Study on brain glucose metabolic networks in Parkinson's disease patients with visual spatial dysfunction by ^{18}F -FDG PET imaging

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Aim: To assess the changes of brain glucose metabolism and abnormal intracerebral loop in early Parkinson's disease (PD) patients with visual spatial dysfunction by ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET) imaging.

Materials and Methods: This study includes three groups: early PD patients with visual spatial dysfunction ($n = 10$), early PD patients without visual spatial dysfunction ($n = 10$) and healthy controls ($n = 10$). Resting-state ^{18}F -FDG PET was performed to obtain the imaging of brain glucose metabolism. Statistical Parametric Mapping (SPM) was used for data analyses to compare the brain glucose metabolic changes among different groups.

Results: Compared with the healthy controls, early PD patients (with/without visual spatial dysfunction) showed hypermetabolism in putamen, globus pallidus, thalamus, pons, cerebellum and primary motor cortex, and hypometabolism in part of the occipital and temporal lobes. Compared with early PD patients without visual spatial dysfunction, those with visual spatial dysfunction further showed hypometabolism in visual regions including bilateral lateral prefrontal cortices and posterior parietal lobules, besides occipital and temporal lobes.

Conclusion: The occurrence of abnormal glucose metabolism in the brain visual processing areas was closely associated with visual spatial dysfunction in PD patients.

Keywords: Parkinson's disease; visual spatial dysfunction; brain glucose metabolism; positron emission tomography.

Introduction

This study assessed the brain glucose metabolism in early Parkinson's disease (PD) patients with/without visual spatial dysfunction and healthy controls with matched age by using ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET). Statistical parametric mapping (SPM) was used to analyze the changes of brain glucose metabolism among different groups, aiming to investigate the brain regions with abnormal glucose metabolism in early PD patients and supply the imaging evidence for the pathogenesis of PD with visual spatial dysfunction.

Materials and Methods

Patient recruitment

PD was diagnosed strictly according to the UKPD Brain Bank Criteria, and Montreal Cognitive Assessment (MoCA) was used to assess the concomitant visual spatial dysfunction. Ten early PD patients with visual spatial dysfunction, 10 without, and 10 healthy controls with matched age and gender were recruited. This study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants.

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¹⁸F-FDG PET brain imaging

In PET center of Huashan hospital, ¹⁸F was produced by using RDSIII accelerator (CTI company, USA), and ¹⁸F-FDG was synthesized by using automated synthesis module (PET Co., Ltd., Beijing). The radiochemical purity and mark rate were both > 95%.

The PD patients should withdraw PD medicines at least 12 h before PET scanning, and adjuvant drugs like levodopa should be avoided in case of their influence on brain glucose metabolism. All PD patients and healthy controls were required to fast for at least 6 h before PET scanning.

A 185 MBq injection of ¹⁸F-FDG was administered intravenously under standardized conditions (in a quiet, dimly lit room with patients' eyes open). A 20-s CT transmission scan was first performed for attenuation correction, and a 10-min three-dimensional (3D) brain emission scan was then acquired at 45-min post injection with a state-of-the-art PET scanner (Siemens Biograph 64 HD PET/CT, Siemens, Germany). During the scanning procedure, subjects' heads were immobilized using a head holder. PET image datasets were reconstructed iteratively by FBP to obtain the transverse section, coronal plane and sagittal plane images of brain.

Data analysis

The reconstructed images by SUN SPARK workstation were transmitted into PC image workstation via Microsoft FIP software, which were then converted from ECAT7 format to Analyze7 by using MRIcro software. ¹⁸F-FDG PET images were spatially normalized to the SPM PET template that was aligned to the Montreal Neurological Institute (MNI) brain space with linear affine transformation and nonlinear iteration, using the SPM12 software package (Wellcome Department of Cognitive Neurology, London, UK) running on MATLAB

Version 2016a (Mathworks Inc, Sherborn, MA, US). The normalized PET images were then smoothened by a Gaussian filter of 10 mm full width at half maximum (FWHM) over a 3D space to increase signal to noise ratio for statistical analysis, with matrix 79 × 95 × 79, voxel 2 mm × 2 mm × 2 mm.

To identify the brain areas displaying different glucose metabolism, we respectively compared the PET images of two PD groups with those of the healthy controls with SPM software. Simple fixed-effects *t*-test for each voxel was performed. Clusters of at least 100 contiguous voxels, with threshold two-tailed uncorrected *P* = 0.001, were considered to be significantly different in hypermetabolism or hypometabolism. For all statistical analyses, Talairach client was used to convert the MNI coordinates to Talairach coordinates.

Results

The 20 recruited PD patients were all diagnosed as class Hoehn–Yahr I–II according to the UKPD Brain Bank Criteria. There was no difference in the age and gender of the three groups (*P* > 0.05): 55.7 ± 6.7 years old (ranging from 42 to 70), 7 males and 3 females in early PD patients with visual spatial dysfunction; 55.7 ± 8.5 years old (ranging from 42 to 68), 8 males and 2 females in the early PD patients without visual spatial dysfunction; 54.6 ± 6.4 years old (ranging from 40–70), 7 males and 3 females in the healthy controls.

