



Review

The contribution of TMS–EEG coregistration in the exploration of the human cortical connectome

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ABSTRACT

Recent developments in neuroscience have emphasised the importance of integrated distributed networks of brain areas for successful cognitive functioning. Our current understanding is that the brain has a modular organisation in which segregated networks supporting specialised processing are linked through a few long-range connections, ensuring processing integration. Although such architecture is structurally stable, it appears to be flexible in its functioning, enabling long-range connections to regulate the information flow and facilitate communication among the relevant modules, depending on the contingent cognitive demands. Here we show how insights brought by the coregistration of transcranial magnetic stimulation and electroencephalography (TMS–EEG) integrate and support recent models of functional brain architecture. Moreover, we will highlight the types of data that can be obtained through TMS–EEG, such as the timing of signal propagation, the excitatory/inhibitory nature of connections and causality. Last, we will discuss recent emerging applications of TMS–EEG in the study of brain disorders.

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1. Introduction

In the past, the major focus of research defining the brain–behaviour relationship was to identify the segregated brain regions recruited by a given task. More recent developments have emphasised the importance of distributed networks at all levels, from individual neurons to neural populations and brain regions. Such an approach is therefore moving neuroscience from a topological perspective on the mapping of “important brain areas” to a hodological perspective on “system interactions”. Neurons in the brain are clustered in regions with different cytoarchitectonical and functional properties, which are heavily interconnected through bidirectional connections in large-scale networks. This architecture relates to functional networks, in that cognitive efficiency – from perception to movement control and from executive functions to emotions – does not only rely on the local processing of information in specialised areas but also on the integration of information (i.e., connectivity) through the coordinated activity of multiple areas (Driver et al., 2009; Sporns et al., 2004). Accordingly, imbalances in connectivity patterns have been proposed to be strongly associated with neurological (e.g., Alzheimer’s disease – AD: Tijms et al., 2013; Vecchio et al., 2014 and brain damage: Catani et al., 2013) and psychiatric disorders (e.g. schizophrenia, Buckholz and Meyer-Lindenberg, 2012; Frantseva et al., 2012).

A crucial goal of neuroscience studies is to define the human “connectome”, a complete map of the neural connections in the human brain, both in terms of structural and functional connectivity, which will enable a better comprehension of the brain–behaviour relationship (Behrens and Sporns, 2012; Sporns, 2013). Towards this goal, neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have been employed in the vast majority of studies. This field has greatly benefitted from multidisciplinary approaches such as the integration of graph theory in neuroimaging. Graph theory is a mathematical tool to quantify the properties of complex networks and describe the interrelationships between network elements (nodes) by means of connections (edges), which in this case represent brain regions and their connections, respectively (Baronchelli et al., 2013; Minati et al., 2013).

Nevertheless, we still face several important challenges in this field, ranging from the methodological limitations of our investigative equipment (Johansen-Berg, 2013) to the limitations concerning the complexity of analyses and *a priori* assumptions that are needed with graph theory (Buckner et al., 2013; De Reus and van den Heuvel, 2013a; Fornito et al., 2013). For this reason, cross validation through independent methodologies may be critical for overcoming the limitations of single methodologies in defining how the brain connectome supports cognitive functioning.

Here, we outline how a multimodal imaging approach combining transcranial magnetic stimulation (TMS) and electroencephalography (EEG) has contributed and might contribute to the understanding of the functional connectome. TMS–EEG offers a unique insight into effective connectivity, the description of causal interactions between regions, including how well the activation of one region explains the activation of another (Friston et al., 1993a). Notably, this approach provides a causal model on the origins of activation in neural activity patterns and might define the functional strengths between regions.

We first review the TMS–EEG literature probing the motor system during the resting state. We then review the TMS–EEG literature on connectivity in different task contexts. By comparing TMS–EEG studies with fMRI-based functional connectomics, we will show how it is possible to test and validate the general principles of functional brain architecture inferred by graph theory, i.e., the organisation and configuration of brain networks, and provide further insights into the properties of the connectome as a function

of a brain state or specific cognitive task. Last, we will underline recent emerging applications of the TMS–EEG approach in brain disorders.

2. Effective connectivity through TMS–EEG coregistration

Neuroimaging techniques, such as EEG, fMRI and PET, can reveal the functional connectivity between areas as result of “temporal correlations between spatially remote neurophysiological events” (Friston et al., 1993b). Obtaining measures of effective connectivity with these techniques requires complex causal models, such as dynamic causal modelling and Granger causality (Friston et al., 2013; Stephan and Roebroeck, 2012), based on pre-existing neuroanatomical, neuropsychological and functional neuroimaging data (Stephan et al., 2008). Effective connectivity includes a definition of causality, which these techniques cannot provide *per se*. Therefore, their inferential power on effective connectivity relies on *a priori* assumptions about the involved network and about the validity of the implemented model.

The integration of TMS with the above mentioned neuroimaging techniques, i.e., PET, fMRI and EEG, may be a useful empirical method to test functional integration and causality, i.e., effective connectivity (Shafi et al., 2012, 2013). Each combination allows focusing on different aspects of TMS-induced changes in brain activity. TMS–PET and TMS–fMRI coregistration can reveal the spatial profiles of transcranial brain stimulation effects with high spatial resolution, including subcortical structures (Siebner et al., 2009). Nevertheless, these techniques have a reduced temporal resolution and can only detect modulations arising a few seconds (fMRI) or even minutes (PET) post-stimulus, because such neuroimaging techniques are based on changes in blood flow and oxygenation.

