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Regional Metabolic Changes Influencing Three-Dimensional Perception in Parkinson's Disease

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Background and Purpose Stereopsis refers to the perception of depth and awareness of the distance of an object from the observer that results from the brain receiving visual stimuli from both eyes in combination. Patients with idiopathic Parkinson's disease (PD patients) typically experience problems with vision, eyeball movements, and visual perception due to degeneration of the cells that generate dopamine in the brain. We therefore hypothesized that stereopsis is affected more by visual cortical dysfunction in idiopathic PD than by retina and subcortical structural dysfunction.

Methods We analyzed stereopsis in 12 PD patients and 7 healthy controls using a three-dimensional (3D) television (TV). Before allowing patients to watch TV, we examined their visual acuity and strabismus using the Titmus Stereo Fly Test, and evaluated their cognitive function using cognitive tests. The patients watched 3D and two-dimensional (2D) versions of a movie with an approximate duration of 17 minutes, and then completed a questionnaire about stereopsis. All subjects underwent brain F-18 fluorodeoxyglucose (FDG) positron-emission tomography after watching the 3D version of the movie. One week later, subjects watched the 2D version of the same movie under the same conditions. Each scan was analyzed using statistical parametric mapping (version 8) software.

Results The visual cortex was activated less in the PD patients than in the healthy controls when watching the 2D or 3D movie. However, there was no significant difference between watching 2D and 3D movies in the PD patients or healthy controls.

Conclusions The lower activation of the primary visual cortex in PD patients suggests the presence of dysfunction of the visual cortex. In addition, there was less activation of the visual association cortex in PD patients when watching a 3D movie than in controls under the same conditions. This might be one reason why PD patients do not recognize real and dynamic stereopsis. These findings have clinical significance since they suggest that safety needs to be considered when making devices or programs using 3D or virtual reality for use by patients with various cerebral degenerative diseases.

Keywords neurodegenerative diseases; Parkinson's disease; depth perception; vision disparity.

INTRODUCTION

Numerous studies have investigated the motor symptoms associated with idiopathic Parkinson's disease (IPD), but nonmotor symptoms, and particularly visual spatial perception, have received little attention. Patients with idiopathic Parkinson's disease (PD patients) have problems in visual-spatial perception as well as retinal disparity and eyeball movements due to the death of dopamine-generating cells in the brain.[1-5]

Visual attention and visual-spatial perception of PD patients are observed to be particularly impaired in tests of line orientation, memory for spatial location, and three-dimen-

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sional (3D) mental rotation.[6-8] Since 3D perception involves the fusion of binocular images in the cerebral cortex, PD patients may have deficits in 3D perception. Kim et al.[9] reported that PD patients have deficits in 3D perception based on tests using classical methods. The present study assessed 3D perception using the Titmus Stereo Fly Test (TSFT), which is a common clinical test performed to measure 3D perception by binocular disparity without considering monocular cues such as contrast, relative size and height of the object, texture gradients, motion parallax, accommodation, or binocular cues.

Studies using functional magnetic resonance imaging (fMRI) have found that visual association cortexes such as V2, V3, V3A, V7, V4, V3A, and V7 are associated with 3D perception.[10,11] The visual association cortex (V5 area) is especially important in 3D perception and motion perception. The damage seen almost throughout the entire neocortex increases during Braak stages 5 and 6 of IPD.[12] The visual association cortex is also involved. To evaluate the cortical function of patients, it was considered appropriate to use 3D television (TV) as an evaluation tool to provide practical movement stimulation to PD patients.

F-18 fluorodeoxyglucose (FDG) is an analogue of glucose, which is the main energy source of the brain. FDG positron-emission tomography (PET) can accurately display neural activity during sustained stimulation.[13,14] We considered that because the mechanism underlying a 3D TV test differs from that of the TSFT, it may be useful for detecting response differences for stimuli involving 3D moving images.

We hypothesized that PD patients have visual perception deficits due to a dysfunctional visual association cortex compared with healthy controls and that these deficits appear more significant when watching 3D TV than when watching two-dimensional (2D) TV. We compared assessments of PD patients and healthy controls performed using both the TSFT and the 3D TV method. Statistical parametric mapping (SPM) was used to analyze regional differences in brain metabolism between the two groups that underwent FDG PET scans.

We therefore evaluated the correlation of brain metabolism between 2D and 3D visual perception and cortical function in PD patients, and aimed to identify the cause of visual dysfunction in PD patients.

