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The neurophysiology of language: Insights from non-invasive brain stimulation in the healthy human brain

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ABSTRACT

With the advent of non-invasive brain stimulation (NIBS), a new decade in the study of language has started. NIBS allows for testing the functional relevance of language-related brain activation and enables the researcher to investigate how neural activation changes in response to focal perturbations. This review focuses on the application of NIBS in the healthy brain. First, some basic mechanisms will be introduced and the prerequisites for carrying out NIBS studies of language are addressed. The next section outlines how NIBS can be used to characterize the contribution of the stimulated area to a task. In this context, novel approaches such as multifocal transcranial magnetic stimulation and the condition-and-perturb approach are discussed. The third part addresses the combination of NIBS and neuroimaging in the study of plasticity. These approaches are particularly suited to investigate short-term reorganization in the healthy brain and may inform models of language recovery in post-stroke aphasia.

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1. The basic physiology of non-invasive brain stimulation techniques

This review aims at elucidating how non-invasive brain stimulation can contribute to a better understanding of the neurophysiology of language. Non-invasive brain stimulation methods like transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) complement correlative neuroimaging approaches by enabling the researcher to characterize the causal contribution of the stimulated area to a given (language) task. Moreover, these techniques can be used to shed light on mechanisms of plasticity in language networks in both the healthy brain and patients suffering from aphasia. This review deals with the application of non-invasive brain stimulation in the healthy language system with a particular focus on the application of repetitive TMS (rTMS), since these protocols represent the most commonly used approach to interfere with speech and language functions in the majority of studies to date. For recent reviews on the potential of non-invasive brain stimulation in facilitating recovery after stroke-induced aphasia, the reader is referred to Devlin and Watkins (2007), Hamilton, Chrysikou, and Coslett

(2011), Hartwigsen and Siebner (2013) or Holland and Crinion (2012).

1.1. Transcranial magnetic stimulation (TMS)

TMS was introduced as non-invasive technique for electrical stimulation of the human cortex in the 1980s (Barker, Jalinous, & Freeston, 1985). When investigating brain functions with TMS, it should be borne in mind that the effects of TMS critically depend, among others, on the stimulation parameters, the targeted cortical area(s), the employed task and the timing of the stimulation (Siebner, Hartwigsen, Kassuba, & Rothwell, 2009; Siebner & Rothwell, 2003). Some of these issues with a particular relevance for the study of language will be discussed in the next sections.

1.1.1. Some basic mechanisms of TMS

TMS is a valuable tool for studying language functions since it permits causal conclusions to be drawn regarding the contribution of the stimulated area to a specific brain function (Paus, 2008; Walsh & Cowey, 2000).

On the physiological level, a single TMS pulse causes electro-magneto-electric stimulation of neuronal axons, particularly in superficial regions of the cerebral cortex. TMS directly and noninvasively interacts with cortical processing by passing a brief and strong current through a stimulation coil, which induces a perpendicular time-varying magnetic field that penetrates the

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scalp without attenuation. This magnetic field will induce a weak and short-lived current at the site of stimulation that can temporarily excite or inhibit the stimulated area (Bestmann, 2008; Hallett, 2000). The term "magnetic stimulation" might appear misleading since the strong time-varying magnetic field that is induced in the TMS coil is only used as a means to generate an electric field in the brain. The majority of studies have investigated the physiological mechanisms of TMS in the human motor system because its effects can easily be quantified by recording the TMS-induced motor evoked potential as a measure of neuronal excitability. When applied over the primary motor cortex, TMS can depolarize corticospinal tract neurons and evoke contralateral hand muscle movements. The size of these motor evoked potentials reflects the excitability of the corticospinal system (Bestmann, 2008). For other brain regions, such direct measures are difficult to obtain. TMS-induced effects on cognitive functions such as language are usually quantified either as changes in behavioural performance (i.e., the speed and accuracy of a specific task) or changes in neural activation (see Section 3). For comprehensive review on the basic physiology of TMS, see (Amassian & Maccabee, 2006; Bestmann, 2008; Hallett, 2000; Pascual-Leone, Walsh, & Rothwell, 2000; Ziemann et al., 2008).

Despite the increased application of TMS in the study of motor function and cognition across the last few years, the events that lead to neuronal excitation at the cellular level are still poorly understood. For instance, the relevance of cellular and gyral shapes, the grey matter boundaries, the local variations in tissue conductivity, and the role of background neural activity for the effects of non-invasive brain stimulation are largely unknown (Miniussi, Ruzzoli, & Walsh, 2010; Sandrini, Umilta, & Rusconi, 2011; Siebner, Hartwigsen, et al., 2009). Previous studies in the motor cortex suggested that for many coil orientations, the cortical grey matter is the predominant target of the TMS pulse (Di Lazzaro et al., 2004). Thielscher, Opitz, and Windhoff (2011) used anatomical modelling of the individual gyrification pattern to characterize the effect of the current direction on the electric field distribution in the cortical grey matter of the primary motor and somatosensory cortex. The authors reported that the highest field strengths occur at the gyral crowns that are perpendicular to the local electric field orientation, implicating that the gyral geometry has a strong impact on the electric field induced by the TMS pulse. This suggests that the TMS coil handle should be oriented perpendicular to the target structure to optimize the (behavioural and electrophysiological) effects of TMS. These results have important implications for the study of language. So far, many studies relied on a coil orientation with the handle pointing at 45° to the sagittal plane that is optimal with respect to the size of the motor evoked potential when TMS is applied over the primary motor cortex (e.g., Brasil-Neto, Cohen, et al., 1992; Ni et al., 2011). However, the gyral anatomy might be different in areas outside the primary motor cortex. Hence, it might be worthwhile to use neuronavigated TMS based on frameless stereotaxy and adjust the coil orientation to the cortical anatomy of the target structure when TMS is given over language areas.

1.1.2. Different TMS protocols and timing issues

In principle, TMS can be applied in two different approaches: TMS can either be given before a language task (i.e., "offline") or during a task (i.e., "online"). Particularly, the online approach provides a means of transiently disrupting ongoing neural processing in the stimulated cortex while subjects perform a given (language) task and thus permits causal conclusions with respect to the contribution of the stimulated area to a specific brain function (Hartwigsen & Siebner, 2012; Paus, 2008; Siebner, Hartwigsen, et al., 2009; Walsh & Cowey, 2000). Online TMS protocols range between the application of single pulses, paired pulses and short high-frequency bursts of repetitive TMS (rTMS). While the majority of studies targeting language areas used rTMS to interfere with a specific language function (e.g., Gough, Nobre, & Devlin, 2005; Papagno, Fogliata, Catricala, & Miniussi, 2009; Romero, Walsh, & Papagno, 2006; Sliwinska, James, & Devlin, 2014; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2011 see below for details), some language studies also applied single, double, or triple pulse protocols in a chronometric fashion (e.g., Coslett & Monsul, 1994; Devlin, Matthews, & Rushworth, 2003; Schuhmann, Schiller, Goebel, & Sack, 2009; Sliwinska, Khadilkar, Campbell-Ratcliffe, Quevenco, & Devlin, 2012; Stoeckel, Gough, Watkins, & Devlin, 2009). This means that TMS is given at distinct time-points during a task to perturb intrinsic neural activity in the stimulated area. As a single TMS pulse interferes with ongoing neural activity for several tens of milliseconds, this approach provides sufficiently high temporal resolution to identify the time period during which the stimulated region makes a critical contribution to a given task (see also Section 3.1).

The perturbation of intrinsic brain activity with short bursts of rTMS is often referred to as "virtual lesion". An important advantage of such (r)TMS-induced lesions relative to studies of structural brain lesions is that there is insufficient time for functional reorganization to occur during online TMS. Thus, the acute perturbation effect should not be confounded by chronic processes mediating functional recovery locally and at the systems level (Walsh & Cowey, 1998, 2000). However, it should be mentioned that the TMS-induced disruption of neural activity in one area might also lead to a "paradoxical improvement" in task performance. For instance, several studies reported *faster* reaction times with different online or offline rTMS protocols over temporal or frontal language areas (Andoh & Paus, 2011; Andoh et al., 2006; Nixon, Lazarova, Hodinott-Hill, Gough, & Passingham, 2004; Sparing et al., 2001). The observation of a paradoxical improvement in cognitive tasks after a "virtual lesion" can be explained within the framework of the "state dependency" concept. It was argued that the TMS-induced activity or "neural noise" (Ruzzoli, Marzi, & Miniussi, 2010) is not totally random and may not be independent of the task-induced neural activity or brain state (i.e., "state dependency", see Pasley, Allen, & Freeman, 2009; Silvanto, Muggleton, & Walsh, 2008). TMS may induce neuronal activity that adds to the ongoing neural activity as a complement to the extant activity determined by state and task demand. Depending on the neuron population that will be activated, the induced activity can be considered both as noise and as part of the signal (Miniussi et al., 2010). Hence, the induced noisy activity may be synchronized with the ongoing relevant signal (Ermentrout, Galan, & Urban, 2008), thereby rendering the signal stronger (Miniussi, Harris, & Ruzzoli, 2013). In other words, behavioural facilitation may result from an optimum level of noise.

In the language system, state dependent effects were demonstrated in studies employing TMS in a priming approach during speech production. A number of studies reported behavioural facilitation when single pulse TMS or high-frequency rTMS was given immediately before picture naming over left-hemispheric language areas (e.g., Mottaghy, Sparing, & Topper, 2006; Mottaghy et al., 1999; Sparing et al., 2001; Topper, Mottaghy, Brugmann, Noth, & Huber, 1998; Wassermann et al., 1999). For instance, in a study by Sparing et al. (2001), naming latencies were decreased immediately after 20 Hz rTMS of Wernicke's area, but only at relatively high intensities (i.e., with 55% of maximum stimulator output relative to conditions with intensities of 35% or 45%). These authors suggested that the facilitatory effect of rTMS over Wernicke's area could be explained by a facilitation of lexical processes through a pre-activation of language-related neural networks (see also Topper et al., 1998). In contrast, other studies reported decreased behavioural accuracy when online rTMS bursts were applied during picture naming over frontal or temporal language

areas (Flitman et al., 1998; Wassermann et al., 1999). These studies stress the influence of the timing of the TMS intervention as well as the employed task and the stimulation protocol and intensity.

Offline TMS, on the other hand, is well suited to induce plasticity in the targeted brain network and can be easily combined with different imaging techniques (see Section 4.1 for details). Offline TMS usually refers to the application of rTMS. Such protocols are given continuously as long trains at a constant rate (i.e., continuous rTMS, often applied at a frequency of 1 Hz) or intermittently as repetitive bursts (i.e., intermittent or burst-like rTMS) to induce lasting functional effects in the stimulated area and connected sites (Siebner & Rothwell, 2003; Ziemann et al., 2008). These protocols can modulate brain activation for a longer time period of about 30–45 min after the end of the stimulation and thus allow for the induction of rapid functional reorganization in the stimulated area and in connected brain regions (Lee, Siebner, & Bestmann, 2006; Rossi & Rossini, 2004). Notably, such "remote" effects may even occur over large distances at interconnected sites within the same hemisphere as well as in contralateral areas. Usually, the applied rTMS protocol is "inhibitory" with respect to its effects on motor cortical excitability. When applied over the primary motor cortex, such (low-frequency) rTMS protocols appear to produce a transient reduction in cortical excitability as assessed by the size of the motor evoked potential (Fitzgerald, Fountain, & Daskalakis, 2006). Due to these inhibitory effects, it is generally assumed that the rTMS intervention induces a lasting suppression of neural excitability in relevant areas (Siebner & Rothwell, 2003). However, as noted above, the effects of a particular rTMS protocol on cognitive functions may strongly depend on the given context. The offline approach bears some analogies to acute stroke, because offline rTMS may give rise to an acute adaptive reorganization within the non-stimulated functional nodes of the networks to compensate for the rTMS-induced suppression of neural activity in those components of the network that have been perturbed with rTMS (O'Shea, Johansen-Berg, Trief, Gobel, & Rushworth, 2007; Rossi & Rossini, 2004).