TMS–EEG consists of measuring electrical brain activity (*via* EEG) after brief non-invasive brain stimulation (*via* TMS) and provides an empirical measure of effective connectivity because the activation induced by the TMS in the targeted area propagates to anatomically and functionally connected regions (O’Shea et al., 2008; Siebner et al., 2009). The millisecond temporal resolution of the EEG provides two important advantages in the study of brain connectivity. First, information about the temporal pattern of the responses induced by the TMS contributes to defining the causal relationships in the connections across brain areas. Indeed, we can assume that if area A is active prior to area B, then area A might cause increased (or reduced) activity in area B through excitatory (or inhibitory) connections between the two areas (Sporns et al., 2004). Second, it allows the investigation of the temporal evolution of communication between regions and to unfold the connectivity patterns throughout task execution, highlighting short time windows of information exchange. In addition, the delivery of the TMS pulses is under explicit experimental control (Miniussi et al., 2013; Sack and Linden, 2003), thereby allowing researchers to successfully differentiate the connectivity pattern of different cognitive processes related to the execution of specific tasks (Morishima et al., 2009) or to different brain states (Massimini et al., 2005). Last, EEG provides a direct measure of the electrical signals generated by neuronal activity and enables researchers to derive the excitatory/inhibitory nature of network connections (Daskalakis et al., 2012). These features of TMS–EEG can be of great help to study the temporal sequence of neural activity that determine the interactions between brain areas, that is typically modelled by graph theory in the neuroimaging field to represent networks of communication.

A simple way to evaluate cortico-cortical connectivity is by studying the spatio-temporal distribution of TMS-evoked potentials (TEPs) after a single TMS pulse, also called the inductive

TMS–EEG approach (Miniussi and Thut, 2010). After a TMS pulse over a cortical region, the spread of the induced activity can be traced via the waveform and topography of the TEP over the scalp, providing a direct measure of brain connectivity (e.g., Bonato et al., 2006; Ilmoniemi et al., 1997; Komssi et al., 2002).

Single-pulse TMS and trains of pulses can also trigger (Paus et al., 2001) or enhance brain oscillations (Thut and Miniussi, 2009; Thut et al., 2011), when these trains are frequency-tuned to the underlying brain oscillations of the target cortical area (entrainment), defined as the rhythmic TMS–EEG approach (Miniussi and Thut, 2010). Brain oscillations are thought to represent a mechanism through which information is processed within a network, forming dynamic assemblies of neurons through synchronisation in specific frequency bands (Buzsaki, 2006; Watrous et al., 2013).

Last, TMS-induced coherence of cortical areas can be used for the identification of effective connections during a task, based on the notion that a bound is created by the synchronisation of oscillatory activity. Several methods have been developed to estimate interactions between brain regions based on the amplitude and phase of EEG oscillations, e.g., directed coherence, imaginary coherence, phase-locking value, phase-lag index, etc. A detailed description of these methods, their breakthroughs and their pitfalls, can be found in recent methodological papers (Greenblatt et al., 2012; Sakkalis, 2011; Schoffelen and Gross, 2009).

Briefly, the spatial-temporal pattern of the brain responses to TMS can contribute to defining causal relationships in the connections across brain areas and can reveal their activation at the time of stimulation. By examining the responses within the network when one of its nodes is stimulated, TMS–EEG coregistration provides

measures of effective connectivity that may test the predictions of graph theory models in terms of brain interactions more directly and along a causal dimension.

3. Distributed networks from neuroimaging and graph theory

Graph theory analyses of structural and functional neuroimaging have suggested a hierarchical modular organisation of the human connectome that is organised to rapidly and efficiently transfer information through minimal wiring (Bassett and Bullmore, 2006; Bullmore and Sporns, 2012; Ercsey-Ravasz et al., 2013). Brain connectivity architecture may resemble a “small world” network that is characterised by modules (or sub-networks) that perform segregated and highly specialised processing and that are linked through a few long-range connections that ensure integrated processing (Achard et al., 2006; Bassett and Bullmore, 2006; Sporns et al., 2004) (Fig. 1).

Modules of nodes correspond to functional networks of areas, e.g., the motor network, visual network, dorsal attention network, default mode network, medial lobe memory network and fronto-parietal control network (Power et al., 2011; Smith et al., 2009). Areas of the same network have stronger anatomical connections (Wang et al., 2013) and inherent biases in their interactions (Chu et al., 2012; Deco et al., 2013; Smith et al., 2009), as indicated by high local clustering, i.e., the high probability of two neighbouring nodes being connected to each other.

Long-range connections link areas that participate in multiple networks, called “hubs”, and ensure fast information exchange

