



Neurorehabilitation in Stroke: The Role of Functional Connectivity

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Commentary

In the last decade, important progress has been made with regard to clinical recovery in patients with disabling neurological conditions such as ischemic and hemorrhagic stroke. Until recently, the lack of effective treatment for stroke left patients with impaired cognition and severe physical disability with no hope of clinical recovery. Nowadays, rehabilitation represents a growing field that applies the knowledge from medicine, neuroscience, psychology and bioengineering that has allowed patients with neurological disability due to stroke to increase their life expectancy and enjoy a better quality of life [1].

Despite the advancement in neurointerventional surgery and medical treatment options (e.g., tissue plasminogen activator) applied within a few hours of stroke onset, stroke remains the main cause of permanent disability in Europe and the USA [2]. Early rehabilitative interventions such as intensive physiotherapy, neuropsychological rehabilitation or application of cutting-edge technologies, including robot-assisted therapy are associated with a high degree of physical and cognitive recovery. However, not all patients achieve considerable improvement of their neurofunctional disorders, and current functional indexes are unable to predict clinical outcome after rehabilitation. Thus, an important clinical question in stroke is whether specific measures of neural function can help predict which patients will benefit to a greater or lesser extent from rehabilitative interventions.

In an attempt to answer this question, new research looks at changes in neuronal reorganization or functional connectivity dynamics following neurorehabilitation in patients with stroke [2,3]. It is known that after focal lesions, cerebral networks reorganize themselves both functionally and structurally to compensate for the effects of the lesion and for those of remote areas. Hence the analysis of functional connectivity can help us to understand the effect of stroke on cerebral networks and why some patients make a better recovery than others [4]. The aim of this work is to discuss the potential role of functional connectivity and brain network reorganization in predicting neurorehabilitation outcomes after stroke.

Motor outcomes

Clinical examination and neuropsychological assessments show limited value to predict post-stroke rehabilitation outcome. It has been proposed that neuroimaging and functional measures may potentially have a role in clinical decision making for rehabilitation therapy after stroke [3]. A recent review of the use of non-invasive brain stimulation techniques to monitor and modulate the excitability of intracranial neuronal circuits highlights that transcranial magnetic stimulation can produce lasting effects on brain motor function. Of note, functional connectivity between premotor and primary motor cortex assessed with fMRI has been found predictor of good clinical response to transcranial magnetic stimulation [5]. These findings suggest that cortical stimulation may be a promising approach to improve synaptic dysfunction and functional reorganization of motor networks after stroke, enhancing clinical recovery [2]. In support to this view, other studies exploring the effects of robotic therapy on brain function pointed out that motor recovery after stroke is best predicted by neuroimaging

measures, including interhemispheric functional connectivity within the motor network [3]. Based on these studies, a successful motor recovery produced by conventional physiotherapy, robot-assisted therapy, or transcranial magnetic stimulation over the motor cortex is likely mediated by cortical network reorganization. These interventions, however, have none or little effects on neurocognitive deficits, which are common manifestations of cortical stroke.

Cognitive Outcomes

A recent line of research indicates that intensive neurocognitive rehabilitation appears to be of value in the recovery from stroke-related cognitive symptoms such as neglect after right hemisphere infarction [6]. Cognitive training using virtual reality games has successfully achieved improvements in attention and memory functions in patients with stroke [7]. Moreover, low-frequency repetitive magnetic stimulation over the contralesional opercular area has demonstrated to be effective in language recovery in patients with post-stroke aphasia [8]. A combined intensive language training and transcranial magnetic stimulation is thought to improve clinical recovery, although the long-term effects of the magnetic cortical stimulation are yet unknown [9]. These studies are clinically relevant with regard to therapeutic effects of cognitive training and cortical stimulation. However, they do not address the question of a possible role for functional network organization in the neuropsychological improvement observed after cognitive rehabilitation in stroke.

A study using electroencephalography (EEG) provides support to the notion that functional connectivity is disrupted by focal ischemic lesions, and that this disruption underlies cognitive impairment. Compared to healthy subjects, patients with ischemic stroke exhibited decreased alpha coherence between the perilesional area and cortical regions critical to the behavioral deficits (e.g., language, motor, executive functions) observed in their clinical and neuropsychological assessments. This functional abnormality predicted cognitive performance, suggesting a role for alpha band connectivity in the processing of cognitive functions [10]. These findings are consistent with the fact that alpha band coherence of clinically dysfunctional areas like the right parietal lobe is able to predict the effects of cortical stimulation on parietal network functions, including visuospatial attention [5].

Using fMRI, a functional disintegration of the Default Mode

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Network (DMN) associated with cognitive deficits has been found three months after stroke [11]. The DMN is a brain circuit that is specifically active during rest and temporally deactivated during performance of sensorimotor or cognitive tasks. This intrinsic functional organization during rest allows the brain to allocate resources and ready itself for changes in internal and external environments [12]. Functional and structural connectivity abnormalities of the DMN have consistently been reported in cognitive disorders [12,13]. This evidence paves the way for the investigation of network reorganization related to recovery induced by neurocognitive rehabilitation in stroke.

Functional Connectivity – Evidence from our Group

Using magneto encephalography (MEG), our group has evaluated how cognitive interventions may induce reorganization of functional brain networks and predict improvement of cognitive functions in patients with focal brain insult, in particular traumatic brain injury [14]. Prior to rehabilitation, the patients showed increased functional connectivity in slow frequencies (i.e., delta band) and decreased connectivity in the alpha band, as measured with coherence. These results indicate a shift towards slow rhythms in brain connectivity typically seen after brain damage. After the rehabilitative intervention, patients showed a reduction in the number and strength of local and long-range connections in delta band that correlated with improvements in cognitive functioning. Interestingly, this occurred in parallel with a recovery in alpha band connectivity (i.e., increase in number and strength of alpha band connections) which correlated positively with improvements in neuropsychological test performance and with increased autonomy in daily competences.

Using a graph theory approach, we were able to describe how the architecture of neural networks in patients with traumatic brain injury changes from a random organization to a more “small world” configuration, recovering a number of hubs closely linked to network efficiency [15]. We additionally used data mining methods to predict the post rehabilitation state of these patients, and found that rehabilitation discriminated several patients from healthy controls based on their cognitive performance.

Conclusion

Taking together, EEG/MEG evidence from stroke and traumatic brain injury suggests that alpha band functional connectivity might represent a reliable predictor of clinical improvement induced by neurorehabilitation or cortical stimulation. The topographic distribution of changes in alpha functional connectivity may vary depending on the location of the stroke lesion and the specific cognitive functions affected or the deficits targeted by the rehabilitation. Nevertheless, resting-state DMN connectivity may be involved as a sign of intrinsic functional network reorganization after stroke rehabilitation. Overall, brain functional connectivity could be considered as an important method for evaluating and monitoring the process of recovery after brain damage, and for predicting patients that will benefit to a greater extent from specific rehabilitative interventions. Studies aiming to identify brain connectivity and plasticity changes induced by neurorehabilitation in stroke are strongly encouraged.

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