Motor Control Network Effective Connectivity in Regulating Muscle Force Output

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ABSTRACT

Objective of the study: This study aimed at characterizing output features of the higher-order motor control centers (hoMCCs), including secondary (premotor cortex [Pre] and supplementary motor area [SMA]) and association (prefrontal cortex [PFC]) motor regions to the primary motor cortex (M1) during graded force tasks. It is well known that one of the major roles of the primary motor cortex (M1) is controlling motor output such as muscle force. However, it is unclear how the hoMCCs interact with M1 in regulating voluntary muscle contractions. Methods: fMRI data was acquired during graded force tasks and fMRI-based effective connectivity (EC) and muscle force analyses were performed to study the relationship between hoMCCs-M1 effective connectivity and voluntarily exerted handgrip force. Results: The results show that there is a consistent information flow from the hoMCCs to M1 under all force conditions, suggesting a hierarchical control mechanism in the brain in regulating voluntary muscle force. Only the premotor cortex exhibited a significant role in mediating the level of force production through its EC with M1 but that role diminished when the exerted force was high, suggesting perhaps a ceiling and/or fatigue effect on the EC. A flip in the direction of EC from the primary sensory cortex (S1) to the hoMCCs (PFC, SMA, and Pre) at lower force levels while at higher forces EC was observed from the hoMCCs to S1. Conclusion: The hoMCCs regulate M1 output to produce desired voluntary muscle force. Only the Pre-to-M1 connectivity strength directly correlates with the force level especially from low to moderate levels. The hoMCCs are involved in modulating higher force production likely by strengthening M1 output and downgrading inhibition from S1 to M1.

1. INTRODUCTION

In volitional motor control, movement commands are generated based on the goal, effort, kinematics, and dynamics of the motor task. It has been well documented that the activity of the primary motor cortex (M1, single cell or macro electrophysiological and neuroimaging signals) is proportional to voluntary muscle force [1-4]. The role of M1 in controlling voluntary force has been studied extensively in both non-human primates and human participants. For example, in 1980's, researchers demonstrated a relationship between motor cortex neuron discharge rate and monkey finger pinch force [1], showing a linear relationship between the discharge rate and static finger pinch force [2-4]. A number of neuroimaging studies have shown a proportional relationship between voluntary muscle force and level of brain activation [5-9] in healthy humans. A similar positive relationship between scalp EEG-derived movement-related cortical potentials (MRCP) and voluntary elbow-flexion force and EMG signals was reported in young human subjects [10].

Despite this knowledge, it is not well known how other cortical fields, especially higher-order motor control centers (hoMCCs), interact with M1 in making voluntary muscle contractions. Previous research by our research group has shown activations across the network of entire motor control hierarchy [9, 11] and a strong functional connectivity between the M1 and hoMCCs [12-14] in control of voluntary force in humans; however, no studies have examined directional control or connectivity from the hoMCCs to M1. The purpose of this study was to characterize output features of the hoMCCs to M1 during graded force tasks using fMRI data-based effective connectivity (EC) analysis. The hoMCCs regions explored in this study included the prefrontal cortex (PFC), the supplementary motor area (SMA), and premotor cortex (Pre). Activation of the primary sensory cortex (S1) and its relation with M1 and hoMCCs were also analyzed. We selected these hoMCC regions based on findings of the previous fMRI studies by our group discussed in this section and specifically based on [9] study that has shown linear relationship between intensity of fMRI signals of PFC, SMA, and Pre and voluntary muscle force. PFC is known to play a role in regulating endurance by increasing connectivity with Pre to modulate cortical drive [12, 15, 16] and SMA is known to modulate motor strategy through communication with M1 [17-19]. We hypothesized a proportional relationship between strength of directional connectivity from hoMCCs to M1 and voluntary muscle force during the graded motor task.

2. METHODS

2.1. Subjects

Six healthy and young subjects (all males, right-handed, age = 31.3 ± 6.5) participated in the study. Subjects performed a handgrip task in a magnetic resonance scanner and the handgrip force data were recorded during the experiment using a customized pressure transducer system. The force measurement system consisted of handgrip device, hydraulic pressure transducer, water reservoir, and an amplifier. The system was custom-designed and was described in details in previous publications [6, 20].