Compared with the healthy controls, early PD patients without visual spatial dysfunction showed hypermetabolism in bilateral lentiform nuclei (putamen), superior frontal gyri, paracentral gyri, paracingulate cortices, pons, thalamus, cerebellum and right postcentral gyrus, left lentiform nucleus (lateral globus pallidus), right superior occipital gyrus; hypometabolism was shown in bilateral insula and cuneus gyri and left lingual gyrus (Table 1).

Table 1. Brain regions with changed glucose metabolism in early PD patients without visual spatial dysfunction.

Brain regions	Side	K_E	Coordinates			$Z_{\max}$	t	P
			X	Y	Z			
Hypermetabolism								
Lentiform nucleus (putamen)	B	1544	18	14	−8	4.48	5.89	< 0.001
Paracentral gyrus	B	933	14	−32	48	4.34	5.62	< 0.001
Paracingulate cortex	B		16	−18	46	4.22	5.39	< 0.001
Pons	B	4217	6	−28	−36	4.18	4.99	< 0.001
Cerebellum	B		−38	−66	−46	3.91	4.82	< 0.001
Postcentral gyrus	R		54	−6	30	3.76	4.11	< 0.001
Lentiform nucleus (lateral globus pallidus)	L	116	−20	16	−10	3.37	5.06	< 0.001
Thalamus	B		−14	−10	0	3.99	4.95	< 0.001
Superior occipital gyrus	R	78	40	−78	14	3.95	4.88	< 0.001
Superior frontal gyrus	B	115	16	44	−2	3.81	4.64	< 0.001
Hypometabolism								
Insula	B	123	40	18	−10	3.94	4.87	< 0.001
Cuneus gyrus	B	653	6	−92	2	4.45	4.32	< 0.001
Lingual gyrus	L	356	−10	−36	−2	4.54	3.11	< 0.001

Table 2. Brain regions with changed glucose metabolism in early PD patients with visual spatial dysfunction.

Brain regions	Side	K_E	Coordinates			$Z_{\max}$	t	P
			X	Y	Z			
Hypermeterabolism								
Lentiform nucleus (putamen)	B	3413	30	-12	0	4.48	4.12	< 0.001
Paracingulate cortex	B		-14	-30	46	5.98	7.90	< 0.001
Paracentral lobule	L		-8	-20	56	5.59	4.27	< 0.001
Pons	B	5515	2	-36	-42	5.99	4.65	< 0.001
Cerebellum	B		-14	-52	-72	6.42	5.22	< 0.001
Postcentral gyrus	R	933	54	-8	30	4.34	4.16	< 0.001
Lentiform nucleus (lateral globus pallidus)	B	132	-26	-14	-12	6.86	3.15	< 0.001
Thalamus	B		16	-22	4	5.21	4.08	< 0.001
Hypometabolism								
Lingual gyrus	B	422	-10	-36	-2	4.54	5.85	< 0.001
Cuneus gyrus	B	751	6	-92	2	4.45	5.09	< 0.001
Lateral dorsal prefrontal cortex	B	186	26	28	52	4.52	5.99	< 0.001
Parietal lobule	B		-38	-50	42	3.88	4.31	< 0.001
Angular gyrus	B		-48	-68	28	3.57	4.25	< 0.001
Insula	B	518	-44	-12	6	4.01	4.99	< 0.001

Figure 1. The brain glucose metabolic network of early PD patients with and without visual spatial dysfunction. Compared with healthy controls, early PD patients with/without visual spatial dysfunction showed hypermetabolism in putamen, globus pallidus, thalamus, pons and cerebellum, which had bigger area in those with visual spatial dysfunction. Compared with early PD patients without visual spatial dysfunction, those with visual spatial dysfunction showed new brain regions with hypometabolism, including bilateral lateral dorsal prefrontal cortices and parietal lobules, besides occipital and temporal lobes.

Note: Red indicates the increased glucose metabolism and blue indicates the decreased metabolism.

Compared with the healthy controls, early PD patients with visual spatial dysfunction showed hypermetabolism in bilateral lentiform nuclei (putamen and lateral globus pallidus), paracingulate cortices, pons, thalamus, cerebellum and right post-central gyrus, left paracentral lobule; hypometabolism was shown in bilateral lingual gyri, cuneus gyri, lateral dorsal prefrontal cortices, parietal lobules, angular gyri and insula (Table 2).

Compared with early PD patients without visual spatial dysfunction, those with visual spatial dysfunction showed more brain regions with hypometabolism, mainly the visual cognition-related brain regions including bilateral lateral dorsal prefrontal cortices, parietal lobules and angular gyri, besides insula, lingual gyrus and cuneus gyrus (Fig. 1).

