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► **To cite this version:**

Ana Luísa Marques, Natasha Taylor, Daniel Roquet, Steven Beze, Carine Chassain, et al.. Structural and Functional Correlates of Hallucinations and Illusions in Parkinson's Disease. *Journal of Parkinson's disease*, 2022, 12 (1), pp.397-409. 10.3233/JPD-212838 . hal-03647518

HAL Id: hal-03647518

<https://hal.science/hal-03647518v1>

Submitted on 20 Apr 2022

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Research Report

Structural and Functional Correlates of Hallucinations and Illusions in Parkinson's Disease

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Accepted 17 October 2021

Abstract.

Background: Visual illusions (VI) in Parkinson's disease (PD) are generally considered as an early feature of the psychosis spectrum leading to fully formed visual hallucinations (VH), although this sequential relationship has not been clearly demonstrated.

Objective: We aimed to determine whether there are any overlapping, potentially graded patterns of structural and functional connectivity abnormalities in PD with VI and with VH. Such a finding would argue for a continuum between these entities, whereas distinct imaging features would suggest different neural underpinnings for the phenomena.

Methods: In this case control study, we compared structural and resting state functional MRI brain patterns of PD patients with VH (PD-H, $n = 20$), with VI (PD-I, $n = 19$), and without VH or VI (PD-C, $n = 23$).

Results: 1) PD-H had hypo-connectivity between the ILO and anterior cingulate precuneus and parahippocampal gyrus compared to PD-C and PD-I; 2) In contrast, PD-I had hyper-connectivity between the inferior frontal gyrus and the postcentral gyrus compared to PD-C and PD-H. Moreover, PD-I had higher levels of functional connectivity between the amygdala, hippocampus, insula, and fronto-temporal regions compared to PD-H, together with divergent patterns toward the cingulate. 3) Both PD-I and PD-H had functional hypo-connectivity between the lingual gyrus and the parahippocampal region vs. PD-C, and no significant grey matter volume differences was observed between PD-I and PD-H.

Conclusion: Distinct patterns of functional connectivity characterized VI and VH in PD, suggesting that these two perceptual experiences, while probably linked and driven by at least some similar mechanisms, could reflect differing neural dysfunction.

Keywords: Parkinson's disease, hallucinations, illusions, neuroimaging, visuo-perception

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INTRODUCTION

Visual hallucinations (VH), defined as a perception without existing stimuli, are one of the most frequent non-motor symptoms of Parkinson's disease (PD), and typically present across a spectrum ranging from minor hallucinations to complex hallucinations. In contrast, visual illusions (VI), defined as a false perception of an existing stimulus, are generally considered part of the prodrome towards fully formed visual hallucinations in PD, and are frequently classified as minor hallucinations [1, 2]. However, this sequential relationship has not been clearly demonstrated and longitudinal clinical, imaging and/or pathological studies addressing this specific question are lacking in PD [3, 4].

In other conditions such as schizophrenia, it has been shown that the perception of VI is not related to the strength of VH [5]. Indeed, patients with schizophrenia may even have a reduced susceptibility to visual illusions compared to healthy controls [6]. Thus, whilst one might intuitively regard visuo-perceptive phenomena as being symptomatically related, they may arise from discrete and separable neural substrates.

Previously, neuroimaging techniques have been used to investigate structural, functional and metabolic changes in PD patients with and without VH [7–14], either including well-structured or minor VH [7, 10], and have reported alterations in multiple regions related to different functions such as visuospatial processing, attention and memory [7]. Indeed, morphometric studies identified atrophy in lingual gyrus, cingulate, precuneus, superior frontal gyrus and inferior frontal gyrus (SFG and IFG), hippocampus, fusiform gyrus in PD patients with VH [7–10, 15–17]. Functional studies have generally highlighted decreased activity in posterior brain regions (occipital, parietal, temporal) corresponding to visual pathways, and increased activity of frontostriatal circuits during visual stimuli processing, suggesting an aberrant top-down visual processing over the normal bottom-up processing, as one of the factors predisposing to VH in PD [11, 18]. However, these findings have not been consistent across all studies, and no alterations in posterior activation during presentation of visual stimuli have been reported in other studies, but instead a significant reduction in the activation of the anterior cingulate gyrus, inferior, middle and superior frontal gyri [19]. More recently, the role of abnormal connectivity of the default mode network (namely in regions such as middle frontal

gyrus, posterior cingulate and precuneus) and dorsal attention network in the pathophysiology of VH in PD has been suggested [12, 20]. However, those studies did not discriminate between VH and VI, which are not differentiated in the majority of studies, which could explain some of the reported discrepancies. Indeed, less work has been focused on VI in PD and very few studies so far have addressed the question of brain changes that could be specifically related to either VI or VH [4, 21–23].

One study has shown that the metabolic pattern observed in PD patients with kinetopsia (illusion of movement) was similar to the one observed in PD patients with VH, whereas the misidentification of objects had a different pattern that only partially overlapped with VH [4]. Recently, our own team demonstrated that PD patients with VH had generalized retinal and brain atrophy compared to those with VI, regardless of the disease duration [22]. This finding is in line with another study reporting decreased age-adjusted global grey matter volume in Parkinsonian patients with VH compared to those with VI [24]. Yet, these observations failed to resolve whether the brain changes underpinning PD-H simply represent progression from more subtle modifications in PD-I or if these phenomena arise from discrete mechanisms.