2.2. Participant's Consent

The protocol was approved by the local Institutional Review Board and all the participants signed an informed consent before participating in the study.

2.3. Motor Task

The maximum voluntary contraction (MVC) of handgrip force was performed before starting the MRI experiment. During the MRI experiment, subjects performed right handgrip contractions at 20%, 35%, 50%, 65% and 80% of their own MVC levels with visual feedback of the force and target displayed in real-time based on the pressure sensor data. These five targets were chosen to explore a set of force levels that incrementally ranges from low effort (20% of MVC) to higher effort (80% of MVC) force tasks. Dura-

tion of each contraction was 25 s followed by a 3-min rest. Eleven fMRI scans were collected during the last 22 seconds of each contraction condition or level, and each condition was repeated only once (Figure 1). Three subjects performed the force tasks in an ascending order and three in descending order. This eliminates possible dependence that one level of force grip generated to the next one. Force output data was collected using metal free handgrip device connected to a pressure transducer (EPX-N1 250 PSIG; Entran Devices, Fairfield, N.J.). The transducer was connected to an amplifier and the amplifier output was recorded by a data acquisition system (Spike 2; Cambridge Electronic Design, Cambridge, UK) in real-time. Detailed procedures are described in Dai *et al.* [9].

2.4. Image Acquisition

All images were acquired using a Siemens 1.5T Vision scanner. Functional images were acquired using a T2* weighted gradient-echo, EPI sequence (TR/TE = 2300/22 ms; interleaved order). At each force level, the fMRI images were acquired during rest period followed by handgrip contraction period. Eleven scans of brain images were collected at each force level or rest period and the duration of the data collection period was ~25.3 seconds. Each scan covered 20 slices (6 mm/slice). High-resolution T1-weighted images were also acquired for identification of anatomical regions in the brain. Both T1-weighted (anatomic) images and functional images were collected in the transverse plane.

2.5. Data Analysis

The fMRI images were preprocessed and image motion detection and correction were performed before the statistical comparisons. A general linear model was fitted for every voxel to detect brain activation at all force levels based on a canonical hemodynamic response function (HRF). Average cortical activation at the five force levels showed activation of M1, Pre, S1, SMA, PFC, cingulate and parietal cortices. Subsequently, representative time courses were extracted from the following five region of interests (ROIs) in each force task: primary motor cortex (M1, Brodmann' area [BA] 4), supplementary motor area (SMA, BA 6) and premotor area (Pre, BA 6) areas, dorsal lateral prefrontal cortex (PFC, BA 46) and primary sensory cortex (S1, BA 1, 2, 3). The ROIs were selected based on findings in a previous work by [9], a study by our group that showed activation of these regions during the same task and linear relationship between fMRI signal intensity and force levels. AMOS (Analysis of a Moment Structures) 16.0 SPSS module (SPSS. Inc.) was used to find the best path models which best fit the extracted time course data using structural equation modeling (SEM). AMOS is part of SPSS package that is used to perform SEM analysis. The procedure
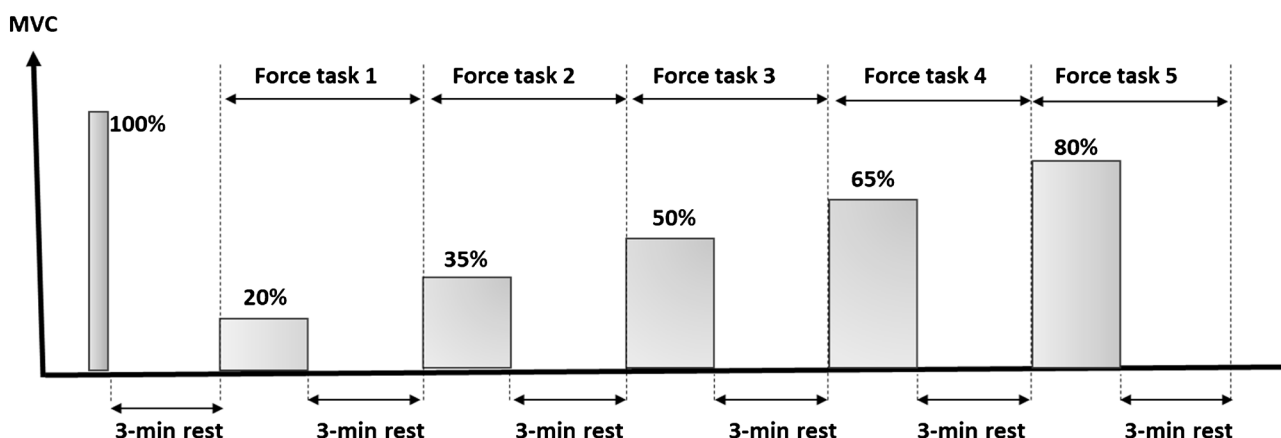
Figure 1. All subjects completed a single MVC trial lying in the scanner before the fMRI-force task experiment. The levels of force for the subsequent force tasks were determined based on the MVC force. Each contraction (force task) lasted 25 s while fMRI brain images were acquired followed by a 3-min rest.

