Ventral striatal dopaminergic defect is associated with hallucinations in Parkinson's disease

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Abstract

Background: Visual hallucinations (VHs) are a common complication of Parkinson's disease (PD). The pathogenesis of VHs in PD is still largely unclear. The aim of this study was to investigate the dopaminergic mechanisms of VHs and specifically whether the degree of striatal dopamine transporter (DAT) or extrastriatal serotonin transporter (SERT) function can predict the appearance of VHs in patients with PD.

Methods: Twenty-two PD patients scanned with [^{123}I]FP-CIT single photon emission computed tomography at an early stage of their disease who later developed VHs were identified and compared with 48 non-hallucinating PD patients. The groups were matched for age, medication, disease duration and motor symptom severity. Clinical follow-up after the scan was a median (range) of 6.9 (3.8 – 9.6) years. Imaging analyses were performed with both regions-of-interest-based and voxel-based (SPM) methods for the striatal and extrastriatal regions.

Results: The median interval between the scan and the emergence of VHs was 4.8 years. Patients who developed VHs had 18.4 % lower DAT binding in the right ventral striatum ($p=0.009$), 16.7 % lower binding in the left ventral striatum ($p=0.02$) and 18.8 % lower binding in the right putamen ($p=0.03$) compared to patients who did not develop VHs.

Conclusions: Low striatal DAT function may predispose PD patients to VHs, and the regional distribution of the findings suggests a particular role of the ventral striatum. This is in line with non-PD research that has implicated ventral striatal function in psychosis.

Introduction

Hallucinations are a common problem in Parkinson's disease (PD). The outpatient prevalence of these complications has been estimated to be approximately 25 % [1], and it may be as high as 75 % when minor hallucinations (sense of presence or shadows in the visual periphery) are included [2]. Thus, the quality of life of a large proportion of PD patients and caregivers is affected by hallucinations, and this is associated with higher rates of hospitalization and nursing home placement [2, 3]. Most commonly, the hallucinations in PD are visual [4] that are typically well formed, complex and recurrent, and they can be associated with delusions such as phantom boarder symptom (patient imagines that there are uninvited people living in their home) or delusion of spousal infidelity and abandonment [5]. Auditory hallucinations may coexist with more common visual hallucinations (VHs) [2]. Although a large proportion of PD patients will eventually develop VHs during the disease course, it remains unclear which factors predict the emergence of these complications.

There are multiple theories explaining the emergence of VHs in PD [3, 6]. The prevalent view of hallucinations as a simple side effect of dopaminergic medications appears insufficient [5, 7]. Dopaminergic medications, especially dopamine agonists, may cause the hyperstimulation or hypersensitivity of mesolimbic dopamine D2 and D3 receptors, and this could play a key role in the pathogenesis of hallucinations [2, 5, 8]. On the other hand, there are drug-naïve patients who suffer from hallucinations, even at premotor stages [9]. Furthermore, the dose or the duration of dopaminergic medications appears to have no association with hallucinations [5]. However, hallucinations in PD patients most often emerge in medicated patients at advanced disease stages and the symptoms respond to the reduction of the dose of dopaminergic medication or to treatment with antipsychotics, suggesting that the brain's

dopamine function is nevertheless important in pathophysiology. To our knowledge, only two previous studies have attempted to predict hallucinations in PD on the basis of dopaminergic imaging [10, 11]. These studies have suggested that reduced caudate nucleus and/or putamen dopamine transporter (DAT) binding may be associated with the development of hallucinations, but the studies did not investigate or were not able to demonstrate limbic or extrastriatal DAT binding abnormalities.

Therefore, we sought to examine whether PD patients who develop VHs show a specific pattern of dopaminergic or serotonergic loss compared to patients who remain free from hallucinations. As [^{123}I]FP-CIT can be considered specific for dopamine function only in the dopaminergically highly active striatum[12], we employed methods to investigate both striatal DAT and extrastriatal cortical binding, which reflects the levels of the serotonin transporter (SERT). It was hypothesized that PD patients who develop VHs show more severe monoaminergic impairment, particularly within the limbic system.