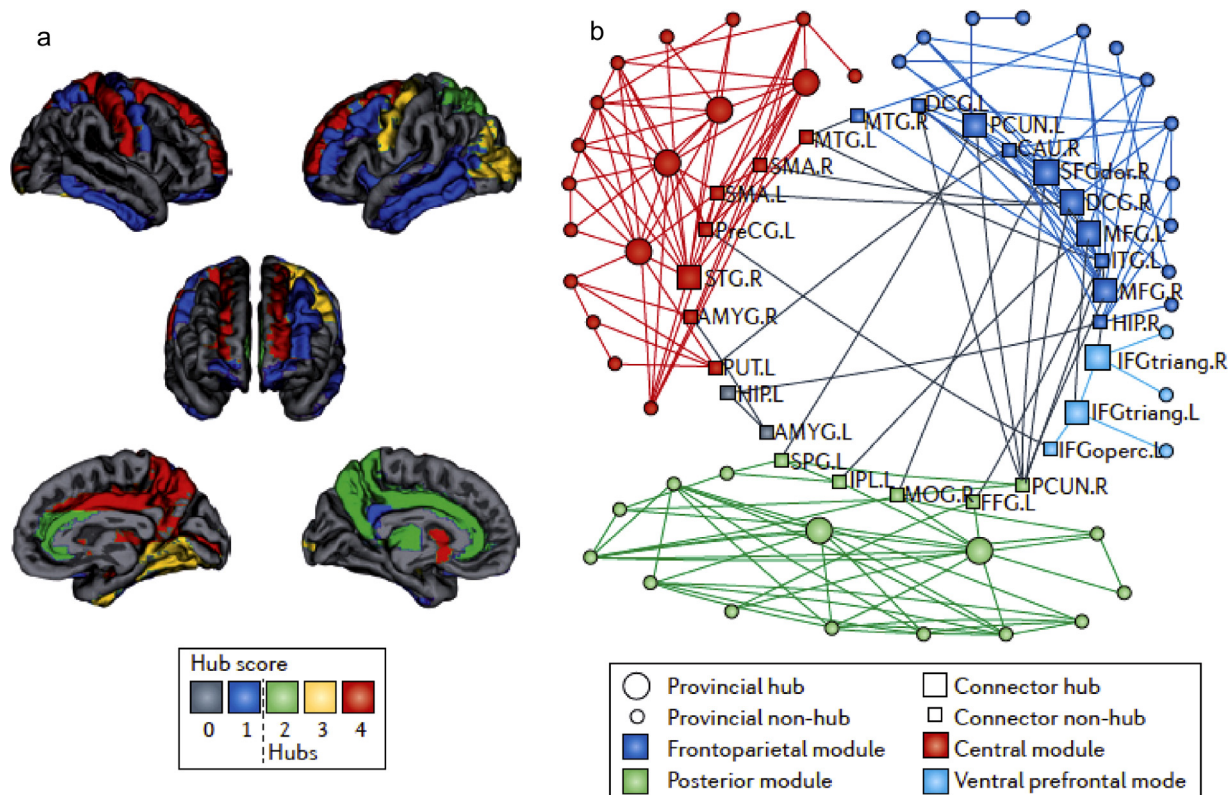


Fig. 1. Hierarchical modular organisation of the human connectome. (a) Hubs: regions with a higher number of connections, higher value of betweenness centrality, a shorter path length and highly clustered among themselves are called ‘hubs’ and are indicated in the figure by a ‘hub score’ of 2 or higher. Hubs include fronto-parietal regions and subcortical regions. (b) Modules of nodes: functionally related nodes (circles) are spatially close and densely interconnected through short-range connections, forming modules or sub-networks. The hubs (squares) of each module mediate most of the longer-distance inter-modular connections. Here, four major modules are shown, comprising frontal (dark blue), central (red) and posterior (green) brain regions and inferior frontal regions (light blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

From Bullmore and Sporns (2012).

across networks by shortening the average path length, i.e., the minimum path length between any two pairs of nodes in the network. Hubs are central and influential on global network functioning because they have a higher number of connections (high degree), are waypoints for the shortest path in the network (betweenness centrality) and tend to be densely interconnected with other hubs, forming a “rich club”. Although there is no complete agreement on the localisation of areas included in the rich club, hubs have been found in association areas within bilateral fronto-parietal regions and subcortical regions (Gong et al., 2009; Van den Heuvel and Sporns, 2011).

Although the structural connectome is highly stable (at the macroscale), the functional connectome appears to be flexible as different cognitive states are associated with changes in the weight of functional connections. There is evidence that the resting state may be associated with a stronger modular structure compared with conditions of high cognitive demand (Di et al., 2013; Kitzbichler et al., 2011). During the resting state, a cost-efficient network reconfiguration has been suggested, in which the activity of weak long-range connections is reduced and more segregated modules of stronger connections increase the efficiency of local communication (Ercsey-Ravasz et al., 2013). In other words, areas that work together to subtend a cognitive function (e.g., movement, attention and memory) tend to be more strongly connected and also more segregated from other modules in the resting state. Graph theory models further suggest that the communication across these locally clustered and specialised networks is ensured by brain hubs and the central infrastructure of the rich club (De Reus and van den Heuvel, 2013b; Van den Heuvel and Sporns, 2011). The connections of brain hubs are shaped by contingent cognitive demands (Chadick and Gazzaley, 2011; Cocchi et al., 2013) to facilitate communication between relevant modules, as suggested by the flexible hub theory (Cole et al., 2013). This small-world architecture constrains the functioning of brain connections, possibly by maximising the complexity or adaptivity of a function while also minimising wiring costs (Bassett and Bullmore, 2006; Bullmore and Sporns, 2012).

4. Cortical networks in healthy controls: the contribution of TMS–EEG

According to graph theory models, the nodes of specialised networks and hubs of the rich club should show different connectivity profiles: the former should mainly connect with other nodes of the same functional network, especially during the resting state, whereas the latter should show a high number of intermodular connections. TMS–EEG can be employed to empirically test these predictions about network architecture. We will show that TMS–EEG studies on network dynamics at rest and during cognitive processes are in line with specialised network segregation (which is more pronounced during the resting state), with dense connectivity through brain hubs, and support what has been suggested by graph theory models.

4.1. Cortico-cortical connectivity within functional networks

In line with resting-state neuroimaging, TMS–EEG has revealed functionally isolated networks when participants are at rest, as depicted in Fig. 2. As an example, let us consider the motor network, identified by fMRI as including the left and the right motor regions and the supplementary motor area (Biswal et al., 1995; Patriat et al., 2013; Smith et al., 2009).