started by constructing possible path model matrices for each force level data to describe the causal relations between source and target regions in the models and model covariance is then identified based on a maximum likelihood algorithm. Regression analysis was used to estimate the coefficient of the path links in the most optimal path model matric at each force level. Effective Connectivity (EC) was evaluated across all force levels by estimating the coefficient of the paths. All statistical analysis was done using Brainvoyager QX 1.7 (Brain Innovation Inc., Netherland), statistical threshold was set to $p < 0.05$ and False Discovery Rate (FDR) was employed to correct for multiple comparisons.

Our previous study demonstrated that fMRI signal within motor cortical network increases proportionally with muscle activation indicated by real-time force and EMG measurements [9]. Many brain regions showed this relationship. This finding implies more synchronized activities or strengthened intrinsic functional connections among these brain regions as brain increases its descending command to the motor neuron pool in the spinal cord as the force output increases [14].

3. RESULTS

3.1. Linear Relationship between Force Task Amplitude and fMRI Time Course

Analysis of time course of voxels in the left M1, contralateral to the performing hand, showed a linear relationship between the force and amplitude of BOLD signal (Figure 2). The relationship is statistically significant ($p < 0.05$) with FDR correction.

3.2. Effective Connectivity (EC) in Different Force Tasks

SEM showed the same path model for lower force levels (20%, 35%, and 50%) versus higher force levels (65% and 80%) except for the EC between PFC and S1 regions. Under the lower force conditions, information flow started from S1 to other regions including PFC. At the higher force levels, information
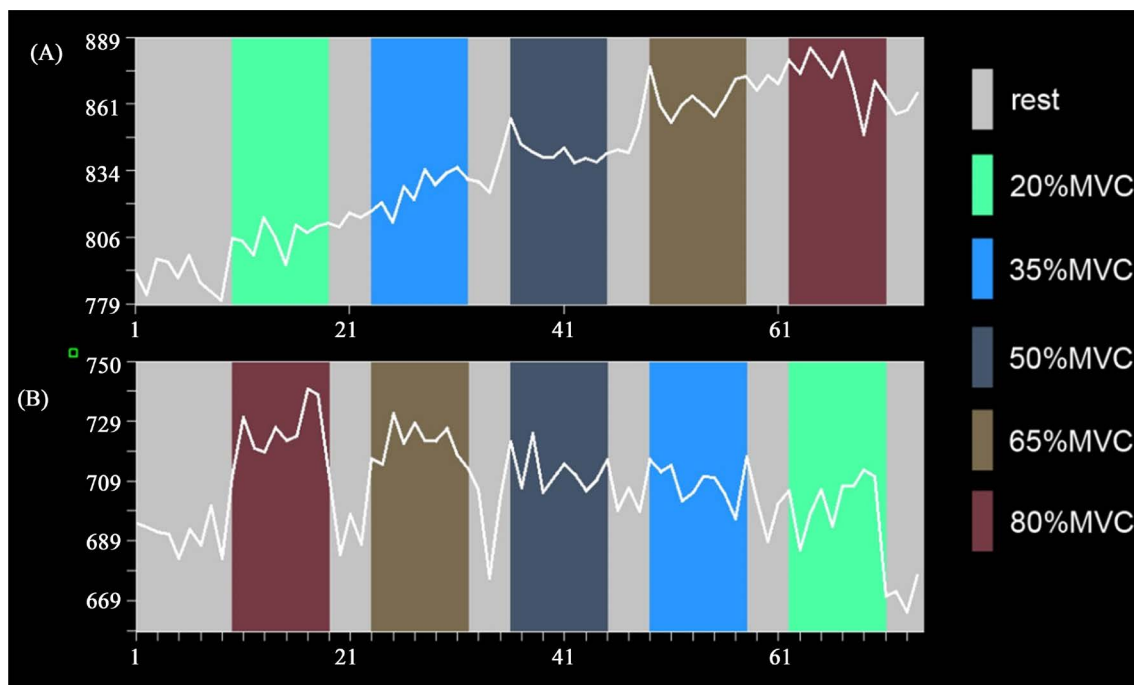

