

1 Exploring Bottom-Up Visual Processing and Visual Hallucinations in 2 Parkinson's Disease with Dementia

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19 Abstract

20 Visual hallucinations (VH) are a common symptom of Parkinson's disease with dementia (PDD),
21 affecting up to 65% of cases. Integrative models of their etiology posit that a decline in executive
22 control of the visuo-perceptual system is a primary mechanism of VH generation. The role of
23 bottom-up processing in the manifestation of VH in this condition is still not clear. Here we
24 compared amplitude and latency patterns of reversal visual evoked potentials (VEPs) in healthy
25 controls (n=21) and PDD patients (n = 34) with a range of VH severities. PDD patients showed
26 increased N2 latency relative to controls, but patients reporting complex VH (n=17) did not
27 demonstrate any relationship between VEP measurements and their hallucination severity as
28 measured on the neuropsychiatric inventory hallucinations subscale (NPIHal) score. Our VEP
29 findings support previous reports of declining visual system physiology in PDD. However, no
30 notable major relationships between the integrity of the visual pathway and VH were found.

31 **1 Introduction**

32 Visual symptoms are common in Parkinson's disease (PD), and include double vision, dry or painful
33 eyes, poor contrast sensitivity, problems with color vision, and blurring of vision or lowered acuity
34 (Biousse et al., 2004; Davidsdottir et al., 2005; Archibald et al., 2009; Urwyler et al., 2014; Weil et
35 al., 2016). Such problems have been linked to the physical decline of retinal function over the course
36 of disease development with depletion of retinal dopamine (Nguyen-Legros, 1988), and retinal nerve
37 fiber layer thinning (Lee et al., 2014). Electrophysiological measures of visual health, such as the
38 visual evoked potential (VEP), and the electroretinogram (ERG), have been widely used to support
39 the diagnosis of PD as indirect measures of health and integrity of early bottom-up visual processing
40 pathways. Measurements of scalp potentials, as well as scotopic alpha and beta waves generated on
41 the retina during foveal stimulation typically demonstrate a slowing of peak activity in PDD patients
42 relative to controls (Bodis-Wollner and Yahr, 1978; Calzetti et al., 1990; Nowacka et al., 2015),
43 acting as indirect support for pathological evidence of a decline in pre-geniculate visual function
44 (Nguyen-Legros, 1988; Lee et al., 2014).

45 In 45% of PD cases without dementia (Aarsland et al., 1999; Fénelon et al., 2000), and up to 65% of
46 cases with dementia (PDD) (McKeith et al., 2005), patients will also experience visual hallucinations
47 (VH). The early presence of VH is a strong predictor of cognitive decline (Aarsland et al., 2003), as
48 well as increased mortality and overall reduced quality of life for patients and their carers (Goetz and
49 Stebbins, 1993; 1995). Models of VH in Lewy body dementias (including dementia with Lewy
50 bodies (DLB), and PDD) have posited that VH are a product of the inefficient integration of multiple
51 perceptual sub-divisions of the visual system (Collerton et al., 2005; Shine et al., 2011). The
52 framework for healthy visual perception involves the prediction of sensory inputs expected from the
53 salient features of images (based upon long-term memory of similar images and current context)
54 which are then matched to the actual sensory inputs to minimize any discrepancy between the two.
55 Thus, perception needs to balance predictions and sensory information. Impairments in cognitive
56 control across executive networks in PDD lead to difficulties balancing these processes, thus
57 impairing the accuracy of matching the visual input to expectations. Despite the precise etiology of
58 VH being unclear, variations in the frequency of visual hallucinations over the course of disease
59 progression suggests that these hallucinations reflect a complex relationship between declining
60 sensory function and dysfunctional predictions (Collerton et al., 2005; Onofri et al., 2007; Fenelon,
61 2008; Llebaria et al., 2010; Sanchez-Castaneda et al., 2010; Shine et al., 2011).