In sum, online and offline TMS represent complementary approaches that enable the researcher to investigate the functional relevance of the targeted brain area and allow for the investigation of rapid reorganization and plasticity within a (language) network. The changes in neural activity evoked by TMS can be quantified with different methods. For instance, TMS-induced disruptions on the behavioural level are usually measured as changes in reaction times and/or error rates. Effects of TMS on electrophysiological parameters or neural activation, on the other hand, can be assessed with motor evoked potentials or neuroimaging read-outs.

1.2. Transcranial direct current stimulation (tDCS)

Electrical stimulation of animal and human body parts dates back to the days of Galvani's first experiments on bioelectricity in the 18th century (Galvani, 1791). In the 1950s and 1960s, tDCS has been mainly used in animal research. These studies demonstrated that the effects of tDCS are primarily based on a modulation of the resting membrane potential (Bindman, Lippold, Redfearn, & Physiology, 1964; Creutzfeld, Fromm, & Kapp, 1962; Malenka & Nicoll, 1999; Purpura & McMurtry, 1965; Terzuolo & Bullock, 1956); see (Nitsche & Paulus, 2000). tDCS was re-introduced as a means to induce plasticity in the healthy human brain in 2000 by Nitsche and Paulus (2000). Over the last 15 years, this technique has increasingly been used in the study of motor and cognitive functions to modulate cortical excitability for longer time periods in healthy subjects and patients with brain lesions.

1.2.1. Some basic mechanisms of tDCS

tDCS modulates cortical excitability via tonic cortical stimulation. To this end, weak direct electrical currents (1–2 mA) between two electrodes are applied to the scalp over a relatively extended time period of usually 5–20 min. tDCS has been shown to elicit polarity-dependent excitability changes in the cortical area under the stimulation electrodes, presumably due to direct current-induced modulation of the resting membrane potential. Studies in the motor cortex showed that anodal tDCS increases motor-cortical excitability while cathodal tDCS decreases it (Antal et al., 2004; Kincses, Antal, Nitsche, Bartfai, & Paulus, 2004; Nitsche & Paulus, 2000). Similar to TMS, tDCS can also be applied before a certain task (offline) or during task processing (online).

Of note, the physiological mechanisms during stimulation are probably different from those responsible for short and long-lasting after-effects (Bindman, Lippold, & Redfearn, 1962; Brunoni et al., 2012; Stagg & Nitsche, 2011), for review, see (Monti et al., 2013). Indeed, evidence from animal studies suggests that the acute online tDCS effects are mediated by membrane depolarization for anodal stimulation and membrane hyperpolarization for cathodal stimulation (Purpura & McMurtry, 1965). In contrast, it was proposed that long-term potentiation and long-term depression might be likely candidates for the long lasting after effects (Hattori, Moriwaki, & Hori, 1990; Islam, Aftabuddin, Moriwaki, Hattori, & Hori, 1995; Malenka & Nicoll, 1999; Moriwaki, 1991). Importantly, the effects of tDCS depend on the interaction of electric flow direction and neuronal geometry (Nitsche & Paulus, 2000).

Several studies on motor and cognitive functions showed that performance changes induced by tDCS persisted beyond the period of stimulation for up to 6–12 months after the intervention (Cohen Kadosh, Soskic, Iuculano, Kanai, & Walsh, 2010; Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009; Reis et al., 2009).

The effects of tDCS on task processing can be quantified with behavioural measures, neurophysiological parameters or neuroimaging read-outs. For example, the amplitude of the motor-evoked potential can be used to measure changes in the excitability of the motor system after tDCS application over the primary motor cortex.

Additional transcranial stimulation techniques such as transcranial alternating current stimulation or transcranial random noise stimulation have been introduced more recently. So far, these methods are mainly applied in the motor or visual system to directly modulate cortical rhythms (for a recent review, see Antal and Paulus (2013)). Future studies will prove whether these techniques may also be suitable as interventional tools to modulate language functions in the healthy brain and in patients with brain damage.

2. Critical issues for the application of non-invasive brain stimulation in language studies

A prerequisite for all studies employing non-invasive brain stimulation is the use of adequate control sites and conditions. In general, active control regions are preferable to placebo (sham) stimulation. This is of particular relevance for the application of (online) TMS over language areas since TMS can yield unpleasant side effects (e.g., muscle twitches) that might induce substantial discomfort, especially when applied in inferior frontal regions at higher stimulation intensities (Hartwigsen, Price, et al., 2010). The side effects of the stimulation procedure might cause unspecific behavioural effects that can substantially confound the results. As a second general remark, different stimulation sites should be targeted in different sessions several days apart to prevent any carry-over effects of the stimulation procedures when offline stimulation is used.

2.1. Coil or electrode placement

When applying TMS over the cortical target area of interest, it needs to be borne in mind that the induced 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 stimulation intensity and the responsiveness of the targeted tissue. Commercially used standard coils usually reach a penetration depth of approximately 2–3 cm (Sandrini et al., 2011; Weyh & Siebner, 2007). Hence, only cortical neuronal tissue is within the range of TMS while deep cerebral grey matter nuclei cannot be stimulated directly with TMS. The penetration depth is thus sufficient to effectively stimulate the fronto-parieto-temporal language areas at the hemispherical surface (Hartwigsen & Siebner, 2012). Recently, h-shaped coils for so called "deep TMS" were introduced as a potential means for the treatment of psychiatric disorders such as depression (Harel et al., 2014; Levkovitz et al., 2007). It was demonstrated that these coils modulate cortical excitability to a maximum depth of up to 6 cm (Bersani et al., 2013; Roth, Amir, Levkovitz, & Zangen, 2007), thus allowing for a direct stimulation of deeper brain structures like the cingulum. However, these coils are not used in the routine application yet.

Another limiting factor of the TMS approach is the focality of the stimulation. 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. As a rule of thumb, standard figure-of-eight coils usually provide a spatial resolution of approximately 1–1.5 cm (Walsh & Rushworth, 1999), depending on the specific tissue that is being stimulated (Sandrini et al., 2011). Mapping studies in the motor system demonstrated even higher resolutions of up to 0.5–1 cm when single pulses were applied over the primary motor cortex (Brasil-Neto, McShane, Fuhr, Hallett, & Cohen, 1992; Pascual-Leone, Bartres-Faz, & Keenan, 1999; Wilson, Thickbroom, & Mastaglia, 1993). Note that the focality of the TMS procedure is also influenced by the employed stimulation intensity, frequency and duration. The focality is generally lower when high-frequency bursts are applied as compared to the application of single pulses, since the former protocols produce stronger spreads of excitation (Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994; Pascual-Leone et al., 1999).

Accurate placement of the TMS coil over the cortical area of interest is crucial. The motor response evoked by TMS can be used to functionally localize the primary motor cortex. In this context, TMS produces an overt response, which can be used to determine the appropriate site of stimulation. A similar approach has been adopted for TMS of the visual cortex by positioning the coil at the site where TMS most reliably elicits a phosphene. However, note that the successful induction of phosphenes critically depends on the individual subject's perception and cannot be quantified by objective external measures. For most other cortical areas, no such responses can be elicited. Therefore, other strategies have to be used to guarantee accurate coil placement. Neuronavigated TMS based on frameless stereotaxy is the method of choice for exact coil placement and continuous monitoring of the coil throughout the TMS experiment (Denslow, Bohning, Bohning, Lomarev, & George, 2005; Herwig et al., 2003; Neggers et al., 2004; Sack, Kohler, Linden, Goebel, & Muckli, 2006; Schonfeldt-Lecuona et al., 2005).

With the relatively large stimulation electrodes, tDCS is considerably less focal than TMS. Hence, in comparison with TMS, tDCS is less suitable to investigate functional–anatomic subdivisions within language areas but might be preferable for therapeutic purposes (e.g., in post-stroke rehabilitation, see Monti et al., 2013). Placement of the tDCS electrodes over the language area of interest is usually guided by the 10–20 EEG system.

2.2. Remote effects and stimulation intensity

An increasing body of research uses neuroimaging techniques to map TMS-evoked changes in neural activity throughout the brain (Sandrini et al., 2011; Siebner, Bergmann, et al., 2009). One consistent finding across these studies is that TMS gives rise to functional changes in connected cortical and subcortical areas (Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2003; Lee et al., 2003; Rossi & Rossini, 2004; Siebner et al., 2003). In addition to the focal stimulation of neuronal tissue at the primary target site, TMS can influence intrinsic activity in remote brain areas because of transsynaptic spread of excitation via cortico-cortical and cortico-subcortical projections. For instance, it has been shown that a conditioning TMS pulse given to one primary motor cortex can inhibit the cortico-motor excitability of the primary motor cortex in the opposite hemisphere (Di Lazzaro et al., 1999; Ferbert et al., 1992). In sum, the effects of a TMS pulse may not only be caused by effects at the site of stimulation but may also be mediated via axons projecting to remote cortical areas. Like the local effects induced in the targeted cortical area, the remote effects critically depend on the intensity of stimulation.

Of note, the induced magnetic and electric field of the TMS pulse decreases rapidly with increasing distance from the coil (see above). The intensity of TMS is usually calibrated to the excitability of the primary motor hand area by using the motor threshold as reference, mainly because of a lack of more appropriate procedures. Yet, it remains unclear for which cortical areas the motor threshold of the primary motor cortex works as a good predictor in terms of regional excitability (Boroojerdi et al., 2002). It was argued that when using the motor threshold of the primary motor hand area to individually adjust the intensity of stimulation, the intensity should be corrected for differences in the scalp-to-cortex distance between the primary motor cortex and the area that is actually targeted with TMS (Stokes et al., 2005, 2007).

It needs to be borne in mind that TMS may cause adverse effects, especially if rTMS is used with high frequencies. These effects range from mild headache to the induction of epileptic seizures. Therefore, adherence to the published safety guidelines (Rossi, Hallett, Rossini, & Pascual-Leone, 2009; Wassermann, 1998; Wassermann, Cohen, Flitman, Chen, & Hallett, 1996; Wassermann, Grafman, et al., 1996) is mandatory.

For tDCS application, usually the standard protocols introduced by Nitsche and Paulus (2000) and Nitsche et al. (2003) are used without any adaptation to individual thresholds. Recent combinations of tDCS with resting state functional MRI demonstrated that tDCS induces changes in brain activity in large scale (language) networks (e.g., Meinzer, Lindenberg, Antonenko, Flaisch, & Floel, 2013; Pena-Gomez et al., 2012). Accordingly, it was suggested that (anodal) tDCS might modulate endogenous low-frequency oscillations that are not restricted to the targeted area but also spread to functionally connected brain areas (Meinzer et al., 2013). In comparison with TMS, an important advantage of tDCS is the apparent absence of any significant side effects when using standard protocols. Specifically, tDCS has not been reported to provoke seizures since the standard intervention protocols are well below the threshold of eliciting action potentials (Nitsche et al., 2003). Therefore, compared with TMS, tDCS may be a viable option for stimulation of the perilesional cortex after stroke where the threshold to induce seizures is lower. Moreover, in contrast to TMS, it is relatively easy to blind the subject and examiner to the type of tDCS (i.e., placebo or verum stimulation), which enables a double-blind study design. This makes tDCS an appealing form of neurostimulation in chronic stroke populations (Holland & Crinion, 2012).

3. The functional relevance of language-related brain activity

Previous studies investigated the functional anatomy of language comprehension and production in the healthy brain with online TMS. Most of these studies focused on the application of

unifocal TMS (i.e., TMS over a single brain area) to the left inferior frontal and posterior superior temporal gyrus. Aside from the investigation of the "classic" language areas, TMS studies have also contributed to elucidate the role of middle frontal cortex, premotor and motor regions as well as parietal areas in speech and language production and perception (see below for details).

3.1. Unifocal TMS studies on language production and comprehension

The functional relevance of language-related brain activity reported in neuroimaging studies is usually investigated with a high-frequency online rTMS approach. For extensive review on the application of online rTMS in language areas, the reader is referred to Devlin and Watkins (2007), Floel (2012) or Hartwigsen and Siebner (2012).