We hypothesized that the existence of overlapping but graded patterns of structural and functional abnormalities in PD with VI and VH would argue for a continuum between these entities, whereas distinct functional connectivity features would suggest different neural underpinnings for the phenomena. To test this hypothesis, we assessed group-wise local changes of voxel values throughout the entire brain, and we analyzed the resting state functional connectivity associated with VH and VI in PD, focusing on the following regions: lateral occipital cortex (mid-level visual region involved in shape and object identification) [25], lingual gyrus (supplementary visual cortex) [26], and occipital fusiform gyrus (responsible for high-level visual processing, and for memory multisensory integration and perception) [27], amygdala and insula (involved in emotional processing and emotional modulation of perception) [28], hippocampus (involved in encoding and retrieval of memories, conscious observation and anticipation, and mental imagery) [29], precuneus (involved visuo-spatial imagery, self-processing and consciousness) [30], and inferior/middle/superior frontal gyrus (IFG, MFG, SFG) (involved in retrieval of autobiographical memories and reality

136 monitoring) [31–34]. Those regions were selected
 137 as they were previously reported to be impaired in
 138 structural and functional MRI studies conducted in
 139 PD patients with VH [7].

140 MATERIALS AND METHODS

141 *Study design and settings*

142 The participants were a subset drawn from our
 143 previous study [22], that included eighty four PD
 144 patients, either with VI (PD-I; $n=28$), VH (PD-
 145 H; $n=28$), and without any VI or VH (PD-C;
 146 $n=28$) matched for age and sex, who were recruited
 147 from the Parkinson expert center, Neurology Depart-
 148 ment, Clermont-Ferrand University Hospital, France,
 149 between March 2018 and April 2019. Among these
 150 patients, 68 underwent MRI (PD-I: $n=22$, PD-H:
 151 $n=23$, PD-C: $n=23$) and were included in the cur-
 152 rent study. We assessed the characteristics of VH and
 153 VI, severity of PD, as well as dopaminergic treat-
 154 ment, general cognitive and specific visuo-perceptive
 155 functions. Neuroimaging evaluated brain volumetry
 156 and functional connectivity for all patients. The pro-
 157 tocol was approved by the South-West & Overseas
 158 II ethical committee, France (clinicaltrials.gov num-
 159 ber NTC03454269). All patients gave their written
 160 informed consent as per the Declaration of Helsinki.

161 *Participants*

162 We included PD patients who met the United King-
 163 dom Parkinson's Disease Society Brain Bank criteria
 164 [35], and the presence of VI or VH was defined using
 165 the scale for outcomes in PD psychiatric compli-
 166 cation (SCOPA-PC) [36], together with patient and
 167 caregiver interviews. Inclusion criteria required that
 168 VI or VH had to occur at least once a week within
 169 the past 3 months. VI was defined by the false per-
 170 ception of an existing stimulus [37], while VH was
 171 defined as a visual perception in the absence of an
 172 external stimulus [24]. We only considered visual
 173 misperception as VI and we distinguished them from
 174 sense of presence and passage hallucinations. Among
 175 68 PD patients ($n=23$ PD-C; $n=22$ PD-I; $n=3$ PD-
 176 H), we excluded from our analysis six patients who
 177 reported coexisting VH and VI ($n=3$ PD-H with
 178 mild VI, and $n=3$ PD-I with mild VH), in order
 179 to avoid any confounding effect on the brain struc-
 180 tural and functional characteristics related to VI or
 181 VH (Supplementary Material Flow Diagram). We
 182 excluded patients with neurological diseases other

183 than PD or psychiatric conditions characterized by
 184 VH, patients with cognitive impairment (Montreal
 185 Cognitive Assessment (MoCA) [38] score $<21/30$)
 186 or with conditions incompatible with MRI scanning
 187 (e.g., claustrophobic, severe camptocormia, weight
 188 restrictions, congestive cardiac failure, severe dysk-
 189 inesia or tremor). Treatment with antipsychotics
 190 represented a further exclusion, as well as modifi-
 191 cations of anti-parkinsonian treatments within the
 192 month before inclusion.

193 *Clinical and neuropsychological assessments*

194 The characteristics and severity of visual hallu-
 195 cinations or illusions were assessed according to
 196 the Psycho-Sensory hAllucinations Scale (PSAS)
 197 [39]. The presence of other modalities such as
 198 sense of presence, passage hallucinations, auditory,
 199 olfactory and cenesthesia hallucinations was also
 200 noted. We assessed the duration and severity of
 201 PD (according to Movement Disorder Society -
 202 Unified Parkinson's Disease Rating Scale (MDS-
 203 UPDRS) [40] and Hoehn & Yahr stage [41], and
 204 noted the dopaminergic treatment doses (expressed as
 205 total Levodopa equivalent dose (LED)) [42], as well
 206 as other treatments users (antidepressants, benzodi-
 207 azepine, cholinesterase inhibitors, antiepileptics).

208 Cognitive profile (including Mattis dementia rat-
 209 ing scale [43], and the copy of the complex figure
 210 of Rey-Osterrieth [44]), sleep quality (Parkinson's
 211 disease sleep scale (PDSS-2) [45], probable REM
 212 Sleep Behavior Disorder (screened with REM Sleep
 213 Behavior Disorder Single-Question (RBD-1Q) [46],
 214 and excessive daytime sleepiness (Epworth scale)
 215 [47] were assessed. Subjective ophthalmological
 216 complaints (vision loss, visual field impairment,
 217 metamorphopsia, halos, diplopia, color vision com-
 218 plaint, epiphora, eye pains) were noted during a semi
 219 structured interview with an ophthalmologist. All
 220 clinical and neuropsychological assessments, as well
 221 as neuroimaging, were performed with participants
 222 on their regular antiparkinsonian treatment.