Figure 2. Sample time course of a cluster of voxels in left M1 when the subject performed the force tasks in an ascending order (panel A) and descending order (panel B). X axis shows the scan volume number and Y axis shows the BOLD signal intensity. It is clear that BOLD signal increases or decreases with increased or decreased force levels.

flow originated from PFC to S1. Under both lower and higher force task conditions, the information flowed from PFC to M1 and SMA, from Pre to M1, and from SMA to M1 (**Figure 3** & **Figure 4**). These models are statistically significant ($p < 0.05$) with FDR correction. There was a gradual increase in the EC from the Pre to M1 among force levels 20%, 35%, 50% and 65%. No such increase was seen from 65% to 80% MVC (**Figure 5**).
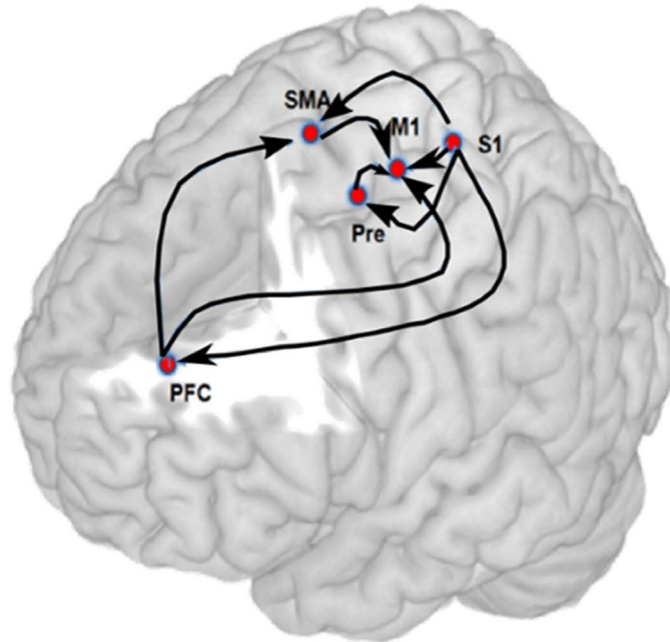
Figure 3. Path model for force modulation involving force levels of 20%, 35% and 50% MVC. Information flow started from S1 to other regions in the motor-control network including M1 and hoMCCs. There is direct modulation of M1 by all hoMCCs regions (S1, Pre, PFC, and SMA).
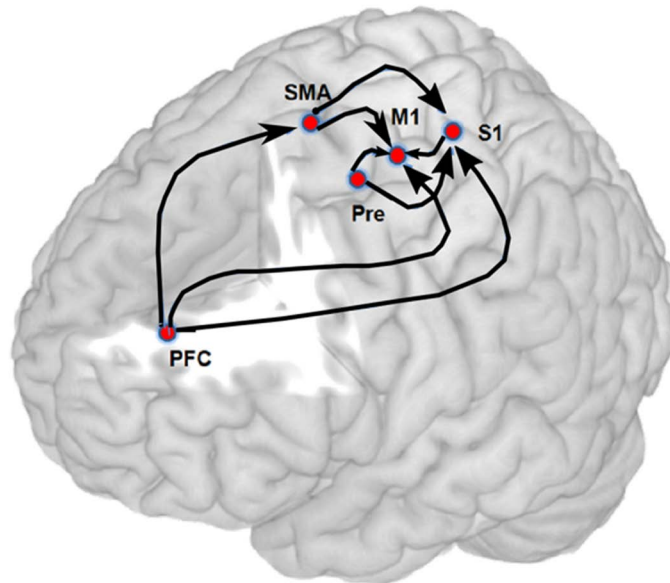
Figure 4. Path model for force modulation involving force levels of 65% and 80% MVC. Direction of information flow at higher force levels began from the PFC to S1, SMA, and M1. Information flow started from Pre to M1 and S1 and from PFC, S1, and SMA to M1.
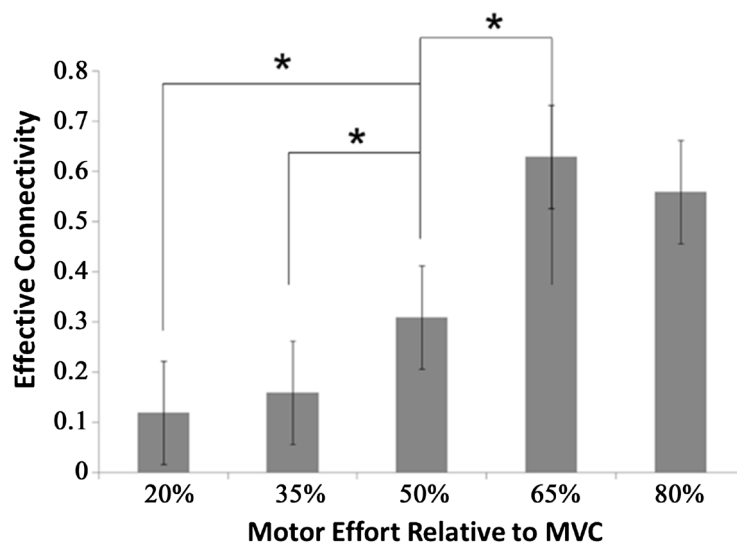
Figure 5. Estimated EC from Premotor cortex (Pre) to M1. Significant increases in EC were found in force modulation from 20% to 65%MVC force levels. No significant increase was found in force modulation from 65% to 80%MVC. *Significant difference in EC at P < 0.05.

4. DISCUSSION AND CONCLUSIONS

