主論文

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Altered striatal circuits underlie characteristic personality traits in Parkinson's disease

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Abstract

Patients with Parkinson's disease (PD) have been suggested to share personality traits characterized by low novelty-seeking and high harm-avoidance. Although a link between novelty-seeking and dopamine is hypothesized, the link is not fully supported by 6-[^{18}F]fluoro-L-dopa positron emission tomography (PET) studies. Meanwhile, tractography studies with magnetic resonance imaging (MRI) link personality to the connectivity of the striatum in healthy subjects. Here, we investigated neurochemical and anatomical correlates of characteristic personality traits in PD. Sixteen PD patients and 28 healthy controls were assessed using the Temperament and Character Inventory. All patients and 17 randomly selected controls were scanned with 2β-carbomethoxy-3β-(4-fluorophenyl)-[*N*-^{11}C-methyl]tropane ([^{11}C]CFT) PET to measure striatal dopamine transporter availability. All subjects were scanned with MRI to evaluate the connectivity of the striatum using probabilistic tractography. PET findings revealed no correlation of novelty-seeking and harm-avoidance with [^{11}C]CFT uptake in patients or controls. Novelty-seeking correlated positively with the connectivity strength of the striatum with the hippocampus and amygdala in both patients and controls. Harm-avoidance and the fibre connectivity strength of the striatum including ventral area with the amygdala correlated negatively in patients and positively in controls, which differed significantly between the groups. Our data support the notion that the fibre connectivity of the striatum with limbic and frontal areas underlies the personality profile. Further, our findings suggest that higher harm-avoidance in PD is linked to alterations of the network including the nucleus accumbens and amygdala.

Introduction

Parkinson's disease (PD) is related to characteristic personality traits described as industrious, inflexible and introspective [1,2]. As expected from the personality traits, life-style behaviours such as smoking cigarettes are less common in patients with PD [3]. However, a small percentage of patients develops compulsive dopaminergic drug use and impulse control disorders (ICD) after the initiation of dopaminergic therapy, and one risk factor for this is a higher score on the personality measure of novelty-seeking (NS) [4-6].

Cloninger proposed a self-report measure of personality dimensions, the Temperament and Character Inventory (TCI) [6]. One dimension is NS, which is described as the tendency to respond positively to novel stimuli and is hypothesized to be associated with an elevated dopamine response. Another dimension is harm-avoidance (HA), which is defined as a bias in the inhibition of behaviour and is postulated to be related to serotonergic activity. Several studies have suggested a role for dopamine in personality in PD, who score lower on an NS measure than healthy controls [7,8]. In addition, NS is related with genetic polymorphism of the dopamine D4 receptor in healthy subjects [9,10]. PET imaging of the dopaminergic system, however, reveals controversial findings. One study with nine patients reported that NS correlated with 6-[^{18}F]fluoro-L-dopa ([^{18}F]DOPA) uptake in the left caudate nucleus [11], whereas another study with 47 patients found no correlation between NS and any brain region investigated, as well as an unexpected positive correlation between HA and [^{18}F]DOPA uptake in the right caudate nucleus [8]. A number of studies also report that patients with PD have a higher HA score than healthy controls, although the neurobiological basis of this finding is not clear [8,12,13].

Recent tractography studies in healthy human subjects linked personality traits to the fibre connectivity strength of the striatum with the limbic system and frontal lobe [14,15]. These MRI findings using diffusion-weighted images (DWI) support the notion that personality dimensions such as NS and HA can be defined in terms of individual differences in percept-based habits, which are regulated by the striatum [16]. This notion is consistent with findings from animal studies, indicating the involvement of the basal ganglia network in forming habitual behaviours [17,18]. Data from previous studies suggest that individual differences in NS relate to the fibre connectivity strength of the anterior striatum involving ventral area with a subcortical network including the hippocampus and amygdala [15], while individual differences in HA correlate with the connectivity of the anterior

striatum involving ventral area with a cortico-subcortical network including the amygdala and orbitofrontal cortex [14].

Here, we examined the neural correlates of characteristic personality traits in patients with PD from neurochemical and anatomical standpoints. We assessed the nigrostriatal dopaminergic system utilizing 2β-carbomethoxy-3β-(4-fluorophenyl)-[*N*-^{11}C-methyl]tropane ([^{11}C]CFT) PET, and the fibre connectivity of the striatum with the limbic system and frontal lobe using probabilistic tractography. The aim of the present study was to investigate a possible relationship of personality traits with neurochemical and anatomical changes observed in PD, which may provide clues to the clinical significance of characteristic personality traits.

Methods

Participants

We recruited 16 patients with PD, and 28 age- and sex-matched healthy controls (Table 1). All subjects were right-handed. Of the patients with PD, eleven patients were undergoing treatment with L-DOPA (mean dose 290 mg, range 100-500 mg/day) plus carbidopa, three were also receiving a dopamine agonist (either pramipexole [one patient taking 0.375 mg/day and the other taking 0.5 mg/day] or ropinirole [one patient taking 3 mg/day plus amantadine 200 mg/day]). Two patients were taking a dopamine agonist alone (pramipexole [one patient taking 0.5 mg/day] or ropinirole [one patient taking 3 mg/day]). Three were taking no medication. Patients were examined in a practically defined off-state after withdrawal of L-DOPA for at least 12 h and dopamine agonists and amantadine for at least 24 hours. All subjects were examined using the personality questionnaire and MRI. All patients and 17 healthy controls (age 62.5 ± 5.1 years, 9 females) randomly selected from among the recruited subjects were also scanned with PET. All subjects were interviewed to exclude the presence of ICD.

Personality measures

All subjects filled out the Japanese version of the TCI [6,19]. We focused on the temperament factors (NS, HA, reward-dependence, and persistence) especially NS and HA, based on earlier reports that PD shows a characteristic personality profile of low NS, high HA, but similar reward-dependence and persistence compared with healthy controls [2,20]. We limited confirmatory planned analysis on personality measures of NS and HA without corrections for multiple comparisons. Personality

measures of reward-dependence and persistence were presented as reference and did not submit for further imaging data analysis. The personality measures were acquired on the day of the MRI examination.