METHODS

Participants

We prospectively and systematically recruited 12 PD patients from the Movement Disorders Unit of Korea University Anam Hospital. All patients met the clinical diagnostic criteria for IPD according to the UK Parkinson's Disease Society Brain Bank.[15] The patients had no history or symptoms of dementia, abnormal brain lesions on conventional brain magnetic resonance imaging (MRI), or other neurological disorders. Ten of the 12 patients underwent F-18-FP-CIT PET at the time of being diagnosed as PD. Seven age- and sex-matched healthy controls who had no history of any neurological disorder or abnormal lesion in brain MRI were also recruited. None of the subjects in this study had any laboratory findings or history of diabetes mellitus, and they were not taking drugs that would affect cerebral glucose metabolism at the time of PET scanning. PD patients were categorized according to the Hoehn and Yahr stage (H&Y stage)[16] based on the Unified Parkinson's Disease Rating Scale (UPDRS).[17]

Ophthalmological examinations were conducted on the PD patients and healthy controls. The subjects did not have strabismus, nystagmus, ocular motility disturbance, visual field defects, or poor visual acuity in either eye (Snellen fraction ≤20/40). We measured conventional stereopsis using a TSFT plate (Stereo Optic Company, Chicago, IL, USA). Stereopsis testing was performed at a distance of 40 cm under 200-lux illumination. Dementia was excluded based on scores for the Korean version of the Mini Mental State Examination (K-MMSE) and the Montreal Cognitive Assessment (MoCA). All PD patients received levodopa or a dopamine agonist during the study.

This study was approved by the Institutional Review Board, at Korea University Anam Hospital (2011AN0208) and met the standards of the Declaration of Helsinki, and all participants provided written informed consent prior to their inclusion.

Protocol

All PD patients and healthy controls underwent brain FDG PET after watching the 3D version of a movie in a designed room (Fig. 1). One week later, they visited the hospital again and watched the 2D version of the same movie under the same conditions. At both visits, FDG was injected when the movie began. The subjects were then transferred to an adjacent room to rest when the movie had finished. Scans were acquired 40 minutes after the start of the visual stimulation. The participants wore polarized glasses while viewing the 3D TV, which had a diagonal dimension of 52 inches. We showed 3D and 2D versions of the same movie (title: drama of general "Kye Back" in Baekje dynasty produced by Munhwa Broadcasting Center in Korea), which lasted approximately 17 minutes. The sound volume, screen brightness, and unnecessary movements and disturbances were controlled during each experiment.

FDG PET imaging

FDG was administered via an intravenous injection. Within

40 minutes after the FDG injection, PET scans were obtained for 10 minutes with the patient's eyes closed in a dimly lit room with little or no auditory stimulation after they had finished watching the movie. Image acquisition was performed using a high-resolution PET-computed tomography (CT) scanner (Gemini TF; Philips Medical Systems, Cleveland, OH, USA). The scanner generated 90 contiguous transverse slices with an intrinsic resolution of 4.4-mm full-width half-maximum (FWHM) in all directions and an axial field of view of 18 cm. Attenuation correction was performed using a low-dose CT scan and 16-slice multidetector helical CT unit. Acquired data were reconstructed iteratively using a 3D row-action maximum-likelihood algorithm with an image size of 512×512 pixels.

Statistical analysis

The SPSS software package (version 15.0 for Windows, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Non-normally distributed epidemiological data were analyzed using nonparametric tests (Wilcoxon rank-sum tests). The results from the TSFT were analyzed based on the binocular disparity being considered abnormal when this was at least 60 arcsec. Answers were analyzed using Pearson's chi-square test. Each scan was analyzed using SPM software (version 8, Wellcome Department of Cognitive Neurology, London, UK) running under MATLAB (version R2011b, MathWorks, Natick, MA, USA). All images were normalized by the PET template and smoothed using a 12-mm FWHM isotropic Gaussian kernel to compensate for interindividual anatomical variability and to increase the signal-to-noise ratio. Smoothed images for each group were compared using the two-sample *t*-test while controlling for age and sex as nuisance variables in SPM. The intensity of all images was normalized using proportional scaling to reduce confounding by global effects. The criterion for statistical significance was $p<0.05$ (corrected) with an extent threshold of >500 contiguous voxels.

RESULTS

Epidemiological data

Twelve PD patients (six males and six females aged 63.5±10.7 years, mean±SD) and seven healthy controls (four males and three females aged 67.9±4.4 years) were enrolled in this study. In the PD patient group, the H&Y stage and UPDRS motor score were 2.17±0.70 and 24.8±10.6, respectively, and the disease duration was 9.83±10.10 months. There was no between-group difference in K-MMSE score, MoCA score, corrected visual acuity, or ophthalmological stereopsis function in log seconds of arc in the TSFT (Table 1).

