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Neural correlates of progressive reduction of bradykinesia in de novo Parkinson's disease

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ABSTRACT

Background: A progressive reduction in the speed and amplitude of repetitive action is an essential component of bradykinesia, which is called sequence effect (SE). Because SE is specific to Parkinson's disease (PD) and is suggested to be associated with motor arrest, its features are of great interest. The aim of this study was, for the first time, to find the neural correlates of SE and to demonstrate whether dopaminergic deficit is correlated with SE.
Methods: We enrolled 12 patients with de novo PD at a tertiary referral hospital. Correlations between SE severity and alterations in gray and white matter were studied. The association between severity of the SE and striatal dopaminergic deficits was also analyzed.
Results: There was a significant negative correlation between the volumetric changes in the anterior cingulate cortex (ACC) and the inferior semilunar lobule of the cerebellum and the degree of SE. There was a significant correlation between the long association fibers (the superior longitudinal fasciculus, the uncinate fasciculus, and the inferior fronto-occipital fasciculus) connecting the frontal lobes to the temporal, parietal, and occipital lobes and SE. There was a significant negative correlation between SE in the more affected hand and the caudate dopamine transporter binding in the more affected hemisphere.
Conclusions: Our results suggest that the ACC and the cerebellum (inferior semilunar lobule) are associated with the severity of SE. Taken together with DTI findings, the present study proposes that ACC may have an important role. Our data show that the caudate dopaminergic activity may be related to SE.

1. Introduction

The progressive reduction in speed and amplitude of repetitive action is called the sequence effect (SE) [1]. SE is a unique feature of Parkinson's disease (PD) and an essential component of bradykinesia. Other movement disorders displaying slowness, such as progressive supranuclear palsy and dystonia, do not have a SE [2,3]. The clinical significance of SE is related to motor arrest; SE provokes motor arrest and may also be a preceding condition. Motor arrest has a deleterious impact on daily life. A typical example of motor arrest is freezing of gait, and it has been reported that SE contributes to the development of freezing of gait [1].

The structural brain abnormality associated with SE has not yet been identified. We inferred that derangement of a setting mechanism that adjusts the extent of movement may cause the SE. The basal ganglia (BG) is a possible candidate, because it is suggested that it is associated with the control of movement amplitude [4,5]. However, BG is not the only one area involved in the extent of movement (i.e., amplitude, distance of movement), and the

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supplementary motor area (SMA), the premotor cortex, the sensorimotor cortex (SMC), and the cerebellum have also been reported to be involved [6–8]. Electrophysiologic studies have shown correlations between movement amplitude and cortical neuronal discharge rate in the primary motor cortex, the premotor cortex, the superior parietal cortex, and the cerebellum [8]. Some studies have suggested that cortical structures might be more critical than BG in the maintenance of constant movement amplitude, and more closely involved in scaling movement amplitude. The dorsal premotor cortex and supplementary motor cortex play a role in the maintenance of sequential movements [9].A correlation was found between unctional activity in the motor/premotor cortex, intraparietal sulcus, and cerebellum and movement amplitude, but not with BG was [10].

The etiology of SE is unclear. Nigral dopaminergic deficit is the main cause of PD, but it seems to be unrelated to the SE because previous studies did not demonstrate a response to dopaminergic medication [1,5]. However, no studies have examined the correlation between dopaminergic activity and SE.

The aim of our study was to determine the neural correlates of SE and whether dopaminergic deficit is correlated with SE. We hypothesized that the premotor and supplementary motor cortex would be more closely associated with SE than the BG. We also hypothesized that the striatal dopaminergic system would be unrelated to SE.

2. Patients and methods

2.1. Patients

Twelve patients with de novo PD (mean age 60.3 ± 9.1 years; 10 women) participated in this study. A previous study reported that SE is observed in de novo PD [11]. All patients were recruited at Yonsei University Severance Hospital between 2010 and 2012. PD was diagnosed according to the UK Brain Bank criteria [12]. Hoehn and Yahr stage (H&Y stage), the Unified Parkinson's Disease Rating Scale (UPDRS), the Korean version of the Mini-Mental State Examination (K-MMSE), disease duration, and the Beck Depression Inventory (BDI) were evaluated (Table). Handedness was evaluated with the Edinburgh Handedness Inventory (EHI) [13,14]; nine patients were right-handed and three were ambidextrous. The more affected hand was determined based on the clinical features (initially affected hand on history or more affected symptoms and signs). All patients provided written informed consent and the study was approved by our institution review board.

2.2. Behavioral assessment

We modified a repetitive pentagon drawing test that was used to measure the SE in several previous studies [2]. Participants were asked to trace a regular pentagon in which each side was 17 cm. The vertices of the segments were marked with a circle of 1.5 cm diameter. The movement time for each segment was defined as the time taken for the pen tip to move from one vertex to the next. Pentagon drawing was recorded using a digitizing tablet (WACOM Intuos3 PTZ-1231W, A3 wide, 488 × 305 mm) with high spatial (0.05 mm) and temporal resolution (200 Hz sampling rate). The movement times were stored in a personal computer.