Neuropsychological data analyses

To examine the relations between characteristic personality and severity of motor symptoms in patients, we determined the Pearson's correlation coefficient between NS and HA scores, and the UPDRS part III score. To assess the relation with mood symptoms, we determined the Pearson's correlation coefficient between NS and HA scores, and HAM-D score. The relation with medication for PD was evaluated between NS and HA scores, and L-DOPA equivalent daily dose, which was calculated for each patient according to the formula described in a previous study [21].

Imaging data acquisition

Striatal dopamine transporter availability was assessed with [^{11}C]CFT (or [^{11}C]WIN 35,428) PET [22]. All patients with PD and 17 healthy controls were examined after bolus injection of 370 MBq/1.5 ml [^{11}C]CFT solution with a 10-ml saline flush using a GE Advance Tomograph (GE/Yokogawa, Tokyo, Japan) with the interslice septa retracted, acquiring 35 slice images with 4.25-mm interslice spacing. The axial dimensions and pixel size of the reconstructed images were 128 × 128 and 1.95 mm. The data were corrected for effects of radiation attenuation using a transmission with two rotating ^{68}Ge sources. A dynamic study over 20 min (4 × 5 min) was performed beginning at 60 min after bolus injection of [^{11}C]CFT.

MRI data were scanned on a 3 Tesla Trio (Siemens, Erlangen, Germany) equipped with an eight-channel phased-array head coil [23]. DWI was performed in an axial orientation with the following parameters: repetition time = 10,500 ms; echo time = 96 ms; flip angle = 90°; field of view = 192 × 192 mm; slices = 70; voxel size = 2 × 2 × 2 mm. The diffusion weighting was isotropically distributed in 81 directions using a b value of 1500 s/mm^2. Nine volumes with no diffusion weighting (b = 0 s/mm^2) were also acquired at points throughout the acquisition. T1-weighted anatomical images were acquired using the MP-RAGE sequence: repetition time = 2000 ms; echo time = 4.38 ms; flip angle = 8°; field of view = 176 × 192 mm; slices = 160; voxel size = 1 × 1 × 1 mm. A dual-gradient

field map in an axial orientation was also obtained: repetition time = 511 ms; echo time 1/ echo time 2 = 5.19/7.65 ms; flip angle = 60°; field of view = 192 × 192 mm; slices = 46; voxel size = 3 × 3 × 3 mm.

Mask definition

For the objective of this study, masks were defined on the striatum, limbic system and frontal lobe [15]. For subcortical structures, masks were created using FIRST [24] in the FMRIB software Library (FSL) [25]. We specified the putamen, caudate nucleus and nucleus accumbens. The striatum was provided as a combined structure of these three. We also identified the hippocampus and amygdala. To create cortical masks, T1-weighted anatomical images of individual subjects were processed through an automated anatomical reconstruction and labelling procedure using Freesurfer (version 5.1; http://surfer.nmr.mgh.harvard.edu/). This process provided five cortical masks, including the lateral prefrontal cortex (LPFC), anterior cingulate cortex (ACC), middle cingulate cortex (MCC), posterior cingulate cortex (PCC), and precuneus. Based on anatomical landmarks, previous functional MRI and post-mortem studies, three other cortical masks (the medial orbitofrontal cortex [MOFC], lateral orbitofrontal cortex [LOFC] and dorsolateral prefrontal cortex [DLPFC]) were defined (Supplementary Methods). We combined Freesurfer cortical masks of the entire cerebral cortex and FIRST subcortical areas (hippocampus and amygdala) for creating a whole brain grey matter mask. Full description of mask definition is provided in Supplementary Methods.

PET data analysis

The index of specific [^{11}C]CFT binding was calculated in the whole brain as a (region-cerebellum)/cerebellum ratio at 60 to 80 min post-injection [22]. For the reference region, circular regions of interest (ROI) of 31.2 mm in diameter were defined on each cerebellar hemisphere in five contiguous planes with Analyze software (version 11.0, Biomedical Imaging Resource, Mayo Foundation, Rochester, MN, USA) [26].

For the ROI analysis, masks defined on the T1 images of each individual subject were converted into PET space using the linear registration tool in FSL. The regionally computed values of specific [^{11}C]CFT binding were submitted to evaluate relations with personality scores by applying a linear regression analysis. For NS, the personality measure with an *a priori* hypothesis, we set the level of significance at an uncorrected $P < 0.05$. For HA, Bonferroni corrections were used to correct for

multiple comparisons of spatially distributed data (i.e., 6 striatal regions) and corrected *P* values below 0.05 were considered statistically significant.

Specific [^{11}C]CFT binding images were also interrogated to localize individual differences in striatal dopamine transporter availability at a voxel level using the general linear model implemented in FSL. First, specific binding images were registered to the individual T1 anatomical images using the rigid body transformation, and then normalized to Montreal Neurological Institute (MNI) 1-mm space by using individual T1 with the nonlinear registration tool in FSL. The relationship between specific binding images and personality scores was evaluated by the general linear model. A $P < 0.05$ was considered significant for the spatial extent test on the clusters with the height threshold set at $Z > 2.58$, and corrected for multiple comparisons over the whole brain.

To verify data validity, we also performed a regression analysis between the UPDRS part III score and [^{11}C]CFT uptake in patients with PD. We assumed negative correlation between the two parameters as reported previously [27].

In addition to parkinsonian motor symptoms, we observed group differences in the HAM-D score as reported in previous studies [28-30]. Therefore, statistical evaluation of NS was conducted with the HAM-D scores partialled out as well. For HA, HAM-D scores were not included in the regression model to avoid a multicollinearity problem as the HA score and HAM-D score significantly correlated in patients and tended to correlate in controls in the present study as shown below, consistent with previous studies suggesting that increased HA score is associated with the presence of depression in patients with PD [12,31] as well as in the general population [32-34]. We also performed exploratory analyses on the relationship between HAM-D score and [^{11}C]CFT binding.

