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A regulation role of the prefrontal cortex in the fist-edge-palm task: Evidence from functional connectivity analysis

Hengyi Rao,[a,b,*] Xin Di,[a] Raymond C.K. Chan,[a,c,d,*,1] Yulong Ding,[a] Binbin Ye,[a] and Dingguo Gao[a]

[a] *Department of Psychology, Center for Functional Brain Imaging and First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, 510275, China*
[b] *Department of Psychiatry and Center for Functional Neuroimaging, University of Pennsylvania, Philadelphia, PA 19104, USA*
[c] *Neuropsychology and Applied Cognitive Neuroscience Laboratory, Institute of Psychology, Chinese Academy of Sciences, Beijing, 100101, China*
[d] *Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, 100101, China*

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The Fist-Edge-Palm (FEP) task is a motor sequencing task that is widely used in neurological examination. Deficits in this task are believed to reflect impairment in the frontal lobe regions. However, two recent functional brain imaging studies of the FEP task using conventional subtraction analysis failed to demonstrate FEP-induced activation in the prefrontal cortex (PFC), which contradicts existing neuropsychological literature. In this study, psychophysiological interaction (PPI) analysis was used to reanalyze our previous neuroimaging dataset from 10 healthy subjects in order to evaluate the changes of functional connectivity between the sensorimotor cortex and the prefrontal regions during the performances of the FEP task relative to simple motor control tasks. The PPI analysis revealed significantly increased functional connectivity between bilateral sensorimotor cortex and the right inferior and middle frontal cortex during the performance of the FEP task compared with the control tasks. However, regional signal changes showed no significant activation differences in these prefrontal regions. These results provide evidence supporting the involvement of the frontal lobe in the performance of the FEP task, and suggest a role of regulation, rather than direct participation, of the prefrontal cortex in the execution of complex motor sequence tasks such as the FEP task.

Keywords: Motor sequencing; Fist-Edge-Palm; Effective connectivity; Prefrontal cortex

Neurological soft signs (NSS) refer to minor abnormalities and difficulties in sensory perception, motor coordination, and complex motor sequencing that may accompany psychiatric diseases such as schizophrenia (Chan et al., 2004; Chan and Gottesman, in press; Chen et al., 2005; Dazzan and Murray, 2002; Tosato and Dazzan, 2005). Although various semi-quantitative scales have been established and widely used to rate psychomotor performance in psychosis (Buchanan and Heinrichs, 1989; Chen et al., 1995; Ismail et al., 1998), there are surprisingly few studies that have examined the neural basis of NSS in clinical patients and healthy subjects. This lack of converging evidence limits the scope of understanding the neuropathological origin of poor NSS performance (Chan and Toulopoulou, 2006; Dazzan and Murray, 2002; Tosato and Dazzan, 2005).

Recent advances in brain imaging techniques have led to a growing interest in integrating neuroimaging methods to study motor coordination and motor sequencing (e.g., Chan et al., 2006; Dazzan et al., 2004, 2006; Jancke et al., 1999; Nitschke et al., 2003; Schroder et al., 1999; Ullen et al., 2003; Umetsu et al, 2002). Imaging studies that visualize the brain activation patterns induced by NSS tasks in healthy subjects, such as the Fist-Edge-Palm (FEP) task, may be able to provide direct anatomical and physiological evidence to validate the efficacy of NSS tasks in detecting deficits in motor cortical and subcortical function. In the FEP task, subjects are required to successively place their hand in each of the following postures: a fist resting vertically (i.e., Fist), a palm resting vertically (i.e., Edge), and a palm resting horizontally (i.e., Palm). Since its introduction by Luria (1966), the FEP task has been widely used to detect voluntary movement disorders, and is believed to reflect frontal lobe damage (Motomura et al., 1989). However, two recent independent studies using blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) in healthy subjects found no association between the FEP task and frontal lobe activation. In one of the studies, Umetsu et al (2002)

* Corresponding authors. Rao is to be contacted at Center for Functional Neuroimaging, University of Pennsylvania, 3W Gates, 3400 Spruce Street, Philadelphia, PA 19104, USA. Fax: +01 215 349 8260. Chan, Institute of Psychology, Chinese Academy of Sciences, No.4 DaTun Road, Beijing, 100101, China.
E-mail addresses: hengyi@gmail.com (H. Rao), edsrhy@zsu.edu.cn (R.C.K. Chan).
[1] Fax: +86 10 6483 6274.

