



Multiscale topological properties of functional brain networks during motor imagery after stroke



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ABSTRACT

In recent years, network analyses have been used to evaluate brain reorganization following stroke. However, many studies have often focused on single topological scales, leading to an incomplete model of how focal brain lesions affect multiple network properties simultaneously and how changes on smaller scales influence those on larger scales. In an EEG-based experiment on the performance of hand motor imagery (MI) in 20 patients with unilateral stroke, we observed that the anatomic lesion affects the functional brain network on multiple levels. In the beta (13–30 Hz) frequency band, the MI of the affected hand (*Ahand*) elicited a significantly lower smallworldness and local efficiency (E_{loc}) versus the unaffected hand (*Uhand*). Notably, the abnormal reduction in E_{loc} significantly depended on the increase in interhemispheric connectivity, which was in turn determined primarily by the rise of regional connectivity in the parieto-occipital sites of the affected hemisphere. Further, in contrast to the *Uhand* MI, in which significantly high connectivity was observed for the contralateral sensorimotor regions of the unaffected hemisphere, the regions with increased connectivity during the *Ahand* MI lay in the frontal and parietal regions of the contralaterally affected hemisphere. Finally, the overall sensorimotor function of our patients, as measured by Fugl–Meyer Assessment (FMA) index, was significantly predicted by the connectivity of their affected hemisphere. These results improve on our understanding of stroke-induced alterations in functional brain networks.

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Introduction

Most brain functions result from the organization of several neuronal assemblies in a complex and dynamic system (Varela et al., 2001). The term “organization” can be defined as the coherent interdependence of various parts that constitute the whole. Functional connectivity (FC) approaches have been introduced to operationally describe the coherent dependence across spatially remote neurophysiological processors (Friston, 1994); such approaches are effective tools for assessing the organization of the brain, based on the activity of multiple cerebral regions.

Over the past decade, graph theory has been introduced as a mathematical approach to characterize the complexity of anatomic and functional brain networks (Bullmore and Sporns, 2009). In functional

neuroimaging, a graph is an abstract representation of a pattern of connectivity, in which nodes represent various areas of the brain and links correspond to significant interactions between the activities of regions of the brain. Many groups have exploited graph-based approaches to examine the changes in functional (data-driven) and effective (model-based) connectivity in several brain disorders (He and Evans, 2010). In this regard, many computational studies have focused on understanding how the brain reorganizes its functional structure after stroke from a network-based perspective.

Graph theory approaches have allowed the effect of stroke on the organization of the brain to be studied from neuroimaging signals that are recorded during resting states and motor/cognitive tasks through various noninvasive techniques, such as functional MRI (fMRI) (Nomura et al., 2010; Wang et al., 2010), EEG (De Vico Fallani et al., 2009), MEG (Westlake et al., 2012), and DTI (Crofts et al., 2011). Although the extent to which the application of such approaches impact the study of stroke-related disturbances in cortical connectivity is unknown, they have been reviewed comprehensively, based on recent meta-analyses (Grefkes and Fink, 2011; Westlake and Nagarajan, 2011).

These reviews have highlighted that stroke lesions can lead to i) critical deviation from optimal “small-world” network topologies

Abbreviations: MRI, Magnetic Resonance Imaging; PET, Positron Emission Tomography; MEG, MagnetoEncephalography; EEG, ElectroEncephalography; DTI, Diffusion Tensor Imaging; *Ahand*, Affected hand; *Uhand*, Unaffected hand; *Ahemi*, Affected/Ipsilesional hemisphere; *Uhemi*, Unaffected/Contralesional hemisphere; MI, Motor imagery; FC, Functional connectivity.

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that support processing of segregated and integrated information (Bassett and Bullmore, 2006), ii) altered interhemispheric connectivity, and iii) abnormal region centrality in the ipsilesional and contralesional hemispheres, possibly due to compensatory mechanisms. Although this evidence suggests that stroke modulates several topological attributes of the functional brain network, ranging from small (e.g., single-node connectivity) to large scales (e.g., connectivity of the entire system), a unifying framework that simultaneously describes the changes in network properties on different scales (Alstott et al., 2009) and their relationships (Vázquez et al., 2004) has not been established and is rarely and poorly applied in analyses of functional brain networks.

In this study, we applied a multilevel graph analysis on functional brain networks obtained from EEG signals that was designed to examine multiple topological scales simultaneously. Based on the peculiarity of functional brain networks to be embedded in a physical space that is coincident with the anatomic substrate (Doron et al., 2012; Honey et al., 2007), we aimed to characterize the FC patterns on several scales: i) the entire brain (large scale), ii) the 2 hemispheres (intermediate scale), and iii) each node in the 2 hemispheres (small scale). This framework was adopted to describe the possible brain connectivity disturbances in stroke.

Specifically, the functional brain network was studied under a motor/cognitive condition, represented by mental simulation of hand movements, also called motor imagery (MI). MI can be defined as a dynamic state during which the representation of a specific motor action is rehearsed internally without any overt motor output and is governed by the principles of central and peripheral motor control (Decety, 1996). Thus, the practice of action mental imagery by triggering neural activations of relevant brain motor areas is an alternative approach for examining the motor system, even in the absence of movement execution (Page et al., 2007; Sharma et al., 2006).