62 In this investigation we sought to characterize the components of early bottom-up processing in PDD
63 patients, using the pattern reversal visual evoked potential, and to relate the response features to the
64 complexity of the VHs experienced. Based on available evidence of physiological decline in PDD we
65 predicted that we would observe a general reduction in the amplitude of the VEP components, as
66 well as an increase in the P1 latency (Matsui et al., 2005). In addition we expected baseline visual
67 acuity and visual perception, to demonstrate a decline in those with a more severe and frequent
68 complex VH. This should also extend to an association between VEP P1 and N2 measurements with
69 VH experience, as both of these are thought to be contingent upon attentional and perceptual
70 processes (Haider et al., 1964; Luck 2005), which are, in particular, disrupted by Lewy body
71 pathology (Shine et al., 2011; Taylor et al., 2011).

72 **2 Methods**

73 **2.1 Participants**

74 A total of 21 healthy controls, and 38 Parkinson's disease with dementia (PDD) patients were
75 recruited from the North East of England. Ethical approval was granted by the Newcastle National
76 Health Service (NHS) Health Research Authority (HRA) (REC reference: 13/NE/0252; R&D
77 reference: 6691). The diagnosis of PDD was confirmed by two independent and experienced
78 clinicians (Charlotte Allan, John-Paul Taylor) and met with the standards described in the
79 international PD diagnostic criteria (Emre et al., 2007). Participants were excluded from the study if
80 baseline assessment revealed the presence of comorbid factors including stroke, non-PD related
81 dementia, and/or visual dysfunction secondary to glaucoma. All procedures related to the study were
82 explained to the participants and written informed consent was obtained prior to participation.

83 **2.2 Clinical assessments**

84 All participants were assessed on their level of global cognitive function using the Mini Mental State
85 Exam, (MMSE, (Folstein et al., 1975); maximum score of 30) and the Cambridge Cognitive Test
86 Battery (CAMCOG total score, (Roth et al., 1986; Roth et al., 1988); maximum score of 107). Motor
87 function was assessed using the total (left and right) score from the Unified Parkinson's disease
88 rating scale section three (UPDRS-III, (Fahn et al. 1987); maximum score of 57).

89 The integrity of the participant's visual acuity was assessed using a detailed screening questionnaire,
90 computerized Freiburg acuity testing (Bach, 1996), and the LOGMAR (Logarithm of the Minimum
91 Angle of Resolution) scale of visual acuity. Visuo-perceptual function was assessed using
92 performance on motion sensitivity, (Wood et al., 2013), angle discrimination (Wood et al., 2013),
93 and performance on the pareidolic imagery test (Uchiyama et al., 2012).

94 **2.3 Visual Hallucinations**

95 The hallucination subscale of the Neuropsychiatric Inventory (NPIHal) (Cummings et al., 1994) was
96 used for assessing VH occurring in the previous month, with the NPIHal score (frequency × severity
97 of hallucinations) derived as a measure. For reliability, patients and carers were independently asked
98 about the occurrence of VH in the month before using the North-East Visual Hallucinations
99 Interview (NEVHI) (Mosimann et al., 2008). Any discrepancies in the reporting of VH (Urwyler et
100 al., 2015) were discussed with both parties and the assessor, with reformulation of NPIHal scores
101 (wherever the patient seemed to lack insight, primacy was given to caregiver opinion).

102 Participants were classed as active visual hallucinators (PD-VH, n=17) if they had complex VH in
103 the month preceding their interview; otherwise, they were classed as non-hallucinators (controls
104 (n=21) and PD-NVH(n=17)). Participants with minor VH (e.g., passage or feeling of presence) but
105 no complex VH in the last month were included in the PD-NVH group. This distinction was made
106 due to the different etiologic basis to complex VH even though minor VH typically precede complex
107 VH. Patients in this study map onto the same categories used in previously published research from
108 our lab (see Firbank et al., 2018).