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compared both right- and left-hand FEP tasks to relatively simple motor tasks, and revealed that the FEP task induced activation in multiple cortical regions, including the sensorimotor cortex, premotor cortex, parietal cortex, and supplementary motor areas, but not in the prefrontal cortex. In another study, we compared the right-hand FEP task to a relatively simple palm pronation/supination (PS) task and palm tapping (PT) task, and replicated significant activation in the motor network and the lack of activation in the prefrontal regions during the performances of the FEP task (Chan et al., 2006). These results are inconsistent with previous evidence from neuropsychological testing showing that patients with frontal lobe lesions exhibit deficits in the performance of the FEP task (Motomura et al., 1989).

A possible explanation for the discrepancy may be that during the FEP task the frontal lobe is involved in the functional integration or regulation of neural activity underlying motor sequencing, rather than being directly activated. If this is the case, previous imaging studies using conventional subtraction analysis would not be able to examine the potential role of the prefrontal regions in the FEP task, since such analysis can only reveal regionally specific effects in the context of functional specialization. To test this hypothesis, we re-analyzed our previous FEP imaging data (Chan et al., 2006) using an approach of functional connectivity analysis in addition to the conventional analysis, in order to estimate the functional integration between the sensorimotor cortex and the prefrontal regions when subjects were executing the FEP and simple control motor tasks.

Currently, there are several approaches available to functional connectivity analysis, such as psychophysiological interaction (PPI) analysis, dynamic causal modeling (DCM) and structural equation modeling (SEM) for fMRI data (for a review, see Di and Rao, 2007; Penny et al., 2004) and coherence analysis for electroencephalographic (EEG) data (for a review, see Koenig et al., 2005). Although SEM and DCM are widely used to evaluate effective connectivity, both methods require all regions of interest to be defined *a priori* to test specific hypotheses regarding the extent to which the functional connectivity between these pre-determined regions can be changed by perceptual or cognitive conditions. In contrast, PPI analysis is a more exploratory approach that searches for specific brain regions that show significant changes in functional connectivity to another region under different perceptual or cognitive conditions (Friston et al., 1997). Due to the lack of regional activations in the prefrontal cortex (PFC) induced by the FEP task, the present study examined whether any prefrontal regions are involved in the integration or regulation of neural activity underlying motor sequencing. More specifically, the aim of the present study was to identify any frontal lobe regions where coupling between these areas and the sensorimotor cortex (SMC) significantly differed between the complex FEP task and the control motor tasks. Therefore, the PPI approach was adopted in this study. By utilizing one regressor that represents the deconvolved activation time course in a given volume of interest (i.e., the physiological variable), a second regressor that represents the psychological variable of interest, and a third regressor that represents the product of the previous two regressors (i.e., the psychophysiological interaction term), PPI analysis is able to detect regionally specific responses in one brain area in terms of interactions between a cognitive or sensory process and activity in another region (Friston et al., 1997). The activation time course in the SMC was defined as the physiological variable, and motor tasks with varying degrees of motor complexity were defined as the psychological variable for the PPI analysis. We predicted that such analysis would reveal a significant interaction between task complexity and functional connectivity between the PFC and SMC. In particular, there would be greater PFC–SMC coupling found during the performance of the FEP task relative to the control motor tasks, but no change of activation level would be found in these prefrontal regions.

Methods

Participants

Ten healthy right-handed subjects (7 female; mean age = 22.9 ± 2.0 years) participated in the study. All of the subjects were free of any neurological illnesses or psychiatric diseases. Written informed consent was obtained from all of the subjects before the testing session.

Tasks and procedures

Three right-hand motor tasks of varying motor complexity were used. These tasks, which include the following, increase in complexity: (1) the simple palm tapping (PT) task, in which subjects were required to repeat only one manual action, specifically, tapping the right palm in a prone position; (2) the intermediate complex pronation/supination (PS) task, in which subjects were required to alternatively perform two manual actions, specifically, tapping the right palm in the prone and supine positions respectively; and (3) the complex FEP task, in which subjects were required to successively place their right hand in the following postures: a fist resting vertically (fist), a palm resting vertically (edge), and a palm resting horizontally (palm). A resting condition without any hand movement was used as the control baseline of the PT task, and the PT task was used as the control baseline of the PS and FEP tasks. Subjects were taught to practice the tasks before the scanning in order to ensure that they perform the motor actions correctly at a constant rate and frequency. Each motor action in the three tasks was required to be executed in a similar time interval and duration throughout the entire experiment. For example, if a subject used 1 s to execute the PT task, he/she was instructed to use 2 s to execute the PS task and 3 s to execute the FEP task. This orientation ensured that each subject was aware of the task demands in each of the three conditions and performed similarly across the different motor tasks.