Online TMS has contributed to a better understanding of the role of the inferior frontal gyrus (IFG, Broca's area) and posterior superior temporal gyrus (STG, Wernicke's area) in language production (see also Section 1.1.2). For instance, Flitman et al. (1998) reported increased errors during picture naming when high-frequency (10–15 Hz) rTMS was applied to left IFG vs. right IFG. More recently, Pobric, Jefferies, and Ralph (2007) demonstrated that the anterior temporal lobe is also critically engaged in picture naming and word comprehension, highlighting the significance of this area for semantic processing (see also Pobric, Jefferies, & Lambon Ralph, 2010). Other studies reported facilitatory effects of single pulses or repetitive high-frequency online rTMS over left-hemispheric language areas when rTMS was applied immediately before picture naming (Mottaghy et al., 1999, 2006; Sparing et al., 2001; Topper et al., 1998; Wassermann et al., 1999). More recently, Schuhmann, Schiller, Goebel, and Sack (2012) used a chronometric triple-pulse TMS approach to demonstrate that the essential contribution of frontal and temporal areas to picture naming differs with respect to their critical time window. The authors reported increased response latencies when TMS was applied over left middle temporal gyrus around 225 ms after picture onset, while Broca's area became functionally relevant at 300 ms and Wernicke's area at 400 ms post picture onset. These data provide new insight into the temporal characteristics of speech production and complement studies employing electroencephalography or magnetoencephalography to investigate the temporal signature of word production (Indefrey & Levelt, 2004).

Online TMS has also been used to explore the role of secondary motor areas in speech production and perception. For instance, Tremblay and Gracco (2009) showed that high-frequency rTMS over the left pre-supplementary motor area selectivity interfered with the volitional but not forced selection of words and oral gestures, highlighting the role of this area in (verbal) response selection. Cattaneo, Devlin, Salvini, Vecchi, and Silvanto (2010) investigated the role of the left ventral premotor cortex in word comprehension. The authors employed a priming experiment where subjects had to decide whether a target stimulus was an exemplar of a tool category. The presentation of target stimuli was preceded by related primes (presentation of the word "tool") or unrelated ones (presentation of the word "animal"). Single pulse TMS over left ventral premotor cortex selectively abolished the priming effect for primed relative to unrelated targets. This study provides causal evidence for a role of the left ventral premotor cortex in semantic encoding processes and further supports the notion that the TMS effect may be strongly state or context dependent (see Section 1.1.2).

Using fMRI-guided low-frequency rTMS, Andoh et al. (2006) investigated the role of left posterior superior temporal gyrus (pSTG) in semantic and phonological processing. Prior to the rTMS application, a functional localizer was performed during fMRI.

Subsequently, the authors applied stereotactically guided effective or sham 1 Hz rTMS over left pSTG or posterior IFG while subjects performed a language-fragment-detection task. The authors reported a facilitation of response speed after rTMS over the pSTG but not pIFG that was stronger for native than for foreign languages, suggesting a role of this area in lexical processing. These results demonstrate that even "standard" virtual lesion rTMS protocols may result in paradoxical facilitation effects.

In a priming approach, the same group (Andoh et al., 2008) tested whether a priming session of rTMS at different frequencies over left pSTG would modulate the effects of low-frequency rTMS over the same area during auditory word detection. In that study, two different virtual lesion protocols were applied before the task, consisting of either 600 pulses of 1 Hz rTMS or 600 pulses of continuous theta-burst stimulation (cTBS) at 50 Hz. Subsequently, 300 pulses of real or sham 1 Hz rTMS were applied during a word-detection task. Priming with 1 Hz rTMS facilitated the detection of native words, whereas priming with cTBS facilitated the detection of foreign words. Accordingly, it was suggested that the priming frequency of the TMS protocol plays a crucial role in word detection in the auditory stream.

Other studies investigated the role of the anterior vs. posterior part of the IFG in word comprehension. To this end, the left IFG was targeted with high-frequency online rTMS during phonological and semantic judgement tasks in several previous studies (e.g., Devlin et al., 2003; Gough et al., 2005; Hartwigsen, Price, et al., 2010; Kohler, Paus, Buckner, & Milner, 2004; Nixon et al., 2004; Romero et al., 2006). These studies provided evidence for a functional–anatomical double dissociation within the left IFG, with the anterior part (aIFG) being necessary for decisions on the meaning of word stimuli (i.e., semantic processing) and the posterior part (pIFG) being more engaged in decisions on the sound of words (i.e., phonological processing). Other studies found that beyond the IFG, the inferior parietal cortex also contributes to phonological decisions (Hartwigsen, Baumgaertner, et al., 2010; Kirschen, Davis-Ratner, Jerde, Schraedley-Desmond, & Desmond, 2006; Pattamadilok, Knierim, Kawabata Duncan, & Devlin, 2010; Romero et al., 2006; Stoeckel et al., 2009) or verbal working memory (Deschamps, Baum, & Gracco, 2014). For instance, Romero et al. (2006) demonstrated that the left supramarginal gyrus (SMG) makes a critical contribution to phonological decisions in healthy volunteers. In that study, 5 Hz online rTMS over either left SMG or pIFG relative to a control site in the vertex significantly disrupted judgments on visually presented words in different tasks, suggesting an involvement of both regions in short term retention of verbal material as well as phonological judgments. This is consistent with the findings of Kirschen et al. (2006) who reported that TMS over the inferior parietal lobe significantly modulates phonological short-term memory.

Many previous online TMS studies contributed to a better understanding of the role of the left motor cortex in speech perception (for detailed reviews, see Devlin & Watkins, 2007; Papeo, Pascual-Leone, & Caramazza, 2013). In one of the initial studies, Watkins, Strafella, and Paus (2003) reported facilitation of motor evoked potentials (MEPs) recorded from lip muscles (i.e., orbicularis oris) when subjects listened to speech while viewing noise or viewed lip movements of continuous speech while listening to white noise. The facilitation of the MEP amplitudes was restricted to the stimulation of left but not right primary motor cortex. These results provide evidence for an observation–execution matching process, linking speech-related visual and auditory input in a somatotopically specific fashion to effective representation in the primary motor cortex (Watkins et al., 2003). In another study, Watkins and Paus (2004) combined TMS and positron emission tomography to demonstrate that the increased excitability of the primary motor cortex lip areas as measured by an increase in the

MEP amplitudes was positively correlated with an increase in the regional cerebral blood flow in pIFG during speech listening. These results indicate that the excitability of the primary motor cortex lip representation is influenced by input from the pIFG during speech perception. It was suggested that the reported increase in motor excitability of the speech production system could reflect covert imitation or internal speech that might improve comprehension of the percept (Devlin & Watkins, 2007; see also Murakami, Ugawa, & Ziemann, 2013).

TMS has also been used to demonstrate a differential engagement of different subareas within the left middle frontal gyrus in the production of grammatical categories (Cappelletti, Fregni, Shapiro, Pascual-Leone, & Caramazza, 2008; Shapiro, Pascual-Leone, Mottaghy, Gangitano, & Caramazza, 2001). These studies showed that an intact function of left anterior midfrontal gyrus is essential for efficient verb but not noun processing.

3.2. Multifocal TMS studies and meta-linguistic processes

While conventional paradigms apply unifocal online rTMS over a single cortical area, more recent language studies also have started to include multifocal rTMS over two or more areas simultaneously (Hartwigsen, Baumgaertner, et al., 2010; Hartwigsen, Price, et al., 2010). The multifocal TMS approach offers the possibility to study interhemispheric or intrahemispheric interaction and compensation by comparing the effects of unifocal TMS over one area with the effects of simultaneous, multifocal stimulation over two sites.

In two studies, we demonstrated that the involvement of frontal and parietal areas in phonological judgements is not restricted to the left hemisphere. Both studies investigated the contribution of homolog regions in both hemispheres to phonological decisions with a novel approach in which rTMS was applied either unilaterally over left or right-hemispheric regions or simultaneously to both hemispheres (Hartwigsen, Baumgaertner, et al., 2010; Hartwigsen, Price, et al., 2010). In one study (Hartwigsen, Price, et al., 2010), high-frequency rTMS was applied over either the left, right or bilateral pIFG or aIFG (see Fig. 1A and B) in two groups of volunteers performing phonological and semantic judgements. In the phonological task, subjects had to indicate via button press whether a high-frequent German noun consisted of two or three syllables. The semantic task required the subject to decide whether the same word represented a natural or man-made item (Fig. 1C and D). This design allowed us to investigate whether right pIFG activation with phonological processing reported in previous fMRI studies (Chee, O'Craven, Bergida, Rosen, & Savoy, 1999; Devlin et al., 2003; Poldrack et al., 1999; Shibahara, 2004; Tremblay, Monetta, & Joanette, 2004) would be necessary for accurate and efficient phonological decisions in the healthy brain. The simultaneous application of rTMS over left and right pIFG enabled us to test whether both areas can compensate a virtual lesion to the respective other area. We found that rTMS over pIFG but not aIFG selectively interfered with phonological but not semantic judgements irrespective of the stimulated hemisphere (left, right or bilateral), indicating that both the left and right pIFG equally contribute to efficient phonological processing (Fig. 1E and F). Interestingly, the intensity threshold for inducing a disruptive rTMS effect on phonological decisions was identical for both hemispheres. In another study (Hartwigsen, Baumgaertner, et al., 2010), we used the same experimental paradigm to demonstrate that efficient modality-independent phonological judgements require both the left and the right SMG in healthy subjects. These results suggest that both hemispheres equally contribute to efficient phonological decisions in the healthy brain without any evidence for an acute compensation of a "virtual lesion" induced in the homolog cortical area in the opposite hemisphere.

A contribution of right-hemispheric brain regions to language has also been demonstrated by several uni-focal studies that compared the effects of rTMS over both hemispheres during different language tasks (e.g., Harpaz, Levkovitz, & Lavidor, 2009; Hoekert, Vingerhoets, & Aleman, 2010; Lauro, Pisoni, Zerboni, & Papagno, 2007; Papagno et al., 2009; Pobric, Mashal, Faust, & Lavidor, 2008; van Rijn et al., 2005). For instance, Papagno et al. (2009) applied 15 Hz rTMS over either left IFG, left or right pSTG, left inferior parietal cortex or vertex (control site) while participants decided whether a letter string represented a real word or not. The authors reported impaired task processing for abstract words when rTMS was applied to left pSTG, while concrete words were disrupted with TMS over right pSTG. Relative to vertex stimulation, TMS over left IFG also decreased accuracy for abstract but not concrete words while parietal TMS did not interfere with task performance. This suggests a differential involvement of both hemispheres in the storage of abstract and concrete items, with abstract lexical entries being stored in left pSTG and left IFG, and concrete items being represented in right pSTG. However, the result from another TMS study (Lauro et al., 2007) rather pointed towards an involvement of the right temporal cortex in the processing of abstract semantic judgments, since 5 Hz online rTMS of the anterior inferior right but not left temporal lobe selectively interfered with abstract but not concrete semantic judgments. These diverging results may indicate that different subareas within the right (and left) hemisphere may contribute differentially to the lexical processing of abstract vs. concrete words.

In sum, these results challenge the notion that language comprehension is generally restricted to the left hemisphere. These studies rather point towards a general contribution of the right hemisphere to meta-linguistic tasks such as supra-segmental phonological processing, emotional prosody perception, novel metaphor processing or ambiguous word comprehension.

3.3. The condition-and-perturb approach in language networks

More recently, we adopted a novel condition-and-perturb rTMS approach (Hartwigsen et al., 2012), see also (O'Shea et al., 2007; Sack, Camprodon, Pascual-Leone, & Goebel, 2005; Strens, Fogelson, Shanahan, Rothwell, & Brown, 2003), combining offline rTMS conditioning over one area with subsequent online perturbation over another area within the same network (Hartwigsen et al., under review). That study addressed the joined functional contribution of inferior frontal and parietal areas to phonological and semantic word decisions. The condition-and-perturb approach can be used to change the functional weight within a certain (language) network and investigate rapid reorganization within the same hemisphere. A schematic illustration of this approach is given in Fig. 2. Fig. 2A shows the expected contribution of two areas in the left hemisphere to a semantic language task. As displayed in Fig. 2B, the conditioning of region A with offline rTMS before the task may decrease the functional contribution of this area to a given task. In turn, the task-related contribution of area B in the same hemisphere may be enhanced. The upregulation of region B may help to maintain task performance at a normal level. If area B is additionally perturbed with online rTMS, the total lesion load should be increased. Consequently, the summation of the lesion effects over area A and B may decrease task performance (Fig. 2C).