MRI data analysis

DWI were analysed using FSL as described in our previous study [23]. Probabilistic tractography was run from all voxels in the mask within the striatum as the seed to reach each of the two subcortical (hippocampus and amygdala) and eight cortical (MOFC, LOFC, LPFC, DLPFC, ACC, MCC, PCC, and precuneus) masks as well as the grey matter mask of the entire cerebral cortex plus subcortical areas (hippocampus and amygdala) as the targets. The calculation resulted in 11 maps in which the value of each voxel in the striatum corresponded to the number of samples reaching the target assigned to that map. Then, the voxel values in each map for the two subcortical and eight cortical masks were

converted into proportions by dividing by the values in the map for the grey matter mask of the entire cerebral cortex plus subcortical areas (hippocampus and amygdala), which we defined as tract strength for each target mask. We calculated the proportion by dividing the voxel values in each map for the masks of interests by the value for the mask of the grey matter mask of the entire cerebral cortex plus subcortical areas since similar methods were used in a previous tractography study linking personality to striatal fibre connectivity strength [15]. These proportion maps were warped into MNI 1-mm space. The associations of the strength of white matter fibre tracts and personality scores were analysed by applying a general linear model. The threshold for the spatial extent test on the clusters was set at $P < 0.05$ with the height threshold set at $Z > 2.58$, and corrected for multiple comparisons over the whole brain.

Because of group differences in the HAM-D score in the present data set, we also performed a statistical evaluation of NS with HAM-D score included in the regression model. For HA, HAM-D scores were not included to avoid a multicollinearity problem in the present data set. The individual effect of HAM-D on the fibre connectivity strength was also examined by applying a regression analysis.

Results

Personality measures and neuropsychological data

Patients with PD had a tendency of lower NS scores compared with healthy controls, although the group difference did not reach the level of statistical significance ($P = 0.09$: Table 2). Patients exhibited significantly higher HA scores than controls ($P < 0.05$). Group differences of other personality measures did not reach statistical significance.

NS scores in PD tended to correlate negatively with the UPDRS part III ($P = 0.06$) and HAM-D ($P = 0.06$) scores. No correlation between NS score and HAM-D score was detected in controls ($P = 0.54$). A positive correlation between the HA score and UPDRS part III ($P < 0.05$) was found in patients, as well as between HA score and HAM-D score in both patients ($P < 0.001$) and controls ($P < 0.01$). Neither NS score nor HA score correlated significantly with the L-DOPA equivalent daily dose. When threshold levels of significance in these 10 analyses were adjusted for multiple comparisons by Bonferroni correction (i.e. $P < 0.005$ in individual hypothesis tests), a

significant correlation was observed only between HA score and HAM-D score in patients and a trend towards significance was found between HA score and HAM-D score in controls.

Dopamine transporter availability assessed with [^{11}C]CFT PET

In the ROI analysis, NS score did not significantly correlate with specific [^{11}C]CFT binding in any of the striatal regions in either group (Table 3). The correlation was non-significant when the effects of the HAM-D score were partialled out. HA score did not significantly correlate with [^{11}C]CFT binding in any of the striatal regions in either group (Table 3).

The voxel-based analysis of [^{11}C]CFT binding revealed no significant correlation between NS score and voxels within the striatum in patients or controls. The correlation remained non-significant when the effects of HAM-D score were included in the regression model. HA score was also not significantly correlated with voxels within the striatum in patients or controls.

By contrast, our data set reproduced negative correlation between the UPDRS part III score and [^{11}C]CFT uptake in the putamen in patients with PD ($P < 0.05$ corrected: peak MNI coordinates [-25, -9, 12] and [31, -10, -1]: left/right = x [-/+], caudal/rostral = y [-/+] and ventral/dorsal = z [-/+]).

The HAM-D score did not significantly correlate with [^{11}C]CFT binding in any of the striatal regions in ROI analyses in either group. The HAM-D score was not significantly correlated within the striatum in the voxel-based analysis in patients or controls.

Probabilistic tractography assessed with MRI

We first calculated tract strength from the striatum to the two subcortical (hippocampus and amygdala) and eight cortical (MOFC, LOFC, LPFC, DLPFC, ACC, MCC, PCC, and precuneus) targets (Supplementary Figure). We then evaluated whether tract strength of these fibres link to individual differences in the personality measures.

The NS score was significantly positively correlated with the fibre connectivity strength between the hippocampus and anterior striatum including ventral area in both PD patients ($P < 0.05$ corrected: Fig 1a and Table 4) and healthy controls ($P < 0.05$ corrected: Fig1b and Table 4). Statistical parametric maps were superimposed on the MNI152 T1 1-mm template. When the effect of HAM-D score was included in the regression model, the statistical significance of the correlation in patients was

only slightly weaker ($Z > 1.9$, $P < 0.05$ cluster corrected) and the correlation in controls remained statistically significant ($P < 0.05$ corrected).

In patients with PD, the NS score also correlated significantly with the fibre connectivity strength from the striatum to the amygdala, MOFC, ACC, PCC, and precuneus ($P < 0.05$ corrected), whereas in healthy controls it correlated significantly with the fibre connectivity strength from the striatum to the amygdala, LOFC, LPFC, and DLPFC ($P < 0.05$ corrected). When the effect of the HAM-D score was included in the regression model, the significant correlation with connectivity to the amygdala was only slightly weaker in patients ($Z > 2.3$, $P < 0.05$ cluster corrected), and remained significant in controls ($P < 0.05$ corrected).

Individual differences in the HA score correlated negatively with the fibre connectivity strength between the right anterior striatum including ventral area and the amygdala in PD patients ($P < 0.05$ corrected: Fig 2a and Table 5). The HA score also correlated with the fibre connectivity strength between the right anterior striatal region involving ventral area and the amygdala in healthy controls ($P < 0.05$ corrected: Fig 2b and Table 5), although the correlation in healthy controls was positive. Because the HA score differed significantly between patients and controls in the present data set, we conducted a group comparison of the slopes of regression lines, and the results revealed a significant difference in the right anterior striatum including ventral area between groups ($P < 0.05$ corrected: Fig 2c).

In patients, stronger fibre connectivity between a region in the left striatum and the LOFC had a lower HA score ($P < 0.05$ corrected: Fig 3a and Table 5). Connectivity strength between the left striatum and the LOFC also correlated negatively with the HA score in controls ($P < 0.05$ corrected: Fig 3b and Table 5). A group comparison of the slopes of the regression lines revealed no significant differences.

