

Evaluation of the Areas Involved in Visual Cortex in Parkinson's Disease Using Diffusion Tensor Imaging

Somayeh Mohammadi Jooyandeh¹, Aida Kamalian², Sepideh Shiranvand²,
Mahsa Dolatshahi², Mohammad Hadi Shadmehr², Thomas C. Baghai¹,
Farzaneh Rahmani², Ahmad Shojaie³, and Mohammad Hadi Aarabi^{3,*}

¹ Department of Psychiatry and Psychotherapy, University of Regensburg,
Regensburg, Germany

² Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran,
Iran

³ Basir Eye Health Research Center, Tehran, Iran
Mohammadhadiarabi@gmail.com

Abstract. Parkinson's disease (PD) is a progressive neurodegenerative disorder assumed to involve different areas of CNS and PNS. In PD patients and in primates with experimental Parkinsonism indicating that retinal dopamine deficiency is an important factor in the pathogenesis of PD visual dysfunction. Visual signs and symptoms of PD may include defects in eye movement, pupillary function, and in more complex visual tasks. In this study, we evaluated the areas involved in visual cortex in PD by diffusion tensor imaging to assess the structural change in PD.

Keywords: Diffusion tensor magnetic resonance imaging, Connectomics, Parkinson disease and Visual Cortex.

1 Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder affecting middle aged and elderly people. It is a disease defined with deficiency of dopamine in areas of the midbrain causing a variety of movement problems such as shaking, rigidity, slowness of movement and difficulty with walking and gait. Sensory problems of PD may include visual loss, loss of smell, auditory problems [1]. In PD patients and in primates with experimental Parkinsonism retinal dopamine deficiency is an important factor in the pathogenesis of PD visual dysfunction. Visual signs and symptoms of PD may include defects in eye movement, pupillary function, and in more complex visual tasks involving the ability to determine interval of the shape of an object and visual hallucination (VH) [2, 3]. The findings show that basic visual sensory function, and visual perception are impaired also in nonmanic patients with mild to moderate PD. Among numerous advanced MR techniques Diffusion-weighted image (DWI) and diffusion tensor imaging (DTI) are methods that have been used in recent years to find changes of white

matter integrity because of their sensitivity to the local diffusion behavior of water molecules in brain tissue [4]. The utilization of DWI and DTI have proved to be effective in differential diagnosis of PD and Parkinson variants, such as Multiple system atrophy and progressive supranuclear palsy [5]. So far, DTI has been widely practical for the quantitative evaluation in many types of brain disease, including amyotrophic lateral sclerosis [6], schizophrenia [7], Parkinson's disease [8], NMO [9], and multiple sclerosis [10], and it has also been used in the quantitative evaluation of the optic nerves in normal brain [11], idiopathic demyelinating optic neuritis [12], and indirect traumatic optic neuropathy [13]. Other imaging techniques including PET and functional MRI studies have shown reduced activation of the ventral/lateral visual association cortices and the primary visual cortex (VC) in particular [2]. While few studies have been done on DTI.

In our study, we aimed to calculate healthy and PD visual cortex brain connectivity matrices for average tract length and average fiber volume and compare them directly through Network Based Statistics (NBS).

2 Method

2.1 Participants

Participants involved in this research were recruited from Parkinson's Progression Markers Initiative (PPMI) [14]. DWI images were obtained for 18 patients (7F 11M, mean age 73.33) and 12 controls (4F 8M, mean age 71.50). Participants were tested and confirmed negative for any neurological disorders apart from PD. The participants' PD status was confirmed by Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the loss of dopaminergic neurons were observed in DaTscans. Every participant involved in this research has signed informed written consents in order to share their unidentified clinical data to investigators.

2.2 Data Acquisition

Data used in the preparation of this paper was obtained from Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data/) [14]. This dataset was acquired on a 3 Tesla Siemens scanner, producing 64 DWI (repetition time = 7748ms, echo time = 86ms; voxel size: $2.0 \times 2.0 \times 2.0mm^3$; field of view = $224 \times 224mm$) at $b = 1000s/mm^2$ and one b0 image along with a 3D T1-weighted structural scan (repetition time = 8.2ms, echo time = 3.7ms; flip angle = 8° , voxel size: $1.0 \times 1.0 \times 1.0mm^3$; field of view = $240mm$, acquisition matrix = 240×240).

2.3 Diffusion MRI Data Processing and Network Construction

The DWI data were analyzed and processed in ExploreDTI [15]. The diffusion tensor was estimated using a weighted linear least square regression procedure

proposed in [16]. For subject motion correction and eddy-current induced geometrical distortion, DWI data were rigidly registered with MNI atlas [17]. During this processing step, we adjusted the B-matrices with appropriate reorientations and included the required signal intensity modulation with the Jacobian determinant of the spatial transformation [18]. Whole-brain tractography was performed using a deterministic algorithm.

Fibers were reconstructed by placing seed points on a uniform grid across the data set at $2mm$ isotropic resolution and by following the main diffusion direction (as defined by the principal eigenvector) unless the fiber tract entered a voxel with a $FA < 0.2$ or it made a high angular turn considered to be anatomically implausible (angle $> 30^\circ$). The step size was set at $0.5mm$. The whole-brain fiber tracts were then parcellated using the automated anatomical labeling (AAL), a widely used atlas to derive nodes in graph theoretical analyses of neuroimaging data [19]. The mentioned atlas divides brain into 6 cortical regions. The interregional connectivity between the 6 ROIs demarcated on the AAL template was computed by applying the ROI masks to the reconstructed fiber tracts using ExploreDTI. In this fashion we determined the volume and average tract length that originated in one ROI (i) and terminated in another one (j), for all 6 ROIs defined on the atlas, creating a 6×6 connectivity matrix (CM).

