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Research Report

Parkinson's disease-related modulation of functional connectivity associated with the striatum in the resting state in a nonhuman primate model

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ABSTRACT

The goal of this study was to describe Parkinson's disease (PD)-related modulation of functional connectivity (FC) associated with the striatum in the resting state in a nonhuman primate model of early-stage PD. Weekly intravenous injections of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (0.5 mg/kg body weight) were performed until parkinsonian motor symptoms developed in four macaques. After 13 weeks of MPTP treatment, all monkeys displayed parkinsonian symptoms. During the course of the experiment, each animal underwent four magnetic resonance imaging scans and four positron emission tomography (PET) scans with the vesicular monoamine transporter 2 (VMAT2)-selective ligand 9-[^{18}F] fluoropropyl-(+)-dihydrotetrabenazine, performed prior to the beginning of MPTP administration as well as after 4, 9, and 13 MPTP injections. The FC profile of the striatum was evaluated using a seed voxel correlation approach and post hoc region of interest analysis on resting-state functional magnetic resonance imaging data. The PET images were subjected to region of interest analysis to examine brain regional reductions in VMAT2 density in the PD model. Significant reductions in the connectivity pattern of the striatal regions were observed: limbic striatum and left hippocampus; caudate nucleus/associative and

Abbreviations: [^{18}F] AV-133, 9-[^{18}F] fluoropropyl-(+)-dihydrotetrabenazine; ACC, anterior cingulate cortex; ANOVA, analysis of variance; BG, basal ganglia; CA, caudate nucleus/associative; CN, caudate nucleus; DLPFC, dorsolateral prefrontal cortex; FC, functional connectivity; fMRI, functional magnetic resonance imaging; ITG, inferior temporal gyrus; LS, limbic striatum; MEG, magnetoencephalography; MFG, middle frontal gyrus; MPTP, 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine; OMPFC, orbital and medial prefrontal cortex; PA, putamen/associative; PCG, postcentral gyrus; PD, Parkinson's disease; PET, positron emission tomography; PM, putamen/motor; ROI, region of interest; SMA, supplementary motor area; STG, superior temporal gyrus; SUR, specific uptake ratio; WM, cortical white matter; VMAT2, vesicular monoamine transporter 2

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brain regions, including the right pre-supplementary motor area and bilateral dorsolateral prefrontal cortex; putamen/associative region and left inferior temporal gyrus or right orbital and medial prefrontal cortex; and putamen/motor and cortical structures, including the right superior temporal gyrus and bilateral postcentral gyrus. Subsequent PET studies showed the progressive loss of striatal VMAT2 in the striatum with the presentation of parkinsonism. Significant differences between the specific uptake ratio reductions in each striatal subdivision were not found. By using a long-term, low-dose MPTP-lesioned nonhuman primate model, this study demonstrated PD-related decreased corticostriatal FC in a resting state; moreover, altered sensorimotor integration was also found in early-stage PD.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder clinically characterized by a variable combination of bradykinesia or akinesia, tremor, rigidity, and postural instability. In addition, it is often accompanied by various non-motor manifestations, such as cognitive disorder, emotional disturbance, and autonomic nervous system dysfunction (Aarsland et al., 1999; Zesiewicz et al., 2003). Dysfunction of the basal ganglia (BG) plays a crucial role in PD. The striatum, which is the major component of the BG, works in concert with the cortex (Haber, 2003). Dysfunction within individual circuits between the striatum and the cortex is associated not only with movement disorders but also with neuropsychiatric disorders. Therefore, it is important to investigate the dynamic changes in these circuits in PD comprehensively and systemically.

In the past years, methodological advances in neuroimaging, i.e., magnetoencephalography (MEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI), have allowed for the remapping of the brain's functional network. MEG studies (Stoffers et al., 2008; Vardy et al., 2011) have identified some cortical regions with altered connectivity in PD, but they have failed to observe changes in subcortical structures. Recently, two studies (Hirschmann et al., 2011; Litvak et al., 2011) performed MEG in combination with subthalamic local field potential recordings in PD patients at rest to identify the causal relationship between the subthalamic nucleus and the cortex. Moreover, PET studies (Eckert et al., 2007; Lozza et al., 2004; Polito et al., 2012), which describe metabolic brain networks, have identified specific regional patterns associated with motor and cognitive symptoms in PD.

fMRI, a neuroimaging technology, has been used to study PD for many years, but most studies have focused on the altered connectivity associated with the performance of a specific task, which requires a certain cognitive process. Recently, several studies (Baudrexel et al., 2011; Helmich et al., 2010; Krajcovicova et al., 2012; Rektorova et al., 2012; Seibert et al., 2012; Wu et al., 2009; Wu et al., 2011; Tessitore et al., 2012; Hacker et al., 2012; Liu et al., 2013) reported interesting results using a novel experimental approach, resting-state fMRI, which allows for the investigation of the intrinsic functional architecture of the brain by examining spontaneous fluctuations in the blood oxygen level-dependent signal of fMRI (Biswal et al., 1995). These studies were performed on PD patients and did not focus on the functional connectivity (FC) alteration with the progression of PD. Wu et al. (2009) found that FC decreased in the supplementary motor area (SMA), left dorsolateral prefrontal cortex (DLPFC), and left putamen, but increased in the left cerebellum, left primary motor cortex, and left parietal cortex in PD patients compared with healthy subjects. Another study (Wu et al., 2011) reported an increased FC of the pre-SMA and the right primary motor cortex as well as a decreased FC of the pre-SMA and the left putamen. Seibert et al. (2012) found that corticostriatal functional correlations decreased in the bilateral prefrontal regions in PD dementia patients relative to elderly control subjects. While two studies (Krajcovicova et al., 2012; Rektorova et al., 2012) failed to find any difference in the default mode network (DMN) among the PD patient group, PD dementia patient group and healthy control group, another study (Tessitore et al., 2012) found a decreased FC of the right medial temporal lobe and bilateral inferior parietal cortex within the DMN in PD patients compared with healthy controls. Helmich et al. (2010) revealed decreased FC of the posterior putamen and the inferior parietal cortex as well as increased FC of the anterior putamen and the inferior parietal cortex. Hacker et al. (2012) found markedly lower striatal correlations with the thalamus, midbrain, pons and cerebellum. Baudrexel et al. (2011) revealed increased FC of the subthalamic nucleus and cortical motor areas in PD patients. Disrupted FC of the dentate nucleus in the resting state in PD patients was found in one study (Liu et al., 2013).

In this study, we set out to describe PD-related longitudinal modulation of FC associated with the striatum in the resting state in an MPTP-lesioned nonhuman primate model by fMRI using a seed voxel approach, in which a voxel is selected as a reference and the time course of this region is then cross-correlated with that of all other voxels in the whole brain to produce an FC map (Biswal et al., 1995).

PET imaging studies with the vesicular monoamine transporter 2 (VMAT2)-selective ligand 9-[^{18}F] fluoropropyl-(+)-dihydrotetrabenazine ([^{18}F]AV-133) were performed to follow the degeneration of dopaminergic innervation in this PD model. VMAT2 is the transporter responsible for packing monoamine neurotransmitters (dopamine, serotonin, and norepinephrine) from the cytoplasm into vesicles for storage and subsequent synaptic release. It is proposed as the gold standard of dopaminergic neuron markers based on the fact