The HAM-D score did not correlate significantly with the fibre connectivity strength of the striatum to the amygdala or the hippocampus in patients with PD. The HAM-D score correlated significantly with the fibre connectivity strength of the striatum to the amygdala ($P < 0.05$ corrected), but not the hippocampus, in controls.

Finally, we directly compared the connectivity strength of the striatum and cortical/subcortical masks between patients and controls. The connectivity strength of the hippocampus and amygdala was higher in the posterior putamen in patients than in controls ($P < 0.05$ corrected: peak

MNI coordinates for hippocampus [-32, -14, 7]: for amygdala [-29, -5, -8] and [29, -8, -5]). In contrast, the connectivity strength of the LOFC was lower in the posterior putamen in patients than in controls ($P < 0.05$ corrected: peak MNI coordinates [-28, -12, -3] and [26, -4, -5]). Since these areas were localized in the posterior putamen, it is unlikely that these differences influence the relationship between personality traits and the fibre connectivity strength in the anterior striatum observed in the present study.

Discussion

The present findings are consistent with previous reports that patients with PD share a characteristic personality profile of lower tendency in NS and higher HA compared with healthy controls. NS and HA scores in patients and controls did not correlate with [^{11}C]CFT uptake in any striatal region investigated. The NS score correlated positively with the fibre connectivity strength of the anterior striatum including ventral area with the hippocampus and amygdala in both patients and controls. HA score and fibre connectivity strength of the anterior striatum including ventral area with the amygdala were negatively correlated in patients and positively correlated in controls, and the slopes of regression lines were significantly different between the groups.

The hypothesized relationship between NS and dopamine was not supported by the present findings. The present PET results demonstrated no correlation between NS score and [^{11}C]CFT uptake in any of the striatal regions studied in patients or controls [8,11] while our data set reproduced negative correlation between the UPDRS part III score and [^{11}C]CFT uptake in the putamen in patients [27]. It is possible, however, that the association between NS and dopamine was not detected in the present study because of a low signal-to-noise ratio with [^{11}C]CFT PET methodology, especially in regions other than the striatum. It might also be possible that the present findings were impacted by the properties of the radiotracer, though CFT has been shown to be relatively selective for dopamine transporter [35]. Alternatively, the hypothesized association may be due to the relationship between NS and insular dopamine D2 receptor availability, as reported in patients with PD [36] and in young healthy subjects [37].

The association between HA and dopamine in the right caudate nucleus reported in unmedicated patients with PD [8] was not found in the present study as in a previous study [11]. This might be due to subject characteristics as medicated patients were involved in the latter studies. The

lack of an association between HA and dopamine, however, is also supported by a behavioural study showing no modification of HA score after 12 weeks of dopamine agonist medication [38].

An association of the HA score was detected, instead, with the HAM-D score in patients. Although the HA and HAM-D scores correlated, the HAM-D score did not significantly correlate with the fibre connectivity strength of the striatum with the amygdala or hippocampus. In contrast, the HA score correlated significantly with fibre connectivity strength in patients with PD. Thus, it would be inappropriate to attribute the altered connectivity pattern between the striatum and amygdala observed in PD to the effect of the HAM-D score instead of HA.

The NS score correlated with the fibre connectivity strength of the anterior striatum including ventral area with the hippocampus and amygdala in both patients and controls. Involvement of the hippocampus in processing novel stimuli has been demonstrated in human single neuron recording [39] and functional MRI studies [40]. Direct stimulation of the hippocampus in rodents increases exploratory behaviour [41]. Human functional MRI studies also suggest the involvement of the amygdala in processing novel stimuli [42]. Differences in the gene expression of stress-related molecules in the amygdala are linked to individual differences in novelty-seeking behaviour in rats [43]. In addition, an MRI study in younger healthy subjects aged 22 to 36 years reported a link between NS score and the fibre connectivity strength of the anterior striatum with the hippocampus and amygdala using the same tractography methodology [15]. It is therefore reasonable to propose that the neural network involving the anterior striatum, hippocampus, and amygdala underlies the personality trait of novelty-seeking behaviour.

The HA score correlated with the fibre connectivity strength of the striatum with the amygdala and LOFC in both patients with PD and healthy controls. Destruction of the basal nucleus in the amygdala reduces fear-avoidance behaviour in rats [44]. The basal nucleus in the amygdala has rich fibre connections with the nucleus accumbens, and their interaction is proposed to play a key role in active coping with fear [45]. In addition, a human functional MRI study revealed that the striatal area that is functionally connected with the amygdala overlaps the area activated when learning to avoid aversive stimuli [46]. The LOFC is an important brain region for evaluating punishers, which may lead to a change in ongoing behaviour [47]. Human functional MRI studies revealed that the LOFC is activated in responding to punishment [48]. Moreover, spatial patterns of amygdala and LOFC connectivity within the striatum in the present study were similar to those demonstrated in monkeys

[49]. These lines of evidence support the notion that the neural network involving the striatum, amygdala, and LOFC is associated with the personality trait of habitual, harm-avoidance behaviour.

The HA score correlated negatively with the fibre connectivity strength of the anterior striatum including ventral area with the amygdala in patients and positively in controls in the present study. The operating mode in the nucleus accumbens at a single site switches reversibly between fear generation mode and positive desire generation mode by a different stimulation pattern of dopaminergic D1 and D2 signalling [50]. In addition, neuronal firing in the nucleus accumbens evoked by basolateral amygdala input is modulated by dopaminergic transmission at the site [51]. It seems therefore possible that properties of neural networks involving the nucleus accumbens and amygdala are altered by abnormal dopaminergic inputs. Indeed, MRI studies in PD suggest that dopamine depletion leads to a remapping of brain networks possibly associated with motor and non-motor symptoms [52]. Alterations of functional connectivity with resting state functional MRI were also shown between the striatum and amygdala in PD [53]. Moreover, a previous study using the same tractography methodology reported changes in fibre connectivity strength between the sensorimotor cortex and the striatum and thalamus in patients with PD [54]. Thus, we consider that the present findings indicate that changes in the neural network underlie the personality trait and that these changes are related to higher HA scores in patients with PD.