Table 1. Demographics, clinical data, and brain volumes of PD patients and healthy controls

	PD patients	Healthy controls	*p*
Sex, male:female	6:6	4:3	NS
Age (yr)	63.5±10.7	67.9±4.4	NS
K-MMSE score	26.5±2.0	28.1±1.3	NS
MoCA score	23.7±3.5	26.3±2.5	NS
Disease duration (month)	9.83±10.10	-	-
H&Y stage	2.17±0.70	-	-
UPDRS motor score	24.8±10.6	-	-
Corrected visual acuity, left	0.8±0.2	0.8±0.3	NS
Corrected visual acuity, right	0.8±0.2	0.8±0.3	NS
Log seconds of arc in TSFT	342.5±842.7	268.6±363.3	NS

Data are mean±SD values.
H&Y, Hoehn and Yahr; K-MMSE, Korean version of the Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; NS, not significant; PD, Parkinson's disease; TSFT, Titmus Stereo Fly Test; UPDRS, Unified Parkinson's Disease Rating Scale.

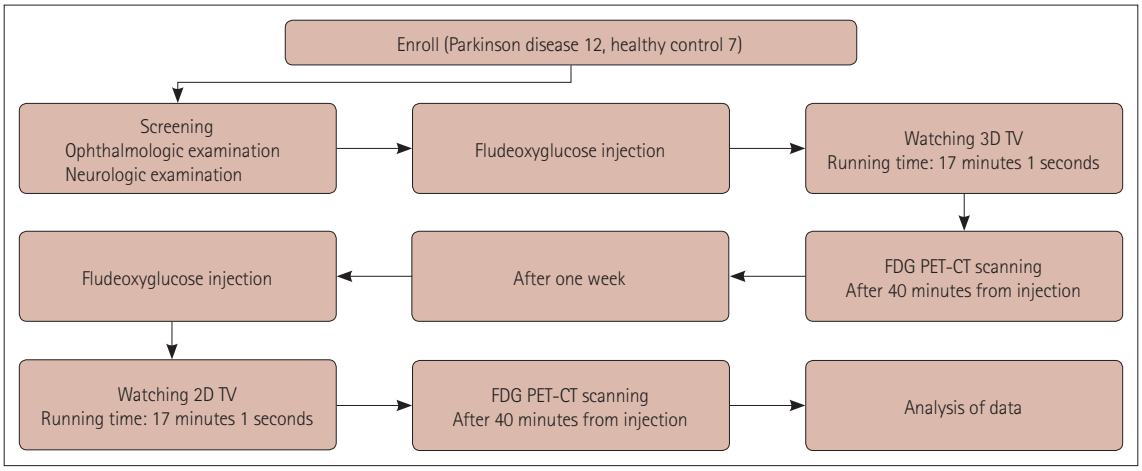

Fig. 1. Flowchart of the study protocol. FDG, F-18 fluorodeoxyglucose; PET, positronemission tomography.

Analysis of the TSFT

The PD patients and healthy controls were classified based on their arcsec values on the TSFT. Binocular disparity was normal in five (41.7%) PD patients and two (28.6%) healthy controls (Pearson's chi-square=3.26, p=0.568) (Table 2). The results of the TSFT did not differ between the two groups.

SPM analysis of FDG PET image

The SPM analysis of FDG PET images revealed differences in brain activation between the healthy controls and the PD patients in the primary visual cortex and visual association cortices when watching 3D TV (Brodmann areas 17–19) (Fig. 2 and Table 3), and in the primary visual cortex when watching 2D TV (cluster-level corrected p<0.01 using the family-wise error) (Fig. 3 and Table 3). However, there were no areas with different brain activation between watching 2D and 3D TV in the healthy control group or the PD patient group.

Table 2. Results of the TSFT for PD patients and healthy controls

Group	TSFT		Pearson's chi square	p
	Normal patients (<60 arcsec)	Abnormal patients (≥60 arcsec)		
IPD	5	7	3.26	0.568
Control	2	5		

IPD, idiopathic Parkinson's disease; PD, Parkinson's disease; TSFT, Titmus Stereo Fly Test.