109 **2.4 EEG**

110 **2.4.1 Visual Evoked Potential Presentation and Recording**

111 The VEP adhered to the specifications proposed by the International Society for Clinical
112 Electrophysiology of Vision (Odom et al., 2010) (ISCEV). Participants viewed a black and white
113 checkerboard pattern whilst the checks (visual angle of 0.6°) reversed phase at a rate of 1Hz
114 (switching to the opposite phase every 500ms), for 200 sweeps, with a brief rest period (3000ms)
115 after 100 sweeps. During stimulus presentation a pink dot was placed in the center of the display as a

116 focus point, which the participant was instructed to look at. This was intended to prevent wandering
117 gaze during the check reversal and was presented on top of a grey background during the rest period.
118 The stimulus was generated on a Dell OptiPlex 755 (Microsoft Windows XP) using Matlab v2012a
119 (The MathWorks, 2012), and presented using a Dell U2412M 24-inch LCD monitor (resolution:
120 1920 x 1200 pixels refresh rate: 60Hz). Pattern reversal visual evoked potentials were recorded
121 during three separate viewing conditions (both eyes, left eye, right eye), using an ASA-LAB 136
122 system amplifier and the ASA-LAB recording software (version 4.9.1) in combination with a 128
123 Ag/AgCl channel Waveguard cap (10-5 system, (Oostenveld and Praamstra, 2001) Advanced Neuro
124 Technologies). The ground electrode was placed on the right clavicle, and Fz was used as the
125 reference electrode. Electrode impedance was kept below 5k Ω , and no filters were applied during the
126 acquisition of EEG data.

127 **2.4.2 Pre-Processing**

128 Signal processing and measurement was performed using Matlab v2012a (The MathWorks, 2012),
129 with the EEGLab (Delorme and Makeig, 2004), ERPLab (Lopez-Calderon and Luck, 2014), and
130 current source density (Kayser and Tenke, 2006) (CSD) toolboxes. Individual sweeps were split into
131 epochs of 400ms, a baseline period of 100ms prior to stimulus presentation, and a post-stimulus
132 period of 300ms. Epochs were baseline corrected using the mean of the data in the pre-stimulus
133 period and filtered using a 0.1 to 45Hz bandpass filter. Individual channels with a kurtosis value
134 greater than three standard deviations from the cap-wide mean were removed and recreated after pre-
135 processing using spherical interpolation (Perrin et al., 1989; Ferree, 2000; Delorme and Makeig,
136 2004; Ferree, 2006). After removing trials containing blinks, muscular activity, and drifting
137 potentials (impedance related artefacts), broad spatial effects of the electric field were attenuated by
138 applying a Laplacian transform (Kayser and Tenke, 2006). This approach was applied to reduce the
139 likelihood of false positives in spatially distant locations when defining the occipital region of
140 interest (ROI).

141 **2.4.3 Measurement**

142 To account for individual variance in the timing of synaptic communication the VEP components
143 were measured within windows defined by the global field power (GFP) for each individual. The
144 VEP components elicited three GFP maxima following stimulus presentation, each of which was
145 used as the center point for the corresponding component window (GFP maxima \pm 10ms). The
146 occipital ROI was defined by measuring the amplitudes of the P1 component for the grand average of
147 the control data set and using the 20 electrodes with the greatest amplitude as the limit for the ROI.
148 Individual subject measurements of peak latency and mean amplitude were taken from the average
149 VEP waveform within the occipital ROI. To account for potential inter-ocular latency differences we
150 estimated the difference between P1 peak latency measurements for the left and right eyes.

151 **2.4.4 Statistical Analysis**

152 All statistical tests were performed using the Statistical Package for the Social Sciences (SPSS,
153 version 22). Demographic and baseline factors were compared using independent samples t-tests. We
154 compared the measurements of amplitude and latency separately for each component using univariate
155 analysis of variance controlling for age and inter-ocular latency difference between the left and right
156 eyes. Effect sizes were estimated using the partial eta squared measure (η^2). To explore the
157 relationship between the variance within our physiological measurements and VH experience in the
158 hallucinating PDD group, we performed Spearman's correlations between each VEP measurement
159 and NPI hallucination subset score. To help identify any variance in our measurements accounted for
160 by clinical and/or demographic factors we performed additional Spearman's correlations between the

161 VEP measurements and each value. Significance for all tests was determined using an alpha criterion
162 of $p < 0.05$, and Bonferroni corrected for multiple comparisons (corrected alpha criterion of $p < 0.016$).
163 Where appropriate un-corrected correlations are reported to highlight trends within individual results.