Several aspects of our methods are important for interpreting the findings. First, we recruited patients receiving dopaminergic medications as well as those that never received dopaminergic medications. In a previous behavioural study, drug-naïve patients with PD had lower NS scores than healthy controls, while the same patients had higher NS scores than controls after 12 weeks of dopamine agonist therapy [38]. The same study also detected no significant effect of dopamine agonist administration on the HA score. Although this study raises a question as to why previous studies found that chronically medicated patients had lower NS scores than healthy controls [7,8], it is possible that the dopaminergic medications affected the present findings, especially with regard to NS. Second, the present technique of probabilistic tractography does not provide definitive evidence for connectivity, but rather estimates the likelihood of connectivity [55,56]. Nonetheless, the technique is thought to be sensitive to examine anatomical patterns in the fibre connectivity of the striatum with the limbic system and frontal lobe [15,23]. Third, we evaluated subjects with a mean age of approximately 65 years. Dimensions of temperament such as NS and HA are generally consistent, but still variable, across the

life course [57]. Thus, differences between individual healthy subjects, especially in age, could contribute to the differences in the results between the present study and previous tractography studies linking personality to striatal fibre connectivity strength using similar methods [15,58].

In summary, the pattern of dopamine transporter availability in the present study does not support the hypothesized role of dopamine in personality. Instead, the present findings support the idea that the fibre connectivity strength of the striatum with limbic and frontal areas underlies personality traits. The present results suggest that neural correlates of NS involve the network comprising the striatum, hippocampus, and amygdala. The present findings further suggest that the characteristic personality feature of higher HA in PD is related to alterations in the network of the anterior striatum, including the nucleus accumbens, with the amygdala.

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Compliance with ethical standards

All subjects provided written informed consent in accordance with the Declaration of Helsinki and the dictates of the Ethics Committee of Kyoto University Graduate School of Medicine prior to their inclusion in the study. All experimental protocol and relevant issues of the study were approved by the Ethics Committee of Kyoto University Graduate School of Medicine.

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Fig. 1

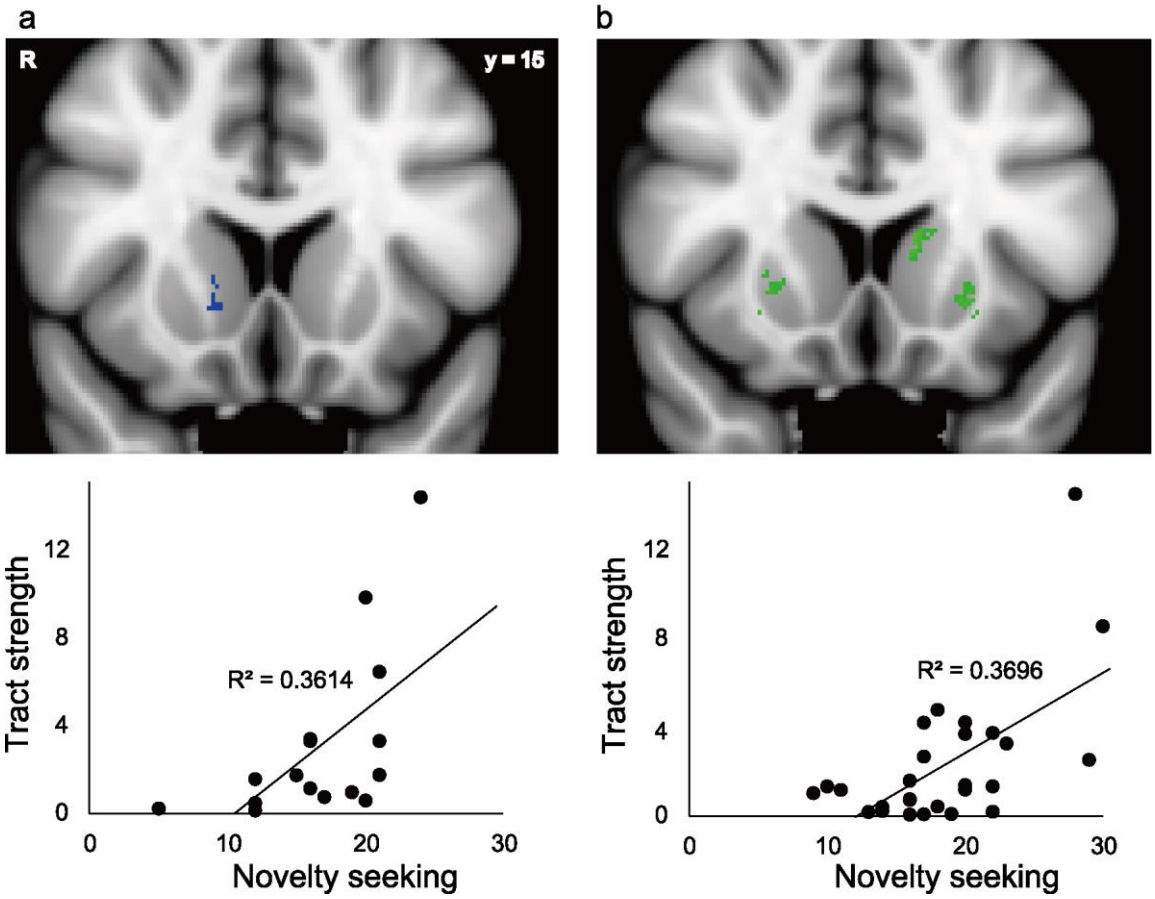

Fig. 1 The novelty-seeking (NS) score and fibre connectivity strength tracking from the striatum to the hippocampus. NS score correlated positively with the fibre connectivity strength between the anterior striatum including ventral area and hippocampus in both (a) patients with Parkinson's disease ($P < 0.05$ corrected) and (b) healthy controls ($P < 0.05$ corrected). Statistical parametric maps were superimposed on the MNI152 T1 1-mm brain template in this and related figures. Tract strength averaged across the statistical peak cluster is plotted against NS score in individual subjects. R, subject's right side