The major findings are that 1) there was a linear relationship between the M1 BOLD signal amplitude and voluntary handgrip force; 2) the premotor cortex to M1 effective connectivity increased linearly from 20% to 65% MVC handgrip force but the increase ceased from 65% to 80%; 3) information flow during 20% to 35% and 50% MVC force was from S1 to SMA, PFC, and Pre regions, but the direction of flow was reversed from Pre, SMA, and PFC to S1 under the higher force condition (65% and 80% MVC); and (iv) the information flow was consistent from PFC to M1 and SMA, from Pre to M1, from S1 to M1, and from SMA to M1 under both lower and higher force task conditions.

The observed linear relationship between the M1 BOLD signal amplitude and voluntary grip force was not surprising since it agrees with previous research that showed similar relationship between EEG-derived movement related cortical potential (MRCP) and voluntary muscle activation [10] and between fMRI activation and output force [6, 9].

One of the major findings in this study is the Strengthened Pre-to-M1 connectivity in generating higher forces. Progressive strengthening of EC was found in the path from the Pre to M1 when the force increased from 20% to 65% MVC (Figure 5). One explanation for this EC relationship between the Pre and M1 might be that the Pre plays a major role in modulating output of the M1 to the spinal cord motoneuron pool during voluntary force production. Animal studies have shown that the dorsal Pre modulates grasp force in a grasping task [21] and ventral Pre is involved in predictive scaling of grip force during grasping task based on previous experience of grasped object [22, 23]. Our human fMRI study [9] found a linear relationship between the Pre activation level and handgrip force. Strong anatomic connectivity exists between the Pre and M1 in humans quantified by diffusion tensor imaging [24, 25] and the Pre is a major source of input to M1 using fiber tracing [26, 27] and single cell recording [28, 29] techniques in animals.