223 *Imaging acquisition and analysis*

224 *Acquisition*

225 MRI scans were performed at 3T on a General
 226 Electric (3T Discovery MR 750, GE Medical Sys-
 227 tems, Milwaukee, Wis; 32 Ch head coil, gradients:
 228 40/200, software: DV24R02) ($n=44$ patients; 17 PD-
 229 C, 15 PD-H, 12 PD-I) and a Siemens scanner (3T
 230 Magnetom Vida, Siemens Healthcare, Erlangen, Ger-
 231 many; 64 Ch head coil, hypergradients XT gradients:

Table 1

Demographical, clinical, and neuropsychological characteristics of parkinsonian patients with visual illusions, with visual hallucinations and controls

	PD-C (n = 23)	PD-I (n = 19)	PD-H (n = 20)	p
Age (y)	69.21 ± 8.76	68.31 ± 6.8	70.2 ± 7.35	0.54
Sex (M/F)	14/9	10/9	12/8	0.85
Education level (y)	17.72 ± 3.28	17.9 ± 3.71	18.95 ± 3.81	0.75
Disease duration (y)	6.21 ± 5.06	9 ± 5.33	11.15 ± 6	0.004^b
Hoehn and Yahr (score 0–21)	2.32 ± 1.00	2.5 ± 0.81	2.9 ± 0.88	0.15
MDS-UPDRS Total (score 0–260)	49.91 ± 31.01	55.94 ± 24.74	75.9 ± 31.6	0.01^b
MDS-UPDRS I (score 0–52)	8.47 ± 4.96	13.26 ± 6.02	18.25 ± 6.07	< 0.001^{a,b,c}
MDS-UPDRS II (score 0–52)	10.73 ± 8.93	13.26 ± 5.09	17.8 ± 9.1	0.01^b
MDS-IPDRS III (score 0–132)	28.69 ± 18.07	27.89 ± 14.30	33.9 ± 18.48	0.43
MDS-UPDRS IV (score 0–24)	2 ± 2.77	2.94 ± 3.23	5.95 ± 5.26	0.03^b
SCOPA-PC (score 0–21)	0.30 ± 0.55	3.45 ± 1.87	4.78 ± 3.10	< 0.001^{a,b}
PDSS (score 0–60)	10.78 ± 6.66	13.83 ± 6.34	13.65 ± 5.81	0.20
Epworth (score 0–24)	6.86 ± 4.51	8.63 ± 6.09	8.3 ± 5.62	0.55
RBD (%)	6 (26%)	8 (42%)	14 (70%)	0.01^b
Ophthalmological complaints	9 (23%)	11 (57%)	6 (30%)	0.19
PSAS (score 0–23)	0	8.63 ± 2.61	10.3 ± 3.77	< 0.001^{a,b}
Auditory hallucinations (%)	0 (0%)	0 (0%)	3 (15%)	0.056
Olfactory hallucinations (%)	0 (0%)	0 (0%)	5 (25%)	0.004^b
Cenesthetic hallucinations (%)	0 (0%)	0 (0%)	1 (5%)	0.62
Passage hallucinations (%)	0 (0%)	0 (0%)	2 (10%)	0.11
Presence sensation (%)	1 (4%)	3 (15%)	2 (10%)	0.45
LED total (mg/day)	953.49 ± 521.44	1061.36 ± 439.69	1012.79 ± 627.29	0.68
LED DA (mg/day)	143.46 ± 173.41	212.45 ± 230.09	266.17 ± 634.88	0.35
DA users (%)	15 (65%)	15 (78%)	11 (55%)	0.28
Rivastigmine users (%)	1 (4%)	0 (0%)	2 (10%)	0.50
Antiepileptic users (%)	2 (8%)	5 (26%)	3 (15%)	0.38
Antidepressant users (%)	1 (4%)	10 (52%)	8 (40%)	0.001^{a,b}
Benzodiazepine users (%)	0 (0%)	7 (36%)	6 (30%)	0.002^{a,b}
Opioid users (%)	0 (0%)	1 (5%)	0 (0%)	0.29
MoCA	25.88 ± 2.52	26.4 ± 2.74	25.53 ± 2.36	0.66
Mattis				
Total (score 0 to 144)	132.78 ± 9.98	132.78 ± 9.14	127.45 ± 9.14	0.04
Attention (score 0 to 37)	36.08 ± 0.90	35.61 ± 0.97	35.4 ± 1.81	0.36
Initiation (score 0 to 37)	32.65 ± 4.68	30.72 ± 4.46	29 ± 5.06	0.03^b
Construction (score 0 to 6)	5.69 ± 0.63	5.55 ± 0.61	5.7 ± 0.47	0.57
Conception (score 0 to 39)	36.26 ± 3.95	36.66 ± 2.95	36.4 ± 3.40	0.94
Memory (score 0 to 25)	22.08 ± 2.52	21.94 ± 2.41	20.95 ± 2.66	0.33
Rey-complex figure (score 0 to 36)	28.2 ± 10.4	27.5 ± 10.25	24.52 ± 10.18	0.20

Mattis, Mattis Dementia Rating Scale; MoCA, Montreal Cognitive Assessment (Score 0 to 30); PD-C, control patients with Parkinson's disease; PD-H, patients with Parkinson's disease and visual hallucinations; PD-I, patients with Parkinson's disease and visual illusions; PDSS, Parkinson Disease Sleep Scale; PSAS, Psychosensory Hallucinations Scale; RBD, REM sleep behavior disorder; SCOPA-PC, scale for outcomes in Parkinson's disease-psychiatric complication; Results are expressed as means ± standard deviation, and number of patients (%). The comparisons between 3 groups were performed using chi-squared or Fisher's exact tests for categorical variables and the analysis of variance (ANOVA) or Kruskal-Wallis test for quantitative parameters. When appropriate (omnibus p -value less than 0.05), a *post-hoc* test was applied for multiple comparisons (^a $p < 0.05$ between PD-I and PD-C; ^b $p < 0.05$ between PD-H and PD-C; ^c $p < 0.05$ between PD-I and PD-H).