Fig. 2

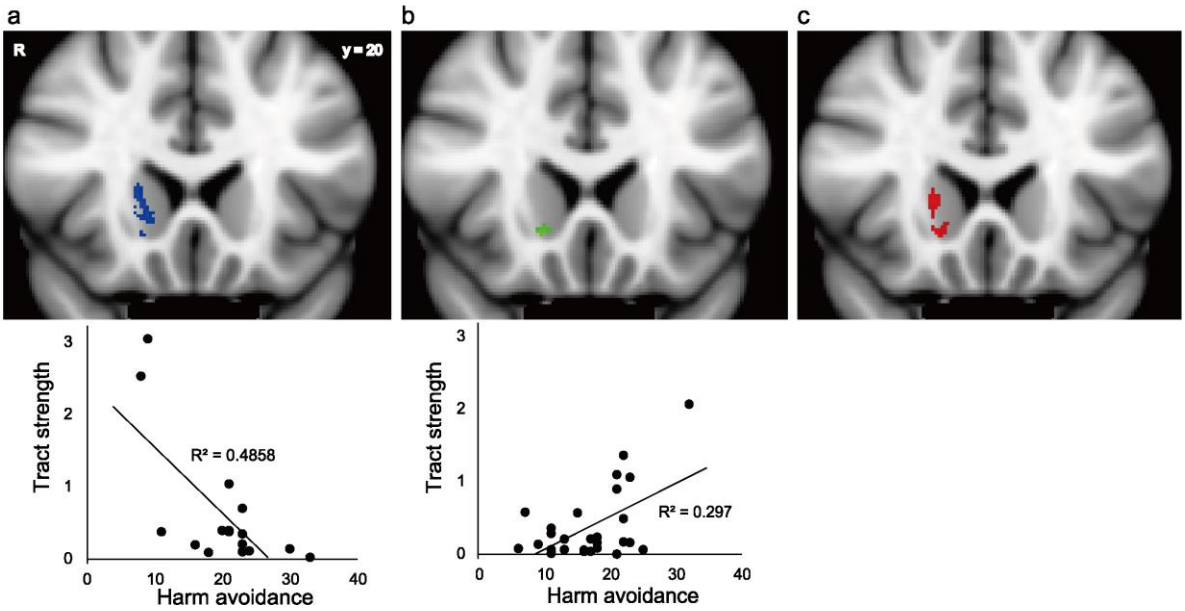

Fig. 2 The harm-avoidance (HA) score and fibre connectivity strength tracking from the striatum to the amygdala. HA score and the fibre connectivity strength between the anterior striatum including ventral area and amygdala was significantly (a) negatively correlated in patients with Parkinson's disease ($P < 0.05$ corrected) and (b) positively correlated in healthy controls ($P < 0.05$ corrected). Tract strength averaged across the statistical peak cluster is plotted against HA score in individual subjects. (c) The regression slopes of the HA score and the fibre connectivity strength of the anterior striatum including ventral area and amygdala differed significantly between patients with Parkinson's disease and healthy controls ($P < 0.05$ corrected). R, subject's right side