164 **3 Results**

165 **3.1 Demographics & Clinical Scores**

166 Demographic results are summarized in Table 1. All groups were matched for age and there were no
167 significant differences in duration of PD or levodopa dose between the PDD-VH and PDD-NVH
168 groups. PDD patients displayed a significant reduction in global cognitive function, UPDRS motor
169 score relative to controls, with the PDD-VH group global cognitive function and motor function were
170 significantly worse when compared to the PDD-NVH group.

171 **3.2 Visual Integrity & Visual Perceptual Scores**

172 Visual acuity and perceptual scores are summarized in Table 1. There was a pattern of overall decline
173 in visual integrity within the PDD patients relative to the control group, characterized by a significant
174 reduction in decimal and LOGMAR measurements of visual acuity. As expected, PDD-VH patients
175 showed a characteristic significant increase in the number of false perceptions reported during the
176 pareidolia task compared to PDD-NVH patients.

177 **[Table 1 Here]**

178 **3.3 Visual Evoked Potential**

179 Amplitude tended to be smaller, and latency later in PDD vs controls, although this was not
180 significant, except for N2. There were no significant differences between PDD-VH vs PDD-NVH.
181 (see Table 2). Follow up simple effects analysis demonstrated that N2 latency in controls was
182 significantly less than PDD-VH ($p = .022$) and PDD-NVH group ($p = .03$), but the N2 latency did not
183 differ between the VH and NVH group.

184 **[Table 2 Here]**

185 **3.4 Clinical Correlations**

186 Visual hallucination experience, as measured using the NPIHal subscale was not significantly related
187 to the measurements of any of the VEP components. In PDD-VH patients there were no significant
188 correlations between any of the VEP measurements, demographic, and clinical factors.

189 **4 Discussion**

190 In healthy participants, the VEP reflects a combination of many pre-striate and cortical processes. It
191 is noted that a decline in visual pathway integrity following structural changes to the retina can affect
192 the latency and amplitude (Bodis-Wollner and Onofrij, 1982; Bhaskar et al., 1986; Nowacka et al.,
193 2015; Miri et al., 2016). In earlier studies the VEP has consistently been shown to be affected by PD
194 neuropathology, indicating substantial decline in the quality of bottom-up visual processing
195 (Archibald et al., 2009; Bodis-Wollner & Yahr, 1978; Nowacka et al., 2015). Following the
196 hypothesis that disrupted bottom-up processing of visual input is associated with the generation of
197 VH in PDD we investigated whether the VEP could be used as a marker of hallucination
198 symptomology.

199 In accordance with previous research (Mosimann et al., 2004; Emre et al., 2007; Archibald et al.,
200 2009; Possin, 2010; Landy et al., 2015) the PDD patients demonstrated a reduction in visual acuity,
201 impaired visual perception, impoverished motor ability, and compromised global cognition. Analysis
202 of the pattern reversal VEP data revealed a significant increase in the PDD N2 latency relative to
203 controls, especially in PDD-VH, and non-significant reduction in the PDD P1 amplitude. P1 and N2
204 (N140) are both linked to physical properties of the stimulus such as luminance, brightness, position
205 on the retina, and associated attentional demands (Van Voorhis and Hillyard, 1977; Hillyard and
206 Munte, 1984; Luck et al., 1994; Johannes et al., 1995; Ito and Gilbert, 1999; Johannes et al., 2003).
207 Further, the N2 (N140) has been reported to be associated with increased disease severity (Talebi et
208 al, 2014). In patients with PDD there are often abnormalities associated with the structure and
209 function of the retina, including changes in morphology and dopaminergic signaling (Archibald et al.,
210 2009), which have previously been linked to reduced conduction velocity in early visual processing
211 (Regan and Neima, 1984; Bodis-Wollner et al., 1987; Jones et al., 1992; Price et al., 1992; Pieri et
212 al., 2000; Holroyd et al., 2001; Nowacka et al., 2015). Source localization of these components
213 places the generating sources deep within the secondary visual cortex (Di Russo et al., 2002; Di
214 Russo et al., 2005); although their cognitive associations suggest that their activity is governed as
215 part of a higher order visual processing network. Given the lack of association between the VEP
216 components and clinical measurements in our study it is unclear what relationship exists between the
217 primary visual cortex and its bottom-up and top-down inputs in this context. However, our
218 experimental design is limited in the scope to which we can draw conclusions on the nature of
219 pathological change within the executive system and the link between attention and passive
220 perception of the VEP stimulus.

