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Brain Research

Research Report

Disrupted connectivity of motor loops in Parkinson's disease during self-initiated but not externally-triggered movements

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ARTICLE INFO

Article history:
Accepted 15 March 2013
Available online 30 March 2013

Keywords:
Basal ganglia
Cerebellum
Functional MRI
Functional cerebral connectivity
Structural equation modeling

ABSTRACT

Parkinson's disease (PD) reportedly includes altered connectivity of neural loops involving the basal ganglia and cerebellum, although little is known regarding any changes in the connectivity of motor loops. The goal of this study was to further understand the connectivity within the basal ganglia–thalamo-motor (BGTM) and cerebro-cerebellar (CC) loops in PD. Twelve PD patients and 12 age-matched control subjects performed a protocol involving self-initiated (SI) and externally-triggered (ET) finger movements, while being scanned with functional magnetic resonance imaging. Compared with the control subjects, the PD subjects showed hypo-activation in the bilateral putamen, right supplementary motor area and hyper-activation in the right premotor cortex. In the sensorimotor cortex and cerebellar hemisphere, PD subjects tended to show hyper-activation in a main effects analysis, but hypo-activation in a linear effects analysis. Analysis using structural equation modeling (SEM) revealed significant positive interactions within the right BGTM loop during the SI task and within the right (right cerebral hemisphere–left cerebellum) CC loop during the ET task. SEM also revealed task-related quantitative changes between the thalamus and the motor cortices in the control subjects. We found that the PD patients showed reduced connectivity in the right BGTM loop and inter-hemispheric connections in SEM, which is the first demonstration of this phenomenon. Interestingly, PD patients exhibited preserved connectivity within the right CC loop during the ET task. These results suggest disruption of cortico-striatal processing and preservation of relatively intact neural circuits that do not involve the basal ganglia in PD.

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http://dx.doi.org/10.1016/j.brainres.2013.03.027

1. Introduction

The connections between the basal ganglia and cerebellum are organized into discrete circuits or 'loops' that reciprocally interconnect a large and diverse set of cerebral cortical areas (Alexander et al., 1990; Middleton and Strick, 2000). It has been consistently found that the basal ganglia–thalamo-motor (BGTM) loop is involved in the pathogenesis of Parkinson's disease (PD; Delong, 1990). Significant impairments in movement initiation (akinesia) and reductions in the amplitude and velocity of voluntary movements (bradykinesia) are characteristics of hypokinetic disorders, of which PD is the best-known example (Delong, 1990). Electrophysiological and metabolic studies of the basal ganglia in animal models suggest that these clinical symptoms are likely to be caused by alterations in connectivity within the BGTM loop, as described in the classic model of PD (Delong, 1990). Many neuroimaging studies have reported altered functional activities within the BGTM loop in PD, such as hypo-activation in the contra-lateral putamen (Put) and supplementary motor area (SMA) (Buhmann et al., 2003; Jahanshahi et al., 1995; Playford et al., 1993; Rascol et al., 1997). The cerebellum is another important structure in motor control, and it is known to influence cerebral cortical activity via the cerebro-cerebellar (CC) loop. Previous studies of PD patients have shown increased activity in the cerebellum compared with healthy controls (Cerasa et al., 2006; Haslinger et al., 2001; Rascol et al., 1997; Sabatini et al., 2000; Samuel et al., 1997). Recent neuroimaging studies reported decreased percentage of activation in the regions within the BGTM during a self-initiated (SI) task and enhanced or preserved activation within the CC loop during an externally-triggered (ET) task in PD (Lewis et al., 2007; Sen et al., 2010).