Imaging data acquisition

The functional imaging data was originally acquired in a GE 1.5T Signa scanner (General Electric, Waukesha, WI, USA) with a standard GE birdcage-type RF coil using a standard T2*-weighted EPI sequence. The EPI parameters were: TR = 3s, TE = 60 ms, FOV = 24 cm × 24 cm, Matrix = 64 × 64, flip angle = 60°, 12 axial slices (7 mm thick/2 mm sp, from superior to inferior). The spatial resolution for the functional images was 3.75 mm × 3.75 mm × 9 mm. High-resolution anatomic images were also obtained using the standard T1-weighted sequence (66 axial slices, 2.0 mm thick/interleaved, FOV = 24 cm × 24 cm, Matrix = 256 × 256).

The study utilized a block design. For each subject, three 246-s long functional runs consisting of four repeated cycles of the motor task and the corresponding baseline condition were conducted, one for each of the three motor tasks. An on-off light signal in the MRI room was used to instruct the subjects to switch between the motor task and the baseline condition. The first two volumes of each run were discarded to eliminate the effects of EPI onset. The scan order of the

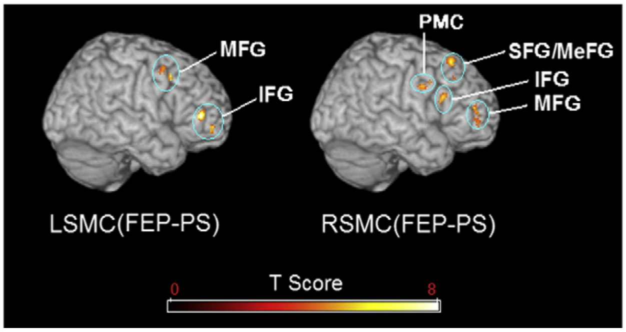

Fig. 1. Right frontal regions showing greater connectivity with the left and right sensorimotor cortex (LSMC and RSMC) during the performance of the FEP task compared with the PS task. Activated clusters were displayed at the threshold of uncorrected $p<0.001$ and cluster size larger than 15 voxels. IFG: inferior frontal gyrus; MFG: middle frontal gyrus; SFG/MeFG: superior/medial frontal gyrus; PMC: premotor cortex; FEP: fist-edge-palm; PS: palm pronation/supination.

motor tasks was counter-balanced across the subjects, and a minimum 2-min rest interval was given between the two successive runs.

Conventional imaging data analysis

Imaging data processing and analysis were carried out using the Statistical Parametric Mapping software package (SPM5, Wellcome Department of Cognitive Neurology, UK, implemented in Matlab 6, Math Works, Natick, MA). The functional imaging time series were realigned to correct for head movements, coregistered with a high-resolution anatomical image, normalized to a standard Montreal Neurological Institute (MNI) template, and spatially smoothed with an 8 mm FWHM Gaussian kernel. Conventional analyses were first conducted on the individual-level using voxel-wise general linear modeling (GLM) and three contrasts were defined between the tasks and the corresponding baselines, namely PT vs. rest, PS vs. PT, and FEP vs. PT. Group-level random effect analyses were then conducted using one-sample *t*-tests. A threshold of uncorrected $p<0.001$ and cluster extent size larger than 15 voxels was used to identify the activations associated with each contrast. No prefrontal activations were found for any of these contrasts. The peak activation in the left SMC from the group-level analysis for the contrast of PT vs. Rest was used to define the reference region for the PPI analysis.

PPI analysis

After conventional analysis, PPI analysis was conducted to estimate functional integration during the task execution under different motor complexity conditions. Because the motor tasks in the present study were only completed with the right hand by all subjects, the left SMC was determined *a priori* as the reference region for the PPI analysis. This region was defined by using a sphere with a radius of 8 mm and a center at the peak activation in the left SMC activation (MNI coordinates = [−30 −28 54], from the conventional analysis of the contrast of PT vs. Rest). Because the FEP task activated both sides of the SMC, the right SMC was also defined as an additional reference region by flipping the left SMC to the right hemisphere.

Voxel-wise PPI analysis was first conducted at individual-level for the left and right SMC in order to identify if any other brain areas connecting to the SMC showed a significant increase in functional coupling (the slope of regression) during a more complex motor task (e.g., the FEP task) compared with a control task (e.g., the PT or PS task). For each subject, the activation time course signal in the reference region (i.e., the first eigenvariate time series, adjusted by effect of interest) was extracted from the conventional GLM and entered into the PPI analysis as the first regressor representing the physiological variable. A second regressor representing the motor tasks with different levels of complexity was entered into the PPI analysis as the psychological variable. The psychophysiological interaction between task complexity and activation signal in the reference region was designated as the regressor of interest in the PPI analysis. Group-level random effect analysis was then conducted on the individual results using one-sample *t*-tests for the contrasts of PS vs. PT and FEP vs. PT. Group-level paired *t*-tests were conducted for the contrast of FEP vs. PS. Areas of significant activation were identified at a threshold of uncorrected $p<0.001$ and cluster extent size larger than 15 voxels. Using this threshold level, the PPI analysis identified several prefrontal regions in which the activity showed significantly increased coupling to activity in the SMC during performance of the more complex FEP task relative to the simple PS task. These prefrontal activation areas were defined as regions of interest in which BOLD signal changes were calculated to further

