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[¹⁸F]Fluoroethoxybenzovesamicol in Parkinson's Disease Patients: Quantification of a Novel Cholinergic Positron Emission Tomography Tracer

Cholinergic denervation is closely related to motor and nonmotor symptoms in Parkinson's disease (PD).¹ The novel PET tracer [¹⁸F]fluoroethoxybenzovesamicol ([¹⁸F]FEOBV) is a presynaptic cholinergic marker that binds to the vesicular acetylcholine transporter and therefore is expected to be a sensitive in vivo marker for cholinergic denervation. Previously, [¹⁸F]FEOBV has been evaluated in Lewy body dementia, Alzheimer's disease, and healthy controls.²⁻⁴ Furthermore, [¹⁸F]FEOBV was implemented in PD research by evaluating the role of vesicular acetylcholine transporter binding in the clinical symptomatology of falling and freezing.⁵ We aimed to further quantify [¹⁸F]FEOBV as a cholinergic PET tracer in PD by comparing PD and controls and evaluating the test-retest variability in both groups.

A total of 10 PD patients (median [interquartile range] disease duration 7.16 [3.08] years) and 10 healthy age/gender/educational level-matched controls (HCs) underwent [¹⁸F]FEOBV PET scanning on medication at 210 minutes after injection and 30 minutes in duration.² Group characteristics can be found in the supplementary materials. Scores on the Montreal Cognitive Assessment (median [interquartile range] for HCs 29.0 [1.25] and PD 27.5 [1.75]) suggest a lower cognitive performance in PD patients when compared with HCs ($P = .057$). A total of 5 PD patients and 5 HCs underwent a second scan within 2 weeks after the first scan. Standard uptake values were obtained, correcting for the subject's weight and the injected activity. No partial volume correction was performed. A standard uptake values ratio (SUVr) was generated using the supratentorial white matter as a reference region.⁴ The volume of interest analysis was performed using an a priori set of standard volumes of interest, automatically adjusted to the subject's anatomy. A between-group comparison was performed using an independent t test with Bonferroni correction for multiple comparisons, resulting in a significant difference at the $P < .001$ level. Test-retest reliability and variability were evaluated using intraclass correlation coefficients and absolute test-retest variability.

FIG. 1. Voxel-based analysis with highlighted regions showing regions with significant lower SUVr in PD patients when compared with healthy controls ($P < .001$). SUVr, standard uptake values ratio. [Color figure can be viewed at wileyonlinelibrary.com]

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TABLE 1. Group difference and test-retest variability for [^{18}F]FEOBV uptake

A: Significantly different SUVR between PD and HC in predefined VOIs	HCs		PD	P
	Mean SUVR (SD)		Mean SUVR (SD)	
Posterior temporal lobe	2.06 (0.20)		1.67 (0.19)	<.001
Superior parietal gyrus	1.91 (0.22)		1.52 (0.18)	.001
Lateral occipital region	1.82 (0.20)		1.37 (0.14)	<.001
Lingual gyrus	1.95 (0.22)		1.47 (0.25)	<.001
Cuneus	1.89 (0.24)		1.38 (0.19)	<.001

B: Test-retest variability and reliability for SUVR of cortical regions, basal ganglia and thalamus	HCs		PD	
	VAR, %	ICC (CI)	VAR, %	ICC (CI)
Frontal lobe	5.09	0.922 (0.725 to 0.969)	5.86	0.961 (0.927 to 0.980)
Temporal lobe	5.07	0.882 (0.614 to 0.954)	6.45	0.950 (0.896 to 0.976)
Parietal lobe	4.27	0.906 (0.775 to 0.958)	5.40	0.965 (0.927 to 0.983)
Occipital lobe	4.00	0.838 (0.661 to 0.923)	7.80	0.925 (0.842 to 0.964)
Basal ganglia	8.92	0.953 (0.845 to 0.981)	13.47	0.881 (0.751 to 0.943)
Caudate nucleus	10.09	0.945 (0.763 to 0.987)	16.73	0.731 (−0.144 to 0.934) ^a
Nucleus accumbens	8.60	0.902 (0.518 to 0.977)	14.63	0.790 (−0.104 to 0.949) ^a
Putamen	8.07	0.904 (0.603 to 0.976)	9.04	0.754 (−0.069 to 0.940) ^a
Thalamus	4.93	0.901 (0.431 to 0.978)	5.50	0.954 (0.820 to 0.989)

CI, confidence interval; HCs, healthy controls; ICC, intraclass correlation; PD, patients with Parkinson's disease; SUVR, standard uptake values ratio; VAR, absolute test-retest variability; VOI, volume of interest.

^a $P < .05$. All other P values for ICC $< .001$.

Whole-brain, voxel-based analysis comparing PD patients and HCs demonstrated significantly lower vesicular acetylcholine transporter binding ($P < .001$, uncorrected) in the posterior cortical regions (Fig. 1). In addition, Table 1A shows regions with significantly lower uptake ($P < .001$) in PD patients when compared with HCs on the volume of interest analysis, indicating reduced cholinergic innervation in the occipital lobe and posterior regions of the parietal and temporal lobes in the PD patients. Scatterplots of the significant different regions are provided in Figure 2. These findings are consistent with previously described cholinergic denervation patterns in PD.^{6,7} Table 1B shows the test-retest reliability and variability for cortical and subcortical regions of interest.

FIG. 2. Scatterplot showing SUVR of all PD patients and healthy controls (HC) for significant different regions based on volume of interest analysis. SUVR, standard uptake values ratio.

The intraclass correlation coefficients showed excellent test-retest reliability for the cortical regions and thalamus in both PD patients and HCs. The basal ganglia regions showed slightly higher variability, but with good reliability in the PD patients and excellent reliability in the HCs. A Bland-Altman plot illustrating the agreement between scan 1 and scan 2 can be found in the supplementary materials. Overall, [^{18}F]FEOBV imaging showed a reduced uptake in the occipital and posterior parietal cortices in PD patients, with an overall high retest-reliability in both the cortical and subcortical regions. By comparing PD patients and HCs and evaluating test-retest variability, we demonstrated that [^{18}F]FEOBV can reliably be used to evaluate cholinergic denervation in PD patients and might be beneficial in establishing the relationship between regional cholinergic denervation and clinical symptomatology. ■

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