One obvious advantage of the condition-and-perturb approach relative to the (simultaneous) application of multifocal online rTMS is that neighbouring areas within the same hemisphere can be targeted with standard coils without any restrictions in coil placement. Moreover, the combination of offline conditioning and online perturbation allows for the investigation of rapid reorganization (i.e., a change in the functional weight) within a network.
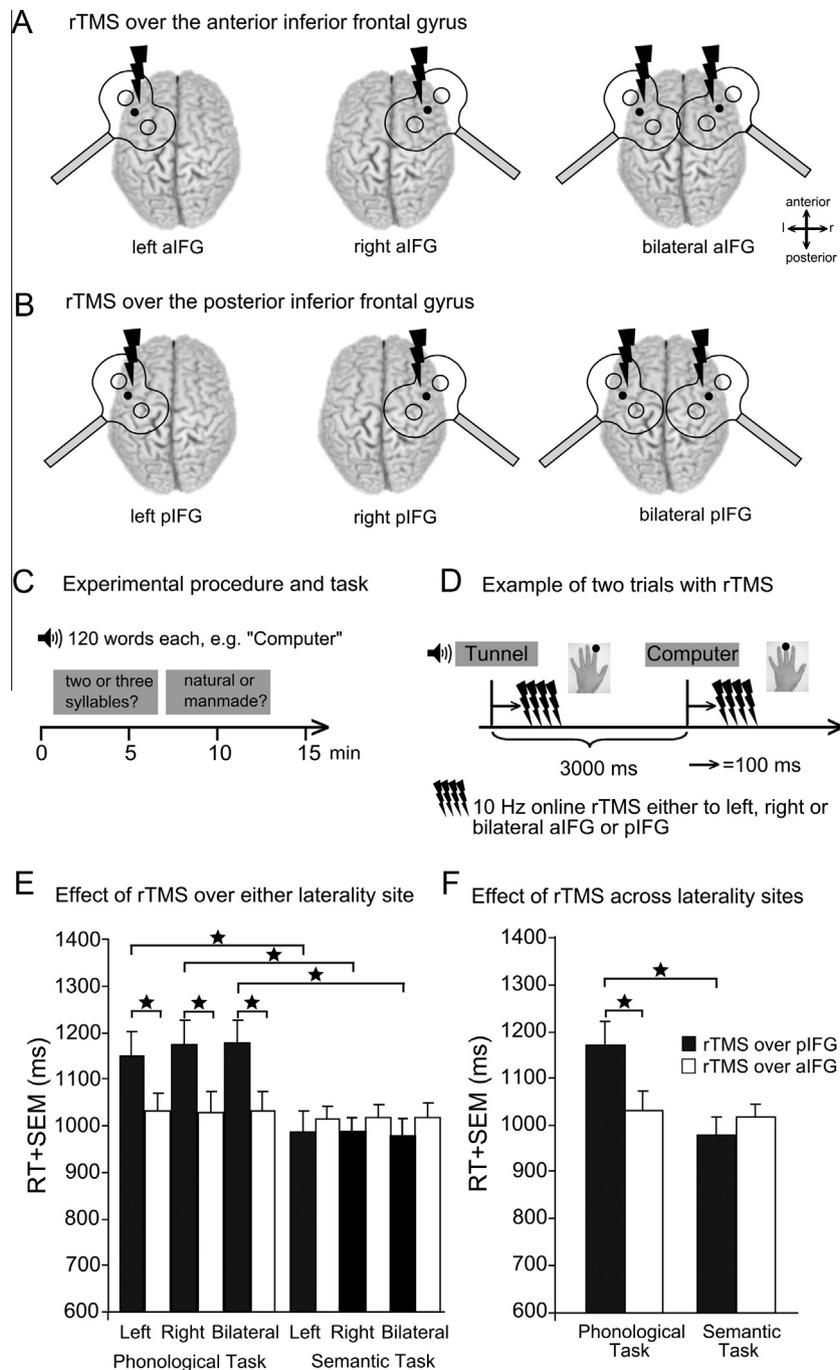
Fig. 1. Effects of multifocal rTMS over the anterior and posterior inferior frontal gyrus (aIFG/pIFG). (A) and (B) Stimulation sites over the left, right and bilateral aIFG and pIFG; respectively. Mean MNI-coordinates were obtained from previous studies (see original study for details). (C) Auditory run of the two blocked tasks. (D) Example of two single trials with rTMS. Each trial had a duration of 3000 ms. A 4-pulse train of 10 Hz online rTMS was applied 100 ms after word onset over left, right or bilateral aIFG or pIFG. Subjects responded with their left index or middle finger. ms = milliseconds; min = minutes. (E) and (F). Both panels display the effects of rTMS over aIFG and pIFG on mean reaction times (RT) for the phonological and semantic task. rTMS over pIFG vs. aIFG selectively affected phonological but not semantic RT independent of the rTMS laterality site (left, right, bilateral). Note that the three rTMS laterality sites are shown separately in (E) for illustrating purposes although the two-way interaction was pooled across rTMS laterality site. Error bars represent onefold standard error from the mean (SEM); $^*p < 0.05$; two-tailed; ms = milliseconds. *Adapted and reprinted from Hartwigsen et al., Neuropsychologia, vol. 48(10), 2010, pp. 3155–3163. Copyright (2010) Elsevier.*

In our recent study (Hartwigsen et al., under review) we tested for a functional–anatomical double dissociation in parieto-frontal networks for word comprehension. Based on previous rTMS studies on phonological and semantic processing (Devlin et al., 2003; Gough et al., 2005; Hartwigsen, Baumgaertner, et al., 2010; Hartwigsen, Price, et al., 2010; Nixon et al., 2004; Romero et al., 2006), see Section 3.1 for details), we expected that left pIFG and SMG should be essential for phonological word decisions while

aIFG and potentially also angular gyrus (AG) might be more engaged in semantic decisions. To investigate whether the functional contribution of one area changes in the presence of a dysfunctional region within the same network, we combined offline rTMS over the parietal areas with subsequent online rTMS over the frontal nodes. We found that decisions on the sound of word stimuli were selectively delayed after offline rTMS over left SMG or online rTMS over left pIFG, but not with rTMS over the semantic
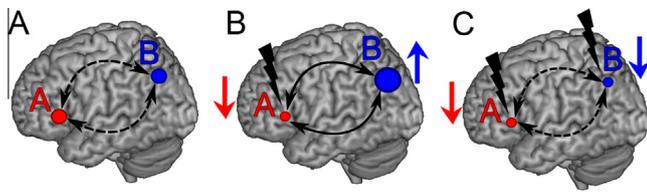
Fig. 2. The condition-and-perturb approach. Schematic illustration of rTMS-induced changes in the functional weight within a language network. (A) Two language regions for semantic processing (see text for details). The functional interaction between both nodes is indicated by the dotted arrows. (B) The rTMS-induced disruption of region A decreases the functional contribution of this area to the semantic task (indicated by the small circle). In turn, the contribution of area B is enhanced as indicated by the large circle. The up-regulation of region B may help to maintain task performance. The functional connectivity between both regions might also be enhanced as indicated by the bold arrows. (C) If area B is additionally lesioned with rTMS, this might result in a decrease in task performance.

control areas. Notably, the unifocal rTMS lesion effect was not enhanced by combining rTMS of SMG with rTMS of pIFG. This suggests that a single focal disruption over one phonological area was already sufficient to delay task performance, without any evidence for an acute compensation of the rTMS-induced lesion effect. In contrast, semantic decisions were only impaired when offline rTMS over ANG was combined with online rTMS of aIFG (see also Fig. 2C), but not after unifocal rTMS over either area alone. This shows that offline rTMS over ANG caused a dysfunction which increased the functional relevance of left aIFG for semantic decisions and sensitized this network to the disruptive effect of online rTMS over aIFG (see Fig. 2 for the hypothesized mechanisms). Hence, these results provide causal evidence that ANG and aIFG both contribute to semantic decisions on the word level and that the functional significance of one area within this network depends on the functional integrity of the other region.

While these findings are generally compatible with previous studies demonstrating disrupted phonological processing after unifocal rTMS over either pIFG or SMG (Gough et al., 2005; Romero et al., 2006), several unifocal rTMS studies reported different results with respect to the effects of rTMS on semantic decisions. For instance, two studies found significantly impaired semantic processing after online rTMS over aIFG (Devlin et al., 2003; Gough et al., 2005), and unifocal online rTMS over ANG also delayed semantic decisions in a recent study (Sliwinska et al., 2014). This contrasts with two previous studies that did not find any disruptive effects of TMS over either aIFG or ANG (Hartwigsen, Baumgaertner, et al., 2010; Hartwigsen, Price, et al., 2010) and seems to be in discordance with the finding of the multifocal TMS study that only combined TMS over both nodes significantly delayed semantic decisions (see above). One possible explanation for these divergent observations might be related to the stimulation intensity of the TMS procedure. Indeed, the TMS intensities were considerably higher in the studies that reported impaired semantic processing after unifocal rTMS (i.e., 55–60% maximum stimulator output or 110% resting motor threshold) compared with those studies that reported negative findings after unifocal perturbations (80–90% active or resting motor threshold, corresponding to a maximum of 30–50% stimulator output). This might indicate that the potential for an acute compensation of the virtual lesion effect between parieto-frontal areas for semantic processing as reported in the multifocal study might be restricted to a moderate focal dysfunction evoked with rTMS at low stimulation intensities. Other possible methodological issues that could have contributed to the divergent results are differences in the employed task and targeted subareas. With respect to the implications of these findings for word comprehension, this might indicate that the semantic network is more robust against focal perturbations than the phonological network. These results again show that the TMS-induced virtual lesion effect

critically depends on the selected stimulation parameters (i.e., the intensity of the TMS protocol) and the employed task.

4. Plasticity in the healthy language network

In recent years, an increasing number of studies combined offline stimulation with neuroimaging techniques to investigate rapid reorganization in the healthy human brain. However, most of these studies were performed in the motor cortex. Yet, relatively few studies used multimodal approaches combining non-invasive brain stimulation and neuroimaging techniques in language areas. A better understanding of the basic mechanisms of adaptive short-term plasticity in language networks is particularly important to advance the current knowledge of reorganizational processes in patients with brain damage and develop effective treatment strategies.

4.1. rTMS studies

Adaptive plasticity in the healthy language system was investigated in a recent study combining high-frequency offline rTMS with subsequent fMRI during word recognition (Andoh & Paus, 2011). In that study, auditory word recognition tasks of native and foreign words were performed during fMRI before and after the application of 10 Hz rTMS over either left or right pSTG in two groups. The authors reported increased task-related activity in the respective contralateral, non-stimulated homologue after rTMS over either hemisphere. These activity increases were interpreted in terms of adaptive short-term compensation. In contrast to the observed changes in neural activation, a significant decrease in reaction times for native relative to foreign words was selectively found after rTMS over left but not right pSTG. While these results support the role of the left pSTG in lexical processing, it remains unclear whether the reported behavioural improvement was related to *increased* task-related activity in the contralateral right hemisphere or *decreased* activity at the site of stimulation in left pSTG (Andoh & Paus, 2011). Future studies investigating TMS-induced changes in the functional influence between the left and right hemisphere might contribute to a better understanding of short-term plasticity during lexical processing.

Interhemispheric interactions between homolog regions were also investigated with a combined TMS-fMRI approach in the auditory system (Andoh & Zatorre, 2013). Subjects performed a melody discrimination task during fMRI before and after continuous theta-burst stimulation over the right auditory cortex. In that study, cTBS increased the task-related activity in the contralateral auditory cortex. The strength of the upregulation of the task-related increase in the contralateral auditory cortex correlated with behavioural performance. Those subjects who showed stronger activity increases had relatively faster reaction times whereas individuals with reduced contralateral activity did not exhibit any behavioural facilitation. Moreover, stronger interhemispheric connectivity between auditory cortices before TMS was associated with faster response times after TMS. These results show that TMS can promote plastic short-term reorganization in the auditory network. Although this study was restricted to the primary auditory cortices, the underlying mechanisms might be similar to the plastic changes observed after focal perturbations in the language system.