Methods

Patients

From 538 consecutive patients scanned with [^{123}I]FP-CIT single photon emission computed tomography (SPECT) imaging in the Department of Nuclear Medicine, Turku University Hospital, Finland, within a six-year period (2007-2012), patients with PD, an abnormal outcome in imaging and sufficient patient clinical history were selected (n = 162). PD diagnoses were based on clinical examinations by certified neurologists. Demographical and clinical data from these patients were gathered from the hospital records at the time of the scan and in median 5.8 years later. From this sample of PD patients, 22 patients were identified identified who developed hallucinations during the follow-up (Table 1). Next, patients with VHs were matched with a group of patients without VHs according to age, sex, duration of follow-up, symptom duration, Hoehn and Yahr stage at the scan, levodopa equivalent daily dose (LEDD) at the scan and LEDD at follow-up. One investigator (E.J.), blinded to the imaging results, selected control patients based on clinical characteristics. The total number of control patients was 48. The local ethical committee accepted this retrospective study protocol, and the requirement to obtain informed consent was waived. The study was conducted according to the principles of the Declaration of Helsinki.

Scanning & image processing

All patients were scanned with a GE Infinia II Hawkeye SPECT/CT (GE Medical Systems, Milwaukee, WI, USA) or Picker Irix gamma camera (Picker International, Uniontown, OH, USA). One hour before tracer injections, patients received oral $KClO_4$ (250 mg, 1 % solution) to protect the thyroid gland. A 185-MBq bolus of [^{123}I]FP-CIT was injected three to four hours before the scanning. Detailed explanation of the scanning protocol and reconstruction has been described elsewhere [13]. BRASS automated analysis software (version 3.6; Hermes

Medical Solutions, Stockholm, Sweden) was used and specific corrections for each scanner were added. Specific binding ratios with an occipital reference (SBRs = (ROI_{target} – $ROI_{occipital}$) / $ROI_{occipital}$) for six regions of interest (ROIs) (right and left caudate, right and left anterior putamen, right and left posterior putamen) were calculated.

For voxel-by-voxel analyses, the reconstructed DICOM files were exported from the BRASS software and converted to NIfTI format. Pre-processing was conducted with Statistical Parametric Mapping (SPM8; http;//www.fil.ion.ucl.ac.ul/spm/software/spm8/) running on Matlab (R2015a; Mathworks Inc., Chicago, IL). The images were warped into the Montreal Neurological Institute (MNI) space using an in-house [^{123}I]FP-CIT-SPECT template [14]. ROIs for the amygdala and the hippocampus were obtained from Automated Anatomic Library (AAL). In addition, ROIs for the right and left ventral striatum that are not included in ALL were drawn using Carimas (version 2.9, Turku PET Centre, Turku, Finland) as described earlier [15]. The occipital cortex was designated as the reference region [16]. SBR images were calculated by scaling the images by the reference region uptake. Finally, the images were smoothed using 8 mm full width at half maximum Gaussian kernel to improve the signal-to-noise ratio and to diminish the effects of minor inter-individual realignment errors.

Statistical analyses

SPSS Statistics (IBM version 24, SPSS Inc., Chicago IL, USA) were used for statistical analyses with ROIs. The differences between the patients with or without hallucinations were calculated using independent samples *t* tests. *P* values < 0.05 were considered significant. To estimate the predictive value of a decrease in the ventral striatal binding, logistic regression analyses were performed with brain regions that were significantly associated with development of hallucinations.

Voxel-by-voxel analyses were conducted using the general linear model across the entire brain, limiting the search volume to regions with binding equal to or higher than the reference region. Regional SBRs were compared between patients with and without hallucinations, and in patients who developed hallucinations associations between regional SBRs and the time interval between scanning and the emergence of hallucinations were studied. Both analyses were conducted with and without covariates (sex, age and Hoehn and Yahr score). Family wise error (FWE) correction was applied at the cluster level and corrected P values less than 0.05 were considered significant. The results were visualized using MRIcron (www.mccauslandcenter.sc.edu/mricro/mricron/) [17].