232 60/200, software: XVA 11-A) ($n = 24$ patients; 6 PD-
 233 C, 8 PD-H, 10 PD-I), due to change of scanner at
 234 our site during the study. The precise technical char-
 235 acteristics of each sequence have been harmonized
 236 between the two scanners in order to achieve the
 237 most homogeneous imaging data possible. A partic-
 238 ular effort has been made on the definition of TR,
 239 TE, flip angle (α), bandwidth, acceleration, tempo-
 240 ral and spatial resolution, and field of view. This step

241 was carried out using a NIST test object associated
 242 with a quality control procedure to quantify various
 243 geometric and signal parameters [48]. MRI scanners,
 244 scans protocol and parameters were qualified after
 245 images quality analysis by the CATI platform (Centre
 246 d'Acquisition et de Traitement d'Images, Multicen-
 247 ter Neuroimaging Platform, Paris, France) to confirm
 248 the acquisition reproducibility. Acquisition parame-
 249 ters are detailed in the Supplementary Material.

249 *Volumetric brain analysis*

250 Pre-processing (Supplementary Material) and
 251 analysis were performed using Statistical Parametric
 252 Mapping software (SPM12, Wellcome Trust Centre
 253 for neuroimaging, London, UK, <http://www.fil.ion.ucl.ac.uk/spm/>) implemented in Matlab 2018a. A
 254 voxel-wise one-way ANOVA was performed to
 255 compare grey matter intensity across groups, with
 256 PD duration (years since symptoms onset), scanner
 257 manufacturer (Siemens or GE) and total intracra-
 258 nial volume as regressors of non-interest. Age and
 259 sex were not included as covariates since groups
 260 were matched for these variables. Statistical anal-
 261 ysis combined a p uncorrected <0.001 threshold
 262 at the voxel level and an extent threshold of 100
 263 adjacent voxels. Clusters which survived a mul-
 264 tiple comparison correction (Family Wise Error
 265 rate) $p_{FWE} < 0.05$ at the cluster level were explicitly
 266 labelled in the tables. Neuroanatomical regions of sig-
 267 nificance were visualized and identified using *xjview*
 268 toolbox (<https://www.alivelearn.net/xjview>).
 269

270 *Resting state fMRI analysis*

271 Preprocessing (Supplementary Material) and seed-
 272 based connectivity analysis were performed using
 273 Conn functional connectivity toolbox (19.b) (<http://www.nitrc.org/projects/conn>, RRID:SCR_009550)
 274 [49], which streamlines functions from SPM12.
 275 A seed-based connectivity analysis calculates the
 276 functional connectivity between a selected region of
 277 interest (ROI), the seed, with all the voxels in the
 278 brain. The analysis estimates the Fisher-transformed
 279 bivariate correlation coefficient between the seed
 280 BOLD signal and all the voxels BOLD signal
 281 across time. The following ROIs were selected (FSL
 282 Harvard-Oxford cortical/subcortical atlas, maximum
 283 probability threshold 25%, 1 mm, <https://identifiers.org/neurovault.collection:262>): putamen, caudate,
 284 lateral occipital cortex, lingual gyrus and occipital
 285 fusiform gyrus, amygdala and insula, hippocampus,
 286 precuneus and inferior/middle/superior frontal gyrus
 287 (IFG, MFG, SFG) [31–34].
 288

289 Then, we compared seed-to-voxel connectivity
 290 maps across participant groups using a general-
 291 ized linear model to perform multivariate regressions
 292 looking at contrasts between participant groups and
 293 controlling for age, duration of disease, benzo-
 294 diazepam and antidepressant treatments and MRI
 295 scanner type. We performed parametric statistical
 296 testing, for comparisons between the three groups
 297 using two-sample t -tests for between two group dif-
 298 ferences and one-way ANOVA. We calculated the
 299

uncorrected p -value and false-discovery rate, with
 statistical significance specified at $p < 0.05$.

302 *Statistical analysis of clinical data*

303 Statistical analyses were performed using Stata
 304 software version 15 (StataCorp, College Station, US).
 305 For continuous data, the assumption of normality
 306 was assessed with the Shapiro-Wilk test. The com-
 307 parison between groups for categorical data were
 308 performed using Chi-squared test and when appropri-
 309 ate Fisher's exact test, whereas the comparisons for
 310 continuous variables were carried out using ANOVA
 311 and Kruskal-Wallis test when assumptions required
 312 for ANOVA were not met. The homoscedasticity
 313 was analyzed using the Bartlett test. When appro-
 314 priate (omnibus p -value < 0.05), *post-hoc* tests for
 315 two by two multiple comparisons were applied, respec-
 316 tively Tukey-Kramer after ANOVA, Dunn's test after
 317 Kruskal-Wallis and Marascuilo procedure after Chi-
 318 squared and Fisher exact tests. All statistical tests
 319 were two-sided and a p -value < 0.05 was considered
 320 statistically significant.

321 **RESULTS**

322 *Clinical characteristics*

323 Sixty-two PD patients were analyzed for clini-
 324 cal and brain volumetric data ($n = 23$ PD-C, $n = 19$
 325 PD-I, $n = 20$ PD-H), and 58 patients analyzed for rest-
 326 ing state functional data ($n = 21$ PD-C, $n = 19$ PD-I,
 327 $n = 18$ PD-H) after exclusion of corrupted files (Sup-
 328 plementary Material Flow Diagram). Demographic
 329 and clinical characteristics of patients together with
 330 group effects are shown in Supplementary Table 1).

331 *MRI analyses*

332 *Volumetry*

333 Whole-brain voxel-based morphometry analyses
 334 revealed no grey matter volume difference between
 335 PD-I and PD-H or between PD-I and PD-C groups.
 336 Decreased volume was observed in PD-H versus PD-
 337 C in the bilateral supramarginal, middle and superior
 338 temporal gyrus, and middle occipital gyrus ($p < 0.001$
 339 uncorrected) but did not survive the multiple com-
 340 parisons correction ($p_{FWE} < 0.05$) (Supplementary
 341 Table 1 and Supplementary Figure 1).