In the next step we used NBS for group analysis [20]. NBS is a method based on the principles underlying traditional cluster-based thresholding of statistical parametric maps to control family-wise error rate (in the weak sense) when mass-univariate testing is performed at every connection of the graph. The gain in power offered by NBS increases as the number of nodes and links is increased, which serves well in our complex neural network. In brief, by using NBS, the presence of every link is utilized to yield greater power than a generic procedure to control FWER.

3 Result

T-test statistics were applied with threshold of 2.9 and significant results (p-values for average tract length was 0.0202 (Table 1) (Figure 1). The NBS identified two subnetworks of reduced connectivity in de novo PD patients ($P < 0.05$, corrected for multiple comparison).

Table 1. The Significant Pathway

Pathway	Test Stat
Calcarine Right to Lingual Left	2.01
Calcarine Right to Calcarine Left	2.32

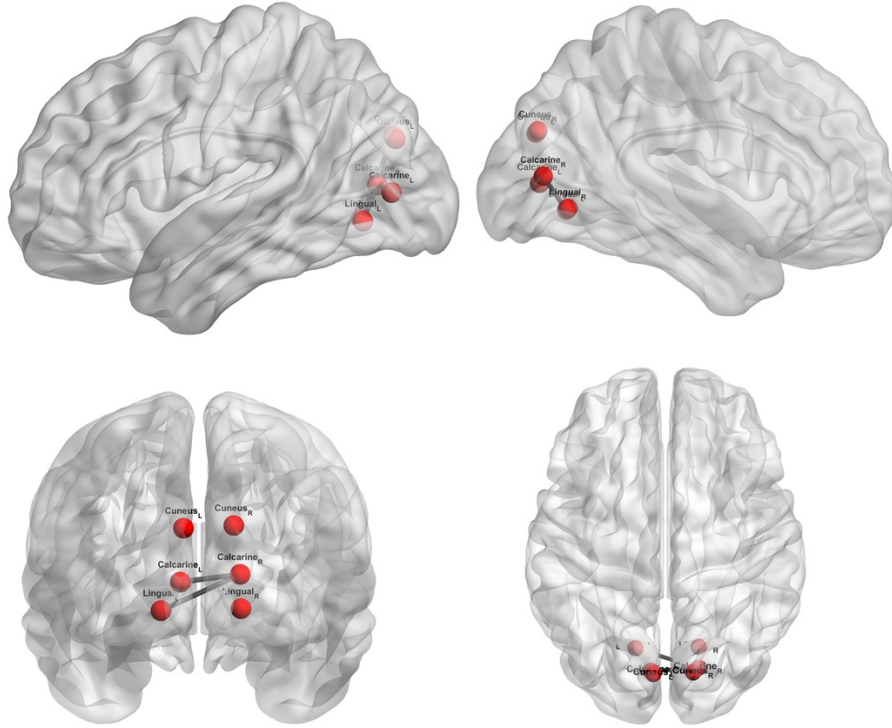


Fig. 1. Graphical illustration of significantly altered connectome pathway: average tract length

4 Discussion and Conclusion

In this study, for the first time, we explore occipital lobe of Parkinson's patients using DTI techniques. Our results suggest that several areas of visual cortex involved in PD including: calcarine (left, right), lingual (left, right), and cuneus. The percentage of disruption of left calcarine to right calcarine/ right calcarine to lingual was more than other areas, and also we show that visual dysfunction can occur in Parkinson's patients and affect their lives, so detection of visual symptoms is important for differential diagnosis and patient management.

Regions of increased activation during the visual hallucinations relative to non-hallucination events included the bilateral cingulate gyrus (anterior, middle, and posterior), bilateral insula (including the claustrum), right medial frontal gyrus, right postcentral gyrus, right thalamus (near the medial dorsal nucleus), and right brainstem (near the red nucleus). Regions of decreased activation during the visual hallucinations relative to non-hallucination periods included the visual system on the right side (inferior occipital gyrus, lingual gyrus, and fusiform gyrus), the right cingulate gyrus, right superior temporal gyrus and the left

middle frontal gyrus. There was no overlap between regions of increased and decreased activation during the visual hallucination events [21].

In PD, the DMN showed reduced connectivity during the resting state, compared to controls. However, connectivity within the PDVH group was greater than the PD nonVH group, particularly across bilateral precuneus/posterior cingulate gyrus and right middle frontal lobe. The decreased functional connectivity within DMN in PD compared to controls is in line with a recent study showing that cognitively unimpaired patients have decreased functional connectivity within the DMN compared to controls [22]. Individuals with greatest hallucination symptoms actually had “higher” connectivity within the disrupted network, which in turn may increase functional connectivity across distant brain regions.

PD patients exhibited decreased short-range functional connectivity densities in regions that were mainly located in the ventral visual pathway and decreased long-range functional connectivity densities in the right middle and superior frontal gyrus, which have been speculated to be associated with visual hallucinations and cognitive dysfunction, respectively. The observed functional connectivity density alterations might be related to the disturbed structural connectivity of PD patients, leading to abnormal functional integration [21]. Morphometric studies based on structural MRI have also documented significant reductions in graymatter volume, cortical thickness, and cortical gyrification, as well as subcortical volumetric atrophy, in PD patients [23].

In a study, we observed focal reductions in both the short- and long-range FCDs of PD patients compared with the healthy controls. Notably, the regions with short-range FCD reduction were mainly located in the ventral visual pathway involving the inferior and middle occipital gyrus, Brodmann’s area 18 and 19, lingual and fusiform gyrus, and inferior temporal gyrus [23].

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