In a recent study (Hartwigsen et al., 2013), we combined offline with subsequent fMRI to investigate the contribution of the right hemisphere to speech production after a focal perturbation of the left hemisphere in the healthy brain. To this end, effective or sham cTBS was applied over either the posterior or anterior IFG before subjects performed a simple overt repetition task on word and pseudoword stimuli in the MR scanner. As expected from previous

imaging studies, left pIFG but not right pIFG exhibited increased task-related activity during pseudoword vs. word repetition at baseline (i.e., with sham cTBS) (Fig. 3A) or after cTBS over aIFG. We did not observe any changes in the task-related connectivity between both areas during pseudoword vs. word repetition after sham cTBS. In contrast, relative to cTBS over aIFG, cTBS over pIFG significantly suppressed task-related activity in the left pIFG during pseudoword vs. word repetition (Fig. 3B, in blue). In turn, we found a strong upregulation of the contralateral homolog area after cTBS of pIFG relative to aIFG (Fig. 3B, in red). Moreover, effective connectivity analyses revealed that this effect was associated with a stronger facilitatory influence from the right pIFG to the left pIFG during pseudoword repetition. Critically, response times became faster as the influence of the right pIFG on left pIFG increased, indicating that homolog areas in the right hemisphere can actively contribute to speech production after a focal left-hemispheric perturbation. Our findings lend further support to the notion that increased activation of homologous right hemisphere areas might support aphasia recovery after left hemisphere damage.

In another multimodal study, Fuggetta, Rizzo, Pobric, Lavidor, and Walsh (2009) combined event-related potentials (ERPs) with rTMS to investigate the neural basis of semantic processing. In that study, rTMS was given over either left or right Wernicke's area or a control site in the occipital cortex during a picture-word verification task. To avoid stimulation-induced artefacts in the EEG signal, TMS application and EEG recordings were separated in time, with the 500 ms train of 10 Hz rTMS starting 750 ms before stimulus onset and the ERP recordings being stimulus-locked. rTMS selectively delayed response latencies for artificial relative to natural items when applied over left Wernicke's area, but not over the right hemisphere or the control site. Interestingly, the dissociation between artificial and natural items with TMS over Wernicke's area had a direct ERP correlate mainly reflected by systematic effects on the late positive complex over the central–parietal electrodes of the right hemisphere. The authors suggested that this amplitude increase reflected a compensatory transfer of language function from the left to the right hemisphere. Accordingly, rTMS might have interfered with post-perceptual categorization processing of natural and artificial stimuli that involve separate

subsystems in distinct cortical areas. The absence of any rTMS effect on natural items might indicate a more bilateral representation of sensory and perceptual features related to the processing of these items. The authors inferred that the rTMS-induced disruption of Wernicke's area might have to some degree been compensated by the functional involvement of the right hemisphere, indicating a functionally relevant integration of right hemisphere activity into the normal language network subserving language comprehension on the word level.

Together, the above cited studies stress the value of multimodal approaches to investigate networks for language comprehension and speech production by combining neuroimaging techniques with TMS. These studies demonstrate how TMS can be used to induce adaptive plasticity in language networks that can be quantified by subsequent neuroimaging.

4.2. tDCS studies

Most of the tDCS studies in the healthy language system applied anodal tDCS over left IFG or STG to facilitate learning tasks or picture naming. A better understanding of the potential of tDCS to improve language functions is of particular relevance for the application in rehabilitation settings. For instance, De Vries et al. (2010) targeted left IFG with tDCS during the acquisition phase of an implicit grammar learning task. This study reported improved performance in a subsequent grammatical decision task after a single 20 min session of 1 mA anodal tDCS over left IFG as compared with sham tDCS and anodal tDCS over right IFG. Particularly, the detection of syntactic violations was improved after anodal tDCS, which might be of relevance for facilitating recovery in some patients with post-stroke aphasia.

In a multimodal approach, Holland et al. (2011) investigated the effects of anodal tDCS over left IFG on behavioural performance and neural activity. Relative to sham tDCS, 2 mA of anodal tDCS significantly facilitated picture naming latencies. Behavioural improvements were accompanied by decreased task-related activity in the stimulated area during concurrent fMRI. Correlational analysis showed that faster naming responses were associated with decreased neural activity in the IFG. The decreased neural
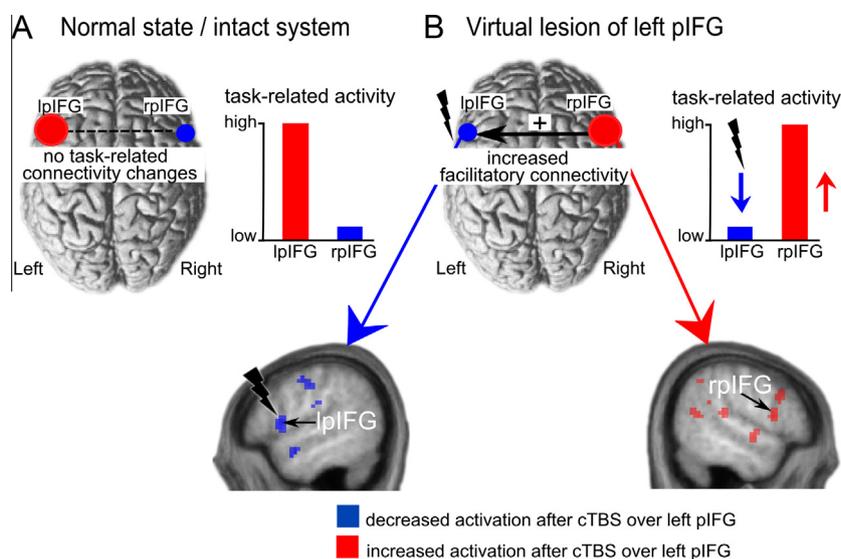
Fig. 3. Illustration of rTMS-induced adaptive plasticity during speech production in the healthy brain. (A) without any rTMS influences, the left posterior inferior frontal gyrus shows increased activation during a pseudoword repetition task (big red circle) while the right homologue does not significantly contribute (small blue circle). There is no significant task-related connectivity between both regions during pseudoword repetition. (B) Continuous theta-burst stimulation (cTBS) over left pIFG decreases task-related activity in the stimulated area (small blue circle) and increases the activity of the right homologue (large red circle). cTBS over left pIFG is followed by an increase in the task-related facilitatory drive from the right to the left pIFG which helps to maintain task-performance (see text for details). *Adapted and reprinted from Hartwigsen et al., Proceedings of the National Academy of Sciences of the USA,* vol. 10(41), *2013,* pp. 16402–16407. Copyright (2013) National Academy of Sciences, USA.

activation in left IFG was suggested to parallel effects of neural priming reported in previous behavioural studies. Accordingly, it was suggested that anodal tDCS during picture naming may facilitate behavioural responses via a regionally specific neural adaptation mechanism in left IFG.

In a complementary multimodal approach, Wirth et al. (2011) combined anodal tDCS over left dorsal prefrontal cortex with EEG during a semantic interference task and picture naming. Relative to sham tDCS, 30 min of anodal tDCS at 1.5 mA resulted in a significant behavioural facilitation that was underpinned by an enhanced electrophysiological semantic interference effect (i.e., increased event-related potentials). These results were taken to reflect a superior tuning of neural responses with language-related generators. Additionally, a significant reduction in delta activity was observed during rest and picture naming after offline tDCS over dorsal prefrontal cortex. These effects were interpreted as neural disinhibition. Together, the behavioural and neural markers identified in this study might be used to inform prefrontal stimulation during speech production in studies on aphasia recovery.

A different approach was used by Javadi, Cheng, and Walsh (2012). These authors applied short-duration tDCS (1.6 s per trial) over the dorsolateral prefrontal cortex during a memory performance task. When applied during word presentation, anodal tDCS significantly increased behavioural performance when subjects had to memorize words. This effect was reversed with cathodal tDCS. In contrast, later stimulation onsets after word presentation did not significantly influence behavioural performance. These results highlight the importance of the timing of the stimulation.

The beneficial effects of anodal tDCS on different language functions might be explained by an increase in the efficiency of task processing locally in the stimulated areas as well as in interconnected language regions. While the precise physiological mechanisms of the tDCS-induced modulation remain elusive, future studies employing tDCS and neuroimaging should focus on the investigation of tDCS-induced changes in the effective connectivity between network nodes to illuminate network interactions during speech and language processes.

Interestingly, a recent study by Fertonani, Brambilla, Cotelli, and Miniussi (2014) suggests that the reported behavioural improvements after anodal tDCS over the left dorsolateral prefrontal cortex may be age-dependent. In their study, anodal tDCS improved naming performance only when it was applied during task execution in elderly subjects, whereas young subjects benefitted from both offline stimulation before the task and online stimulation during the task. These findings may point towards altered synaptic plasticity in the ageing brain, which is of particular importance for the application of tDCS in neurorehabilitation in (older) patients.

Several studies reported behavioural facilitation of speech production, including verbal learning tasks or picture naming with anodal tDCS over left posterior superior temporal cortex (Fiori et al., 2011; Floel, Rosser, Michka, Knecht, & Breitenstein, 2008; Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008). In a study by Meinzer et al. (2014), repeated sessions of anodal tDCS relative to sham tDCS during explicit word learning facilitated the recall of both novel and familiar words. The beneficial tDCS effects were maintained in a follow-up test after 1 week. This observation would be compatible with the notion that repeated sessions of tDCS might induce long-term effects in the stimulated network (Cohen Kadosh et al., 2010; Reis et al., 2009), which implies that tDCS might be used to modulate long-term plasticity in stroke rehabilitation.

To date, relatively few studies investigated the disruptive effects of cathodal tDCS in the healthy language system. For instance, Fiori, Cipollari, Caltagirone, and Marangolo (2014) reported that the repetition of tongue twisters was significantly enhanced after 20 min of anodal tDCS over the left frontal cortex while cathodal tDCS disrupted task performance, with the effects lasting for up to an hour

after the end of stimulation. These data suggest that left inferior frontal cortex is critical for speech repetition.

In another study, Liuzzi et al. (2010) tested the functional relevance of the left primary motor cortex for novel action word learning with cathodal tDCS. 20 min of anodal, cathodal or sham offline tDCS was applied over four consecutive days prior to the learning sessions. Compared with sham stimulation, cathodal tDCS significantly reduced success rates in vocabulary acquisition. Specifically, cathodal tDCS decreased the ability to associatively couple actions with novel words, providing evidence for a causal involvement of left primary motor cortex in the acquisition of novel action-related words.

Cathodal tDCS was also used to probe the relevance of right hemispheric regions in language processing. For instance, a recent study (Rosso et al., 2014) applied 15 min of cathodal and sham tDCS at 1 mA to the right inferior frontal gyrus prior to a picture-naming task. The authors reported decreased response speed after cathodal relative to sham tDCS. The paradoxical facilitation was explained by a tDCS-induced reduction of very slow responses. Notably, the individual behavioural acceleration during picture naming was positively correlated with larger volumes of the tract connecting the right Broca homologue and the right supplementary motor area (SMA), and a stronger intrinsic coupling from the right SMA to the right Broca homologue as revealed by effective connectivity analyses. The authors suggested that the after-effects of tDCS on brain function are at least in part determined by the anatomical and functional connectivity of the targeted region.

In a recent concurrent tDCS-fMRI study, Meinzer et al. (2013) probed the neural correlates of behavioural facilitation induced by anodal tDCS over left IFG during overt semantic word generation. Relative to sham tDCS, anodal tDCS at 1 mA significantly improved word retrieval. The beneficial behavioural effects were paralleled by a reduction in the task-related activity in the left ventral IFG. Moreover, the authors reported increased connectivity between the left IFG and other core areas for language processing, including left middle temporal gyrus and bilateral inferior frontal, inferior parietal and prefrontal regions during resting-state fMRI. These results were taken as evidence for a tDCS-induced modulation of endogenous low-frequency oscillations in the language network that might have induced more efficient task processing in relevant network nodes and might thus explain the observed behavioural improvement.

tDCS has also been used to modulate paralinguistic features in the right hemisphere. One study reported decreased response times to subordinate but not dominant associations after anodal tDCS as compared with sham tDCS over right Wernicke's area (Peretz & Lavidor, 2013). These findings further support the notion of a right-hemispheric contribution to meta-linguistic language processes such as lexical ambiguity resolution.

