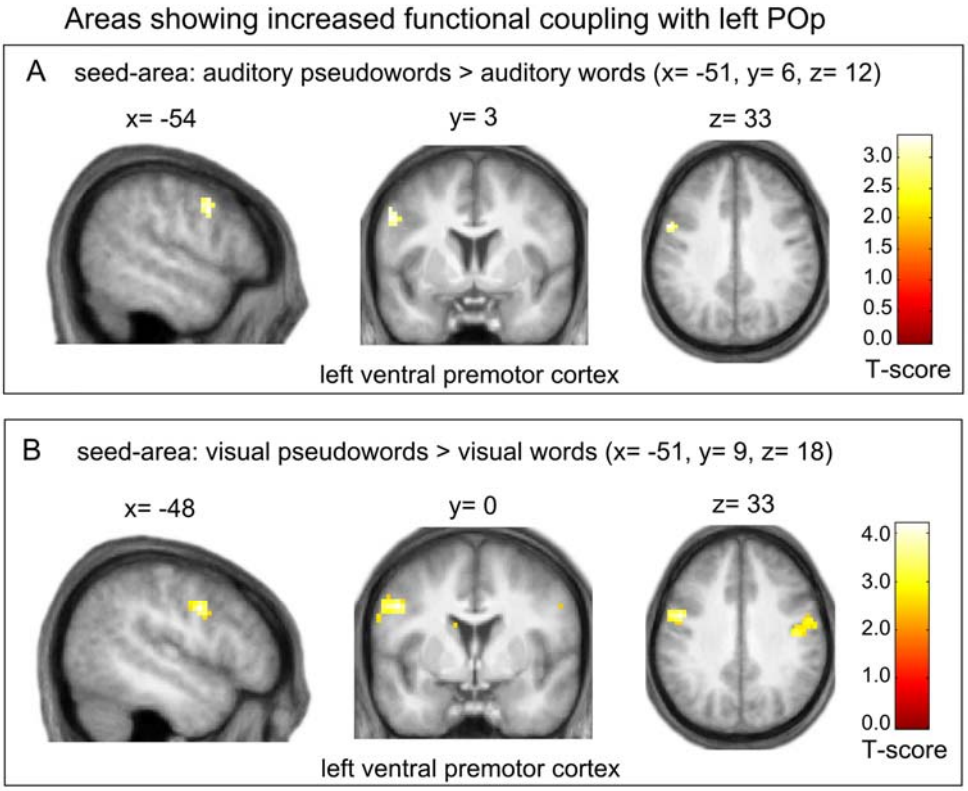
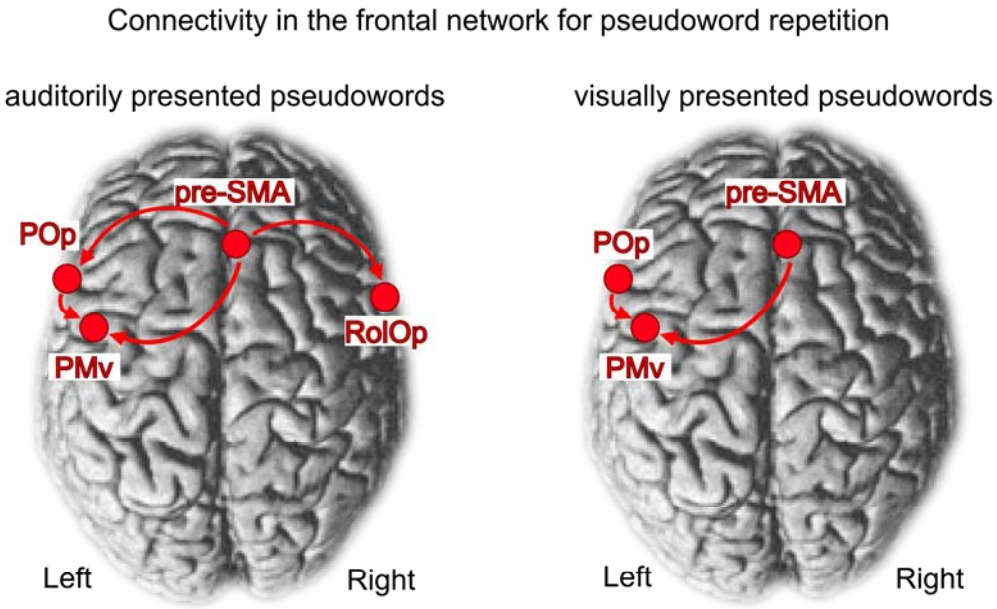