Fig. 3

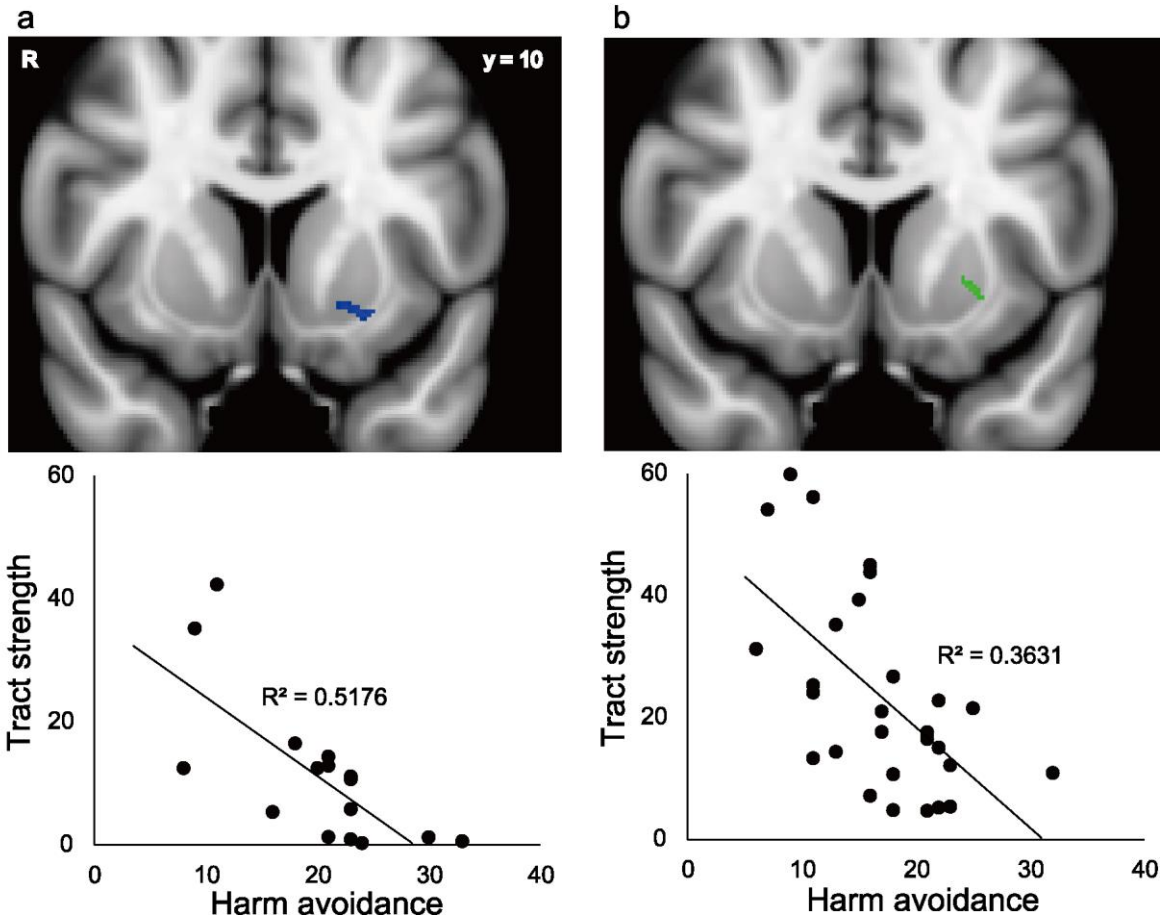

Fig. 3 The harm-avoidance (HA) score and fibre connectivity strength tracking from the striatum to the lateral orbitofrontal cortex (LOFC). HA score and fibre connectivity strength between the striatum and LOFC were significantly negatively correlated in both (a) patients with Parkinson's disease ($P < 0.05$ corrected) and (b) healthy controls ($P < 0.05$ corrected). Tract strength averaged across the statistical peak cluster is plotted against HA score in individual subjects. R, subject's right side

Tables

Table 1. Demographic and clinical characteristics of subject groups

	Parkinson's disease	**Controls**
Number of subjects (female)	16 (10)	28 (10)
Age (years)	66.3 ± 7.2	63.4 ± 5.6
Years since diagnosis	3.0 ± 1.8	—
UPDRS part III (motor examination)	19.3 ± 5.7	—
MMSE	29.1 ± 1.5	28.6 ± 2.2
FAB	16.2 ± 1.3	15.6 ± 1.5
HAM-D*	5.8 ± 4.9	1.6 ± 1.7

mean ± SD. FAB = frontal assessment battery; HAM-D = Hamilton depression rating scale; MMSE = mini mental state examination; UPDRS = unified Parkinson's disease rating scale. The scale was assessed in a practically defined off-state.

* Significant difference between the two groups using two-sample T test ($P < 0.05$).

Table 2. Scores in four temperament factors of temperament and character inventory

	Parkinson's disease	**Controls**	***P* value**
Novelty-Seeking	16.6 ± 4.8	18.5 ± 5.2	0.09
Harm-Avoidance	20.3 ± 6.7	17.0 ± 5.9	< 0.05
Reward dependence	15.3 ± 3.3	15.5 ± 2.2	0.40
Persistence	4.4 ± 1.6	4.2 ± 1.6	0.37

mean ± SD. Statistical comparisons between the two groups using a two-sample T test.

Table 3. Pearson's correlation coefficients between personality scores and specific [^{11}C]CFT binding

	Novelty-seeking				Harm-avoidance			
	Parkinson's disease		**Controls**		**Parkinson's disease**		**Controls**	
Brain region	Right	Left	Right	Left	Right	Left	Right	Left
Putamen	0.14	0.31	-0.10	-0.19	-0.41	-0.52	0.22	0.28
Caudate nucleus	0.35	0.39	-0.04	-0.07	-0.33	-0.37	0.22	0.17
Nucleus accumbens	0.39	0.35	-0.30	0.07	-0.19	-0.03	0.35	-0.01

Table 4. Regions showing significant correlation between novelty-seeking and fibre connectivity strength tracking from the striatum

	Parkinson's disease				Controls			
Target regions	MNI coordinate	Z score	cluster size	r	MNI coordinate	Z score	cluster size	r
Hippocampus	(9, 7, -1)	2.86	192	0.60	(-10, -5, 17)	4.66	755	0.61
Amygdala	(14, 17, 1)	3.18	174	0.68	(-12, 2, 15)	3.84	136	0.60
MOFC	(-10, 5, 7)	3.49	603	-0.68				
LOFC					(22, 14, -12)	3.52	396	0.58
LPFC					(12, 3, 8)	3.76	3447	0.50
DLPFC					(16, 18, -12)	4.15	658	0.62
ACC	(32, -16, 7)	4.30	567	-0.71				
MCC								
PCC	(32, -4, 8)	4.29	507	-0.72				
precuneus	(21, 4, 9)	3.47	179	-0.69				

ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; LOFC = lateral orbitofrontal cortex; LPFC = lateral prefrontal cortex; MCC = middle cingulate cortex; MNI = Montreal Neurological Institute; MOFC = medial orbitofrontal cortex; PCC = posterior cingulate cortex. Coordinates are: left/right = x (-/+), caudal/rostral = y (-/+) and ventral/dorsal = z (-/+) in this and related tables.

Table 5. Regions showing significant correlation between harm-avoidance and fibre connectivity strength tracking from the striatum

	Parkinson's disease				Controls			
Target regions	MNI coordinate	Z score	cluster size	r	MNI coordinate	Z score	cluster size	r
Hippocampus	(-26, -18, -2)	3.61	199	-0.77				
Amygdala	(20, 22, -1)	3.68	495	-0.70	(16, 20, -6)	3.44	242	0.54
MOFC					(29, -2, 9)	3.12	200	0.51
LOFC	(-24, 12, -10)	3.64	238	-0.72	(-27, -1, -5)	3.99	354	-0.60
LPFC								
DLPFC								
ACC	(10, -1, 11)	3.26	478	0.68				
MCC					(10, 20, -4)	3.41	331	0.53
PCC	(-30, -14, -4)	3.35	171	0.68	(-11, 0, 18)	3.15	697	0.50
precuneus					(27, -6, 5)	3.16	160	0.56

ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; LOFC = lateral orbitofrontal cortex; LPFC = lateral prefrontal cortex; MCC = middle cingulate cortex; MNI = Montreal Neurological Institute; MOFC = medial orbitofrontal cortex; PCC = posterior cingulate cortex

Supplementary Material

Altered striatal circuits underlie characteristic personality traits in Parkinson's disease

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Supplementary Methods

Mask definition

For subcortical structures, masks were created using FIRST[1] in the FMRIB software Library (FSL).[2] We specified the putamen, caudate nucleus, and nucleus accumbens. The striatum was provided as a combined structure of these three. We also identified the hippocampus and amygdala.