Table 1
Regions that showed greater functional connectivity to the left and right sensorimotor cortex (SMC) during more complex motor tasks comparing with simpler motor tasks (FEP vs. PS; FEP vs. PT; and PS vs. PT)

Frontal regions	Peak MNI coordinates			Peak Z score	Cluster size	Brodmann area (BA)
	X	*Y*	*Z*			
Connectivity to left SMC (FEP vs. PS)						
R. IFG	52	42	4	4.56	37	45/46
R. MFG	38	14	42	3.73	17	9
Connectivity to right SMC (FEP vs. PS)						
R. SFG/MeFG	6	26	56	3.76	47	8/6
R. IFG	50	18	22	3.65	37	44/45
R. MFG	48	48	12	3.59	20	10
R. PMC	50	−2	32	3.53	20	6
Connectivity to left SMC (PS vs. PT)						
R. MFG	36	36	−20	3.67	19	11
Connectivity to right SMC (PS vs. PT)						
R. MFG	34	34	−16	4.22	49	11
Connectivity to left SMC (FEP vs. PT)						
R. MFG	42	8	48	3.98	34	8/6
Connectivity to right SMC (FEP vs. PT)						
L. Cerebellum	−38	−80	−18	4.10	139	/
L. Thalamus	−4	−20	0	4.01	25	/
L. IPL	−34	−58	42	3.96	17	40
R. IPL	30	−74	40	3.82	32	7/40
R. MeFG/ACC	8	34	30	3.67	26	9/32
R. MFG	32	32	52	3.42	19	8
L. MFG	−52	16	40	3.38	26	9

Threshold was set as uncorrected $p<0.001$ and cluster size larger than 15 voxels. L. left; R. right; IFG: inferior frontal gyrus; IPL: inferior parietal lobule; MFG: middle frontal gyrus; SFG/MeFG: superior/medial frontal gyrus; PMC: premotor cortex; MeFG/ACC: medial frontal gyrus/anterior cingulate cortex; FEP: fist-edge-palm; PS: palm pronation/supination; PT: palm tapping.

confirm that the FEP task did not directly activate the prefrontal cortex when compared with the PS task.

Results

The results from the conventional analysis replicated our previously reported findings that task complexity modulates regional activity in the motor-related brain regions (Chan et al., 2006). Compared with the PT task, the PS task induced greater activity only in the left sensorimotor cortex, whereas the FEP task induced greater activity in multiple cortical regions, including the bilateral SMC and SMA, the left inferior parietal lobule, and the right cerebellum. However, the FEP task did not induce greater activity in the prefrontal regions when compared with the PT or PS tasks, respectively.

Consistent with our hypothesis, the PPI analysis revealed a significant interaction between motor task complexity and SMC activation expressed in the prefrontal regions. Greater functional connectivity to the left SMC was found in the right inferior frontal gyrus (IFG) and middle frontal gyrus (MFG), and greater functional connectivity to the right SMC was found in the right IFG, MFG, superior/medial frontal cortex (SFG/MeFG), and premotor cortex during the FEP task compared with the PS task (Fig. 1 and Table 1). Regional parameter estimates confirmed significant enhancements in functional connectivity in these prefrontal regions during the FEP task compared with the PS task (paired t-tests, all $p<0.001$, Fig. 2). However, regional BOLD signal changes in these prefrontal regions showed no significant activation differences between the FEP and PS tasks (paired t-tests, all $p>0.2$, Fig. 2) or between the FEP and PT tasks (one-sample t-tests, no difference to zero, all $p>0.05$).

The PPI analysis also revealed significantly increased functional connectivity between the right MFG and bilateral SMC in the FEP task and the PS task compared with the simplest PT task (Table 1). Enhanced functional connectivity to the right SMC was also found in the left cerebellum, left thalamus, left MFG, right medial frontal gyrus/anterior cingulate cortex (MeFG/ACC) and bilateral inferior parietal lobule for the FEP task compared with the PT task (Table 1).

Discussion

By applying functional connectivity analysis to our previously acquired imaging data, the present study demonstrates a significant psychophysiological interaction between motor task complexity and neural activity in the SMC within the prefrontal regions. In particular, the inferior and middle prefrontal regions showed greater coupling to the SMC during the performance of a more complex FEP task compared with the relatively simple PS and PT tasks. This finding provides direct evidence supporting the involvement of the frontal lobe in the execution of the FEP task, which is consistent with existing neuropsychological literature. However, no difference in BOLD signal change was observed in these PFC regions during the FEP and PS tasks. These results replicate previous null findings (Chan et al., 2006; Umetsu et al, 2002) and suggest that the FEP task does not involve direct activation in the PFC, but engages greater functional integration between the PFC and SMC.