Since the first studies, TMS–EEG has revealed that induced activity spreads from the stimulated node to other nodes of the same motor network. Activation maps from TEPs using minimum-norm estimates (Ilmoniemi et al., 1997; Komssi et al., 2002) and precise

source localisation (Litvak et al., 2007) have shown that TMS of the primary motor cortex causes the succeeding activation of ipsilateral supplementary/premotor areas and contralateral motor regions, and that these activations depend on the amplitude of the response evoked in the targeted motor cortex (Giambattistelli et al., 2014). Accordingly, transcallosal connectivity (Ilmoniemi et al., 1997) and fast direct signal conduction on the order of 9–20 ms between the homologous motor regions have been reported using TEPs (Komssi et al., 2002) and EEG oscillations (Manganotti et al., 2012). The short conduction time of the TMS-induced activity suggests direct connections, in line with neurophysiological evidence in humans (Civardi et al., 2001; Groppa et al., 2012) and monkeys (Boussaoud et al., 2005; Dum and Strick, 1991; Rouiller et al., 1994).

Interestingly, TMS–EEG studies have revealed the inhibitory versus facilitatory nature of these connections depending on the level of cortical activation. Regarding transcallosal connectivity, a recent study correlated diffusion tensor imaging-based fractional anisotropy in callosal motor fibres with TMS-induced interhemispheric signal propagation in the primary motor cortex (Voineskos et al., 2010). Crucially, the authors reported that sub- and supra-threshold TMS over the primary motor cortex induced, respectively, facilitatory and inhibitory effects over the contralateral homologous area. Such distinct effects are likely due to a different threshold of activation of excitatory and inhibitory circuits, suggesting that the corpus callosum may regulate the communication between hemispheres depending on the level of activation. Likewise, a recent TMS–EEG study reported that the connections between primary motor and premotor areas may be mainly inhibitory during the resting state (Veniero et al., 2012). The authors reported a negative correlation between excitability of the primary motor cortex, measured as the amplitude of the muscular twitch induced by the TMS, and the amplitude of an early TEP component likely generated in the ipsilateral premotor area. In line with fMRI-based graph theory models of cortical connectivity, that have individuated segregated networks of co-varying activity, TMS activations at rest do not reach areas clearly embedded in other specialised networks, e.g., the visual network.

In summary, these studies on the motor system have identified singular nodes of the probed network at rest by the spatio-temporal decomposition of TMS-induced activity. They illustrate that the cortico-cortical spreading of TMS-induced activity remains largely confined to the specialised motor network. Therefore, by showing that activity is confined to a restricted specialised network, they support a modular organisation of functional brain architecture at rest.

4.2. Cortico-cortical connectivity from nodes to brain hubs

Although early latency TMS responses reflect direct connections within functional networks, later components of TEPs reveal further nodes and more complex interactions, suggesting bottom-up signal propagation from lower-degree nodes to brain hubs.

For example, primary motor area stimulation generates the late activation of areas outside the stimulated functional network, involving the cingulate gyrus and temporo-parietal junction (Litvak et al., 2007). These activations, possibly achieved through loops or indirect connections with other nodes, affect areas that have a strict functional relationship with the stimulated network and may correspond to brain hubs. Compelling evidence has also been found in the visual system. Garcia et al. (2011) applied TMS to different areas of the visual system, including the left and right primary visual area, middle temporal cortex, and a ventral temporal region. Interestingly, both site-specific and site-invariant EEG responses were obtained. Site-specific responses were mainly generated at earlier latencies, whereas site-invariant responses increased with latency. Importantly, many of these site-invariant responses seemed to