DISCUSSION

PET is a well-established imaging method used to detect brain neural activity, and FDG PET provides images of the rate of regional glucose metabolism in the brain.[18,19] FDG PET is therefore commonly used to identify glucose hypo- or hypermetabolic lesions, such as primary brain tumors and metastatic tumors, and structures associated with epilepsy and neurodegenerative diseases. Because FDG PET scans may contain considerable artifacts and have low sensitivity and resolution, they have not been used in metabolic activation studies; many

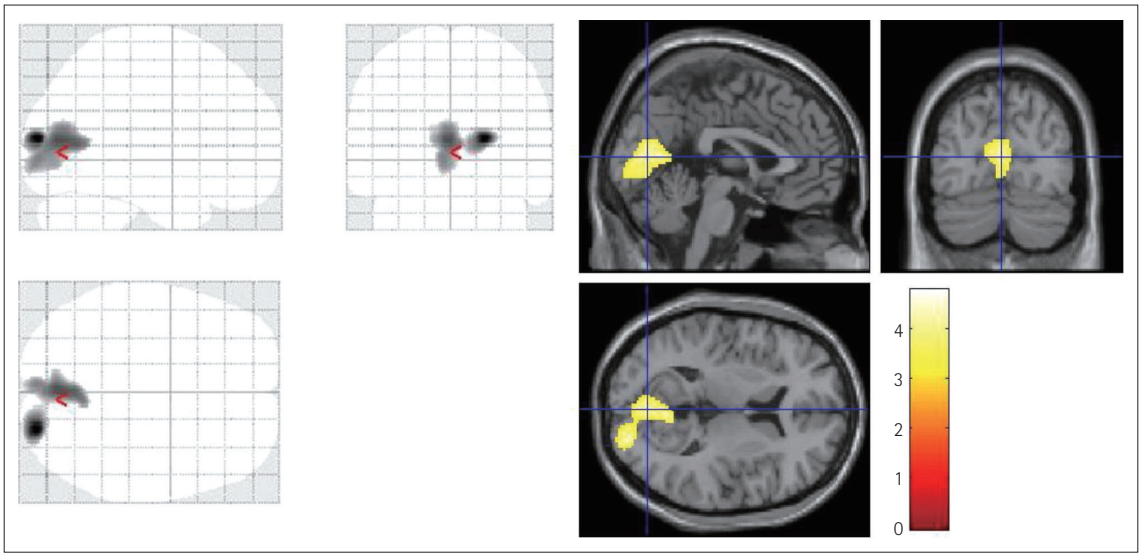

Fig. 2. The difference of glucose metabolism between idiopathic Parkinson's disease (PD) patients and healthy controls when watching 2D TV. Statistical parametric maps superimposed on a standard T1-weighted MRI template showing significant glucose hypometabolism in bilateral primary visual cortex in 12 PD patients compared with 7 healthy controls when watching 2D TV (thresholded at corrected p<0.05 for illustrative purposes). The color bar indicates t values.

Table 3. SPM results of group comparisons (PD patients vs. healthy controls) and correlation analyses when watching 2D and 3D TV

Location	BA	Coordinates (mm)			Peak z	Uncorrected p	Corrected p^{SVC}
		x	y	z			
Significant hypometabolism in PD patients compared with healthy controls when watching 2D TV							
Primary visual cortex	17	22	-88	14	3.70	<0.001	0.003
Significant hypometabolism in PD patients compared with healthy controls when watching 3D TV							
Primary visual cortex	17	-4	-64	0	4.13	<0.001	<0.001
Visual associated cortex	19	12	-68	26	4.07	<0.001	0.005

Coordinates refer to the Talairach space and denote the regions showing maximal changes within each cluster (defined as the voxel with the highest z value). All regions were significant at p<0.01 corrected for multiple comparisons at the voxel level.
BA, Brodmann area; PD, Parkinson's disease; SPM, statistical parametric mapping.