Increased functional connectivity between the frontal regions and the SMC revealed by the PPI analysis during the more complex FEP task compared with the simpler motor tasks is consistent with previous findings from EEG coherence studies (e.g., Astolfi et al., 2004; Manganotti et al. 1998; Serrien and Brown, 2003). Converging evidence from these EEG studies have demonstrated increased task-related coherence during the initiation or execution of various complex motor tasks. Unlike fMRI, which records hemodynamic or metabolic signals and provides an indirect measurement for neural activity, EEG records extra- or intra-cranial scalp electrical potentials and provides a direct measurement of cortical neural activity. The coherence between different EEG channels reflects the inter-regional correlation of oscillatory activities across different frequency bands. More recently, a method of applying coherence and partial coherence analyses to fMRI data to reveal task-related functional connectivity changes has been developed by Sun and colleagues (2004, 2007). Using this novel method, they reported greater connectivity between frontal regions and cortical motor regions during the early novel motor sequence learning (Sun et al.,

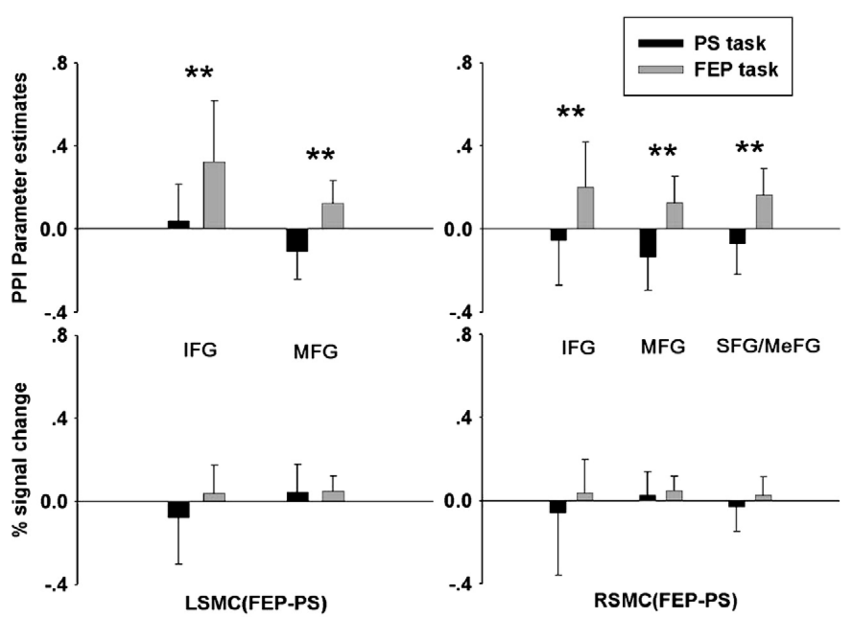

Fig. 2. Regional parameter estimates from the PPI analysis and regional percentage signal changes from conventional subtraction analysis in the right frontal regions. PPI: psychophysiological interaction; IFG: inferior frontal gyrus; MFG: middle frontal gyrus; SFG/MeFG: superior/medial frontal gyrus; LSMC: left sensorimotor cortex; RSMC: right sensorimotor cortex; FEP: fist-edge-palm; PS: palm pronation/supination PT: palm tapping. (**$p<0.001$).

2007). The consistency between the current PPI connectivity observations and existing coherence literature provides further evidence and a multi-modal validation supporting our hypothesis that the frontal lobe is involved in the integration or regulation of neural activity underlying motor sequencing.

The left SMC is the primary area underlying all right-hand movements in right-handed individuals. Increasing activation in this area during more complex motor tasks compared with simple motor tasks has been consistently observed in several studies (Catalan et al., 1998; Kawashima et al., 1998; Umetsu et al; 2002), including our own (Chan et al., 2006). However, it is unclear whether increasing SMC activation in complex voluntary motor tasks is contingent upon the bottom-up processing of additional sensory and motor information, or dependent on top-down regulation from higher brain regions. The current findings support the top-down regulation hypothesis. The regulation from the right prefrontal regions to the SMC is also consistent with the critical role of the prefrontal cortex in cognitive control, goal maintenance and impulsivity inhibition (Miller and Cohen, 2001), all of which are necessary components during the execution of complex motor sequences in a rhythmic and systematic pattern.

