

TMS in cognitive neuroscience: virtual lesion and beyond

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TMS excites axons of cortical neurons, leading in turn to synaptic activation of excitatory and inhibitory target neurons. However, the exact neurophysiological mechanisms of how TMS activates the brain are still relatively unclear (Di Lazzaro et al., 2008; Rotem and Moses, 2008; **Wagner et al., 2009**). Despite this lack of detailed knowledge, TMS is increasingly more often used in cognitive neuroscience to test brain-behavior relation, through its capacity to disrupt task-related neuronal activity ('virtual lesion') (Pascual-Leone et al., 1999; Silvanto and Muggleton, 2008; Walsh and Pascual-Leone, 2003). 'Virtual lesion' is used in this article in its broadest term, i.e. transient alteration of the function of the cortical target induced by single-pulse TMS or short trains of TMS during a cognitive task (online mode), or by TMS plasticity protocols prior to the task (offline mode). The important question is: How valid is TMS as a tool to test brain-behavior relation, if its modes of action are not fully known?

This account will be written from the perspective of TMS applications in the motor system, but the conclusions pertain to any field of cognitive neuroscience. It is currently thought that single-pulse TMS alters ongoing (task-relevant) neuronal activity by exciting many neurons

by virtue of artificially synchronizing their action potentials, followed by long lasting inhibition (cf. [Siebner et al., 2009](#) in this special issue). If TMS alters cognitive task performance, then most people would agree with the statement that the stimulated brain region is causally involved in that task. While this, in its broad sense, is correct, many qualifications exist which may preclude more specific conclusions.

The first problem is that it is still not exactly known which neuronal elements are excited by TMS, and whether the main effect is excitatory or inhibitory. Extracellular single cell recordings in cat visual cortex showed that low-intensity TMS typically results in early excitation (increase in spontaneous and visual stimulus evoked firing rate) followed by long lasting inhibition (Allen et al., 2007; Moliadze et al., 2003). In contrast, high-intensity TMS often led to early inhibition followed by excitation (Moliadze et al., 2003). This indicates that different neuronal elements have different thresholds to TMS. In addition to stimulus intensity, direction of the induced current in the brain and current waveform also influence which neurons are preferentially excited (Di Lazzaro et al., 2008). Furthermore, recent recordings from neuronal cultures indicate that only small subpopulations of neurons (referred to as initiating neurons) are directly excitable by magnetic stimulation (Rotem and Moses, 2008). In summary, the physical properties of the stimulus (intensity, waveform, duration, and polarity) will influence which neurons of the stimulated brain region are excited. Accordingly, the effects of TMS of a given brain region on a given cognitive task may vary (deterioration, improvement, or no change), depending on whether or not neurons involved in the task become inhibited, excited or remain unaffected by TMS. Certainly, this does not invalidate the 'virtual lesion' concept, and many cognitive neuroscientists may not even bother about the exact way of how TMS activates the brain, as long as they can use TMS to somehow alter task-related neuronal activity. Still, it should be a mandatory

minimum standard of all future TMS research to report all details of the TMS protocol, as these matter for the magnitude and direction of TMS-induced cognitive effects. Furthermore, this information may eventually facilitate our understanding of the mechanisms underlying TMS-induced effects.

A second problem is that the effects of TMS on the stimulated brain region are context or state dependent (cf. [Ruff et al., 2009](#) in this special issue). Neuronal excitation thresholds to magnetic stimulation in neuronal cultures show *hysteresis* effects, i.e. they are higher if testing starts with low-intensity stimuli below threshold and intensities are subsequently increased compared to when testing starts from above threshold and intensities are subsequently decreased (Rotem and Moses, 2008). This indicates that excitation threshold is sensitive to the recent history of low (ascending) vs. high (descending) intensity magnetic stimulation. Furthermore, long-term depression-like decreases in excitability induced by 1 Hz repetitive TMS (rTMS) can be reverted to long-term increases in excitability if preceded by cathodal transcranial direct current stimulation (tDCS) which by itself depresses excitability (Siebner et al., 2004). This means that magnitude and direction of (long-term) TMS effects are modifiable by preceding stimulation. Many of the reported interactions (Hamada et al., 2008; Iyer et al., 2003; Lang et al., 2004; Müller et al., 2007; Siebner et al., 2004) follow the rules of homeostatic metaplasticity, but non-homeostatic interactions also exist (Nitsche et al., 2007). Similarly, *previous voluntary* neuronal activity may strongly influence magnitude and direction of subsequent TMS effects (Gentner et al., 2008; Iezzi et al., 2008; Stefan et al., 2006; Ziemann et al., 2004). Furthermore, the level of motor attention strongly affects the magnitude of TMS-induced long-term changes in corticospinal excitability (Stefan et al., 2004). This dependency of TMS effects on context or state is fundamentally important for cognitive neuroscience, as TMS effects during a cognitive task are also context dependent.

