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EDITORIAL

Integrating TMS with EEG: How and What For?

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Transcranial magnetic stimulation (TMS) is a unique tool that utilizes magnetic fluxes to noninvasively stimulate the human cortex. Introduced in 1985 (Barker et al. 1985), it has developed into a powerful research device by virtue of its capacity to stimulate the brain with a relatively good spatial and temporal selectivity (Walsh and Cowey 2000), without the pain associated with transcranial electrical stimulation (TES), and with an excellent safety profile if appropriate guidelines are followed (Rossi et al. 2009). Guided by studies using brain imaging (e.g. functional MRI) that deliver evidence correlating brain activity with specific behaviors, TMS has been employed to induce transient "virtual lesions" in humans under controlled conditions, providing causal evidence linking activity in specific brain areas with behavior (Walsh and Pascual-Leone 2003). TMS is also being actively studied as a therapeutic technique for certain neuropsychiatric conditions (e.g. depression) via protocols that involve repetitive stimulation to induce longer-term changes in brain activity at carefully selected sites (Fregni and Pascual-Leone 2007). While all these TMS approaches are valuable and have provided exciting results, the use of TMS in conjunction with concurrent recordings of brain activity holds promise for further advances in neuroscience as well as neurologic and psychiatric therapeutics along several dimensions.

TMS-EEG and Network Dynamics

A pervasive notion in neuroscience is that a given mental faculty can be localized to a specific part of the brain. This view posits a relatively simple structure-function relationship, in which anatomically distinct brain regions perform specialized, relatively independent computations (e.g. visual cortex is responsible for vision). However, a growing body of evidence from neuropsychological, neurophysiological, and neuroimaging studies in animals and humans suggests that it is the interactions between brain regions organized in functional networks that underlie cognitive processing and determine behavior. Any cognitive function and goal-directed behavior may be best identified with a certain activity profile of specific, spatially-distributed, but interconnected neuronal assemblies occurring in a specific time window and temporal order. Defining network interactions is thus key to understanding cognition. Furthermore, abnormalities in the interactions of network components play a critical role in common and devastating neurological and psychiatric disorders ranging from depression to epilepsy. And, damage to specific functional connectivity networks can lead to distinct neurological syndromes. Finally, both the deficits and functional recovery after strokes or traumatic brain injury may be a function of the architecture and adaptability of these networks. Defining network interactions is thus also key to understanding brain disorders and brain reorganization. For example, identification of the dysfunctions of neural circuitry in a given patient may provide a more direct and powerful therapeutic target, than a given diagnostic label.

This is one of several papers published together in Brain Topographyon the ''Special Topic: TMS and EEG''.

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Despite all this, functional network analysis currently has only a minor role in clinical neuropsychiatry and the *therapeutic* interventions that modulate neural networks in a specific and targeted fashion are still limited. However, the combination of TMS with brain mapping methods promises to enable such studies.

Experimentally in humans it is possible to merge TMS with brain imaging methods such as optical brain imaging or functional magnetic resonance imaging (fMRI) (e.g. Bestmann et al. 2008; Driver et al. 2009). The concurrent recording of EEG during TMS is particularly promising (see Fig. 1) given its exquisite temporal resolution and the provision of a direct measure of brain activity (rather than an indirect index). TMS can deliver a controllable input of known spatial and temporal characteristics to an identifiable brain region and EEG enables the study of local responses and distant interactions between different brain regions within and between neural networks. The behavioral consequences can be correlated with the neurophysiologic impact and the temporal resolution of the EEG enables to distinguish direct consequences of TMS from adaptive responses to the focal disruption within the distributed networks. Such approaches can be applied to different cortical regions in healthy controls across the age span, as well as in patients with a variety of neuropsychiatric disease. This special issue of brain topography includes a series of papers on combined TMS-EEG studies (reviews and original contributions) highlighting the challenges and also the power of this combined methodology.

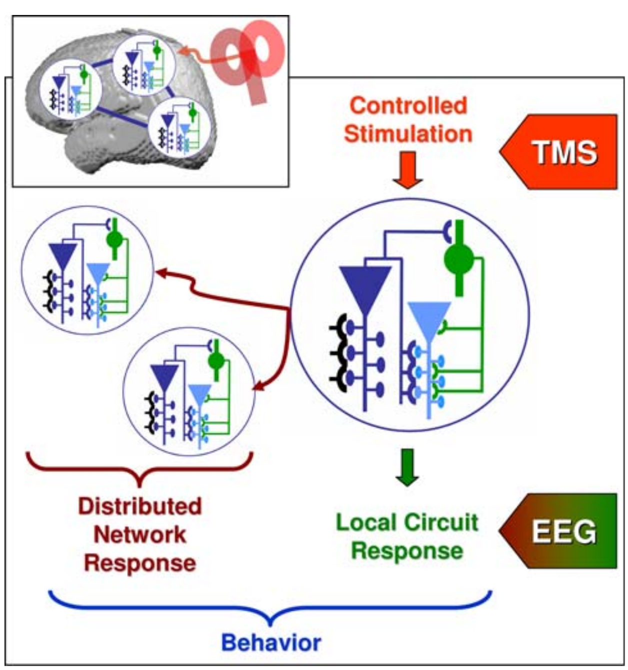

Fig. 1 Schematic representation of the TMS-EEG approach

TMS-EEG and Physiological Underpinnings of TMS

In addition, TMS-EEG can provide valuable insights into the mechanisms of action of TMS. While the physiological basis of TMS is partially resolved, many questions about TMS remain (e.g. Bestmann 2008). There is limited knowledge on the mechanisms of TMS action, including what is stimulated by TMS from the level of the cell to neuronal assemblies or networks, what is changed by TMS in terms of markers of brain activity or neuronal operations, when these TMS changes occur and how long they last. Another unresolved question is why the outcome of TMS is so variable, for instance why the effects of the same TMS design can change from being detrimental to beneficial when put into another experimental setting/task context. In analogy to providing clues on network interactions, it is the combination of TMS with EEG that can contribute significant information here.

