Brain & Language xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Brain & Language

journal homepage: www.elsevier.com/locate/b&l

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

Gesa Hartwigsen *

Department of Psychology, Christian-Albrechts-University Kiel, Germany

ARTICLE INFO

Article history:
Accepted 21 October 2014
Available online xxxx

Keywords:
Broca
Network
Plasticity
Recovery
Reorganization
Transcranial direct current stimulation
Transcranial magnetic stimulation
Speech
Virtual lesion
Wernicke

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.

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 electromagneto-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

* Address: Department of Psychology, Christian-Albrechts-University Kiel, Olshausenstr. 62, D-24118 Kiel, Germany.
E-mail address: hartwigsen@psychologie.uni-kiel.de

http://dx.doi.org/10.1016/j.bandl.2014.10.007
0093-934X/© 2014 The Author. Published by Elsevier Inc.

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

Please cite this article in press as: Hartwigsen, G. The neurophysiology of language: Insights from non-invasive brain stimulation in the healthy human brain. *Brain & Language* (2014), http://dx.doi.org/10.1016/j.bandl.2014.10.007