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Brain effective connectivity during motor-imagery and execution following stroke and rehabilitation

Sahil Bajaj[a,*], Andrew J. Butler[b,c,d], Daniel Drake[b], Mukesh Dhamala[a,d,e]

[a] Department of Physics and Astronomy, Georgia State University, Atlanta, GA, USA
[b] Byrdine F. Lewis School of Nursing & Health Professions, Georgia State University, Atlanta, GA, USA
[c] Department of Veteran's Affairs, Atlanta Rehabilitation Research and Development Center of Excellence, Decatur, GA, USA
[d] Neuroscience Institute, Georgia State University, Atlanta, GA, USA
[e] Center for Nano-Optics, Center for Behavioral Neuroscience, Center for Diagnostics and Therapeutics, Georgia State University, Atlanta, GA, USA

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A B S T R A C T

Brain areas within the motor system interact directly or indirectly during motor-imagery and motor-execution tasks. These interactions and their functionality can change following stroke and recovery. How brain network interactions reorganize and recover their functionality during recovery and treatment following stroke are not well understood. To contribute to answering these questions, we recorded blood oxygenation-level dependent (BOLD) functional magnetic resonance imaging (fMRI) signals from 10 stroke survivors and evaluated dynamical causal modeling (DCM)-based effective connectivity among three motor areas: primary motor cortex (M1), premotor cortex (PMC) and supplementary motor area (SMA), during motor-imagery and motor-execution tasks. We compared the connectivity between affected and unaffected hemispheres before and after mental practice and combined mental practice and physical therapy as treatments. The treatment (intervention) period varied in length between 14 to 51 days but all patients received the same dose of 60 h of treatment. Using Bayesian model selection (BMS) approach in the DCM approach, we found that, after intervention, the same network dominated during motor-imagery and motor-execution tasks but modulatory parameters suggested a suppressive influence of SM A on M1 during the motor-imagery task whereas the influence of SM A on M1 was unrestricted during the motor-execution task. We found that the intervention caused a reorganization of the network during both tasks for unaffected as well as for the affected hemisphere. Using Bayesian model averaging (BMA) approach, we found that the intervention improved the regional connectivity among the motor areas during both the tasks. The connectivity between PMC and M1 was stronger in motor-imagery tasks whereas the connectivity from PMC to M1, SM A to M1 dominated in motor-execution tasks. There was significant behavioral improvement ($p = 0.001$) in sensation and motor movements because of the intervention as reflected by behavioral Fugl-Meyer (FMA) measures, which were significantly correlated ($p = 0.05$) with a subset of connectivity. These findings suggest that PMC and M1 play a crucial role during motor-imagery as well as during motor-execution task. In addition, M1 causes more exchange of causal information among motor areas during a motor-execution task than during a motor-imagery task due to its interaction with SM A. This study expands our understanding of motor network involved during two different tasks, which are commonly used during rehabilitation following stroke. A clear understanding of the effective connectivity networks leads to a better treatment in helping stroke survivors regain motor ability.

1. Introduction

Numerous studies have investigated the characteristics of motor networks following stroke and it has been confirmed that stroke may cause a significant disturbance within the motor system due to direct tissue loss or damage of white matter fibers connecting different motor areas (Inman et al., 2012; James et al., 2009; Silasi and Murphy, 2014; Turken et al., 2008). This may result in temporary or permanent

Abbreviations: DCM, dynamical causal modeling; BMS, Bayesian model selection; BMA, Bayesian model averaging; IU, imagine unaffected; IA, imagine affected; PU, pinch unaffected; PA, pinch affected; MI, motor imagery; ME, motor-execution.

* Corresponding author at: Department of Physics and Astronomy, Georgia State University, Suite 600, 25 Park Place, Atlanta, GA 30303, USA. Tel.: +1 404 413 6073; fax: +1 404 413 6025.
E-mail address: sahil.neuro@gmail.com (S. Bajaj).

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physical disability among stroke survivors. Statistics published by The American Stroke Association and National Stroke Association confirms the importance of investigations related to stroke and interventions to promote recovery following stroke. Therefore, it is essential that we understand the detailed mechanism of reorganization of motor networks following stroke. It is also crucial to understand the effect of intervention on disturbed motor network as motor function is regained.

Motor-imagery and motor-execution tasks have been used to study motor recovery in people following stroke (Butler and Page, 2006; Lehéricy et al., 2004; Mintzopoulos et al., 2009; Sharma et al., 2006). Previous studies have investigated the effects of stroke on motor networks (Confalonieri et al., 2012; James et al., 2009; Jiang et al., 2013; Sharma et al., 2009) but there are little data on the effects of interventions on motor behavior and motor network interactions. Here, by using a dynamical causal modeling (DCM) approach (Friston et al., 2013; Friston et al., 2003; Valdes-Sosa et al., 2011), we investigated effective connectivity among three motor areas: the primary motor cortex (M1), the pre-motor cortex (PMC) and the supplementary motor area (SMA), which are known to interact during motor-execution and imagery tasks.

Mental practice (MP) and physical therapy (PT) are used frequently to improve motor function for people recovering from stroke. The primary goal of such treatments is to help patients regain motor strength or function that was completely or partially lost due to stroke. In the current study, we used either MP or combination of MP and PT. MP is defined as use of internal simulation that originates by creating an experience, which can be auditory, visual, tactile or kinesthetic but without any overt movements (Butler and Page, 2006; Dickstein and Deutsch, 2007). PT involves actual physical exercise, which has been demonstrated to improve learning and restoration of lost skills in stroke survivors.