221 In the context of a mechanism for VH, our sample results suggest that bottom-up processing is not
222 differentially affected between hallucinators and non-hallucinators. This is not unexpected as it
223 follows that in an integrative model of VH we would expect VH content to stem from the interaction
224 of impaired bottom-up processing with dysfunctional top-down control of perception. In our data,
225 complex VH were associated with greater decline in CAMCOG, and UPDRS scores, as well as
226 increased numbers of pareidolia relative to patients without complex VH. The divergence in the
227 cognitive and perceptual profile of the groups supports a deteriorated capacity for effective top-down
228 control, which in this model would be a pre-requisite factor for the generation of complex VH.
229 However, these measures were not significantly correlated with the amplitude or latency of the VEP
230 component measurements suggesting that conduction velocity and basic processing of visual feature
231 information is unimpeded by the integrity of detailed perceptual processing.

232 Within the integrative model of complex VH in Lewy body dementias the importance of bottom-up
233 processing is thought to be its influence on the generation of proto-objects (Collerton et al., 2005;
234 Shine et al., 2011). The frequency and phenomenology of the VH would then depend on the
235 interaction between the executive system and the perceptual processing centers. Therefore, declining
236 visual health and perceptual quality might simply place the individual in an at-risk state for VH
237 development (Firbank et al., 2018) rather than directly impact their generation. Further research is
238 required to model the way pathological effects on top-down processing interact with declining visual
239 health.

240 **4.1 Limitations**

241 There are several limitations. Firstly, the sample size within this study was relatively small.
242 Secondly, we used only a single subjective measure for VH severity. The NPI items are typically
243 collected from the carers of the patient, and do not ask questions about the content of the

244 hallucination. It thus remains possible that there could be a relationship between visual health,
245 bottom-up processing, and VH content that could be accessed by quantifying a scale such as the
246 North East Visual Hallucination Interview (NEVHI) (Mosimann et al., 2008). Furthermore, the range
247 of VH severity scores in our groups was limited making correlative analyses more difficult.

248 **4.2 Conclusion**

249 In summary, PDD patients demonstrated a diminished profile for visual information processing by
250 way of lowered acuity and reduced visual integrity. This was partially reflected in the outcome of the
251 VEP components, although the broad lack of significant differences between PDD-VH, PDD-NVH,
252 and healthy controls implies that bottom-up visual information processing remains reasonably intact.
253 Our findings support a separation between bottom-up information processing and the mechanism of
254 complex VH generation, and instead imply that the reduced visual integrity might act to place the
255 individual in an at risk state for the development of hallucinations in patients with a deteriorated
256 cognitive profile. Future work should focus on a multimodal approach to understanding the
257 interactions between top-down and bottom-up perceptual circuitry and how this is impacted by PDD
258 neuropathology.

259 **5 Conflict of Interest**

260 The authors declare that this research was conducted in the absence of commercial or financial
261 relationships that could be construed as potential conflicts of interest.

262 **6 Author contributions**

263 NM, SG, LR, CA, DC, and J-PT contributed to the conception and organization of the research. NM
264 and AK participated in the execution and data collection. NM, PU and MF designed and
265 implemented the data analysis and interpretation. NM and PU wrote the first draft of the manuscript.
266 All authors approved the final version of this manuscript.

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275 of the pareidolia task.