During the behavioral measurement, participants were instructed to wear a wrist brace to restrict wrist movement and not to move their trunk to minimize body movement. Subjects were asked to draw the pentagon 10 times in a counterclockwise direction, with a pause of 30 s between each repetition; they were instructed to move the pen as quickly as possible. The height of the table on which the tablet was placed was adjusted so that the elbow and shoulder joints were at approximately the same level on the horizontal plane [2] Before starting, they placed the pen tip on the first vertex (starting point). The starting point was the right of the two vertices closest to the participant. On hearing a beep sound, they began to draw a pentagon from the first vertex. After returning to the starting point, they rested for 30 s. Ten movement times for each segment were recorded for both hands independently (right hand first and then left hand). Before data were recorded, participants practiced to become familiar with the task. We calculated mean movement times for each segment and then plotted the mean movement time against the segment of the pentagon. Progressive changes in the averaged movement time (i.e., the SE) were shown by the slope of the linear regression analysis.

2.3. MRI acquisition

MRI data were acquired as previously described [15] using a Philips 3.0 T scanner (Philips Intera; Philips Medical System, Best, the Netherlands) with SENSE head coil (SENSE factor1⁄42). Head motion was minimized with restraining foam pads provided by the manufacturer. High-resolution T1-weighted MRI volumes were acquired axially using fast-spin echo sequence with the parameters of 224 × 224 acquisition and 256 × 256 reconstructed matrices with 182 slices, 220 mm field of view, 0.859 × 0.859 × 1.2 mm^3 voxels, TE 4.6 ms and TR 9.7 ms. Diffusion tensor images (DTI) were then obtained using single-shot echo-planar acquisition from 45 non-collinear, non-coplanar diffusion encoded gradient directions with the following parameters: 128 × 128 acquisition matrix with 70 slices, 220 mm field of view, 1.72 × 1.72 × 2 mm^3 voxels, TE 60 ms, TR 7.384 s, b-factor of 600 s/mm^2, without cardiac gating.

2.4. Structural image processing using FMRIB software library (FSL) – voxel-based morphometry (VBM)

Structural data were analyzed with FSL-VBM [16], an optimized VBM protocol [17] carried out with FSL tools [18]. First, T1 images were brain-extracted and gray matter-segmented before being registered to the MNI 152 standard space using nonlinear registration [19]. The resulting images were averaged and flipped along the *x*-axis to create a left-right symmetric, study-specific gray matter template. Second, all native gray matter images were non-linearly registered to this study-specific template and modulated to correct for local expansion or contraction caused by the nonlinear component of the spatial transformation. The modulated gray matter images were then smoothed with an isotropic Gaussian kernel with sigma of 3 mm. Finally, preprocessed gray matter images were flipped such that the contralateral hemisphere to the more affected limb was displayed on the same side.

2.5. Diffusion tensor imaging analysis using tract-based spatial statistics

A skeleton based analysis of fractional anisotropy (FA) and mean diffusivity (MD) data was carried out using the tract-based spatial statistics (TBSS) [20] component of FSL [18]. First, maps for fractional anisotropy (FA) and mean diffusivity (MD) were created by fitting a tensor model to the raw diffusion data using FDT, and then brain-extracted using the brain extraction tool (BET) [21]. Diffusion data for all subjects were then aligned into a common space using the non-linear registration tool FNIRT [19,22], which uses a b-spline representation of the registration warp field [23]. Next, the mean FA image was created and thinned to create a mean FA skeleton that represents the centers of all tracts common to all study participants. Each subject's aligned FA data was then projected onto this skeleton and flipped so that the contralateral to the more affected limb was displayed on the same side.

2.6. [18F] N-(3-fluoropropyl)-2b-carbon ethoxy-3b-(4-iodophenyl) nortropane (FP-CIT) PET analysis

^{18}F-FP-CIT PET images were obtained 20 min and 90 min after injection of ^{18}F-FP-CIT (5 mCi; 185 MBq) in all 12 patients with a GE PET-CT DSTe scanner (GE Discovery STE, GE Healthcare Technologies, Milwaukee, WI, USA) with three-dimensional resolution of 2.3 mm full width at half-maximum. Quantitative analyses were performed following a previously described procedure [24,25]. Image processing was performed using SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL, London, UK) under Matlab 2013a for Windows (Math Works, Natick, MA, USA) and MRIcro version 1.37 (Chris Rorden, Columbia, SC, USA). Volumes of interest (VOIs) were defined based on a template in standard space. All reconstructed PET images were spatially normalized to Talairach space using a standard 18F-FP-CIT PET template which was made using 18F-FP-CIT PET and T-1 MR images of 13 normal controls. Eight VOIs of bilateral striatal subregions and one occipital VOI were drawn on a co-registered spatially normalized single T-1 MR and 18F-FP-CIT PET template image. The striatum was divided into the anterior caudate, posterior caudate, ventral striatum, anterior putamen, and posterior putamen [26]. Nine VOIs were tested against each subject's spatially normalized 18F-FP-CIT PET image and adjusted when necessary. DAT activity was calculated by non-displaceable binding potential (BPND), which was defined as (mean standardized uptake value of the striatal subregions VOI – mean standardized uptake value of the occipital VOI)/mean standardized uptake value of the occipital VOI [27].

2.7. Statistical analysis

We investigated the anatomic correlation between the SE and brain volume, and between the SE and white matter changes, in both the more affected and less affected hand. The correlation between image parameter (GM, FA, and MD) and behavioral performance (sequence effect), adjusting for the effect of age and gender, was analyzed using the randomize implementation in the FSL toolbox. A total of 5000 permutations were conducted and uncorrected *p*-value images were generated using a threshold free cluster enhancement (TFCE) method.

We carried out multivariate linear regression analysis including subregional DAT uptake and sex difference as independent variables to test whether the SE is correlated with striatal dopaminergic deficiency in the more affected and less affected hand, respectively. Values of $p < 0.05$ were considered significant.