Several studies have reported that cortical activation during MP are identical to PT (Hale, 1982; Livesay and Samaras, 1998). In a study by Altschuler et al. (1999), a comparison was done between movements of the impaired and the healthy arm; they found that several patients regained function of their affected arm when they watched the reflection of their healthy arm moving in a mirror, which may be regarded as an MP task. Recently, a combination of MP and PT has emerged as an effective tool to improve and characterize brain functionality at various stages following stroke (Bajaj et al., 2015; Butler and Page, 2006). It has been mentioned that following intervention PMC develops functional interactions with ipsilesional M1 (Grefkes and Fink, 2014; Silasi and Murphy, 2014). Although the source of the neuronal change associated with these interventions remains unclear. There is debate as to whether an intervention promotes the promulgation of same neuronal population during the recovery period or the intervention recruits other neuronal populations to compensate for the role played by affected neurons. A few studies (Schaechter et al., 2002; Wittenberg et al., 2003) have shown that repetitive task performance may lead to an increase in motor-map size in the affected hemisphere and this might be associated with a shift in laterality of motor cortical activation from damaged to undamaged hemisphere.

Brain activation and effective connectivity have been extensively studied in healthy people using motor-imagery and motor-execution tasks. Motor-imagery tasks (mental rehearsal) can involve a representation of movements in the brain (Jeannerod, 1995; Solodkin et al., 2004). The extent and distribution of activations may differ in motor-imagery and motor-execution, but both motor imagery and motor execution tasks activate the network that involves the core motor areas: M1, SM A and PMC (Bajaj et al., 2014; Cordes et al., 2000; Gerardin et al., 2000; Grefkes et al., 2008; Kasess et al., 2008). These areas are known to be involved in planning, initiation and execution of motor commands. The roles of SM A and PMC have been reported repeatedly during motor-imagery as well as during motor-execution tasks. They send neuronal impulses to M1. Several studies on effective connectivity and directed functional connectivity have reported the interactions of these areas within themselves as well as with areas such as: the basal ganglia, putamen, cerebellum, inferior and superior parietal lobule and other somatosensory areas (Gao et al., 2011; Grefkes et al., 2008; Rehme et al., 2013; Walsh et al., 2008). SM A, M1 and PMC are known to be anatomically connected (Pool et al., 2013; Walsh et al., 2008).

In the present study, our analysis of brain effective connectivity within motor network of stroke patients is based on dynamical network modeling (DCM) (Friston et al., 2003). We hypothesized that either MP or MP + PT would (i) strengthen the effective connectivity on the affected side of the motor cortical network as patients regain motor ability and (ii) reorganize the connectivity pattern in the contralesional hemisphere. We tested these hypotheses by formulating several models using DCM using ordinary differential equations and compared the exceedance probability of each model. Exceedance probability represents the degree of belief about a model having higher posterior probability than the remaining models (Wasserman, 2000). We also explored and compared the role of M1 in affected and unaffected hemispheres during motor-imagery and motor-execution tasks.

2. Materials and methods

2.1. Participants and pre-scan measures

We recorded fMRI data from 13 adult stroke survivors. Three subjects had more than 2 mm of translation or more than 1.5° of rotation about the three axes or their data following intervention was not recorded properly and were excluded from the analysis. Four (2 females, 2 males) of the remaining 10 participants (4 females, 6 males) had left hemiparesis resulting from infarct or hemorrhage located in the thalamus, basal ganglia, caudate and pontomedullary. The remaining six volunteers had right hemiparesis due to infarctions of the middle cerebral, pontine or internal carotid arteries (Supplementary Table 1) (Inman et al., 2012). The mean age of the participants was 60.10 ± 10.52 years. All the participants were independent in standing, toilet transfer, could maintain balance for at least 2 min with arm support and met the criterion of being atleast 18 years old. Upper extremity movement criteria included the ability to actively extend the affected wrist ≥20° and extend 2 fingers and thumb at least 10° with a motor activity log (MAL) score of less than 2.5 (Uswatte et al., 2006). Either MR imaging or computed tomography (CT) was used to confirm the stroke location (Supplementary Table 1). Average stroke latency was 11 months and ranged from 1 to 54 months. The Mini-Mental State Exam (MMSE) (Folstein et al., 1975), Fugl-Meyer Motor Assessments (FMA) (Fugl-Meyer et al., 1975) and MIQ-RS (movement imagery questionnaire-revised for stroke) (Gregg et al., 2010) were used to assess cognitive aspects of mental function, sensation and motor function, and motor-imagery (kinesthetic and visual) ability respectively (Supplementary Table 1). The MMSE consisted of two sets of questions; the first tested orientation, memory and attention whereas the second set tested the participant's ability to name, follow verbal and written commands, write a sentence spontaneously and copy a complex polygon. A maximum score of 30 is indicative of normal cognitive function. The FMA included a total of 33 items including: reflexes, volitional movement assessment, flexor synergy, extension synergy, movement combining synergies, movement out of synergy, normal reflex assessment, wrist movement, hand movement, co-ordination and speed, each with a scale from 0 to 2 (0 for no performance, 1 for partial performance and 2 for complete performance). The total possible score was 66 where a score of nearly 33 represents moderate impairment of the affected upper limb. The MIQ-RS assesses how well people are able to mentally perform movements and consisted of everyday movements e.g. bending, pushing, pulling and reaching for and grasping (Butler et al., 2012; Gregg et al., 2010). Participants rated the level of ease/difficulty on a 7-point scale from 1 = very hard to see/feel to 7 = very easy to see/feel (Confalonieri et al., 2012).