In sum, these studies show that tDCS is a powerful tool to modulate cortical excitability in language networks in the healthy brain and might be of potential benefit in promoting aphasia recovery after stroke. Indeed, an increasing number of studies applied tDCS in patients with post-stroke aphasia to facilitate recovery (see Hamilton et al., 2011; Monti et al., 2013 for review). While the results of these preliminary studies in patients are generally encouraging, the reported effect sizes are not striking. Hence, it remains unclear whether tDCS might enhance language functions after brain damage at a level that is clinically relevant (Hartwigsen & Siebner, 2012) and future studies on larger patient collectives are needed to explore the potential benefit of tDCS in the neurorehabilitation of language functions. Here, it might be worthwhile to use multimodal approaches, combining imaging methods and non-invasive brain stimulation to consider the individual time-course of recovery. This may include the application of different stimulation protocols during different phases of

reorganization after stroke (Chrysikou & Hamilton, 2011; Saur & Hartwigsen, 2012).

5. Conclusions and future directions

Across the last few years, the application of non-invasive brain stimulation in studies of language has substantially increased our knowledge about the causal role of different brain regions in various aspects of language processing. Moreover, these techniques have provided novel insights into the mechanisms of adaptive short-term reorganization and plasticity in the healthy language system. Yet, relatively few studies used multimodal approaches that combine non-invasive brain stimulation with neuroimaging techniques such as fMRI or EEG. The offline combination of brain stimulation and imaging is relatively easy to establish. Recent studies demonstrated that non-invasive brain stimulation induces plastic changes within language networks that are not restricted to the dominant (left) hemisphere. At least after focal perturbations of left-hemispheric language areas, homolog right-hemispheric regions might actively contribute to language function. These findings may be used to inform models on language recovery in patients with post-stroke aphasia in future studies.

Although the concurrent combination of TMS and fMRI is technically challenging and has not been used in the study of language so far, this approach may be particularly suited to probe the immediate effects of focal perturbations on language networks and provide further insights into the neurophysiology of language. Concurrent TMS and fMRI might thus be used in future studies to explore the dynamic aspects of language processing in the healthy system, and elucidate how the functional interactions between language areas are affected by stroke.

Another promising approach might be the application of novel techniques such as transcranial alternating current stimulation or transcranial random noise stimulation. Both methods have been recently applied to synchronize or desynchronize cortical oscillations during motor, perceptual and cognitive tasks such as decision making or learning with specific or random frequencies (Kuo & Nitsche, 2012). The modulation of cognition-related oscillations might prove effective in facilitating language recovery after stroke in future studies.

Acknowledgments

References

Amassian, V. E., & Maccabee, P. J. (2006). Transcranial magnetic stimulation. *Annual international conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society conference, 1*, 1620–1623.

Andoh, J., Artiges, E., Pallier, C., Riviere, D., Mangin, J. F., Cachia, A., et al. (2006). Modulation of language areas with functional MR image-guided magnetic stimulation. *Neuroimage, 29*(2), 619–627.

Andoh, J., Artiges, E., Pallier, C., Riviere, D., Mangin, J. F., Paillere-Martinot, M. L., et al. (2008). Priming frequencies of transcranial magnetic stimulation over Wernicke's area modulate word detection. *Cerebral Cortex, 18*(1), 210–216.

Andoh, J., & Paus, T. (2011). Combining functional neuroimaging with off-line brain stimulation: Modulation of task-related activity in language areas. *Journal of Cognitive Neuroscience, 23*(2), 349–361.

Andoh, J., & Zatorre, R. J. (2013). Mapping interhemispheric connectivity using functional MRI after transcranial magnetic stimulation on the human auditory cortex. *Neuroimage, 79*, 162–171.

Antal, A., Nitsche, M. A., Kruse, W., Kincses, T. Z., Hoffmann, K. P., & Paulus, W. (2004). Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. *Journal of Cognitive Neuroscience, 16*(4), 521–527.

Antal, A., & Paulus, W. (2013). Transcranial alternating current stimulation (tACS). *Frontiers in Human Neuroscience, 7*, 317–321.

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *Lancet, 1*(8437), 1106–1107.

Bersani, F. S., Minichino, A., Enticott, P. G., Mazzarini, L., Khan, N., Antonacci, G., et al. (2013). Deep transcranial magnetic stimulation as a treatment for psychiatric disorders: A comprehensive review. *European Psychiatry, 28*, 30–39.

Bestmann, S. (2008). The physiological basis of transcranial magnetic stimulation. *Trends in Cognitive Sciences, 12*(3), 81–83.

Bestmann, S., Baudewig, J., Siebner, H. R., Rothwell, J. C., & Frahm, J. (2003). Subthreshold high-frequency TMS of human primary motor cortex modulates interconnected frontal motor areas as detected by interleaved fMRI-TMS. *Neuroimage, 20*(3), 1685–1696.

Bindman, L. J., Lippold, O. C., & Redfearn, J. W. (1962). Long-lasting changes in the level of the electrical activity of the cerebral cortex produced by polarizing currents. *Nature, 196*, 584–585.

Bindman, L. J., Lippold, O. C. J., Redfearn, J. W. T., & Physiology, J. O. (1964). The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. *Journal of Physiology, 172*, 369–382.

Boroojerdi, B., Meister, I. G., Foltys, H., Sparing, R., Cohen, L. G., & Topper, R. (2002). Visual and motor cortex excitability: A transcranial magnetic stimulation study. *Clinical Neurophysiology, 113*(9), 1501–1504.

Brasil-Neto, J. P., Cohen, L. G., Panizza, M., Nilsson, J., Roth, B. J., & Hallett, M. (1992a). Optimal focal transcranial magnetic activation of the human motor cortex: Effects of coil orientation, shape of the induced current pulse, and stimulus intensity. *Journal of Clinical Neurophysiology, 9*(1), 132–136.

Brasil-Neto, J. P., McShane, L. M., Fuhr, P., Hallett, M., & Cohen, L. G. (1992b). Topographic mapping of the human motor cortex with magnetic stimulation: Factors affecting accuracy and reproducibility. *Electroencephalography and Clinical Neurophysiology, 85*(1), 9–16.

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., et al. (2012). Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. *Brain Stimulation, 5*(3), 175–195.

Cappelletti, M., Fregni, F., Shapiro, K., Pascual-Leone, A., & Caramazza, A. (2008). Processing nouns and verbs in the left frontal cortex: A transcranial magnetic stimulation study. *Journal of Cognitive Neuroscience, 20*(4), 707–720.

Cattaneo, Z., Devlin, J. T., Salvini, F., Vecchi, T., & Silvanto, J. (2010). The causal role of category-specific neuronal representations in the left ventral premotor cortex (PMv) in semantic processing. *Neuroimage, 49*, 2728–2734.

Chee, M. W., O'Craven, K. M., Bergida, R., Rosen, B. R., & Savoy, R. L. (1999). Auditory and visual word processing studied with fMRI. *Human Brain Mapping, 7*(1), 15–28.

Chrysikou, E. G., & Hamilton, R. H. (2011). Noninvasive brain stimulation in the treatment of aphasia: Exploring interhemispheric relationships and their implications for neurorehabilitation. *Restorative Neurology and Neuroscience, 29*(6), 375–394.

Cohen Kadosh, R., Soskic, S., Iuculano, T., Kanai, R., & Walsh, V. (2010). Modulating neuronal activity produces specific and long-lasting changes in numerical competence. *Current Biology, 20*(22), 2016–2020.

Coslett, H. B., & Monsul, N. (1994). Reading with the right hemisphere: Evidence from transcranial magnetic stimulation. *Brain and Language, 46*(2), 198–211.

Creutzfeld, O. D., Fromm, G. H., & Kapp, H. (1962). Influence of transcortical dc-currents on cortical neuronal activity. *Experimental Neurology, 5*(5), 436–452.

de Vries, M. H., Barth, A. C., Maiworm, S., Knecht, S., Zwitserlood, P., & Floel, A. (2010). Electrical stimulation of Broca's area enhances implicit learning of an artificial grammar. *Journal of Cognitive Neuroscience, 22*(11), 2427–2436.

Denslow, S., Bohning, D. E., Bohning, P. A., Lomarev, M. P., & George, M. S. (2005). An increased precision comparison of TMS-induced motor cortex BOLD fMRI response for image-guided versus function-guided coil placement. *Cognitive and Behavioral Neurology, 18*(2), 119–126.

Deschamps, I., Baum, S. R., & Gracco, V. L. (2014). On the role of the supramarginal gyrus in phonological processing and verbal working memory: Evidence from rTMS studies. *Neuropsychologia, 53*, 39–46.

Devlin, J. T., Matthews, P. M., & Rushworth, M. F. (2003). Semantic processing in the left inferior prefrontal cortex: A combined functional magnetic resonance imaging and transcranial magnetic stimulation study. *Journal of Cognitive Neuroscience, 15*(1), 71–84.

Devlin, J. T., & Watkins, K. E. (2007). Stimulating language: Insights from TMS. *Brain, 130*(3), 610–622.

Di Lazzaro, V., Oliviero, A., Pilato, F., Saturno, E., Dileone, M., Mazzone, P., et al. (2004). The physiological basis of transcranial motor cortex stimulation in conscious humans. *Clinical Neurophysiology, 115*(2), 255–266.

Di Lazzaro, V., Oliviero, A., Profice, P., Insola, A., Mazzone, P., Tonali, P., et al. (1999). Direct demonstration of interhemispheric inhibition of the human motor cortex produced by transcranial magnetic stimulation. *Experimental Brain Research, 124*(4), 520–524.

Dockery, C. A., Hueckel-Weng, R., Birbaumer, N., & Plewnia, C. (2009). Enhancement of planning ability by transcranial direct current stimulation. *Journal of Neuroscience, 29*(22), 7271–7277.

Ermentrout, G. B., Galan, R. F., & Urban, N. N. (2008). Reliability, synchrony and noise. *Trends in Neurosciences, 31*(8), 428–434.

Ferbert, A., Priori, A., Rothwell, J. C., Day, B. L., Colebatch, J. G., & Marsden, C. D. (1992). Interhemispheric inhibition of the human motor cortex. *Journal of Physiology, 453*, 525–546.

Fertonani, A., Brambilla, M., Cotelli, M., & Miniussi, C. (2014). The timing of cognitive plasticity in physiological aging: A tDCS study of naming. *Frontiers in Aging Neuroscience, 6*, 131–139.

Fiori, V., Cipollari, S., Caltagirone, C., & Marangolo, P. (2014). If two witches would watch two watches, which witch would watch which watch? tDCS over the left frontal region modulates tongue twister repetition in healthy subjects. *Neuroscience, 256*, 195–200.

Fiori, V., Coccia, M., Marinelli, C. V., Vecchi, V., Bonifazi, S., Ceravolo, M. G., et al. (2011). Transcranial direct current stimulation improves word retrieval in healthy and nonfluent aphasic subjects. *Journal of Cognitive Neuroscience, 23*(9), 2309–2323.

Fitzgerald, P. B., Fountain, S., & Daskalakis, Z. J. (2006). A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clinical Neurophysiology, 117*(12), 2584–2596.

Flitman, S. S., Grafman, J., Wassermann, E. M., Cooper, V., O'Grady, J., Pascual-Leone, A., et al. (1998). Linguistic processing during repetitive transcranial magnetic stimulation. *Neurology, 50*(1), 175–181.

Floel, A. (2012). Non-invasive brain stimulation and language processing in the healthy brain. *Aphasiology, 26*(9), 1082–1102.

Floel, A., Rosser, N., Michka, O., Knecht, S., & Breitenstein, C. (2008). Noninvasive brain stimulation improves language learning. *Journal of Cognitive Neuroscience, 20*(8), 1415–1422.