In This Special Issue

Recording EEG concurrently to TMS is challenging due to the TMS-induced electromagnetic and physiologic artifacts. The first review paper by Ilmoniemi and Kičić (2009) provides a thorough description of technical problems of recording electrophysiological signals in the presence of a TMS coil/pulse close to the electrodes, and of the strategies to moderate them. This includes aspects to consider prior, during and after EEG recording and to correctly interpret the data (see also Miniussi and Thut 2009).

TMS will induce a cascade of complex parallel and serial effects at different neural levels. Focusing on the immediate effects of single pulse TMS, Ilmoniemi and Kičić provide a detailed account of the cascade of TMS-evoked potentials (TEPs) revealing local impact on the targeted brain region, as well as the distributed network effect. The point is made that besides providing information on the local and distributed brain responses to TMS, these TEPs can be used as electrophysiologic markers to infer the activation/integrity of inhibitory and excitatory mechanisms for any stimulated site across experimental manipulations and neurological/psychiatric disorders. In contrast to Ilmoniemi and Kičić, Thut and Pascual-Leone (2009) focus on long-term aftereffects in EEG after application of repeated TMS pulses (repetitive TMS, or rTMS). This is to characterize their strength, direction (suppressive or facilitative) and duration (in dependence of rTMS protocols). While the rTMS-aftereffects on EEG are found to be robust (present in almost all studies), they are also short-lived (on the order of an hour), further contributing to characterize the safety of rTMS (Rossi et al. 2009) but limiting its versatile use for clinical applications. The paper discusses possible ways of enhancing these effects when desirable, such as when used with therapeutic intent in patients.

The third and fourth papers review the TMS-EEG literature from a cognitive (Miniussi and Thut 2009) or clinical neuroscience perspective (Rotenberg 2009). In Miniussi and Thut (2009), a taxonomy of TMS-EEG applications is proposed (termed (i) "inductive", (ii) "interactive" and (iii) "rhythmic"). Literature is summarized along these classifications, and it is argued that TMS-EEG is crucial to better understanding the neuronal underpinning of the disruptive and beneficial behavioral effects of TMS as well as null results; the latter potentially carried by compensational reorganization after TMS-interference. One example of the inductive approach is provided in Zanon et al. (2009), studying the connectivity of the parietal cortex with TMS-EEG. Alex Rotenberg (2009) then focuses on plausible TMS-EEG applications in epilepsy and similarly reviews findings along three classes: (i) A "diagnostic" use of EEG-responses to TMS in order to measure potential TMS-provoked spikes for seizure focus localization; (ii) a "therapeutic" use of TEP-amplitude as a measure of individual cortical excitability to guide rTMS-treatment for seizure reduction (see also Brodbeck et al. 2009 on rTMS-induced changes in individual spike patterns as a measure of individual treatment susceptibility), or (iii) a "real-time interactive" use to abort seizures by TMS-timing in dependence on underlying EEG patterns (as shown to be effective in animals). The latter finding is in accordance with the notion that TMS-efficacy is state-dependent (Silvanto and Pascual-Leone 2008), corroborated in many TMS-EEG studies (reviewed in Ilmoniemi and Kičić 2009; Thut and Pascual-Leone 2009; Miniussi and Thut 2009).

Most of the contributions in this special issue also emphasize that the TMS-EEG combination is of interest for research on oscillations (Ilmoniemi and Kičić 2009; Thut and Pascual-Leone 2009; Miniussi and Thut 2009, Johnson et al. 2009; see also Thut and Miniussi 2009). While the TEPs' spatiotemporal distribution enables to trace the brain's responses in the target-site and its spreading to remote, connected sites, a pulse (or potentially a pulse train) also induces rhythmic brain activity, preferably oscillating in the natural frequency of the target site (e.g. Paus et al. 2001; Rosanova et al. 2009; but see Johnson et al. 2009 for a negative finding regarding entrainment through a pulse train). Johnson et al. (2009) provide evidence that the most promising approach of understanding the behavioral TMS-effects is by studying the changes to oscillatory activity by TMS, which cannot be conceptualized as noise in their data set. TMS-EEG hence provides the opportunity to study several aspects of oscillatory activity, including their link to behavior, in a unique setting.

Conclusion

Although TMS-EEG recordings are technically challenging, interpretable data can be obtained. TMS-EEG is poised to deliver novel insights into fundamental aspects of brain network dynamics in health and disease, paving the way for EEG-gated neuromodulatory therapeutic intervention and has the potential to provide important information on the physiological underpinning of TMS-action.

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