Results

Twenty of the 22 hallucinating patients had experienced VHs that had emerged concurrently with the initiation or a dose increase of an antiparkinsonian drug (Table 1). In two patients, the type of hallucination was undetermined. The median interval between scan and the emergence of VHs was 4.8 years (range 1 – 96 months).

The demographic data and differences between patients with and without hallucinations are presented in Table 2. There were no differences in the doses of dopaminergic medications (total LEDD) between patients with and without hallucinations. Importantly, also when dopamine agonist LEDD values were separately investigated, no differences between groups were detected. Patients with or without hallucinations did not differ in the presence of other neuropsychiatric symptoms (self-reported depression, anxiety or impulse control disorders) at baseline or follow-up ($p>0.09$). In striatal subregions, patients with hallucinations had significantly lower DAT binding at baseline in both the right and left ventral striatum and in the right putamen (Table 2, Figure 1). In the logistic regression analyses, the odds ratio (95% confidence interval) for 1.0 decrease in SBR was 4.26 (1.34-13.52) in the right ventral striatum, 3.43 (1.12-10.54) in the left ventral striatum and 3.41 (1.05 –11.12) in the right putamen. Additionally, putamen asymmetry was greater in patients with hallucinations compared to patients without hallucinations [asymmetry index = (right-left putamen SBR)/(left+right putamen SBR)]. At follow-up, patients with hallucinations had developed higher Hoehn and Yahr scores compared to patients without hallucinations (Table 2). DAT binding in the right amygdala was lower in patients with hallucinations compared to those without hallucinations ($p=0.038$). No differences were seen in the left amygdala or in the right or left hippocampus.

In the whole-brain voxelwise analyses, patients with hallucinations had lower SBRs in the anterior and ventral parts of the striatum compared to patients without hallucinations (cluster size 2461 voxels, peak at -30 8 -14 mm in MNI coordinates, maximum t-value 3.53, height-threshold t = 2.39, FWE-corrected p =0.01; Fig 2). The finding was right-lateralized and remained significant after adjusting for covariates (FWE-corrected p=0.04). Regional SBRs did not correlate with the time interval between the scan and the emergence of hallucinations in patients with hallucinations. No significant cortical/extrastriatal group-differences were detected. The lowered SBR in the right amygdala in patients with hallucinations compared to patients without hallucinations was not supported by voxel-by-voxel analyses.

Discussion

Our results indicate that PD patients with low ventral striatal DAT density are more vulnerable to hallucinations. The findings are in line with the hypothesis that limbic areas are involved in the genesis of hallucinations in synucleinopathies [2] and with the postulated similar role of the limbic dopaminergic system in the generation of acute schizophrenic psychosis [18].

The present results demonstrated a consistent bilateral difference of 17-18 % in the ventral striatum between the patients with and without VHs. The ventral striatum receives input from the ventral tegmental area, partially comprising the mesolimbic dopaminergic pathway. In PD, the ventral striatal dopaminergic system is generally better preserved than the dorsal striatum [19]. It has been postulated that dopaminergic medications, especially dopamine agonists, may cause dopaminergic hyperstimulation in the ventral striatum, which could be an important mechanism in the pathophysiology of hallucinations in PD [20, 21]. Since previous research in schizophrenic patients has reported positive correlations between ventral striatal dopamine D2 receptor levels and hallucinations [22], we consider it possible that the ventral striatal presynaptic DAT defect is associated with a compensatory up-regulation of dopamine D2/D3 receptors in PD. However, this theory needs verification from neuroimaging studies using double-tracer design with postsynaptic and presynaptic dopaminergic tracers.