Although the motor tasks in the present study were all executed with the right hand, increased connectivity to the SMC was only found in right prefrontal regions rather than the left side. These results are consistent with the functional asymmetry involving the type of information maintained and processed by the right and left frontal cortex. Previous working memory studies have indicated that storage and maintenance of different kinds of information may be localized in the frontal regions in different hemispheres. Specifically, the left frontal regions are more involved in storage for verbal materials, whereas the right frontal regions are more involved in storage for spatial information (Smith et al., 1996; Smith and Jonides, 1999). Greater right-sided lateralization was also reported when executive functions were demanded in the spatial tasks (Wager and Smith, 2003). Since the FEP task involves both maintenance of spatial information (i.e., the three postures of hand) and successive execution of these hand postures, it is not surprising that activity in the right rather than left frontal regions showed enhanced functional coupling to activity in the SMC during the performance of this task in the present study.

In addition to the frontal cortex, other brain regions including the cerebellum, thalamus, and parietal cortex also showed greater effective connectivity with the right SMC during the FEP task compared with the PT task. These areas overlap with the FEP-induced activation areas found by conventional subtraction analysis (Chan et al., 2006), and belong to a motor network that initiates motor orders and the sequencing of actions during motor planning and execution (Haslinger et al. 2002; Dhamala et al. 2003; Debaere et al. 2004). Increased effective connectivity found in these non-frontal lobe regions suggests that the execution of complex motor tasks such as the FEP task may require not only the participation of additional brain regions, but also greater functional coupling between the participating regions and the SMC.

The observation of null activation in the prefrontal regions during complex motor coordination and motor sequencing tasks is quite commonly reported in the literature on hand movement (e.g. Debaere et al., 2004; Dhamala et al., 2003; Haslinger et al., 2002). However, our findings suggest that failure to observe prefrontal activation in one task *cannot* be interpreted as the lack of involvement of the frontal lobe in that task. The level of neural activation may remain constant in control conditions and complex motor tasks, but the strength of connectivity between the prefrontal and other motor regions may vary. It is therefore necessary to exercise caution when giving explanations for and drawing inferences about imaging results using conventional subtraction analysis alone, especially when these results are used to inform clinical decision making. Connectivity analysis such as the PPI method may provide a useful adjunct to conventional functional specialization in estimating the potential role of a specific brain region in functional integration.

Some aspects of the experimental design may limit the clinical relevance of the results reported here. First, the FEP task adopted in the present study was well practiced, in contrast to the “novel” task performed in clinical evaluations, during which patients are naive to the FEP task when they are requested to imitate the action. As we have argued in our previous study (Chan et al., 2006), a practice effect of this nature may have contributed to the null result for the potential activation of the frontal lobe regions. There remains a gap between the task as performed after practice in a highly restricted laboratory environment and the task as performed in a naturalistic task-naive clinical setting.

Second, we were not able to record the behavioral performance of the subjects, including accuracy and speed during scanning. Behavioral performance, such as tapping rates in audibly paced finger-tapping tasks, may modulate the functional coupling between the primary motor cortex and other cortical regions (Newton et al., 2007). Therefore, we cannot rule out the possibility that subjects' accuracy and speed during the performance of the FEP and control motor tasks might affect the observed functional connectivity changes. However, all subjects were instructed to perform the motor actions at a constant speed and in a similar manner. Further, all subjects were given sufficient time to practice the tasks before the scan. Subjects showed no difficulties performing all three motor tasks at a similar rate of speed, and their informal reports after the scan confirmed that they executed and switched between tasks appropriately during the scan. Thus there is no reason to assume that the accuracy and speed committed by the subjects during the scan differed significantly between FEP and control tasks. The performance differences could not fully account for the observed interaction between motor task complexity and PFC–SMC connectivity.

Finally, the present study only recruited healthy volunteers who could perform the FEP task appropriately, but not patients with schizophrenia who may have failed to perform the tasks. Therefore, it is not clear whether the brain activation pattern in a clinical cohort would be the same as or different from the current findings. For example, limited neuroimaging studies (e.g., Schroder et al., 1995, 1999) that have adopted gross motor coordination signs such as pronation/supination have suggested a decreased activation pattern in the SMC and supplementary motor area (SMA) in patients with schizophrenia compared with healthy controls. Given the hypofrontality hypothesis of schizophrenia, we would expect that fine motor coordination required in the FEP task would be further impaired in this clinical group. As suggested by the current findings, PPI analysis is able to detect the potential changes in functional integration, for this reason it may be a promising technique to further investigate NSS in clinical patients. However, future studies that control the practice effect and have concurrent recording of the movement parameters, such as EMG/movement- co-registration, must be conducted to overcome the aforementioned limitations and characterize the neural mechanism underlying FEP performance in healthy subjects as well as clinical patients.