Connectivity of Cortical Networks at rest

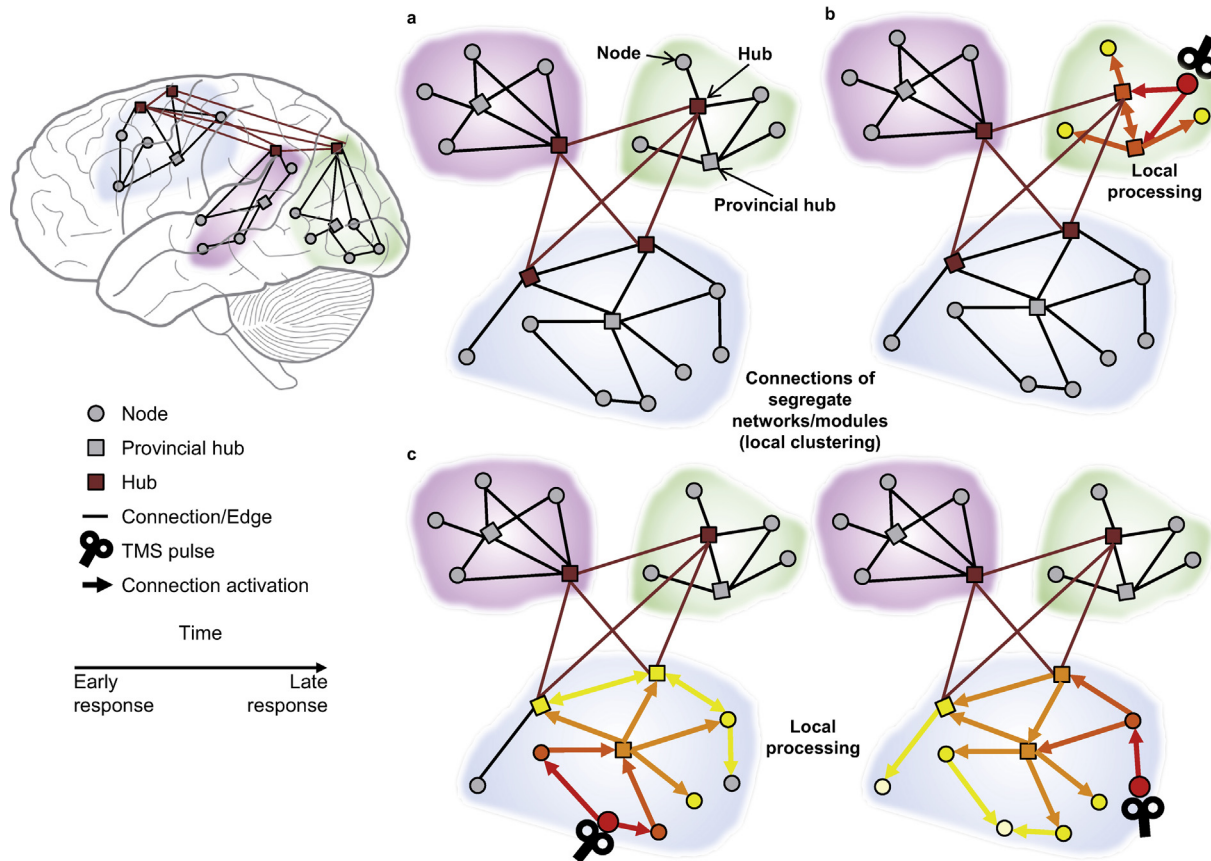


Fig. 2. Testing connectivity during the resting state. (a) Schematic figure of the modular organisation of the brain network, including nodes (grey circles), provincial hubs (grey squares) and hubs of the rich club (red squares), and their short-range (black lines) and long-range (red lines) connections. (b) The spatio-temporal distribution of the brain response to TMS of a lower-degree node is shown. Coloured arrows represent the causal interactions between nodes and the latency of signal propagation from the TMS pulse. After TMS, the activation of the target area travels to other nodes of the same module through short-range connections. (c) When two lower-degree nodes of the same network are stimulated by TMS, the signal propagates within the same module. At first, different nodes (site-specific responses) and eventually the same hubs are activated (site-invariant responses). The figure simulates results from Garcia et al. (2011). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

converge on a frontal and parietal EEG signature, suggesting that the spread of activation from the stimulated lower-degree visual nodes converged to common, heavily interconnected associative areas that can be identified as brain hubs.

To sum up, the TMS–EEG literature on connectivity shows that activity induced in different areas tends to reach a subset of areas that have been identified as brain hubs. The convergence of the signal from nodes to hubs is inline with the putative role of brain hubs in the transmission of information across the brain and with graph theory outcomes that most of the connection routes pass by at least a hub (Van den Heuvel et al., 2012).

4.3. Cortico-cortical connectivity from brain hubs to nodes

Some TMS–EEG studies have targeted multimodal associative and executive areas responsible for higher-order cognitive functions (e.g., Morishima et al., 2009; Taylor et al., 2007), likely corresponding to brain hubs. Work by Morishima et al. (2009) used TMS as a probe to evaluate neural impulse transmission from the prefrontal cortex to downstream, specialised posterior regions while participants were required to attend to specific features of visual stimuli. The authors hypothesised that stimulating the prefrontal areas of the attentional network (Corbetta and Shulman, 2002; Desimone and Duncan, 1995) would induce a spread of activation towards anatomically connected posterior regions and that

the direction and amount of the current spread could be different according to the functional network engaged to accomplish the task in a particular context. In line with these predictions, they found that TMS over the frontal eye field activated two different networks, functionally connecting the target area to distinct posterior visual areas depending on the nature of the to-be-attended visual feature (vertical gratings versus faces), as represented in Fig. 3. Moreover, TMS effects occurred 20–40 ms following the pulse, suggesting that impulse propagation was not due to rerouting via other areas but was instead achieved by the direct transmission of a neural input from frontal to posterior regions.

Others have confirmed that by targeting associated areas with TMS during task performance and assessing the TMS effects on task-related EEG responses, the top-down signals sent to downstream network nodes specialising in stimulus processing can be tracked. This use of TMS–EEG, termed the interactive TMS–EEG approach (Miniussi and Thut, 2010), has been successfully applied in several domains, including perceptual decision-making (Akaishi et al., 2013), controlled behaviour (Akaishi et al., 2010), goal-directed actions (Verhagen et al., 2013), visual search (Taylor et al., 2011), face processing (Mattavelli et al., 2013) and short-term memory (Johnson et al., 2012).

Therefore, the TMS–EEG literature on task-related connectivity from brain hubs shows divergence of TMS-induced activity from these areas depending on the task context. These observations are

inline with dense connectivity through brain hubs and with the suggested role of brain hubs to mediate communication between different modules according to the cognitive context (Cole et al., 2013).

Hence, TMS–EEG reveals dynamic changes to functional connectivity as a result of brain state and the hierarchical level of the targeted node. If the target area is highly interconnected across networks (constituting a hub of the rich club), TMS–EEG has highlighted top-down modulations that establish the information flow across different networks. In contrast, targeting a node of a specialised network appears to mainly illustrate the bottom-up task-related modulations of the connections within that functional network. These state-dependent changes have been previously suggested by analysing fMRI data by means of graph theory and by applying paired-pulse TMS protocols showing that the interactions between brain areas are shaped by ongoing processes (e.g., Buch et al., 2010; Davare et al., 2008, 2009). Altogether, these results illustrate the use of TMS–EEG in the selective investigation of transiently activated cortical networks in the process of accomplishing a cognitive act, reflected in the spread of local TMS effects to connected areas in a state-dependent manner, as shown in Fig. 3.