276 **9 Data Availability**

277 Data pertaining to the obtained results may be provided upon request.

278 **10 Figure Captions**

279 Table 1 | Participant demographics and clinical scores. Data are mean \pm standard deviation. Statistical
280 tests: : Univariate analysis of variance (ANOVA), p-value 2 sided <0.05 significant; PD =

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281 Parkinson's disease, PDD = Parkinson's disease dementia, MMSE = Mini-Mental State Examination,
282 CAMCOG = Cambridge Cognitive Assessment, UPDRS = Unified Parkinson's Disease Rating
283 Scale, HC = Healthy Controls, VH = Visual Hallucination, NVH= No Visual Hallucination; Tests
284 reported used univariate ANOVA with partial eta squared effect size, except for Levodopa, age at
285 onset, duration of PD, and NPI Hal total which used independent samples t-tests and Cohen's D
286 effect sizes.

287 Table 2 | Comparison of the visual evoked potential component (N1, P1 and N2) amplitude and
288 latency. Data are mean \pm standard deviation. Statistical tests: Univariate analysis of variance
289 (ANOVA), df=52, p-value 2 sided <0.05 significant; PDD = Parkinson's disease dementia; HC =
290 Healthy Controls; VH = Visual Hallucination; NVH= No Visual Hallucination; * Posthoc = VH>HC,
291 NVH>HC;

292 **11 References**

- 293 Aarsland, D., Andersen, K., Larsen, J.P., Lolk, A., and Kragh-Sorensen, P. (2003). Prevalence and
294 characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol* 60(3),
295 387-392. doi: 10.1001/archneur.60.3.387.
- 296 Aarsland, D., Larsen, J.P., Karlsen, K., Lim, N.G., and Tandberg, E. (1999). Mental symptoms in
297 Parkinson's disease are important contributors to caregiver distress. *Int J Geriatr Psychiatry* 14(10),
298 866-874.
- 299 Archibald, N.K., Clarke, M.P., Mosimann, U.P., and Burn, D.J. (2009). The retina in Parkinson's
300 disease. *Brain* 132(Pt 5), 1128-1145. doi: 10.1093/brain/awp068.
- 301 Bach, M. (1996). The Freiburg Visual Acuity test--automatic measurement of visual acuity. *Optom*
302 *Vis Sci* 73(1), 49-53. doi: 10.1097/00006324-199601000-00008.
- 303 Bhaskar, P.A., Vanchilingam, S., Bhaskar, E.A., Devaprabhu, A., and Ganesan, R.A. (1986). Effect
304 of L-dopa on visual evoked potential in patients with Parkinson's disease. *Neurology* 36(8), 1119-
305 1121. doi: 10.1212/wnl.36.8.1119.
- 306 Biousse, V., Skibell, B.C., Watts, R.L., Loupe, D.N., Drews-Botsch, C., and Newman, N.J. (2004).
307 Ophthalmologic features of Parkinson's disease. *Neurology* 62(2), 177-180.
- 308 Bodis-Wollner, I., Marx, M.S., Mitra, S., Bobak, P., Mylin, L., and Yahr, M. (1987). Visual
309 dysfunction in Parkinson's disease. Loss in spatiotemporal contrast sensitivity. *Brain* 110 (Pt 6),
310 1675-1698. doi: 10.1093/brain/110.6.1675.
- 311 Bodis-Wollner, I., and Onofrj, M. (1982). System diseases and visual evoked potential diagnosis in
312 neurology: changes due to synaptic malfunction. *Ann N Y Acad Sci* 388, 327-348. doi:
313 10.1111/j.1749-6632.1982.tb50800.x.
- 314 Bodis-Wollner, I., and Yahr, M.D. (1978). Measurements of visual evoked potentials in Parkinson's
315 disease. *Brain* 101(4), 661-671. doi: 10.1093/brain/101.4.661.
- 316 Calzetti, S., Franchi, A., Taratufolo, G., and Groppi, E. (1990). Simultaneous VEP and PERG
317 investigations in early Parkinson's disease. *J Neurol Neurosurg Psychiatry* 53(2), 114-117. doi:
318 10.1136/jnnp.53.2.114.
- 319 Collerton, D., Perry, E., and McKeith, I. (2005). Why people see things that are not there: a novel
320 Perception and Attention Deficit model for recurrent complex visual hallucinations. *Behav Brain Sci*
321 28(6), 737-757; discussion 757-794. doi: 10.1017/S0140525X05000130.
- 322 Cummings, J.L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D.A., and Gornbein, J.
323 (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia.
324 *Neurology* 44(12), 2308-2314.
- 325 Davidsdottir, S., Cronin-Golomb, A., and Lee, A. (2005). Visual and spatial symptoms in Parkinson's
326 disease. *Vision Res* 45(10), 1285-1296. doi: 10.1016/j.visres.2004.11.006.