Fuggetta, G., Rizzo, S., Pobric, G., Lavidor, M., & Walsh, V. (2009). Functional representation of living and nonliving domains across the cerebral hemispheres: A combined event-related potential/transcranial magnetic stimulation study. *Journal of Cognitive Neuroscience, 21*(2), 403–414.

Galvani, L. (1791). *De viribus electricitatis.* The International Centre for the History of Universities and Science (CIS). Università di Bologna.

Gough, P. M., Nobre, A. C., & Devlin, J. T. (2005). Dissociating linguistic processes in the left inferior frontal cortex with transcranial magnetic stimulation. *Journal of Neuroscience, 25*(35), 8010–8016.

Hallett, M. (2000). Transcranial magnetic stimulation and the human brain. *Nature, 406*(6792), 147–150.

Hamilton, R. H., Chrysikou, E. G., & Coslett, B. (2011). Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. *Brain and Language, 118*(1–2), 40–50.

Harel, E. V., Rabany, L., Deutsch, L., Bloch, Y., Zangen, A., & Levkovitz, Y. (2014). H-coil repetitive transcranial magnetic stimulation for treatment resistant major depressive disorder: An 18-week continuation safety and feasibility study. *World Journal of Biological Psychiatry, 15*(4), 298–306.

Harpaz, Y., Levkovitz, Y., & Lavidor, M. (2009). Lexical ambiguity resolution in Wernicke's area and its right homologue. *Cortex, 45*(9), 1097–1103.

Hartwigsen, G., Baumgaertner, A., Price, C. J., Koehnke, M., Ulmer, S., & Siebner, H. R. (2010). Phonological decisions require both the left and right supramarginal gyri. *Proceedings of the National Academy of Sciences of the USA, 107*(38), 16494–16499.

Hartwigsen, G., Bestmann, S., Ward, N. S., Woerbel, S., Mastroeni, C., Granert, O., et al. (2012). Left dorsal premotor cortex and supramarginal gyrus complement each other during rapid action reprogramming. *Journal of Neuroscience, 32*(46), 16162–16171.

Hartwigsen, G., Price, C. J., Baumgaertner, A., Geiss, G., Koehnke, M., Ulmer, S., et al. (2010). The right posterior inferior frontal gyrus contributes to phonological word decisions in the healthy brain: Evidence from dual-site TMS. *Neuropsychologia, 48*(10), 3155–3163.

Hartwigsen, G., Saur, D., Price, C. J., Ulmer, S., Baumgaertner, A., & Siebner, H. R. (2013). Perturbation of the left inferior frontal gyrus triggers adaptive plasticity in the right homologous area during speech production. *Proceedings of the National Academy of Sciences of the USA, 110*(41), 16402–16407.

Hartwigsen, G., & Siebner, H. R. (2012). Probing the involvement of the right hemisphere in language processing with online transcranial magnetic stimulation in healthy volunteers. *Aphasiology, 26*(9), 1131–1152.

Hartwigsen, G., & Siebner, H. R. (2013). Novel methods to study aphasia recovery after stroke. *Frontiers of Neurology and Neuroscience, 32*, 101–111.

Hattori, Y., Moriwaki, A., & Hori, Y. (1990). Biphasic effects of polarizing current on adenosine-sensitive generation of cyclic AMP in rat cerebral cortex. *Neuroscience Letters, 116*, 320–324.

Herwig, U., Abler, B., Schonfeldt-Lecuona, C., Wunderlich, A., Grothe, J., Spitzer, M., et al. (2003). Verbal storage in a premotor-parietal network: Evidence from fMRI-guided magnetic stimulation. *Neuroimage, 20*(2), 1032–1041.

Hoekert, M., Vingerhoets, G., & Aleman, A. (2010). Results of a pilot study on the involvement of bilateral inferior frontal gyri in emotional prosody perception: An rTMS study. *BMC Neuroscience, 11*, 93.

Holland, R., & Crinion, J. (2012). Can tDCS enhance treatment of aphasia after stroke? *Aphasiology, 26*(9), 1169–1191.

Holland, R., Leff, A. P., Josephs, O., Galea, J. M., Desikan, M., Price, C. J., et al. (2011). Speech facilitation by left inferior frontal cortex stimulation. *Current Biology, 21*(16), 1403–1407.

Indefrey, P., & Levelt, W. J. (2004). The spatial and temporal signatures of word production components. *Cognition, 92*(1–2), 101–144.

Islam, N., Aftabuddin, M., Moriwaki, A., Hattori, Y., & Hori, Y. (1995). Increase in the calcium level following anodal polarization in the rat brain. *Brain Research, 684*, 206–208.

Javadi, A. H., Cheng, P., & Walsh, V. (2012). Short duration transcranial direct current stimulation (tDCS) modulates verbal memory. *Brain Stimulation, 5*(4), 468–474.

Kincses, T. Z., Antal, A., Nitsche, M. A., Bartfai, O., & Paulus, W. (2004). Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. *Neuropsychologia, 42*(1), 113–117.

Kirschen, M. P., Davis-Ratner, M. S., Jerde, T. E., Schraedley-Desmond, P., & Desmond, J. E. (2006). Enhancement of phonological memory following transcranial magnetic stimulation (TMS). *Behavioral Neurology, 17*(3–4), 187–194.

Kohler, S., Paus, T., Buckner, R. L., & Milner, B. (2004). Effects of left inferior prefrontal stimulation on episodic memory formation: A two-stage fMRI-rTMS study. *Journal of Cognitive Neuroscience, 16*(2), 178–188.

Kuo, M.-F., & Nitsche, M. A. (2012). Effects of transcranial electrical stimulation on cognition. *Clinical EEG and Neuroscience, 43*(3), 192–199.

Lauro, L. J., Pisoni, A., Zerboni, H., & Papagno, C. (2007). The neural correlates of abstract versus concrete words: Evidence from an rTMS study. *Brain and Language, 103*, 146–147.

Lee, L., Siebner, H., & Bestmann, S. (2006). Rapid modulation of distributed brain activity by Transcranial Magnetic Stimulation of human motor cortex. *Behavioral Neurology, 17*(3–4), 135–148.

Lee, L., Siebner, H. R., Rowe, J. B., Rizzo, V., Rothwell, J. C., Frackowiak, R. S., et al. (2003). Acute remapping within the motor system induced by low-frequency repetitive transcranial magnetic stimulation. *Journal of Neuroscience, 23*(12), 5308–5318.

Levkovitz, Y., Roth, Y., Harel, E. V., Braw, Y., Sheer, A., & Zangen, A. (2007). A randomized controlled feasibility and safety study of deep transcranial magnetic stimulation. *Clinical Neurophysiology, 118*(12), 2730–2744.

Liuzzi, G., Freundlieb, N., Ridder, V., Hoppe, J., Heise, K., Zimerman, M., et al. (2010). The involvement of the left motor cortex in learning of a novel action word lexicon. *Current Biology, 20*(19), 1745–1751.

Malenka, R. C., & Nicoll, R. A. (1999). Long-term potentiation – a decade of progress? *Science, 285*(5435), 1870–1874.

Meinzer, M., Jahnigen, S., Copland, D. A., Darkow, R., Grittner, U., Avirame, K., et al. (2014). Transcranial direct current stimulation over multiple days improves learning and maintenance of a novel vocabulary. *Cortex, 50*, 137–147.

Meinzer, M., Lindenberg, R., Antonenko, D., Flaisch, T., & Floel, A. (2013). Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes. *Journal of Neuroscience, 33*(30), 12470–12478.

Miniussi, C., Harris, J. A., & Ruzzoli, M. (2013). Modelling non-invasive brain stimulation in cognitive neuroscience. *Neuroscience and Biobehavioral Reviews, 37*(8), 1702–1712.

Miniussi, C., Ruzzoli, M., & Walsh, V. (2010). The mechanism of transcranial magnetic stimulation in cognition. *Cortex, 46*(1), 128–130.

Monti, A., Ferrucci, R., Fumagalli, M., Mameli, F., Cogiamanian, F., Ardolino, G., et al. (2013). Transcranial direct current stimulation (tDCS) and language. *Journal of Neurology, Neurosurgery and Psychiatry, 84*(8), 832–842.

Moriwaki, A. (1991). Polarizing currents increase noradrenaline-elicited accumulation of cyclic AMP in rat cerebral cortex. *Brain Research, 544*(2), 248–252.

Mottaghy, F. M., Hungs, M., Brugmann, M., Sparing, R., Boroojerdi, B., Foltys, H., et al. (1999). Facilitation of picture naming after repetitive transcranial magnetic stimulation. *Neurology, 53*(8), 1806–1812.

Mottaghy, F. M., Sparing, R., & Topper, R. (2006). Enhancing picture naming with transcranial magnetic stimulation. *Behavioral Neurology, 17*(3–4), 177–186.

Murakami, T., Ugawa, Y., & Ziemann, U. (2013). Utility of TMS to understand the neurobiology of speech. *Frontiers in Psychology, 4*, 446–452.

Neggers, S. F., Langerak, T. R., Schutter, D. J., Mandl, R. C., Ramsey, N. F., Lemmens, P. J., et al. (2004). A stereotactic method for image-guided transcranial magnetic stimulation validated with fMRI and motor-evoked potentials. *Neuroimage, 21*(4), 1805–1817.

Ni, Z., Charab, S., Gunraj, C., Nelson, A. J., Udupa, K., Yeh, I. J., et al. (2011). Transcranial magnetic stimulation in different current directions activates separate cortical circuits. *Journal of Neurophysiology, 105*(2), 749–756.

Nitsche, M. A., Liebetanz, D., Lang, N., Antal, A., Tergau, F., & Paulus, W. (2003). Safety criteria for transcranial direct current stimulation (tDCS) in humans. *Clinical Neurophysiology, 114*(11), 2220–2222 (author reply 2222-2223).

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *Journal of Physiology, 527*(Pt 3), 633–639.

Nixon, P., Lazarova, J., Hodinott-Hill, I., Gough, P., & Passingham, R. (2004). The inferior frontal gyrus and phonological processing: An investigation using rTMS. *Journal of Cognitive Neuroscience, 16*(2), 289–300.

O'Shea, J., Johansen-Berg, H., Trief, D., Gobel, S., & Rushworth, M. F. (2007). Functionally specific reorganization in human premotor cortex. *Neuron, 54*(3), 479–490.

Papagno, C., Fogliata, A., Catricala, E., & Miniussi, C. (2009). The lexical processing of abstract and concrete nouns. *Brain Research, 1263*, 78–86.

Papeo, L., Pascual-Leone, A., & Caramazza, A. (2013). Disrupting the brain to validate hypotheses on the neurobiology of language. *Frontiers in Human Neuroscience, 7*, 148–155.

Pascual-Leone, A., Bartres-Faz, D., & Keenan, J. P. (1999). Transcranial magnetic stimulation: Studying the brain-behaviour relationship by induction of 'virtual lesions'. *Philosophical Transactions of the Royal Society of London. Series B, Biological sciences, 354*(1387), 1229–1238.

Pascual-Leone, A., Valls-Sole, J., Wassermann, E. M., & Hallett, M. (1994). Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain, 117*(Pt 4), 847–858.

Pascual-Leone, A., Walsh, V., & Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience – virtual lesion, chronometry, and functional connectivity. *Current Opinion in Neurobiology, 10*(2), 232–237.

Pasley, B. N., Allen, E. A., & Freeman, R. D. (2009). State-dependent variability of neuronal responses to transcranial magnetic stimulation of the visual cortex. *Neuron, 62*(2), 291–303.

Pattamadilok, C., Knierim, I. N., Kawabata Duncan, K. J., & Devlin, J. T. (2010). How does learning to read affect speech perception? *Journal of Neuroscience, 30*(25), 8435–8444.

Paus, T. (2008). Combining brain imaging with brain stimulation: Causality and connectivity. In E. M. Wassermann, C. M. Epstein, U. Ziemann, V. Walsh, T. Paus, & S. H. Lisanby (Eds.), *The Oxford handbook of transcranial stimulation* (pp. 539–547). New York: Oxford University Press.

Pena-Gomez, C., Sala-Lonch, R., Junque, C., Clemente, I. C., Vidal, D., Bargallo, N., et al. (2012). Modulation of large-scale brain networks by transcranial direct current stimulation evidenced by resting-state functional MRI. *Brain Stimulation, 5*(3), 252–263.