Areas showing increased functional coupling with left POp
A seed-area: auditory pseudowords > auditory words (x= -51, y= 6, z= 12)
x= -54
y= 3
z= 33
3.0
2.5
2.0
1.5
1.0
0.5
0.0
T-score
left ventral premotor cortex
B seed-area: visual pseudowords > visual words (x= -51, y= 9, z= 18)
x= -48
y= 0
z= 33
4.0
3.0
2.0
1.0
0.0
T-score
left ventral premotor cortex

Figure 6


Connectivity in the frontal network for pseudoword repetition
auditorily presented pseudowords
visually presented pseudowords
pre-SMA
POp
RolOp
PMv
Left
Right
pre-SMA
POp
PMv
Left
Right

Curriculum vitae

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Mitgliedschaften

Seit 2009	Organization for Human Brain Mapping (OHBM)

Preise / Stipendien

2009	OHBM “Trainee Travel Award” for the 15th Annual Meeting of the Organization for Human Brain Mapping; San Francisco, CA, June 18-23, 2009
2009	Reisestipendium des Deutschen Akademischen Austausch-dienstes für das 15. Meeting der OHBM in San Francisco

Publikationen

Peer-reviewed papers

Baumgaertner, A., **Hartwigsen, G.** & Siebner, H.R. (in revision). Modality-independent semantic, phonologic and perceptual word processing in the human brain. *Human Brain Mapping.*

Hartwigsen, G., Siebner, H.R., Deuschl, G., Jansen, O. & Ulmer, S. (in press). Incidental findings are frequent in young healthy individuals undergoing MRI in brain research imaging studies: a prospective single center study. *Journal of Computer Assisted Tomography.*

Hartwigsen, G., Siebner, H.R. & Stippich, C. (in press). Preoperative functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS). *Current Medical Imaging Reviews*.

Hartwigsen, G., Price, C.J., Baumgaertner, A., Geiss, G., Koehnke, M., Ulmer, S. & Siebner, H.R. (in revision). The right posterior inferior frontal gyrus contributes to phonological word decisions in the healthy brain: evidence from dual-site TMS. *Neuropsychologia.*

Hartwigsen, G., Baumgaertner, A., Price, C.J., Koehnke, M., Ulmer, S. & Siebner, H.R. (under review). Efficient phonological decisions require both the left and right supramarginal gyri. A dual-site transcranial magnetic stimulation study. *Proceedings of the National Academy of Sciences of the USA.*

Siebner, H.R., **Hartwigsen, G.**, Kassuba, T. & Rothwell, J.C. (2009). How does transcranial magnetic stimulation modify neuronal activity in the brain? - Implications for studies of cognition. *Cortex 45(9)*,1035-1042.

Ulmer, S., **Hartwigsen, G.,** Riedel, C., Jansen, O., Mehdorn, H. M. & Nabavi, A. (2009). Intraoperative dynamic susceptibility contrast MRI (iDSC-MRI) is as reliable as preoperatively acquired perfusion mapping. *Neuroimage 49(3)*, 2158-2162.

Ward, N.S., Bestmann, S., **Hartwigsen, G.,** Weiss, M., Christensen, L., Frackowiak, R., Rothwell, J.C. & Siebner, H.R. (in press). Low-frequency transcranial magnetic stimulation of left dorsal premotor cortex improves the dynamic control of visuospatially cued actions. *Journal of Neuroscience.*

Bookchapter

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Abstracts (poster / talks)

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Erklärung

Hiermit erkläre ich an Eides statt, dass die vorliegende Abhandlung nach Inhalt und Form meine eigene Arbeit ist.

Kiel, den ……. …….
(Gesa Hartwigsen)