Only a few previous studies have attempted to predict the development of VHs in PD. Ravina *et al* [10] carried out an analysis of PD patients using the PostCEPT cohort that had been scanned with [^{123}I]β-CIT SPECT. The results showed that DAT binding was associated with several motor and non-motor outcomes, including the development of psychosis, after 5-6 years of follow-up. However, the broad association of DAT binding with a wide range of motor

and cognitive outcomes suggested a lack of specificity. Importantly, the investigations were limited to the caudate nucleus and the putamen without limbic, ventral striatal or cortical RIOs. Kiferle *et al* [11] extended investigations to extrastriatal regions in 18 PD patients with VHs and 18 control PD patients who had undergone [^{123}I]FP-CIT SPECT imaging at the time of diagnosis. They reported that patients who developed VHs had significantly lower tracer uptake in the right caudate in comparison with patients without VHs. In our study, in addition to the ventral striatal involvement, the results implied that right putaminal DAT binding is decreased in patients who later develop hallucinations. The results are thus in accordance with the study of Ravina *et al*. [10], and the right-sided caudate nucleus DAT binding deficit was also found in the study by Kiferle *et al.* [11]. Notably, although this work and Kiferle *et al*. employed whole brain voxel-by-voxel analyses, no cortical effects were observed in either study. Furthermore, positive correlations between decreased striatal DAT density and VHs have also been reported in patients with dementia with Lewy bodies [23]. Therefore, our results, together with the available earlier evidence, emphasize the role of motor and limbic striatal dopamine, in contrast to cortical monoaminergic function or SERT, in the development of PD hallucinations. The lack of cortical effects should be interpreted with caution, however, since the signal-to-noise ratio of [^{123}I]FP-CIT SPECT in the cortex is much lower compared to striatal regions. It is also important to note that the number of studies reporting cortical imaging findings in patients with hallucinations is particularly small. At this stage, the lack of positive results cannot be considered as proof of a non-existent cortical mechanism, particularly since the clinical beneficial effect of a 5-HT2A receptor agonist, pimavanserin, indicates that there may be important serotonergic mechanisms in PD hallucinations that are not related to basal ganglia dopamine or cortical SERT levels [4]. Indeed, preliminary findings using [^{18}F]setoperone positron emission tomography have provided evidence supporting a relevant role of cortical $5HT_{2A}$ receptors in mediating VHs in

PD [24]. The development of subtype-specific monoaminergic receptor tracers and other neurotransmitter ligands for positron emission tomography and SPECT will enable the systematic investigation of postsynaptic hallucinogenic mechanisms in PD.

In line with earlier studies [1, 25], our patients with hallucinations also had more advanced motor symptoms at follow-up than patients without hallucinations, even though there were no differences at baseline or in dopaminergic medications between the groups. Whether DAT deficit predicts the worsening of motor symptoms is not clear [26]. It is in any case evident that rather than being dichotomously motor or non-motor, striatal DAT function is associated with a multitude of different clinical end-points. It should also be noted that in addition to dopaminergic functional deficit also other factors, such as longer disease duration, older age at disease onset and sleep disturbances are risk factors for VHs in PD [1, 3]. Some of the other risk factors could also be associated with dopaminergic changes, which underlines the issue of causality: the present findings cannot directly determine causality between striatal dopaminergic loss and VHs, whereas they demonstrate a relationship that could be influenced by a combination of other factors.

There is functional MRI evidence to suggest that ventral striatal activity increases in the remission of psychotic symptoms [27], and there is decreased grey matter density in the ventral striatum in schizophrenia [28]. There are also structural brain changes in PD patients with VHs, as multiple neuroimaging studies have reported changes in visual areas, visual association areas and frontal regions in patients with VHs [29-32]. From a neuropathological point of view, the proteinopathic mechanism could be relevant, as Lewy body/alpha-synuclein distribution has been associated with the emergence of hallucinations in PD [33]. VHs in PD have also been proposed to reflect from the dysfunction of attentional control

networks [34, 35]. Normally, misperceived visual information is corrected by dorsal attention network. When fronto-striatal circuits are damaged in PD this correcting system may not work anymore and VHs arise.

In summary, the relatively lower presynaptic dopamine function in the ventral striatum could be associated with the compensatory up-regulation of postsynaptic dopamine receptors. It is proposed that this is the mechanism that is associated with the greater vulnerability to agonist-induced hallucinations. This theory requires verification from future longitudinal neuroimaging studies with receptor ligands.

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Conflicts of interest

None.

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