342 *Seed-based functional connectivity at rest*

343 *Overlapping features between PD-I and PD-*
 344 *H.* PD-I and PD-H both had functional hypo-
 345 connectivity between left lingual gyrus and left

Table 2
Seed-based functional connectivity in parkinsonian patients with visual hallucinations, with illusions and controls

	P _{FDR} - CORR	K _E	P UNCORR	BETA	T	X (MM)	Y (MM)	Z (MM)		
PD-I > PD-H										
R AMYGDALA	<0.001	<0.001	408	<0.001	0.19	6.54	66	-38	-02	R MTG
	0.003	0.003	268	<0.001	0.19	5.05	8	70	-6	R Frontal pole
	0.01	0.006	223	<0.001	0.18	5.08	-58	24	20	L IFG
L AMYGDALA	0.01	0.02	205	<0.001	0.20	5.45	-58	12	24	L IFG
R HIPPOCAMPUS	<0.001	<0.001	615	<0.001	0.19	5.38	-60	8	18	L IFG (triang.)
	0.001	0.001	394	<0.001	0.17	5.28	-14	20	14	L caudate
L INSULA	0.001	0.002	358	<0.001	0.19	5.07	26	-44	-14	R temporal occipital fusiform cortex
R SFG	<0.001	<0.001	518	<0.001	0.34	5.29	52	18	22	R IFG
L IFG (TRIANG.)	0.01	0.02	239	<0.001	0.18	5.25	-66	-6	18	L post central gyrus
	0.08	0.04	145	0.005	0.12	4.53	14	-46	-4	R lingual gyrus
	0.05	0.03	165	0.03	0.19	5.36	24	-28	-4	R hippocampus
L CAUDATE	0.01	0.03	215	0.001	0.16	5.30	68	-34	-10	R MTG
PD-I > PD-C										
R SFG	<0.001	<0.001	475	<0.001	-0.08	4.23	-2	-54	30	Posterior cingulate gyrus, precuneus
	0.05	0.04	184	0.003	+0.20	5.57	+12	-22	+42	Posterior cingulate gyrus, r precentral gyrus
R LINGUAL GYRUS	0.10	0.04	135	0.006	-0.11	5.65	-40	+4	-38	L temporal pole, L temporal fusiform gyrus
L LINGUAL GYRUS	0.06	0.03	160	0.003	-0.07	-5.64	-36	-16	-30	L parahippocampal gyrus, temporal fusiform gyrus
L IFG (TRIANG)	0.03	0.03	181	0.002	0.12	5.35	-66	-10	34	L postcentral gyrus
PD-H > PD-C										
L INFERIOR LATERAL OCCIPITAL CORTEX	0.009	0.01	258	<0.001	-0.13	5.05	-16	38	10	Anterior cingulate gyrus, L paracingulate
R LINGUAL	0.01	0.01	245	<0.001	-0.14	5.55	36	2	-44	R parahippocampal gyrus, R temporal fusiform gyrus
	0.005	0.01	281	<0.001	-0.16	6.58	-42	4	36	L parahippocampal gyrus, L temporal fusiform gyrus
L LINGUAL	<0.001	<0.001	462	<0.001	-0.17	5.85	-40	-4	2	L insular cortex
	0.01	0.009	250	<0.001	-0.22	5.97	-30	-8	-42	L temporal fusiform gyrus
	0.006	0.004	268	<0.001	-0.20	5.30	36	6	-46	R temporal fusiform gyrus

IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; K_E, cluster size; L, left; PD-C, Parkinson's disease without illusions or hallucinations; MTG, middle temporal gyrus; PD-H, Parkinson's disease with visual hallucinations; PD-I, Parkinson's disease with visual illusions; pFDR, *p* corrected for multiple comparisons using the false discovery rate; pFWE, *p* corrected for multiple comparisons using the family wise error; puncorr, *p* uncorrected; R, right; SFG, superior frontal gyrus; STG, superior temporal gyrus; Triang, triangularis; Beta values, represent Fisher-transformed correlation coefficient values: for the PD-I > PD-H contrast, positive beta values suggest a stronger connectivity between the seed and these regions in PD-I compared to PD-H, while negative beta values suggest a lower connectivity between the seed and these regions in PD-I compared to PD-H; for the PD-I > PD-C contrast, positive beta values suggest a stronger connectivity between the seed and these regions in PD-I compared to PD-C, while negative beta values suggest a lower connectivity between the seed and these regions in PD-I compared to PD-C; for the PD-H > PD-C contrast, positive beta values suggest a stronger connectivity between the seed and these regions in PD-H compared to PD-C, while negative beta values suggest a lower connectivity between the seed and these regions in PD-H compared to PD-C; T values, represent the size of the difference relative to the variation in the sample data; x, y, z (mm), coordinates in MNI space. Age, disease duration, MRI manufacturer, and the presence of benzodiazepine and antidepressant treatment were included as covariates.

parahippocampal region compared to PD-C, with no difference between PD-I and PD-H (Table 2, Fig. 1).

Distinct features between PD-I and PD-H. PD-I had hyper-connectivity compared to PD-H between bilateral amygdala and bilateral IFG, between right hippocampus and left IFG and caudate, and between left insula and right temporal occipital fusiform cortex. PD-I also had hyper-connectivity between right

SFG and right IFG compared to PD-H (Table 2, Fig. 1). PD-I had functional hyper-connectivity between left IFG and left postcentral gyrus both compared to PD-H and PD-C.