To create cortical masks, T1-weighted anatomical images of individual subjects were processed through an automated anatomical reconstruction and labelling procedure using Freesurfer (version 5.1; http://surfer.nmr.mgh.harvard.edu/) in a standard processing stream that included Talairach registration, skull stripping,[3] segmentation of grey and white matter,[4] and probabilistic labelling of cortical structures.[5] This process provided five cortical masks, including the lateral prefrontal cortex (LPFC), anterior cingulate cortex (ACC), middle cingulate cortex (MCC), posterior cingulate cortex (PCC), and precuneus. Based on anatomical landmarks, previous functional MRI and post-mortem studies, three other cortical masks were defined as described below.

We defined the human medial orbitofrontal cortex (MOFC) on the medial part of the orbital gyri spreading from the most medial portion of the orbital H-shaped sulci.[6] We fixed the human lateral orbitofrontal cortex (LOFC), on the lateral part of the orbital gyri extending from the most lateral portion of the orbital H-shaped sulci.[6]

For the dorsolateral prefrontal cortex (DLPFC), we applied human area 46, which was situated on the middle frontal gyrus and in the depth of the middle frontal sulcus.[7] We determined the limit at y = +50 and +29 in the rostrocaudal axis and at z = +36 and +14 in the dorsoventral axis following the overlap among the five reconstructions of the post-mortem brain to the Talairach grid system. The Talairach coordinate system was transformed to the Montreal Neurological Institute (MNI) coordinate system with an automated nonlinear match of the Talairach to the MNI brain (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). Coordinates were described as left/right = x (-/+), caudal/rostral = y (-/+), and ventral/dorsal = z (-/+).

We also combined Freesurfer cortical masks of the entire cerebral cortex and FIRST subcortical areas (hippocampus and amygdala) for creating a whole brain grey matter mask. Thereby, we defined the putamen, caudate nucleus and nucleus accumbens. The striatum was provided as a combined structure. We also identified two additional subcortical masks, eight cortical masks, and a whole brain grey matter mask for each subject.

Supplementary Figure

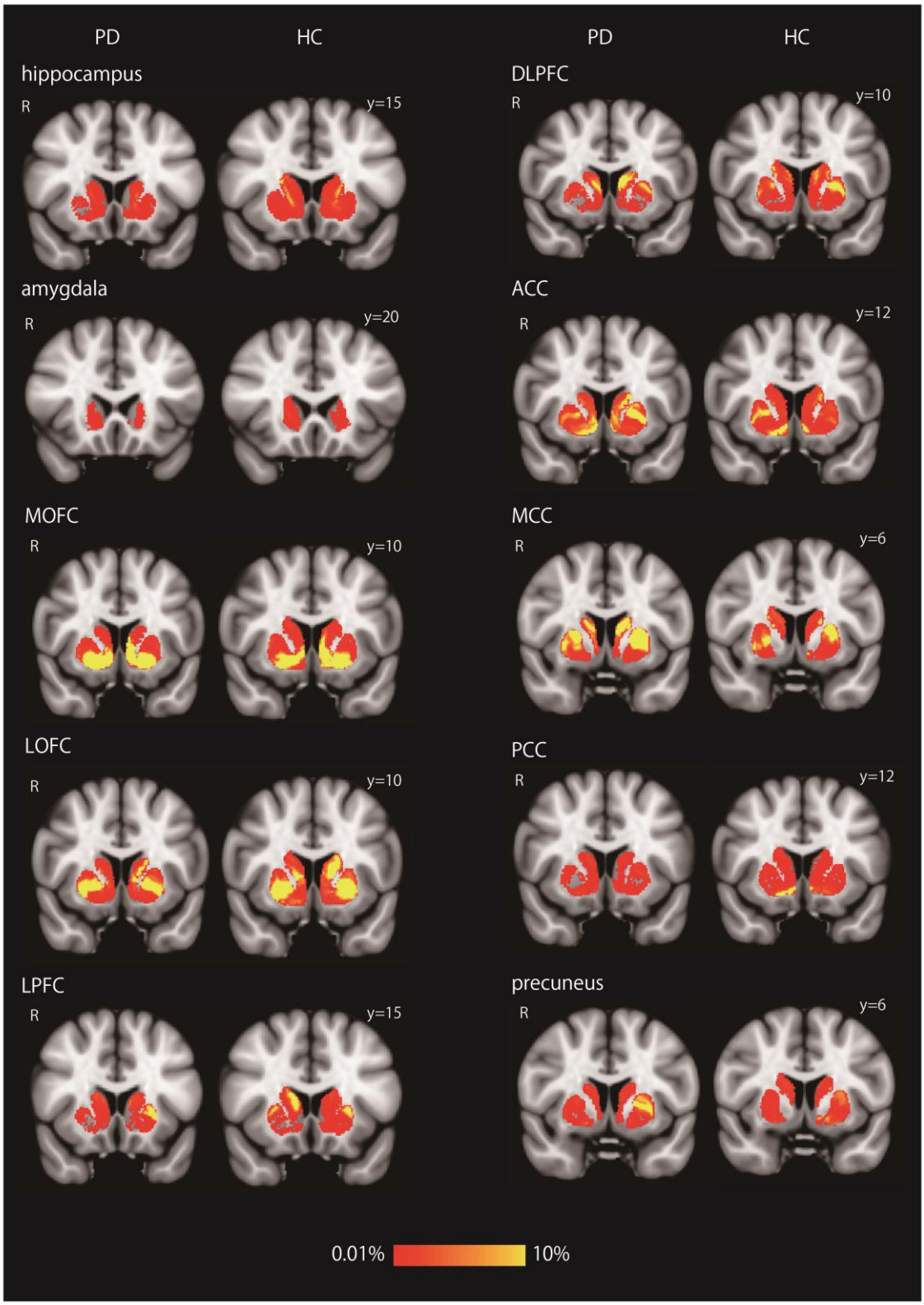

Figure caption

Tract strength from the striatum to each target in patients with Parkinson's disease (PD) and healthy controls (HC). The colour value at each voxel represents the proportion of tracts that run from that voxel and reach each of the targets, compared to the total number of tracts that run from that voxel and reach the whole brain grey matter mask. Voxel value having more than 0.01% is presented. Statistical parametric maps were superimposed on the MNI152 T1 1-mm brain template. R, subject's right side

Supplementary References

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