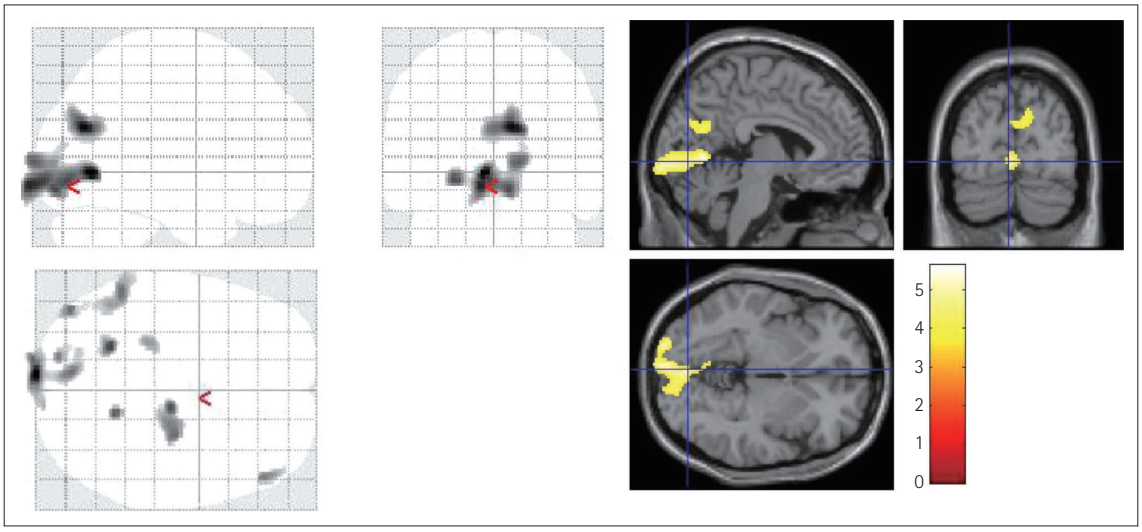

Fig. 3. The differences of glucose metabolism between idiopathic Parkinson disease patients and healthy controls when watching 3D TV. Statistical parametric maps as in Fig. 2, but for 3D TV.

such studies have used f-MRI instead. Few studies have used FDG PET scans to observe glucose metabolism during direct stimulation or motion.[20,21]

Patients undergoing FDG PET should be positioned comfortably in a quiet, dimly lit room several minutes before FDG administration and during the uptake phase of FDG (which lasts at least 30 minutes in our hospital protocol). Therefore, our participants underwent PET scanning 23 minutes after watching the 17-minute TV movie (i.e., 40 minutes after the start of the visual stimulation). The relatively long time for watching 2D and 3D movies with the same content, loudness, and brightness with restricted movement might have contributed to the high image quality and small artifacts in this study. In contrast to most other functional imaging studies, where the tasks must be performed in a supine position during indirect stimulation, FDG PET allows activation to be assessed after watching TV. To the best of our knowledge, this is the first study to investigate cerebral glucose metabolism when stimulating stereopsis in healthy controls and PD patients using voxel-based comparisons of FDG PET images.

A previous study found a large reduction in metabolism in the primary visual cortex in PD patients with dementia and Alzheimer's disease,[22] which also occurs in Lewy body dementia.[23,24] Therefore, a reduction in metabolism in the occipital lobe might be a feature of PD patients with dementia. One study found that the reduction in the visual cortex metabolism in PD patients reflected retinal versus nigrostriatal degeneration.[25] In the present study we found that the primary visual cortex was activated less in PD patients than in healthy controls when watching 2D and 3D movies, while there was no significant difference between watching 2D and 3D movies in the PD patients or healthy controls. The lower activation of the primary visual cortex in PD patients might reflect dysfunction of the visual cortex. In addition, activation of the visual association cortex while watching 3D movies was decreased more in PD patients than in healthy controls. The visual and visual association cortices can influence stereopsis.[26] Activation of the third visual complex (especially the V3A and dorsal V3 areas) and of the region of cortex located immediately in front of the prestriate cortex (V2) was decreased in PD patients when watching 3D movies compared with in healthy controls. This region is a part of the 'where' pathway (dorsal stream) that projects to the posterior parietal cortex, and plays a very important role in perceiving dynamic stereopsis when watching 3D TV.[10] Therefore, decreased 3D perception in PD patients might be influenced more by visual cortical dysfunction than by retina or basal ganglia dysfunction.

The PD patients included in this study did not have dementia symptoms. However, they exhibited decreased metabolic activation of the visual cortex and association cortex while watching 3D TV. Therefore, neural cellular dysfunction or synaptic dysfunction might have already been present in the occipital lobe of those patients with early PD. The symptom of decreased stereopsis might be considered as one of the non-motor symptoms of PD. It is necessary to develop a scale for assessing 3D stereopsis by using 3D TV and to expand this to other diseases, such as Alzheimer's dementia and Lewy body dementia, because these diseases are associated with cortical dysfunction of the occipital lobe.

This was a proof-of-concept study, and the small sample can be considered an important limitation. In addition, although the study involved patients with normal findings in cognitive function tests (K-MMSE and MoCA) and who had no symptoms of Lewy body dementia or PD dementia, the inability to

demonstrate the absence of pathological findings of dementia can also be viewed as a limitation.

This study addressed whether the latest 3D cognitive therapy devices and programs currently being developed, such as treatment programs using virtual reality or 3D TV, can be used stably in patients with cerebral degenerative diseases such as PD. This study has clinical significance in that it suggests that safety needs to be investigated when making devices or programs using 3D or virtual reality for patients with various cerebral degenerative diseases.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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