PD-I had hyper-connectivity between SFG and IFG compared to PD-H. Moreover, we observed in PD-I hypo-connectivity between SFG and posterior cingulate compared to PD-C, whereas PD-H had

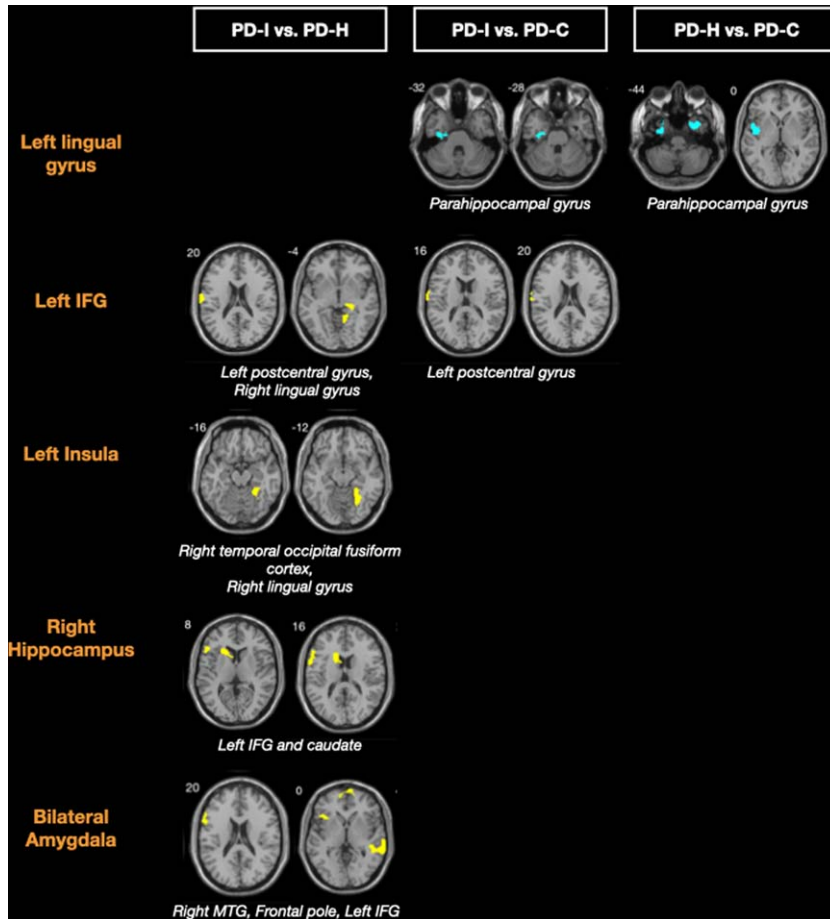


Fig. 1. Seed-based resting state functional connectivity in PD-I, PD-H, and PD-C. For each seed (orange text), differences of functional connectivity between groups are represented; yellow clusters are regions presenting hyper-connectivity with the seed and blue clusters are regions presenting hypo-connectivity with the seed. PD-I and PD-H present a common functional hypo-connectivity pattern between lingual gyrus and parahippocampal region compared to PD-C. Yet, distinct functional patterns are also revealed between VH and VI in PD. PD-I have hyper-connectivity between inferior frontal gyrus (IFG) and postcentral gyrus compared to PD-C and PD-H, and hyper-connectivity between insula and occipital fusiform cortex, and from amygdala, hippocampus towards IFG, compared to PD-H. PD-I, Parkinson's disease patients with visual illusions; PD-H, Parkinson's disease patients with visual hallucinations; PD-C, Parkinson's disease patients without visual hallucinations or illusions.

functional hyper-connectivity between ILO and anterior cingulate and paracingulate.

No other between group differences were reported for other seeds.

Average effect size for each group within clusters with significant between group differences of seed-to-voxel connectivity is represented in Fig. 2.

DISCUSSION

In this study, we compared the volumetric and seed-based functional connectivity characteristics respectively associated with VH and VI in PD. We found no significant structural differences between

PD-I and PD-H. However, PD-I and PD-H showed distinct connectivity patterns, although partially overlapping; suggesting that whilst these symptoms share some partly common neural mechanisms, they are also underpinned by specific functional brain differences.

Volumetric characteristics associated with VH and VI in PD

Using voxel-based morphometry (VBM), we observed no volumetric difference between PD-I and PD-H, nor between PD-I compared to PD-C, but found grey matter atrophy in PD-H compared to

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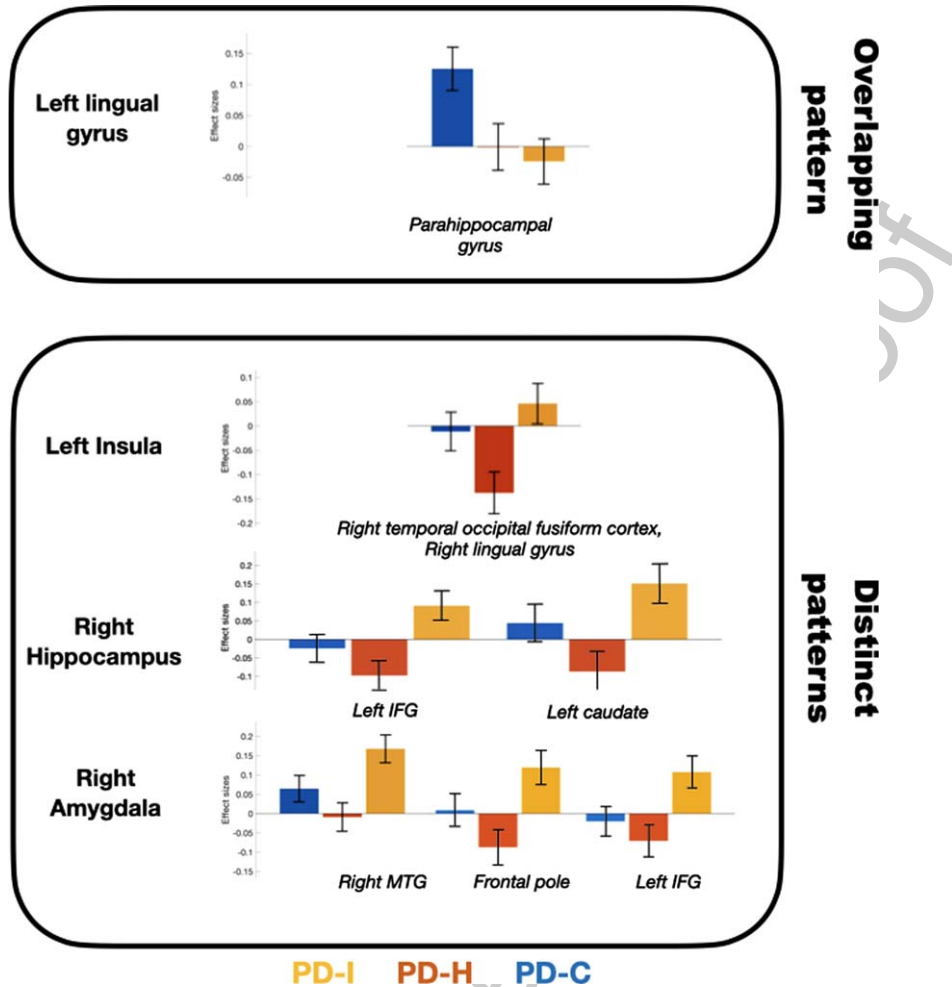


