NeuroImage 49 (2010) 2581–2587

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Effective connectivity of neural networks in automatic movements in Parkinson's disease

Tao Wu [a,b], Piu Chan [a], Mark Hallett [b,*]

[a] Department of Neurobiology, Key Laboratory on Neurodegenerative Disorders of Ministry of Education, Beijing Institute of Geriatrics, Xuanwu Hospital, Capital Medical University, Beijing, China
[b] Human Motor Control Section, Medical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

ARTICLE INFO

Article history:
Received 20 July 2009
Revised 7 September 2009
Accepted 15 October 2009
Available online 22 October 2009

Keywords:
Parkinson's disease
Automatic movement
fMRI
Effective connectivity
Brain networks

ABSTRACT

Patients with Parkinson's disease (PD) have difficulty in performing learned movements automatically. The neural mechanism of this deficiency remains unclear. In the current study, we used functional MRI (fMRI) and psychophysiological interaction (PPI) methods to investigate the changes in effective connectivity of the brain networks when movements become automatic in PD patients and age-matched normal controls. We found that during automaticity, the rostral supplementary motor area, cerebellum, and cingulate motor area had increased effective connectivity with brain networks in PD patients. In controls, in addition to these regions, the putamen also had automaticity-related strengthened interactions with brain networks. The dorsal lateral prefrontal cortex had more connectivity at the novel stage than in the automatic stage in normal subjects, but not in PD patients. The comparison of the PPI results between the groups showed that the rostral supplementary motor area, cerebellum, and cingulate motor area had significantly more increased effective connectivity with several regions in normal subjects than in PD. The changes of effective connectivity in some areas negatively correlated with the Unified Parkinson's Disease Rating Scale (UPDRS). Our findings show that some of the factors related to PD patients having difficulty achieving automaticity are less efficient neural coding of movement and failure to shift execution of automatic movements more subcortically. The changes of effective connectivity become more abnormal as the disorder progresses. In addition, in PD, the connections of the attentional networks are altered.

Published by Elsevier Inc.

A general characteristic of the motor system is that people can perform some learned movements automatically. Automatic movements are performed without attention being clearly directed toward the details of the movement; automaticity is common particularly for movements requiring low levels of precision or for frequently executed movements (Bernstein 1967). After a period of training, even some complex tasks can be executed automatically in healthy people (Wu et al., 2004). In contrast, patients with Parkinson's disease (PD) commonly have difficulties in performing movements automatically. For example, PD patients must direct their attention to walking and think about each step if they are to make adequately long steps; otherwise, their steps become small. It has been observed that PD patients have a greater abnormality of automatic-associated movement than intended voluntary movement, which may be one of the bases of clinical symptoms in the early stage of the disease (Hoshiyama et al., 1994).

Previously, we found that PD patients can achieve automaticity in some relatively simple movements after proper training, but with more difficulty than normals. The automatic process was accompanied by reduced activity in many brain regions in normal subjects; in contrast, only a few areas were less activated in PD patients. PD patients require more brain activity in several regions, such as the cerebellum, premotor area (PMA), and parietal cortex compared with controls to perform automatic movements (Wu and Hallett 2005a). While this study provided some important insights, we still do not completely understand the mechanisms of this deficiency in PD. So far, we have only explored the changes in magnitude of brain activity; however, we did not investigate whether the interactions within brain networks during the process of automaticity are changed in PD. Investigations about interactions among human brain regions may play a more important role in understanding automaticity-related brain functional changes because multiple areas are likely to be involved in the control of a given task. The method used to explore interregional interactions in a given task is analysis of functional connectivity (Friston et al., 1993a) or effective connectivity (Friston et al., 1993b). In a recent study of a young group of healthy subjects, we found that automaticity is accompanied by a strengthened effective connectivity of motor networks even though the magnitude of the activation is decreased in healthy subjects (Wu et al., 2008). We speculate that the difficulty PD patients have in obtaining automaticity

* Corresponding author. Bldg 10, Rm 7D37, 10 Center Drive MSC 1428, Bethesda, MD 20892-1428, USA. Fax: +1 301 480 2286.
E-mail address: hallettm@ninds.nih.gov (M. Hallett).

1053-8119/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.neuroimage.2009.10.051

may be due to abnormalities in achieving enhanced connectivity. To test this assumption, we investigated the effective connectivity of neural networks during the process of automaticity in PD compared with age-matched healthy controls.

Subjects and methods

Subjects

This study represents the further analysis of data already reported (Wu and Hallett 2005a). Clinical data of these patients were previously shown (Wu and Hallett 2005a) and are briefly described here. We have data from 12 patients aged 53 to 77 years old (mean, 61.2 years) and included eight males and four females. Patients were studied after their medication had been withdrawn for at least 12 h. Off medication, their UPDRS scores were from 13 to 37 years (mean, 26.7 years); MMSE was 30 in all subjects. We also had data on 12 age- and sex-matched healthy subjects. The experiments were approved by the institutional review board and all subjects gave their written informed consent.