Based on these considerations, we used the proposed graph approach to study the functional brain networks in stroke patients with unilateral cortico-subcortical damage of the sensorimotor system that caused various degrees of motor impairment in the respective contralateral side (i.e., hemiplegia or hemiparesis). The patients performed MI with their affected (*Ahand*) and unaffected (*Uhand*) hands, the latter of which was used as the reference condition (Jang et al., 2003; Johansen-Berg et al., 2002) to be contrasted to the *Ahand* MI representing the target condition under investigation. FC was estimated from scalp EEG signals, which have high temporal resolution and carry frequency-specific information on motor task-related neural activity (Babiloni et al., 1999; Gerloff et al., 1998).

We hypothesized that our experimental design would allow us to:

- assess the impact of unilateral stroke lesions on multiple brain network properties, estimated during the mental rehearsal of movements, and identify possible dependencies between the network changes on various topological scales; and
- examine the presence of reliable network-based neuromarkers that correlate with poststroke functional motor status, as measured using motor functional scales.

Materials and methods

Between 2011 and 2012, we recruited 20 patients (mean age, 55.5 years; 11 females) who were affected by a first-ever unilateral stroke in the subacute phase (time since event, 8.4 ± 2.8 weeks) on admission for poststroke rehabilitation treatment at Fondazione Santa Lucia (Rome). All patients had suffered unilateral supratentorial (cortico/subcortical) stroke (left hemisphere 11) that was confirmed by structural MRI and resulted in various degrees of motor impairment on the side of the body that was contralateral to the stroke lesion (for patient details, see Table 1). Exclusion criteria were: the

pharmacological treatment with drugs affecting the patient's vigilance and/or the EEG background activity; Mini-Mental State Examination score < 24 (Tombaugh, 2005) and severe cognitive disorders (such as severe hemispatial neglect and language disorders) as evaluated by a neuropsychologist; the presence of other chronic disabling pathologies; orthopedic injuries that could impair reaching or grasping; spasticity of the shoulder, elbow, or finger flexors and extensors that exceeded 3 on the modified Ashworth Scale.

The clinical and functional assessment of all patients comprised the following scales: i) the European Stroke Scale (Hantson et al., 1994); ii) the Medical Research Council scale for muscle strength (Compston, 2010) to assess residual strength in the upper limbs; and iii) the upper limb section of the Fugl–Meyer Assessment (Fugl Meyer et al., 1975) to assess functional motor recovery after stroke. Detailed scale scores relative to the clinical and functional assessment are reported in Table 1. All measurements were made by an expert physician less than 1 week before the EEG data acquisition. All patients gave written informed consent for participation in the study, which was approved by the Ethics committee of the Fondazione Santa Lucia.

EEG recordings and motor tasks

All patients had EEGs recorded within 1 week after hospitalization. Patients were comfortably seated in a dimly lit room, with their upper limbs resting on a cushion, and instructed by a visual cue to perform a kinesthetic type of MI of their hand grasping (Jeannerod, 1994). In order to ensure the correct understanding of the MI task by the patients, several trials of actual execution of the same sustained grasping with the unaffected hand were performed before the recording session (visual cue and timing as the EEG experimental condition). Afterwards, in the EEG experiment, patients were instructed to rehearse “the feeling of movements” acquired during the previous MI task practice. Similar pre-EEG recording session practice was allowed with the affected hand by attempting grasping movements. The recording session comprised 2 runs in which the MI of the hand grasping relative to the unaffected (*Uhand*) and affected (*Ahand*) hand was sustained for 4 s. Each run consisted of 30 trials (8 s each), divided equally between randomly presented *baseline* and *task* trials. The visual cue was presented using dedicated software, i.e., BCI2000 (Schalk et al., 2004), that was synchronized with the EEG amplifiers.

As illustrated in Fig. 1, the visual cue was a small red ball that moved at constant speed along the central vertical line of a screen from bottom to top for 8 s (trial duration). In the *task* trials (panel A), the lower half of the screen was black and the upper half was green. Patients were instructed to be prepared to begin the hand MI as soon as the red ball entered the green area (4 s) and maintain the task until the ball reached the edge of the screen (4 s). In the *baseline* trials (panel B), the screen was black, and patients simply relaxed throughout the trial duration (8 s).

EEG signals were collected from 61 scalp sites that were assembled on an electrode cap per a montage that was modified as an extension of the international 10–20 system. The electrooculogram (EOG) was simultaneously recorded to allow the subsequent rejection of ocular artifacts. EEG data were continuously acquired on a commercial system (Brainproduct GmbH, Munich, Germany) with a 200 Hz frequency sampling; scalp signals were referenced to the linked-ear signal. The data were then band-pass filtered in the 1–45 Hz range and depurated from ocular artifacts using the Independent Component Analysis tool (ICA) and commercial software (Vision Analyzer software; Brainproduct GmbH, Munich, Germany).

To ensure that the MI task was performed without any concomitant voluntary muscular contraction, the electromyographic (EMG) activity that was recorded in the left and right opponens pollicis was monitored throughout the experimental session using disposable surface electrodes that were placed in a bipolar belly–tendon configuration. The

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