5. Cortical networks and brain oscillations in TMS–EEG research

An emerging line of TMS–EEG research focuses on TMS-induced brain oscillations, which extends the TEP approach to the frequency domain, focusing on the oscillatory components of the brain response generated by TMS pulses or trains. TMS is expected to interact with such oscillatory patterns in the directly stimulated cortical area (Thut et al., 2011) and in distant areas belonging to the same neural network (Thut et al., 2012). Therefore, if a group of network elements synchronise at a local level after TMS, we should expect a consequent longer-range synchronisation (interregional coherence) representing information transfer among brain structures. In short, we should expect the induction of the same frequency activity after a delay (phase offset) in all “synchronised” areas of the same network. This outcome would facilitate the localisation of involved areas. Induction of a frequency in the stimulated area may even induce a different frequency in a connected area. Nevertheless, both frequencies would be time locked with the TMS pulse, thereby potentially enabling connected areas to be linked with the stimulated area.

Some preliminary indications that distinct cortical networks are characterised by different oscillatory activity have been reported by Rosanova et al. (2009) who targeted the left frontal, parietal and occipital cortex with single pulse TMS at rest and measured the evoked cortical oscillatory responses. Each cortical area responded at a characteristic frequency, its eigenfrequency (or natural frequency). Most importantly, Rosanova et al. (2009) also showed that the topography of the evoked oscillatory activity was substantially dependent on the targeted region, with little overlap across stimulation sites, thus suggesting that functionally segregated networks can oscillate at different frequencies at rest (see also Brignani et al., 2008; Veniero et al., 2011).

A follow up study using rhythmic TMS, frequency-tuned to the natural oscillatory activity of the target area, revealed the possibility of a frequency-specific enhancement due to a progressive synchronisation of the natural oscillator to the periodic external stimulation (entrainment) (Thut et al., 2011). Interestingly, the stimulation of a node (intra-parietal sulcus) of the attentional network with the TMS rhythmic approach (targeting attention-related frequencies) also led to changes in the behavioural performance, biasing the subjects' perception (Romei et al., 2010, 2011, 2012) and

suggesting that these oscillations and presumably the entrained networks are causally implicated in the probed cognitive process.

Finally, cortical connectivity has been shown to potentially be promoted via paired associative TMS, during which two paired single TMS pulses (Ferreri et al., 2011; Veniero et al., 2013) or two paired rhythmic TMS trains at the same frequency (Plewnia et al., 2008) are applied, with a slight delay, over two interconnected cortical areas. Based on this concept, Veniero et al. (2013) demonstrated that the repeated co-activation of two areas (parietal and primary motor cortex) selectively reinforces communication, measured as interregional coherence, between the targeted regions in two different oscillatory components according to the inhibitory or excitatory motor outcome. Likewise, Plewnia et al. (2008) demonstrated that bifocal rhythmic TMS in the alpha frequency induced a topographically selective enhancement of interregional coherence, mainly at the stimulated frequency, that lasted up to 10 min after stimulation.

Further studies will have to focus on how TMS interacts with oscillatory network activity within the complex multi-frequency workspace of our brain, likely providing additional interesting information on the human connectome from an oscillatory perspective.

6. Clinical applications

When a node is altered, network connections can change in two ways. First, the weight of edges of the affected node can change, i.e., the connections between the target area and the connected areas can be strengthened or weakened. Second, the loss of the affected node and its connections can modulate distant edges and activate alternative (compensatory) paths of information flow. Graph theory indicates that the effects of neural damage may depend on the affected area, i.e., whether it consists of a brain hub or a specialised lower-degree node (Albert et al., 2000). Indeed, the loss of hubs may lead to fragmentation of the brain network into disconnected parts (Tijms et al., 2013). Converging results from modelling studies support that interventions into brain hubs, such as the removal or weakening of a hub's connections (Achard et al., 2006; Van den Heuvel and Sporns, 2011) or lesions in associative cortices, have a much stronger impact on brain architecture than lesions in primary areas (Alstott et al., 2009). These studies indicate that hubs are more important than other nodes for global brain functioning and that their loss may be more difficult to compensate for.

The disruption of neural connectivity has long been associated with many pathological conditions, e.g., AD, autism, aphasic disturbances and agnosias (Frith, 2001; Geschwind, 1965; Vecchio et al., 2014). Therefore, the opportunity to evaluate abnormal connectivity might play a central role in diagnoses and future therapeutic interventions. TMS–EEG can be used to examine normal and modified effective brain connectivity under specific conditions, such as different physiological (Massimini et al., 2005) and pathological states (Ferreri et al., 2014; Ragazzoni et al., 2013; Rosanova et al., 2012), and under pharmacological treatment (Ferrarelli et al., 2010). As such, TMS–EEG could indicate the strengthening or weakening of existing cortico-cortical connections or the recruitment of compensatory networks.