As one example of several others in the field of vision and attention (see also, (Bestmann et al., 2007; Pascual-Leone and Walsh, 2001), visual adaptation to color results in a change of TMS-induced phosphenes from colorless or white to the adapted color (Silvanto et al., 2007). This means that visual adaptation shifts the excitation threshold of neurons coding the adapted color vs. those coding the non-adapted complementary color: the adapted neurons may have become more excitable, and/or the non-adapted neurons less excitable by TMS or the non-adapted neurons may have become more sensitive to TMS-induced inhibition, and/or the adapted neurons less sensitive. While context dependency does not disqualify the 'virtual lesion' concept, it will be mandatory for future TMS research in cognitive neuroscience to carefully control and report state and context conditions.

A third and potentially the most serious problem is that TMS effects usually are not limited to the site of stimulation but spread either physically to neighboring areas, or by propagation of action potentials along cortico-cortical and cortico-subcortical projections to distant sites (Bestmann et al., 2004; Bestmann et al., 2008; Ilmoniemi et al., 1997; Massimini et al., 2005; Paus et al., 1997; Ruff et al., 2009; Siebner et al., 2009). Physical spread means that the induced electrical field unintentionally reaches adjacent brain areas. The strength of the electrical field is less there than at the target site but still may be strong enough to cause unwanted cognitive effects. This possibility can be excluded in control TMS conditions that target these adjacent areas directly at adjusted lower stimulus intensity (Gerschlagner et al., 2001). The propagation of TMS-induced neural activity to connected distant areas, however, cannot be faithfully controlled. One could target connected distant sites directly by TMS in additional control experiments but TMS-induced excitation is different from transsynaptic activation by action potential propagation. In terms of the 'virtual lesion' concept this means that TMS effects on cognition could be caused directly at the stimulated site, but equally

well through modification of neuronal activity at distant sites, or both. Magnitude and direction of these remote effects depend on the TMS effects of the primarily stimulated site. For instance, near threshold focal TMS of one motor cortex results in increased corticospinal excitability of the motor cortex in the opposite hemisphere a few milliseconds later, while higher-intensity TMS results in interhemispheric inhibition (Hanajima et al., 2001). In addition, the extent to which TMS effects in connected distant areas occur is strongly context dependent. Interhemispheric inhibition increases in preparation for and during unimanual contraction from the voluntarily active to the non-active motor cortex (Duque et al., 2007; Vercauteren et al., 2008), probably in order to prevent unwanted mirror co-activation of the non-active motor cortex. Finally, the TMS effects on neuronal activity of the directly stimulated site may be influenced by neuronal activity from other sites. For example, interhemispheric inhibition from the voluntarily non-active to active motor cortex decreases close to movement onset in a unimanual simple reaction time task (Duque et al., 2007; Murase et al., 2004), probably in order to release the active motor cortex from unwanted inhibition from the homologue representation in the motor cortex of the opposite hemisphere.

When returning to the initial question of this opinion paper how valid TMS is to test brain-behavior relation through the 'virtual lesion' approach then a prudent answer is that TMS is indeed a valid tool in cognitive neuroscience as long as interpretation of TMS effects respects all the qualifications given above. Despite these qualifications, there is no true reason to bury the 'virtual lesion' concept. It is still valid to say that TMS-induced alteration of performance in a cognitive task proves the involvement of the stimulated brain region *and* the connected neuronal network in that task.

On the other hand, direction and magnitude of the observed TMS effects on cognition may dramatically vary with stimulus parameters and context. While it may not be ultimately important (and likely impossible) to understand in detail how this happens, this variability provides a great opportunity to go beyond the 'virtual lesion' concept by opening a new window into the brain with a deliberate focus on task and context dependent modifications of functional and effective brain connectivity. With *multifocal TMS* experiments it will be possible to reveal specifically when in a given task a certain cortico-cortical projection is active and whether the interaction from the conditioning to test cortex is inhibitory or facilitatory. For instance, *paired coil TMS* (which is a special case of multifocal TMS and uses two focal coils at different sites) revealed that the connection from posterior parietal cortex to ipsilateral primary motor cortex during the reaction time of a reach task is facilitatory only when planning a reach to contralateral but not to ipsilateral space, and only at two specific time intervals (50 and 125 ms) after an auditory cue (Koch et al., 2008).

In conclusion, inferring function from (virtual) lesion is a long existing and important concept in cognitive neuroscience but data interpretation always bears many caveats and limits. Measuring directly task or context related change in functional connectivity is way more powerful and specific and makes use of the limitations burdening the virtual lesion concept. This can be done with TMS related techniques (multifocal TMS) and will be, in conjunction with other electrophysiological and imaging techniques, the main road to drive on.

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