- 327 Delorme, A., and Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial
328 EEG dynamics including independent component analysis. *J Neurosci Methods* 134(1), 9-21. doi:
329 10.1016/j.jneumeth.2003.10.009.
- 330 Di Russo, F., Martinez, A., Sereno, M.I., Pitzalis, S., and Hillyard, S.A. (2002). Cortical sources of
331 the early components of the visual evoked potential. *Hum Brain Mapp* 15(2), 95-111. doi:
332 10.1002/hbm.10010.
- 333 Di Russo, F., Pitzalis, S., Spitoni, G., Aprile, T., Patria, F., Spinelli, D., et al. (2005). Identification of
334 the neural sources of the pattern-reversal VEP. *Neuroimage* 24(3), 874-886. doi:
335 10.1016/j.neuroimage.2004.09.029.
- 336 Emre, M., Aarsland, D., Brown, R., Burn, D.J., Duyckaerts, C., Mizuno, Y., et al. (2007). Clinical
337 diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord* 22(12), 1689-1707;
338 quiz 1837. doi: 10.1002/mds.21507.
- 339 Fahn, S., Elton, R., and Committee, M.o.t.U.D. (1987). "The Unified Parkinson's Disease Rating
340 Scale," in *Recent Developments in Parkinson's Disease*, eds. S. Fahn, C.D. Marsden, D.B. Calne &
341 M. Goldstein. (Florham Park, NJ: Macmillan Health Care Information), 153-163
- 342 Fénelon, G. (2008). Psychosis in Parkinson's disease: phenomenology, frequency, risk factors, and
343 current understanding of pathophysiologic mechanisms. *CNS Spectr* 13(3 Suppl 4), 18-25. doi:
344 10.1017/s1092852900017284.
- 345 Fénelon, G., Mahieux, F., Huon, R., and Ziegler, M. (2000). Hallucinations in Parkinson's disease:
346 prevalence, phenomenology and risk factors. *Brain* 123, 733-745.
- 347 Ferree, T.C. (2000). "Spline Interpolation of the Scalp EEG." . *Electical Geodesics, Inc.*).
- 348 Ferree, T.C. (2006). Spherical splines and average referencing in scalp electroencephalography.
349 *Brain Topogr* 19(1-2), 43-52. doi: 10.1007/s10548-006-0011-0.
- 350 Firbank, M.J., Parikh, J., Murphy, N., Killen, A., Allan, C.L., Collerton, D., et al. (2018). Reduced
351 occipital GABA in Parkinson disease with visual hallucinations. *Neurology* 91(7), e675-e685. doi:
352 10.1212/WNL.0000000000006007.
- 353 Folstein, M.F., Folstein, S.E., and McHugh, P.R. (1975). "Mini-mental state". A practical method for
354 grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12(3), 189-198. doi:
355 10.1016/0022-3956(75)90026-6.
- 356 Goetz, C.G., and Stebbins, G.T. (1993). Risk factors for nursing home placement in advanced
357 Parkinson's disease. *Neurology* 43(11), 2227-2229.
- 358 Goetz, C.G., and Stebbins, G.T. (1995). Mortality and hallucinations in nursing home patients with
359 advanced Parkinson's disease. *Neurology* 45(4), 669-671. doi: 10.1212/wnl.45.4.669.
- 360 Haider, M., Spong, P., and Lindsley, D.B. (1964). Attention, Vigilance, and Cortical Evoked-
361 Potentials in Humans. *Science* 145(3628), 180-182. doi: 10.1126/science.145.3628.180.