However, no significant difference was found in the magnitude of EC when subject performed the higher force tasks. When driving for high force exertions (such as from 65% to 80% MVC in this study), the input strength from the Pre to M1 might have plateaued with no additional room for further improvement. The M1 may augment its own output for further increase of force by increasing recruitment of more M1 output neurons and/or discharge rate of the active neurons similar to spinal motoneuron/motor unit activities in graded voluntary force tasks [1]. It is also possible that the brain uses different modula-

tion strategies during a prolonged motor task such as by increasing connectivity/input from other regions to M1 in the control network not analyzed in this study [30]. Finally, fatigue may have played a role in contributing to a non-increase or slight decrease in EC from the PRE to M1 when the force was elevated from 65% to 80% MVC. (Almost all subjects experienced fatigue when maintaining the force for 25 s at 65 and especially 80% maximal level indicated by a decline of the force in the second half of the 25-s trial). Functional MRI data have shown that when sustaining a strong voluntary muscle contraction, many primary and higher-order cortical motor areas increased activation level (BOLD signal) first but the activation level declined significantly when the muscle was severely fatigued during later part of the contraction, which was postulated as an effect of inhibition from the sensory cortices processing information from the fatiguing muscle [11]. EEG signal sources estimated during a motor task leading to fatigue demonstrated substantial shifting of source location toward the other hemisphere (ipsilateral to the muscle activation), anterior, and inferior cortical regions under the fatigue condition [30].

The information flow was consistent from the PFC, Pre, S1, and SMA to M1 under both lower and higher force task conditions. The PFC is known to be part of the facilitatory system to aid M1 in increasing motor output during a voluntary motor task [31], while sensory (S1), Pre, and SMA regions are part of an inhibitory network to regulate M1 motor output under condition of motor fatigue [31, 32]. Therefore, the consistent connectivity from these regions to M1 might be explained as for maintaining a balanced input to M1 for generating various levels of muscle output. The flip in the direction of connectivity from the S1 to PFC, Pre and SMA at lower force levels (20%, 35% and 50% MVC) to the reversed direction from the PFC, Pre and SMA to S1 at higher force levels (65% and 80% MVC) may suggest "suppression" of inhibition from the S1 for optimal information flow from M1 to the spinal motoneuron pool. It is well known that group III/IV muscle afferent fibers inhibit both spinal and cortical motoneurons [33] most likely through S1 and other sensory regions. Under high force exertion conditions especially involving fatigue, S1 downregulates excitability of the M1 but the flow of information from the PFC, Pre and SMA may suppress activities of the S1; thereby give rise to M1 excitability and its output.

In conclusion, although the sample size of the study was small (6 participants), the results are clear that there is a consistent information flow from the PFC, Pre, S1, and SMA to M1 under all force conditions, suggesting a hierarchical control mechanism for a relatively simple voluntary motor (handgrip) task involving exerting low and high forces. The strength of effective connectivity (EC) from the Pre to M1 increases progressively from generating low (20%) to moderate (35% & 50%) and to relatively high (65% MVC) forces, indicating an important role of the Pre in regulating descending motor output from the M1. A further increase in force production (65% to 80% MVC) does not intensify EC from the Pre to M1, which could be a consequence of reaching the ceiling and/or fatigue-related inhibition of the Pre. Finally a reversal of information flow from the S1 to the higher order motor control centers (hoMCCs) under higher (65% & 80% MVC) force conditions likely points to the hoMCCs' effort to suppress the S1's inhibitory output to M1 for the purpose of maintaining the descending command from M1 to the spinal motoneuron pool. Future studies in this line of research should focus on better understanding excitatory and inhibitory circuitries in the motor control network that regulates voluntary motor actions.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

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