In summary, we report greater functional coupling between neural activity in the non-activated PFC and the activated SMC during the performance of the FEP task relative to the simple PS and PT tasks, which partly resolves the controversy between previous neuroimaging findings and neuropsychological testing literature. The results suggest that PFC play a role of regulation rather than a role of direct participation in the execution of complex motor sequencing tasks. The FEP task requires not only the direct participation of a distributed network of motor regions, but also the indirect involvement of PFC to enhance functional integration. Our findings support the utility of using the FEP task for neurological examination of frontal lobe dysfunction, particularly for assessing functional integration and regulation of neural activity underlying motor sequencing.

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References

Astolfi, L., Cincotti, F., Mattia, D., Salinari, S., Babiloni, C., Basilisco, A., Rossini, P.M., Ding, L., Ni, Y., He, B., Marciani, M.G., Babiloni, F., 2004. Estimation of the effective and functional human cortical connectivity with structural equation modeling and directed transfer function applied to high-resolution EEG. Magnetic Resonance Imaging 22 (10), 1457–1470.

Buchanan, R.W., Heinrichs, D.W., 1989. The Neurological Evaluation Scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. Psychiat. Res. 27, 335–350.

Catalan, M.J., Honda, M., Weeks, R.A., Cohen, L.G., Hallett, M., 1998. The functional neuroanatomy of simple and complex sequential finger movements: a PET study. Brain 121, 253–264.

Chan, R.C.K., Toulopoulou, T., 2006. Fractionation of executive function in schizophrenia: relationships to clinical and neurological manifestations. In: Douglas, P. (Ed.), Schizophrenic Psychology: New Research. Nova Science Publishers, Inc., Hauppauge, New York, pp. 1–39.

Chan, R.C.K., Gottesman, I.I., in press. Neurological soft signs as candidate endophenotypes for schizophrenia: A shooting star or a northern star? Neurosci. Biobeh. Rev. doi:10.1016/j.neubiorev.2008.01.005.

Chan, R.C.K., Chen, E.Y.H., Cheung, E.F.C., Chen, R.Y.L., Cheung, H.K., 2004. Prediction of neurological signs by neurocognitive performance in schizophrenia. J. Inter. Neuropsychol. Soc. S2, 22.

Chan, R.C.K., Rao, H., Chen, E.E., Ye, B., Zhang, C., 2006. The neural basis of motor sequencing: an fMRI study of healthy subjects. Neurosci. Lett. 398, 189–194.

Chen, E.Y.H., Shapleske, J., Luque, R., McKenna, P.J., Hodges, J.R., Callloway, S.P., Hymas, N.F., Dening, T.R., Berrios, G.E., 1995. The Cambridge Neurological Inventory: a clinical instrument for soft neurological signs and the further neurological examination for psychiatric patients. Psychiat. Res. 56, 183–202.

Chen, E.Y., Hui, C.L., Chan, R.C., Dunn, E.L., Miao, M.Y., Yeung, W.S., Wong, C.K., Chan, W.F., Tang, W.N., 2005. A 3-year prospective study of neurological soft signs in first-episode schizophrenia. Schizophr. Res. 75, 45–54.

Dazzan, P., Murray, R.M., 2002. Neurological soft signs in first-episode psychosis: a systematic review. Br. J. Psychiatry. Suppl. 43, s50–s57.

Dazzan, P., Morgan, K.D., Orr, K.G., Hutchinson, G., Chitnis, X., Suckling, J., Fearon, P., Salvo, J., McGuire, P.K., Mallett, R.M., Jones, P.B., Leff, J., Murray, R.M., 2004. The structural brain correlates of neurological soft signs in AESOP first-episode psychoses study. Brain 127, 143–153.

Dazzan, P., Morgan, K.D., Chitnis, X., Suckling, J., Morgan, C., Fearon, P., McGuire, P.K., Jones, P.B., Leff, J., Murray, R.M., 2006. The structural brain correlates of neurological soft signs in healthy individuals. Cereb. Cortex 16, 1225–1231.

Debaere, F., Wenderoth, N., Sunaert, S., Van Hecke, P., Swinnena, S.P., 2004. Cerebellar and premotor function in bimanual coordination: parametric neural responses to spatiotemporal complexity and cycling frequency. NeuroImage 21, 1416–1427.

Dhamala, M., Pagnoni, G., Wiesenfeld, K., Zink, C.F., Martin, M., Bernsa, G.S., 2003. Neural correlates of the complexity of rhythmic finger tapping. NeuroImage 20, 918–926.

Di, X., Rao, H., 2007. Progress in functional connectivity analysis. Prog. Biochem. Biophys. 34, 5–12.

Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., Dolan, R.J., 1997. Psychophysiological and modulatory interactions in neuroimaging. NeuroImage 6, 218–229.

Haslinger, B., Erhard, P., Weilke, F., Ceballos-Baumann, A.O., Bartenstein, P., Grafin von Einsiedel, H., Schwaiger, M., Conrad, B., Boecker, H., 2002. The role of lateral premotor-cerebellar-parietal circuits in motor sequence control: a parametric fMRI study. Cogn. Brain Res. 13, 159–168.