Discussion

PD is a neurodegenerative disease characterized by progressive destruction of dopaminergic neurons in the nigra-striatum. Most of the previous PD studies focused on exercise symptoms such as resting tremor, slow movement, muscle rigidity and postural reflexes. Recently, non-motor symptoms have been receiving more and more attention, in addition to exercise symptoms. Visual dysfunction is one of the common non-motor symptoms in PD, which mainly manifests as decreased visual acuity and sensitivity, discoloration and visual spatial dysfunction, hallucinations, diplopia and eye movement disorders.¹ These symptoms interfere with the normal life of patients, including difficulties in driving, reading and watching TV, fall and even can not properly identify people's faces. At the same time, due to the progressive characteristics of visual symptoms, PD patients experience reduced self-care ability and social function, which greatly decrease the quality of life for patients and their families, and increase the investment in home-care and social-economic burden in the long run.² Therefore, studies in the mechanisms of PD visual impairment are of great significance for the decision-making and patients' prognosis.

Glucose is the only energy source for brain metabolism, and the functional activities of the nuclei must be accompanied by changes of glucose metabolism. Parkinson's disease-related pattern (PDRP), which can reflect the changes of glucose metabolism in the "cortex-striatum-globus pallidus-thalamus-cortex" loop and the corresponding anatomical/functional pathway, is newly discovered.³⁻⁵ As an effective way to reflect glucose metabolism in the brain, ¹⁸F-FDG PET imaging, combined with SPM analysis, can help to find specific changes of brain glucose metabolism in PD patients.⁶⁻⁹ Thus, our study performed ¹⁸F-FDG PET and SPM analysis in early PD patients with/without visual spatial dysfunction and age-matched healthy controls to investigate the changes of brain glucose metabolism in PD patients with

visual spatial dysfunction and to supply objective evidence for the pathogenesis of visual impairment in PD patients.

Our study used SPM to analyze the whole brain metabolism, and found that compared with healthy controls, early PD patients (with/without visual spatial dysfunction) showed obvious hypermetabolism in putamen, globus pallidus, thalamus, pons, cerebellum and primary motor cortex, while part of other brain areas had decreased metabolism, which was consistent with the previous literatures.^{3,9} This kind of abnormal brain glucose metabolism was consistent with changes in the "cerebral cortex-basal ganglia-thalamus-cerebral cortex" pathway in PD patients. Changes in the local glucose metabolism reflect changes in the afferent synaptic activity of neural networks. The dopamine expression in the nigra-striatum decreases after PD occurs, leading to a decreased direct inhibitory effect on the globus pallidus interna (GPi) in the direct pathway. In the indirect pathway, due to the hyperexcitation of the subthalamic nucleus (STN), the excitability of GPi is strengthened. These two pathways together cause the excessive inhibitory effect of GPi on the thalamus, leading to the decreased excitability of the thalamic motor nuclei on the corresponding cortex. The hypermetabolism of lentiform nuclei observed in this study might be due to an increase of afferent impulses from STN. The metabolism of thalamus was also enhanced by the increased inhibitory impulses from the lentiform nuclei. Another explanation of the increased metabolism in thalamus was the excessive activities of afferent excitatory impulses from the pedunclopontine nucleus, nuclei intralaminares thalami and motor cortex. As the decreased excitability from thalamus to visual cortex, the corresponding visual cortex showed a declined metabolism. The causes of increased cerebellar metabolism were unclear, which might be a functional compensatory of abnormal metabolism in basal ganglia.

We have also found that compared with early PD patients without visual spatial dysfunction, those with visual spatial dysfunction showed hypometabolism in the visual cognition-related brain regions including bilateral lateral dorsal prefrontal cortices, parietal lobules and angular gyri, besides insula, lingual gyrus and cuneus gyrus. Studies have shown that there are two main visual processing pathways in the brain,¹⁰ both of which originate in the primary visual cortex in the occipital lobe. One is the "Where" pathway: "occipital cortex-parietal cortex-striatum-dorsal prefrontal lobe-striatum", located at the top of the brain, the function of which is mainly related to the spatial position of the object and the movement perception; the other is the "What" pathway: "occipital cortex-lower temporal cortex-striatum-thalamus-ventral prefrontal lobe-striatum", located at the ventral part of the brain and is also known as "occipital-temporal pathway", the function of which is to identify the

objective object, and is associated with the formation of object's perception (such as shape, color, texture), so is also called "object-visual pathway". Our study showed that PD patients with visual spatial dysfunction had abnormal glucose metabolism in the visual-spatial processing related "Where" pathway: occipital cortex (hypometabolism)–parietal cortex (hypometabolism)–striatum (hypermetabolism)–thalamus (hypermetabolism)–dorsal prefrontal lobe (hypermetabolism)–striatum (hypermetabolism). Thus, we speculated that the dysfunction of the "Where" pathway due to abnormal glucose metabolism in these brain areas might be one of the causes for visual spatial dysfunction in PD patients.

Conflict of Interest

The authors declare that there is no conflict of interest.

Acknowledgments

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