The basal ganglia should not be viewed in isolation, but, rather, in the context of connections to other brain areas within the loop (Alexander et al., 1990). In fact, connectivity analysis may be more sensitive to changes in PD than measures of the amplitude of activation (Palmer et al., 2010). Several neuroimaging studies have investigated the connectivity within BGTM and CC loops in PD patients. For example, an fMRI study using a psycho-physiological interaction showed weakened striato-cortical and striato-cerebellar effective connections and increased cortico-cerebellar connections during an SI task (Wu et al., 2011). Another fMRI report using local linear discriminant analysis described altered connectivity within the BGTM and CC loops (Palmer et al., 2010). It is important to note, however, that these authors did not investigate some key structures within the BGTM and CC loops such as the globus pallidus, the thalamus and the dentate nucleus of the cerebellum (DN) (Wu et al., 2011) or the premotor cortex and the DN (Palmer et al., 2010). Structural equation modeling (SEM) is a method that has been used to reveal the effective connectivity (Friston, 1994) within the brain in PD (Grafton et al., 1994; Palmer et al., 2009; Rowe et al., 2002), but which did not find distinct differences in the effective connectivity within both loops. Thus, a detailed understanding of the connectivity of the BGTM and CC loops in PD patients has yet to be achieved.

To date, using fMRI combined with a parametric approach and SEM, we described the enhanced connectivity within the BGTM loop during SI finger movements and within the CC loop during ET movements (Taniwaki et al., 2003, 2006). These results also suggested that both SI and ET movements were needed to investigate the connectivity within both loops. Considering previous imaging studies and our findings, we hypothesized that PD patients exhibit decreased connectivity within the BGTM loop and increased or preserved connectivity within the CC loop. In the present study, to understand the connectivity within the BGTM and CC loops in PD, we applied fMRI and SEM to PD patients and healthy control subjects during both SI and ET movements.

2. Results

2.1. Behavioral performance

In the control subjects, very slow movements were performed at a frequency of 0.69±0.19 Hz (mean±S.D.), slow movements at 1.04±0.31 Hz, moderate movements at 1.61±0.35 Hz, fast movements at 2.13±0.32 Hz, and very fast movements at 2.94±0.33 Hz during the SI task. The ET movement rates were almost identical to the rates of the auditory triggers (0.5 Hz trigger, 0.54±0.11 Hz; 1 Hz trigger, 0.99±0.04 Hz; 1.5 Hz trigger, 1.58±0.22 Hz; 2 Hz trigger, 2.06±0.29 Hz; 3 Hz trigger; 3.05±0.26 Hz). During SI movements in the PD group, very slow movements were performed at a frequency of 0.82±0.34 Hz (mean±S.D.), slow movements at a rate of 1.14±0.31 Hz, moderate movements at 1.58±0.25 Hz, fast movements at 1.95±0.28 Hz, and very fast movements at 2.77±0.34 Hz. ET movement rates were almost identical to the rates of the auditory triggers (0.5 Hz trigger, 0.65±0.31 Hz; 1 Hz trigger, 1.04±0.24 Hz; 1.5 Hz trigger, 1.59±0.36 Hz; 2 Hz trigger, 2.00±0.29 Hz; 3 Hz trigger; 2.81±0.32 Hz). No significant differences were observed between the control and PD subjects ($p=0.462$ for SI movements and $p=0.213$ for ET movements, as determined by a repeated measures two-way analysis of variance).

2.2. Foci of activation

2.2.1. Within-group analysis

To separate regional activity within the same task but with different rate-response functions, a parametric approach based on orthogonal basic functions up to the fourth order was used. Regarding main effects, in the control subjects, both tasks caused significant activation in the bilateral posterior Put, ventrolateral nucleus, pars oralis of the thalamus (VLo), ventro-posterior–lateral nucleus, pars oralis of the thalamus (VPLo), SMA, sensorimotor cortex (SMC), ventral premotor cortex (PMv), DN, cerebellar hemisphere (CB), and the right internal segment of the globus pallidus (GPi) (Table 1), which is consistent with previous findings (Taniwaki et al., 2007). In the PD group, there were significant activations of all of these regions except the bilateral Put and left VPLo during the SI tasks (Table 1; Fig. 1A). In the ET tasks, significant activations were observed only in the bilateral SMA, CB and DN, and the right SMC (Table 1; Fig. 1B).

A significant positive linear increase in the magnitude of the blood-oxygen-level- dependent response in parallel with the rate