Tasks

All experimental procedures are only briefly described here. Subjects were asked to perform two sequences of right hand finger tapping, referred to as sequence 4 and sequence 12, based on the number of movements in each unit of the sequence. "Sequence 4" was 1-3-4-2, and "Sequence 12" was 1-4-3-2-2-4-1-3-4-1-2-3, in which 1, 2, 3, and 4 refer to the index, middle, ring, and little fingers, respectively. All sequential movements were self-initiated and self-paced and were executed at 0.5 Hz. Automaticity was evaluated by having subjects perform a visual letter-counting task simultaneously with these sequential movements (dual tasks). The dual tasks were performed only before fMRI scanning to assess whether the subjects achieved automaticity. Before the first scan, all subjects practiced until they could move at the required rate. They briefly practiced each sequential movement. After the first scan, subjects practiced these tasks until they could perform both of the sequential movements from memory 10 times in a row without error as well as the dual tasks accurately.

Functional MRI acquisition

All subjects were scanned on a 1.5-T MRI system (Signa, General Electric, Milwaukee, WI). A response button was used to record finger movements inside the scanner. We used an EPI gradient echo sequence (21 slices, TE = 30 ms, TR = 2500 ms, flip angle = 90°, FOV = 22 × 22 cm, matrix = 64 × 64) to obtain functional images. Data were acquired both before and after the subjects achieved automaticity. Two conditions were contained in each scanning session and were defined as the "rest" and "active" condition, respectively. During the rest condition, subjects were asked to relax and focus on the screen in front of them. The active condition in each session contained either sequence 4 or sequence 12. Each condition lasted 25 s and was repeated five times within a session.

Data analysis

Image analysis was performed with SPM2 software (Wellcome Institute of Cognitive Neurology, London, UK). The magnitudes of brain activations during automatic movements in PD have been previously reported (Wu and Hallett 2005a). Therefore, we only describe the effective connectivity in this study. Automaticity-dependent changes in effective connectivity were assessed using the method of psychophysiological interaction (PPI; Friston et al., 1997). PPI is defined as the change in contribution of one brain area to another due to a change in experimental condition or psychological context (Friston et al., 1997). It aims to explain regionally specific responses in terms of the interaction between the psychological variable and the activity in a specific index area. PPI computes whole-brain connectivity between the time series of the index area and the time series of all other voxels. The analysis is constructed to test for the differences in the regression slope of activity in all areas, on the activity in the index area, under the two conditions (automatic vs. novel condition in the present study). We used first session data as the novel condition and used second session data as the automatic condition. The bi-linear term in PPI represents the interaction between physiological activity and a psychological context input which modulates the connectivity between the index area and the other brain regions and has a directional character (Stephan et al., 2003). In the current study, PPI identifies areas in which the degree of coupling with the index region is significantly modulated by the process of automaticity.

Similar to our previous study (Wu et al., 2008), we chose the left primary motor cortex (M1), bilateral dorsal premotor area (PMA), bilateral dorsal lateral prefrontal cortex (DLPFC), bilateral cerebellum, left putamen, rostral supplementary motor area (pre-SMA), cingulate motor area (CMA), and precuneus as index areas because these regions are thought to be involved in the process of automaticity or are important in motor learning. Separate PPI analyses were conducted for each index area. The mean corrected and high-passed-filtered time series in each index area were obtained on a subject-by-subject basis by extracting the first principal component from all voxel time series in a 5-mm radius sphere centered at the coordinates of the subject-specific activations. The psychophysiological interaction term (referred to as "PPI regressor") was computed as the element-by-element product of the deconvolved extracted time series of the selected index area and a vector coding for the main effect of task (1 for automatic stage, −1 for before automatic stage, 0 elsewhere) (Stephan et al., 2003; Gitelman et al., 2003; Garraux et al., 2005). The PPI regressor was mean corrected to remove subject-specific effects and convolved by the canonical hemodynamic response function to account for possible hemodynamic lag. For each subject, the PPI regressor, the task regressor (representing the automatic minus novel contrast for the main effect of automaticity), and the extracted time series were entered in a first-level model of effective connectivity in which the PPI regressor was orthogonalized with regard to the main effect of the task and the regional time series. Brain areas receiving context-dependent influences from the index areas that were greater during the automatic stage than the novel stage were determined by testing for positive slopes of the PPI regressor, i.e., by applying a *t*-contrast that was 1 for the PPI regressor and 0 elsewhere. Conversely, brain areas receiving context-dependent influences from the index areas that were greater during the novel stage than the automatic stage were determined by testing for negative slopes of the PPI regressor, i.e., by applying a *t*-contrast that was −1 for the PPI regressor and 0 elsewhere. Contrast images from the first-level PPI analysis in each subject were entered into a second-level random-effect model. At the second-level, to detect the regions that receive greater influences from each index area during the automatic stage, the contrast images from each subject showing greater influences during the automatic stage than the novel stage were calculated by a one-sample *t*-test in either patients and controls ($p<0.05$, FWE corrected). Then, contrast images from each subject showing greater influence during the novel stage than the automatic stage were calculated by another one-sample *t*-test to detect the regions that receive greater influences from each index area during the novel stage in each group ($p<0.05$, FWE corrected). In addition, we entered the contrast images from each PD patients and controls showing greater influence during the novel stage than the automatic stage into a two-sample *t*-test model to compare the PPI results between the groups ($p<0.05$, FWE corrected).