A few studies have employed resting-state TMS–EEG to evaluate altered connectivity in specific pathologies such as AD (Casarotto et al., 2011; Julkunen et al., 2008, 2012) or as a tool for diagnostics and early identification of mild cognitive impairment (Julkunen et al., 2008). Julkunen et al. (2008) showed that stimulation of the motor cortex in AD patients was associated with a significant decrease in TMS-induced activity over several brain areas compared with healthy controls. These prominent changes in functional cortical connectivity suggest that large-scale networks are abnormally organised in AD patients due to the alteration of long-range

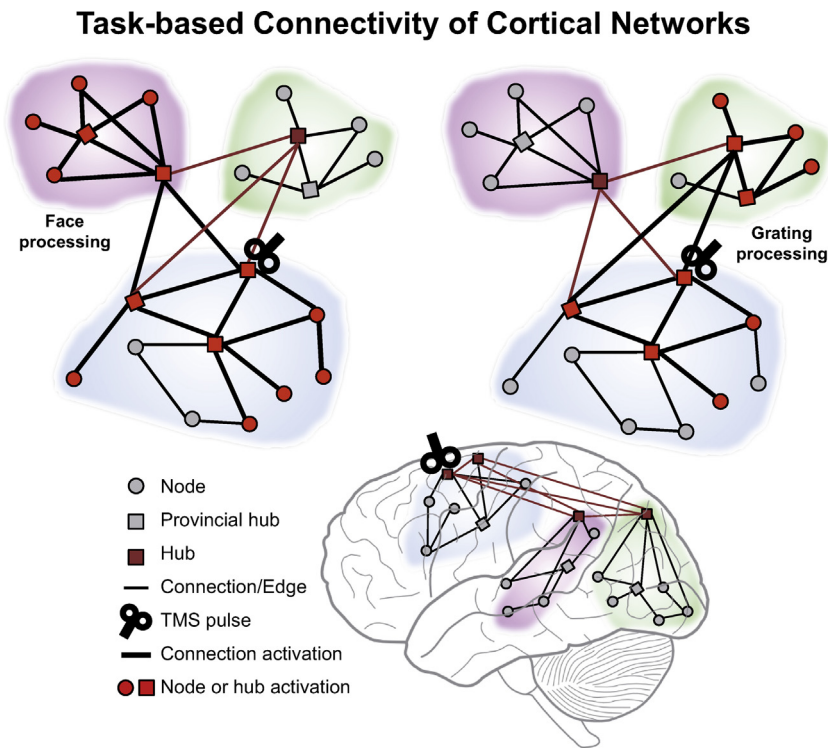


Fig. 3. Testing reveals connectivity during task execution. The figure illustrates the signal distribution in the brain schematically represented by three modules of nodes with long-range connections among them (as in Fig. 2). Task execution increases the connectivity (thick lines) between the functionally relevant modules. TMS-induced responses travel on these connections, i.e., from the target node to the nodes that are more strongly connected during the task. By stimulating a hub, “increased connectivity” within the local stimulated module and along long-distance connections to the functionally relevant downstream modules can be identified. The figure simulates results from Morishima et al. (2009).

connections. Similarly, the application of graph theory to functional connectivity studies in AD supports a global decrease in functional connectivity and a higher vulnerability of hub connections (Stam et al., 2007, 2009; Tijms et al., 2013; Vecchio et al., 2014).

More prominently, TMS–EEG connectivity studies have provided valuable information for the differential diagnosis of consciousness disorders (e.g., vegetative state and minimally conscious state) and hence have related consciousness to signatures of cortico-cortical connectivity. Consciousness has been described as an emergent property of the collective activity of a widespread associative network (Demertzi et al., 2013; Laureys and Schiff, 2012; Tononi, 2004). Although to our knowledge, graph theory has not yet been applied to patients with disorders of consciousness, several neuroimaging studies using both fMRI (Vanhaudenhuyse et al., 2010) and EEG (Varotto et al., 2014) suggest a close relationship between resting-state connectivity in a fronto-temporo-parietal network (resembling the default mode network) and the level of consciousness. In line with these data, two independent TMS–EEG studies (Ragazzoni et al., 2013; Rosanova et al., 2012) have been able to distinguish between patients in a vegetative state and a minimally conscious state based on differences in intra- and interhemispheric connectivity patterns as revealed by TEPs (as illustrated in Fig. 4). In minimally conscious patients, both studies found TMS evoked local activity in the stimulated area and also in more distal, connected cortical sites. This distal activation was limited to the areas homologous to the stimulated one (Ragazzoni et al., 2013). In contrast, in vegetative state patients, TMS-evoked activity (when present) was locally confined to the stimulated hemisphere, indicating strongly compromised effective connectivity. Interestingly, the absence of contralateral TEPs significantly discriminated between the vegetative state and minimal conscious state groups (Ragazzoni et al., 2013).

As reviewed above, TMS–EEG connectivity studies in patients have highlighted the vital importance of stable brain network interactions to ensure normal brain function, characterising disorders by altered connectivity and advancing knowledge of the pathophysiological state of a given condition.

7. Limitations and open questions

So far we have highlighted the advantages of the use of TMS–EEG in the study of the connectome. Here we summarise limitations and confounders with the possible strategies that have been developed for addressing them.

Caution should be taken when studying connectivity through EEG-based coherence measures because the activity from the same source can be recorded from different EEG sensors and induce spurious connectivity patterns. Several methods have been implemented to reduce or exclude spurious connectivity, mainly based on the detection of lagged interactions, excluding zero-phase interactions (e.g., imaginary coherence, partial directed coherence and phase-lag index) (Greenblatt et al., 2012; Palva and Palva, 2012; Sakkalis, 2011; Schoffelen and Gross, 2009). Moreover, volume conduction may be further reduced by performing the connectivity analyses at the source level.