Fig. 2. Average effect sizes in each group within clusters with significant seed-to-voxel differences between PD-I and PD-H. PD-I and PD-H present a common functional hypo-connectivity pattern between lingual gyrus and parahippocampal region compared to PD-. Yet, distinct functional patterns are also revealed between VH and VI in Parkinson's disease. PD-I have hyper-connectivity between insula and occipital fusiform cortex, and from amygdala and hippocampus to IFG compared to PD-H. PD-I, Parkinson's disease patients with visual illusions; PD-H, Parkinson's disease patients with visual hallucinations; PD-C, Parkinson's disease patients without visual hallucinations or illusions.

386 PD-C in the middle occipital gyrus, and parieto-
 387 temporal gyrus, including supramarginal gyrus (un-
 388 corrected statistical threshold), indicating a greater
 389 degree of neurodegeneration in PD-H. Several other
 390 VBM studies have assessed volumetric characteris-
 391 tics associated with VH in PD, and to date, all [8–10,
 392 50–52] but one [17] have reported grey matter vol-
 393 ume differences between PD-H and PD-C, in brain
 394 regions involved in visuospatial-perception, attention
 395 control and memory [7], either using an uncorrected
 396 statistical threshold [7, 8, 52], or with correction for
 397 multiple comparisons [9, 10, 50, 51]. Structural dif-
 398 ferences between parkinsonian patients with minor
 399 VH (defined by the authors as sense of presence,
 400 passage hallucination or illusions) and those with

well-structured VH were previously investigated [4],
 suggesting partly distinct features between complex
 VH and other manifestations described as minor VH.
 However, in that study, visual illusions were not dis-
 tinguished from minor VH. Thus far, only two studies
 have specifically investigated the morphometric char-
 acteristics of PD-I compared to PD-H [22, 24], and
 reported a decrease in total gray matter volume [22,
 24] and left accumbens [22] on brain MRI associ-
 ated with the presence of VH compared to the
 presence of VI in PD, independent of age [24], or
 disease duration [22]. In those studies, including one
 conducted by our group on the same population, a
 different tool was used to perform whole brain struc-
 tural analyses (FreeSurfer), which could explain the

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apparently conflicting results compared to the current study [53, 54]. Indeed, in the current study we performed VBM (which utilizes group-wise comparisons that objectively localize focal changes in voxel values throughout the entire brain volume), whereas Freesurfer enables automatic parcellation of the brain into multiple anatomic regions and quantifies tissue volume in these predefined regions on an individual case basis. Thus, even if more widespread brain atrophy has been suggested in PD-H compared to PD-I [22], as of yet, no data suggests the existence of distinct structural changes associated respectively with VH and VI. Hereby, we are currently unable to distinguish between VH and VI according to morphometric characteristics.

Functional connectivity signatures of VH and VI in PD

While we found no VBM difference between PD-I and PD-H in this study, we identified partly overlapping and distinct resting state functional connectivity patterns associated with the presence of VH and VI in PD, independent of disease duration. These connectivity changes observed in PD-H and PD-I could reflect differential deposits of alpha-synuclein, as it has been reported that patients with synucleinopathies frequently experience hallucinations and illusionary perceptions, related to dysfunction of both associative visual areas and changes of limbic areas or the ventral striatum [55].

Common functional connectivity patterns to PD-I and PD-H from lingual gyrus

Both PD-I and PD-H presented functional hypo-connectivity between the lingual gyrus and the parahippocampal region, in line with occipital functional hypo-connectivity generally reported in PD with VH [7, 11, 56]. Hippocampal functional connectivity with the visual cortices has been previously reported to be lower in parkinsonian patients with VH [57], and as suggested by the authors, this could disrupt visuospatial memory and constitute a common functional impairment to VH and VI in PD.

Contrasting functional patterns in PD-I compared to PD-H: hyper-connectivity from IFG, amygdala, hippocampus, and insula

Some contrasting functional differences were revealed between PD-I and PD-H. PD-I compared to

PD-H and PD-C had hyper-connectivity between the inferior frontal gyrus (involved in retrieval of episodic memories) [31] and postcentral gyrus. PD-I also had increased connectivity compared to PD-H from the amygdala and hippocampus to the IFG, and from the insula to the occipital fusiform cortex, as well as between SFG and IFG.

Hyper-connectivity between IFG and amygdala, encoding positive and negative emotional memories [58, 59], suggests that emotional memory could influence and modify reality monitoring of an existing visual stimulus in PD with VI. Supporting this hypothesis, pronounced functional connectivity between the amygdala, hippocampus, and right IFG has been reported during autobiographical retrieval in the healthy population [31, 60]. Our findings suggest that VI in PD could be associated with a strong influence of anxiety and fears, and prior experiences on interpretation of visual stimuli, as well as hyperacute reality monitoring, consistently with hyper-connectivity between the insula (involved in the detection of salient stimuli) [61] and the occipital cortex.