Ismail, B., Cantor-Craae, E., McNeil, T.F., 1998. Neurological abnormalities in schizophrenic patients and their siblings. Am. J. Psychiatry 155, 84–89.

Jancke, L., Specht, K., Mirzazade, S., Peters, M., 1999. The effect of finger movement speed of the dominant and the subdominant hand on cerebellar activation: a functional magnetic resonance imaging study. NeuroImage 9, 497–507.

Kawashima, R., Matsumura, M., Sadato, N., Naito, E., Waki, A., Nakamura, S., Matsunami, K., Fukuda, H., Yonekura, Y., 1998. Regional cerebral blood flow changes in human brain related to ipsilateral and contralateral complex hand movements—a PET study. Eur. J. Neurosci. 10, 2254–2260.

Koenig, T., Studer, D., Hubl, D., Melie, L., Strik, W.K., 2005. Brain connectivity at different time-scales measured with EEG. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 360, 1015–1023.

Luria, A.R., 1966. Higher Cortical Functions in Man. Basic Books, New York.

Manganotti, P., Gerloff, C., Toro, C., Katsuta, H., Sadato, N., Zhuang, P., Leocani, L., Hallett, M., 1998. Task-related coherence and task-related spectral power changes during sequential finger movements. Electroencephalography and Clin. Neurophysiol. 109 (1), 50–62.

Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci. 24, 167–202.

Motomura, N., Seo, T., Asaba, H., Sakai, T., 1989. Motor learning in ideomotor apraxia. Psychiat. Res. 83, 7–22.

Newton, A.T., Morgan, V.L., Gore, J.C., 2007. Task demand modulation of steady-state functional connectivity to primary motor cortex. Hum. Brain Mapp. 28, 663–672.

Nitschke, M.F., Stavrou, G., Melchert, U.H., Erdmann, C., Petersen, D., Wessel, K., Heide, W., 2003. Modulation of cerebellar activation by predictive and non-predictive sequential finger movements. Cerebellum 2, 233–240.

Penny, W.D., Stephan, K.E., Mechelli, A., Friston, K.J., 2004. Modelling functional integration: a comparison of structural equation and dynamic causal models. NeuroImage 23 (Suppl 1), S264–S274.

Schroder, J., Essig, M., Baudendistel, K., Jahn, T., Gerdsen, I., Stockert, A., Schad, L.R., Knopp, M.V., 1999. Motor dysfunction and sensorimotor cortex activation changes in schizophrenia: a study with functional magnetic resonance imaging. NeuroImage 9, 81–87.

Schroder, J., Wenz, F., Schad, L.R., Baudendistel, K., Knopp, M.V., 1995. Sensorimotor cortex and supplementary motor area changes in schizophrenia: a study with functional magnetic resonance imaging. Bri. J. Psychiatry 167, 197–201.

Serrien, D.J., Brown, P., 2003. The integration of cortical and behavioural dynamics during initial learning of a motor task. Eur. J. of Neurosci. 17, 1098–1104.

Smith, E.E., Jonides, J., 1999. Storage and executive processes in the frontal lobes. Science 283, 1657–1661.

Smith, E.E., Jonides, J., Koeppe, R.A., 1996. Dissociating verbal and spatial working memory using PET. Cereb. Cortex 6, 11–20.

Sun, F.T., Miller, L.M., D'Esposito, M., 2004. Measuring interregional functional connectivity using coherence and partial coherence analyses of fMRI data. NeuroImage 21, 647–658.

Sun, F.T., Miller, L.M., Rao, A.A., D'Esposito, M., 2007. Functional connectivity of cortical networks involved in bimanual motor sequence learning. Cereb. Cortex 17, 1227–1234.

Tosato, S., Dazzan, P., 2005. The psychopathology of schizophrenia and the presence of neurological soft signs: a review. Curr. Opin. Psychiatry 18, 285–288.

Ullen, F., Forssberg, H., Ehrsson, H.H., 2003. Neural networks for the coordination of the hands in time. J. Neurophysiol. 89, 1126–1135.

Umetsu, A., Okuda, J., Fujii, T., Tsukiura, T., Nagasaka, T., Yanagawa, I., Sugiura, M., Inoue, K., Kawashima, R., Suzuki, K., Tabuchi, M., Murata, T., Mugikura, S., Higano, S., Takahashi, S., Fukuda, H., Yamadori, A., 2002. Brain activation during the fist-edge-palm test: a functional MRI study. NeuroImage 17, 385–392.

Wager, T.D., Smith, E.E., 2003. Neuroimaging studies of working memory: a meta-analysis. Cogn. Affect. Behav. Neurosci. 3, 255–274.