Another limitation is related to the use of TMS. Given that TMS induces spreading of activity along active functional connections at the time of stimulation, TMS–EEG may highlight the excitatory/inhibitory interplay between nodes within and across networks, but it might not reveal the complete set of connections of a node. Secondly, most subcortical structures are silent in EEG recordings because only columnar structures contribute to surface recordings. Therefore some properties of the connectome and the distinction between some connectivity models may hardly be obtained with this technique, e.g., the sparsity of

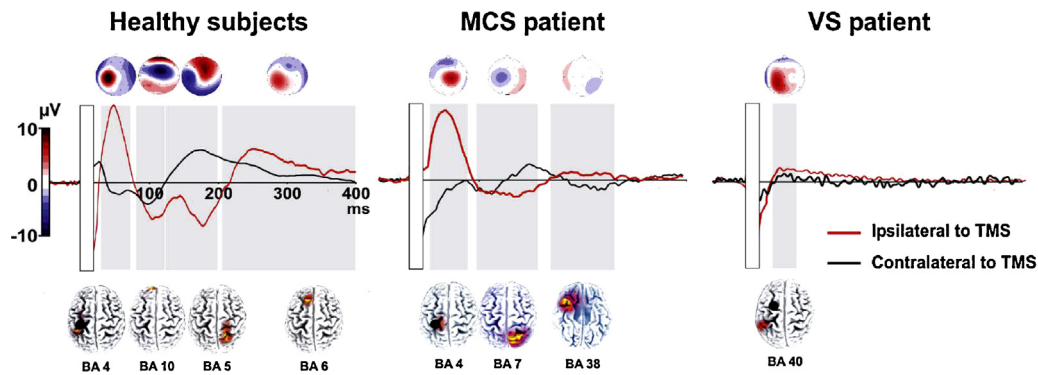


Fig. 4. Altered connectivity in disorders of consciousness. The figure presents the TEPs recorded from the C3 (ipsilateral to TMS – red line) and C4 electrodes (contralateral hemisphere – black line) in a group of healthy controls, a minimal conscious state (MCS) patient and a vegetative state (VS) patient. In all subjects, the left motor cortex was stimulated, as indicated with a black dot on the signal distribution maps reported below waveforms. The responses obtained during the sham condition were point-by-point subtracted from those obtained during real TMS. The time windows in which the signal was significant are indicated with a grey rectangle (i.e., EEG signal exceeding three times the standard deviation of the pre-stimulus activity for at least 20 ms). Grand-averaged scalp topographies and sLORETA localisation maps are reported on the top and bottom, respectively, showing changes over time of the activated areas (BA = Brodmann area). The colour scale on the left shows the range of values for topography maps. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Modified from Ragazzoni et al. (2013).

intermodular connectivity (Bassett and Bullmore, 2006) or the decline of connections with distance (Markov and Ercsey-Ravasz, 2013).

An open question here is how sensitive TMS–EEG may be for tracking alternative routes of neural input transmission as a function of task context and pathological conditions. Graph theory indicates that when a node is altered, network connections can change in two ways. First, the weight of edges of the affected node can change, i.e., the connection between the target area and the connected areas can be strengthened or weakened. Second, the loss of the affected node and its connections can modulate distant edges and activate alternative paths of information flow. TMS–EEG studies might highlight both mechanisms, by looking at the strength of the connections between the target area and the connected network (Shafi et al., 2013) and at the activation of new routes within the network. In the clinical context, it would be interesting to use a TMS–EEG approach to track compensatory activity and the reorganisation of connectivity, i.e., whether alternative routes are adopted to solve a task in pathological conditions and to understand the association between the alternative routes and the preserved abilities. Moreover, establishing whether a hub or a node is altered would aid in the design of more specific neuromodulation and rehabilitation protocols to re-establish degraded functions (Miniussi and Rossini, 2011).

Changes in the neuronal network dynamics are important also for healthy brain functioning, in the context of learning. Indeed, changes in cognitive functions are intimately tied to the capacity of a system to acquire or improve skills through plasticity processes. Repetitive TMS protocols have plasticity inducing properties (Shafi et al., 2013; Siebner et al., 2009), and therefore TMS can be used to temporarily modify activity in a targeted cortical region. These plastic changes in the targeted area may also induce complex widespread alteration in the global functional connectivity and network efficiency that may depend on whether the targeted area is a brain hub or a specialised area of lower degree. In this context by recording EEG activity during plasticity-inducing TMS protocols it may be possible to evaluate how long term potentiation- or long-term depression-like effects act at network level.

8. Conclusions and future perspectives

TMS–EEG coregistration offers a unique opportunity to study effective connectivity at high temporal resolution through simultaneous cortical stimulation and evaluation of induced cortical

activity at both local and global (network) levels. The reviewed findings, inline with previous theorizations by means of fMRI study with graph theory analysis, suggest that TMS-probed connectivity patterns depend on the hierarchical level of the targeted area, revealed by different physiological and behavioural consequences of the stimulation of brain hubs and lower-degree areas. Induced activity in response to the stimulation of lower-degree areas initially spreads within the segregated network in which the area is embedded and eventually reaches more interconnected, higher-degree nodes. In contrast, induced activity from the stimulation of a brain hub quickly reaches specialised areas of a lower degree, depending on the activation state of its connections.

The interfacing of TMS–EEG studies with findings on brain network architecture derived from other neuroimaging techniques has two important advantages. First, it provides empirical validation to models of brain network architecture, such as graph theory. Second, TMS–EEG can provide dynamic measures of the response of the brain when one specific node is targeted, i.e., focusing on specific sub-networks or on specific connections. This information is missing in graph theory models in which global indices of network functioning are employed. However, more specific indices of network functioning are crucial to define the relationship between the activity in a specialised network and a specific cognitive function or dysfunction after neural damage. TMS–EEG coregistration can overcome these limitations and highlight the different contributions of brain hubs and lower-degree specialised nodes in healthy and dysfunctional brain organisation.

The convergence of graph theory models and TMS–EEG studies will provide an excellent method of mapping effective cortical connectivity in a network and its relationship with cognitive functioning, fostering the development of new tools for the diagnosis of neural diseases.

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