Peretz, Y., & Lavidor, M. (2013). Enhancing lexical ambiguity resolution by brain polarization of the right posterior superior temporal sulcus. *Cortex, 49*(4), 1056–1062.

Pobric, G., Jefferies, E., & Lambon Ralph, M. A. (2010). Category-specific versus category-general semantic impairment induced by transcranial magnetic stimulation. *Current Biology, 20*(10), 964–968.

Pobric, G., Jefferies, E., & Ralph, M. A. (2007). Anterior temporal lobes mediate semantic representation: Mimicking semantic dementia by using rTMS in normal participants. *Proceedings of the National Academy of Sciences of the USA, 104*(50), 20137–20141.

Pobric, G., Mashal, N., Faust, M., & Lavidor, M. (2008). The role of the right cerebral hemisphere in processing novel metaphoric expressions: A transcranial magnetic stimulation study. *Journal of Cognitive Neuroscience, 20*(1), 170–181.

Poldrack, R. A., Wagner, A. D., Prull, M. W., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1999). Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage, 10*(1), 15–35.

Purpura, D. P., & McMurtry, J. G. (1965). Intracellular activities and evoked potential changes during polarization of motor cortex. *Journal of Neurophysiology, 28*, 166–185.

Reis, J., Schambra, H. M., Cohen, L. G., Buch, E. R., Fritsch, B., Zarahn, E., et al. (2009). Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proceedings of the National Academy of Sciences of the USA, 106*(5), 1590–1595.

Romero, L., Walsh, V., & Papagno, C. (2006). The neural correlates of phonological short-term memory: A repetitive transcranial magnetic stimulation study. *Journal of Cognitive Neuroscience, 18*(7), 1147–1155.

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology, 120*(12), 2008–2039.

Rossi, S., & Rossini, P. M. (2004). TMS in cognitive plasticity and the potential for rehabilitation. *Trends in Cognitive Sciences, 8*(6), 273–279.

Rosso, C., Valabregue, R., Arbizu, C., Ferrieux, S., Vargas, P., Humbert, F., et al. (2014). Connectivity between right inferior frontal gyrus and supplementary motor area predicts after-effects of right frontal cathodal tDCS on picture naming speed. *Brain Stimulation, 7*(1), 122–129.

Roth, Y., Amir, A., Levkovitz, Y., & Zangen, A. (2007). Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils. *Journal of Clinical Neurophysiology, 24*(1), 31–38.

Ruzzoli, M., Marzi, C. A., & Miniussi, C. (2010). The neural mechanisms of the effects of transcranial magnetic stimulation on perception. *Journal of Neurophysiology, 103*(6), 2982–2989.

Sack, A. T., Camprodon, J. A., Pascual-Leone, A., & Goebel, R. (2005). The dynamics of interhemispheric compensatory processes in mental imagery. *Science, 308*(5722), 702–704.

Sack, A. T., Kohler, A., Linden, D. E., Goebel, R., & Muckli, L. (2006). The temporal characteristics of motion processing in hMT/V5+: Combining fMRI and neuronavigated TMS. *Neuroimage, 29*(4), 1326–1335.

Sandrini, M., Umilta, C., & Rusconi, E. (2011). The use of transcranial magnetic stimulation in cognitive neuroscience: A new synthesis of methodological issues. *Neuroscience and Biobehavioral Reviews, 35*(3), 516–536.

Saur, D., & Hartwigsen, G. (2012). Neurobiology of language recovery after stroke: Lessons from neuroimaging studies. *Archives of Physical Medicine and Rehabilitation, 93*(Suppl. 1), S15–25.

Schonfeldt-Lecuona, C., Thielscher, A., Freudenmann, R. W., Kron, M., Spitzer, M., & Herwig, U. (2005). Accuracy of stereotaxic positioning of transcranial magnetic stimulation. *Brain Topography, 17*(4), 253–259.

Schuhmann, T., Schiller, N. O., Goebel, R., & Sack, A. T. (2009). The temporal characteristics of functional activation in Broca's area during overt picture naming. *Cortex, 45*(9), 1111–1116.

Schuhmann, T., Schiller, N. O., Goebel, R., & Sack, A. T. (2012). Speaking of which: Dissecting the neurocognitive network of language production in picture naming. *Cerebral Cortex, 22*(3), 701–709.

Shapiro, K. A., Pascual-Leone, A., Mottaghy, F. M., Gangitano, M., & Caramazza, A. (2001). Grammatical distinctions in the left frontal cortex. *Journal of Cognitive Neuroscience, 13*(6), 713–720.

Shibahara, N. (2004). Picture-name priming in the cerebral hemispheres: Evidence for phonological access in the right hemisphere. *Perceptual and Motor Skills, 99*(1), 305–314.

Siebner, H. R., Bergmann, T. O., Bestmann, S., Massimini, M., Johansen-Berg, H., Mochizuki, H., et al. (2009). Consensus paper: Combining transcranial stimulation with neuroimaging. *Brain Stimulation, 2*(2), 58–80.

Siebner, H. R., Filipovic, S. R., Rowe, J. B., Cordivari, C., Gerschlager, W., Rothwell, J. C., et al. (2003). Patients with focal arm dystonia have increased sensitivity to slow-frequency repetitive TMS of the dorsal premotor cortex. *Brain, 126*(Pt 12), 2710–2725.

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.

Siebner, H. R., & Rothwell, J. (2003). Transcranial magnetic stimulation: New insights into representational cortical plasticity. *Experimental Brain Research, 148*(1), 1–16.

Silvanto, J., Muggleton, N., & Walsh, V. (2008). State-dependency in brain stimulation studies of perception and cognition. *Trends in Cognitive Sciences, 12*(12), 447–454.

Sliwinska, M. W., James, A., & Devlin, J. T. (2014). Inferior parietal lobule contributions to visual word recognition. *Journal of Cognitive Neuroscience*, 1–12.

Sliwinska, M. W., Khadilkar, M., Campbell-Ratcliffe, J., Quevenco, F., & Devlin, J. T. (2012). Early and sustained supramarginal gyrus contributions to phonological processing. *Frontiers in Psychology, 3*, 161.

Sparing, R., Dafotakis, M., Meister, I. G., Thirugnanasambandam, N., & Fink, G. R. (2008). Enhancing language performance with non-invasive brain stimulation – A transcranial direct current stimulation study in healthy humans. *Neuropsychologia, 46*(1), 261–268.

Sparing, R., Mottaghy, F. M., Hungs, M., Brugmann, M., Foltys, H., Huber, W., et al. (2001). Repetitive transcranial magnetic stimulation effects on language function depend on the stimulation parameters. *Journal of Clinical Neurophysiology, 18*(4), 326–330.

Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *The Neuroscientist, 17*(1), 37–53.

Stoeckel, C., Gough, P. M., Watkins, K. E., & Devlin, J. T. (2009). Supramarginal gyrus involvement in visual word recognition. *Cortex, 45*(9), 1091–1096.

Stokes, M. G., Chambers, C. D., Gould, I. C., English, T., McNaught, E., McDonald, O., et al. (2007). Distance-adjusted motor threshold for transcranial magnetic stimulation. *Clinical Neurophysiology, 118*(7), 1617–1625.

Stokes, M. G., Chambers, C. D., Gould, I. C., Henderson, T. R., Janko, N. E., Allen, N. B., et al. (2005). Simple metric for scaling motor threshold based on scalp-cortex distance: Application to studies using transcranial magnetic stimulation. *Journal of Neurophysiology, 94*(6), 4520–4527.

Strens, L. H., Fogelson, N., Shanahan, P., Rothwell, J. C., & Brown, P. (2003). The ipsilateral human motor cortex can functionally compensate for acute contralateral motor cortex dysfunction. *Current Biology, 13*(14), 1201–1205.

Terzuolo, C. A., & Bullock, T. H. (1956). Measurement of imposed voltage gradient adequate to modulate neuronal firing. *Proceedings of the National Academy of Sciences of the USA, 42*(9), 687–694.

Thielscher, A., Opitz, A., & Windhoff, M. (2011). Impact of the gyral geometry on the electric field induced by transcranial magnetic stimulation. *Neuroimage, 54*(1), 234–243.

Topper, R., Mottaghy, F. M., Brugmann, M., Noth, J., & Huber, W. (1998). Facilitation of picture naming by focal transcranial magnetic stimulation of Wernicke's area. *Experimental Brain Research, 121*(4), 371–378.

Tremblay, P., & Gracco, V. L. (2009). Contribution of the pre-SMA to the production of words and non-speech oral motor gestures, as revealed by repetitive transcranial magnetic stimulation (rTMS). *Brain Research, 1268*, 112–124.

Tremblay, T., Monetta, L., & Joanette, Y. (2004). Phonological processing of words in right- and left-handers. *Brain and Cognition, 55*(3), 427–432.

van Rijn, S., Aleman, A., van Diessen, E., Berckmoes, C., Vingerhoets, G., & Kahn, R. S. (2005). What is said or how it is said makes a difference: Role of the right fronto-parietal operculum in emotional prosody as revealed by repetitive TMS. *European Journal of Neuroscience, 21*(11), 3195–3200.

Walsh, V., & Cowey, A. (1998). Magnetic stimulation studies of visual cognition. *Trends in Cognitive Science, 2*, 103–110.

Walsh, V., & Cowey, A. (2000). Transcranial magnetic stimulation and cognitive neuroscience. *Nature Reviews. Neuroscience, 1*(1), 73–79.

Walsh, V., & Rushworth, M. (1999). A primer of magnetic stimulation as a tool for neuropsychology. *Neuropsychologia, 37*(2), 125–135.

Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalography and Clinical Neurophysiology, 108*(1), 1–16.

Wassermann, E. M., Blaxton, T. A., Hoffman, E. A., Berry, C. D., Oletsky, H., Pascual-Leone, A., et al. (1999). Repetitive transcranial magnetic stimulation of the dominant hemisphere can disrupt visual naming in temporal lobe epilepsy patients. *Neuropsychologia, 37*(5), 537–544.

Wassermann, E. M., Cohen, L. G., Flitman, S. S., Chen, R., & Hallett, M. (1996a). Seizures in healthy people with repeated "safe" trains of transcranial magnetic stimuli. *Lancet, 347*(9004), 825–826.

Wassermann, E. M., Grafman, J., Berry, C., Hollnagel, C., Wild, K., Clark, K., et al. (1996b). Use and safety of a new repetitive transcranial magnetic stimulator. *Electroencephalography and Clinical Neurophysiology, 101*(5), 412–417.

Watkins, K., & Paus, T. (2004). Modulation of motor excitability during speech perception: The role of Broca's area. *Journal of Cognitive Neuroscience, 16*(6), 978–987.

Watkins, K. E., Strafella, A. P., & Paus, T. (2003). Seeing and hearing speech excites the motor system involved in speech production. *Neuropsychologia, 41*(8), 989–994.

Weyh, T., & Siebner, H. R. (2007). Hirnstimulation – Technische Grundlagen [Stimulation of the brain – technical basics]. In H. R. Siebner & U. Ziemann (Eds.), *Das TMS-Buch [The TMS book])*. Heidelberg: Springer.

Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M. A., & Jefferies, E. (2011). The neural organization of semantic control: TMS evidence for a distributed network in left inferior frontal and posterior middle temporal gyrus. *Cerebral Cortex, 21*(5), 1066–1075.

Wilson, S. A., Thickbroom, G. W., & Mastaglia, F. L. (1993). Transcranial magnetic stimulation mapping of the motor cortex in normal subjects. The representation of two intrinsic hand muscles. *Journal of the Neurological Sciences, 118*(2), 134–144.

Wirth, M., Rahman, R. A., Kuenecke, J., Koenig, T., Horn, H., Sommer, W., et al. (2011). Effects of transcranial direct current stimulation (tDCS) on behaviour and electrophysiology of language production. *Neuropsychologia, 49*(14), 3989–3998.

Ziemann, U., Paulus, W., Nitsche, M. A., Pascual-Leone, A., Byblow, W. D., Berardelli, A., et al. (2008). Consensus: Motor cortex plasticity protocols. *Brain Stimulation, 1*(3), 164–182.