Contrasting functional connectivity towards cingulate regions in PD-I and PD-H

Divergent patterns of connectivity between towards the cingulate were also observed in PD-I to PD-C: PD-H had hyper-connectivity from ILO with the anterior cingulate and the anterior paracingulate region compared to PD-C, whilst PD-I had hypo-connectivity from SFG with the posterior cingulate compared to PD-C.

The cingulate cortex has a crucial role in the emergence of VH in PD [62], and it was recently reported that access to consciousness in PD with VH was associated with hypoactivation in the cingulate, suggesting impaired involvement of attentional processing [63]. In particular, the anterior cingulate has a role in focusing attention on behaviorally relevant stimuli [64], whereas the posterior cingulate cortex has a central role in supporting internally-directed cognition, such as autobiographical memories retrieval and conscious awareness [65], and could be differentially involved in VI and VH.

The lateral occipital cortex is a well-known processing center for object recognition [66], and has been reported to activate in fMRI studies in response to pictures of objects, independently of image feature or familiarity [67]. Interestingly, previous neuroimaging studies using regional cerebral

512 blood flow concluded that the inferior lateral temporal
513 cortex (particularly fusiform gyrus), was the region
514 most likely responsible for the complex visual hallucinations reported in Charles Bonnet Syndrome [68].
515 As proposed by the authors, visual loss due to eye
516 pathology in Charles Bonnet Syndrome patients, produces a state of sensory deprivation that releases the
517 visual cortex from regulation by external stimuli that normally has an inhibitory effect on the endogenous
518 activation of the visual cortex. Such a cortical release
519 phenomenon could also occur in PD-H patients secondary to retinal impairment [22], and result in
520 visual hallucinations. Furthermore, reduced activity
521 of the superior frontal gyrus has been demonstrated in
522 healthy individuals who are prone to psychosis [33],
523 and in patients with schizophrenia [69]. Contrasting
524 connectivity between cingulate, SFG and ILO could
525 represent distinct neural mechanisms leading to VH
526 or to VI in PD.
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531 *Visual and non-visual hallucinations*

532 A significant proportion of PD patients with visual
533 hallucinations also had olfactory hallucinations, and
534 one might argue that it may have play a role in the specific pattern of functional alterations observed in the
535 PD-H group. Yet, olfactory, tactile and gustatory hallucinations usually coexist with VH in PD [70] and in
536 other conditions such as schizophrenia [71, 72], and probably involve the alteration of common pathways
537 responsible for reality monitoring. Indeed, a previous
538 longitudinal study showed that whilst visual hallucinations in isolation are classic in early PD, nonvisual
539 hallucinations emerge over time, and the combination
540 of visual with nonvisual hallucinations predominates
541 in later stages of PD [73]. Moreover, the presence
542 of visual/auditory hallucinations and sex has been
543 reported recently to be the main variables predicting
544 the presence of olfactory hallucinations [74], without
545 any association with olfactory impairment [74,
546 75]. Thus, hallucinations in PD may occur in one or
547 multiple sensory modalities, and a common brain network
548 responsible for hallucinations independent of
549 the sensory modality has been suggested by previous
550 studies [76]. In line with this hypothesis, a previous
551 study compared PD patients with one versus multiple
552 hallucinatory modalities, and did not reveal any
553 difference regarding demographic, clinical and medication
554 parameters [72]. Interestingly, we found that
555 other sensory modalities of hallucinations are only
556 reported in PD patients with visual hallucinations and
557 not in PD patients with illusions, thus appearing to

562 be part of a common clinical spectrum related to the
563 functional alterations reported in our results.

564 *Limitations*

565 Our study has several limitations that should be
566 considered when interpreting the results. First, our
567 study is ancillary, and analyses were conducted in
568 a sample whose size was calculated for a previous
569 analysis focusing on retinal thickness. Thus, the sample
570 size may have been too small to identify VBM
571 differences between PD-I and PD-C. However, 62
572 parkinsonian patients were included in our functional
573 data analysis, which is higher than the majority of
574 previous functional neuroimaging studies on parkinsonian
575 patients with VH [7]. Another limitation of
576 this study is the difficulty to distinguish VI from
577 minor hallucinations such as passage hallucinations
578 and sensation of presence. Presence hallucinations
579 could be identified, during patients and caregiver
580 interview, as they are closer to a delusional idea
581 or a social hallucination and defined by the belief
582 that a person is present behind oneself generally, but
583 without associated visual perception. Though, distinguishing
584 VI from passage hallucination can be challenging since
585 it depends on the patient's ability to determine whether
586 there was or not a real visual external stimulation. More
587 precise clinical criteria need to be developed in the future
588 in order to better classify these minor manifestations and
589 illusions. It should also be acknowledged that VI and VH
590 are dynamic phenomena that were not occurring during
591 the scans, even if patients had frequent and recent
592 VI and VH at the moment of inclusion in this study.
593 Thus, functional resting state analysis shows brain
594 patterns at rest that could predispose to the occurrence
595 of VI or VH in PD but does not allow to capture
596 neural activation patterns occurring during an actual
597 hallucinatory/illusory event.
598

599 **CONCLUSION**

600 We show both overlapping and distinct functional
601 signatures related to VI versus VH in PD patients.
602 This advances our current comprehension of illusions
603 and hallucinations in PD, which have to date been
604 limited to considering these phenomena as representing
605 a clinical spectrum from simple to complex hallucinations.
606 Understanding the plurality of the structural and functional
607 characteristics underlying VI and VH in PD may enlighten
608 how these two forms of perceptual experiences overlap
609 and are distinct in

their specific neural dysfunction, which may inform clinical prognosis. Hence longitudinal studies focusing on structural and functional alterations in PD with VI and VH should provide greater insight into the natural history of these phenomena.

ACKNOWLEDGMENTS

This work was funded by Fondation de France (n°76354).

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JPD212838>.

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