- 362 Hillyard, S.A., and Munte, T.F. (1984). Selective attention to color and location: an analysis with
363 event-related brain potentials. *Percept Psychophys* 36(2), 185-198. doi: 10.3758/bf03202679.
- 364 Holroyd, S., Currie, L., and Wooten, G.F. (2001). Prospective study of hallucinations and delusions
365 in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 70(6), 734-738. doi: 10.1136/jnnp.70.6.734.
- 366 Ito, M., and Gilbert, C.D. (1999). Attention modulates contextual influences in the primary visual
367 cortex of alert monkeys. *Neuron* 22(3), 593-604. doi: 10.1016/s0896-6273(00)80713-8
- 368 Johannes, S., Munte, T.F., Heinze, H.J., and Mangun, G.R. (1995). Luminance and spatial attention
369 effects on early visual processing. *Brain Res Cogn Brain Res* 2(3), 189-205. doi: 10.1016/0926-
370 6410(95)90008-x.
- 371 Johannes, S., Wieringa, B.M., Nager, W., Rada, D., Muller-Vahl, K.R., Emrich, H.M., et al. (2003).
372 Tourette syndrome and obsessive-compulsive disorder: event-related brain potentials show similar
373 mechanisms [correction of mechanisms] of frontal inhibition but dissimilar target evaluation
374 processes. *Behav Neurol* 14(1-2), 9-17. doi: 10.1155/2003/326468.
- 375 Jones, R.D., Donaldson, I.M., and Timmings, P.L. (1992). Impairment of high-contrast visual acuity
376 in Parkinson's disease. *Mov Disord* 7(3), 232-238. doi: 10.1002/mds.870070308.
- 377 Kayser, J., and Tenke, C.E. (2006). Principal components analysis of Laplacian waveforms as a
378 generic method for identifying ERP generator patterns: I. Evaluation with auditory oddball tasks.
379 *Clin Neurophysiol* 117(2), 348-368. doi: 10.1016/j.clinph.2005.08.034.
- 380 Landy, K.M., Salmon, D.P., Galasko, D., Filoteo, J.V., Festa, E.K., Heindel, W.C., et al. (2015).
381 Motion discrimination in dementia with Lewy bodies and Alzheimer disease. *Neurology* 85(16),
382 1376-1382. doi: 10.1212/WNL.0000000000002028.
- 383 Lee, J.Y., Kim, J.M., Ahn, J., Kim, H.J., Jeon, B.S., and Kim, T.W. (2014). Retinal nerve fiber layer
384 thickness and visual hallucinations in Parkinson's Disease. *Mov Disord* 29(1), 61-67. doi:
385 10.1002/mds.25543.
- 386 Llebaria, G., Pagonabarraga, J., Martinez-Corral, M., Garcia-Sanchez, C., Pascual-Sedano, B.,
387 Gironell, A., et al. (2010). Neuropsychological correlates of mild to severe hallucinations in
388 Parkinson's disease. *Mov Disord* 25(16), 2785-2791. doi: 10.1002/mds.23411.
- 389 Lopez-Calderon, J., and Luck, S.J. (2014). ERPLAB: an open-source toolbox for the analysis of
390 event-related potentials. *Front Hum Neurosci* 8, 213. doi: 10.3389/fnhum.2014.00213.
- 391 Luck, S.J. (2005). *An Introduction to the Event-Related Potential Technique*. Massachusetts Institute
392 of Technology, Cambridge, Massachusetts: The MIT Press.
- 393 Luck, S.J., Hillyard, S.A., Mouloua, M., Woldorff, M.G., Clark, V.P., and Hawkins, H.L. (1994).
394 Effects of spatial cuing on luminance detectability: psychophysical and electrophysiological evidence
395 for early selection. *J Exp Psychol Hum Percept Perform* 20(4), 887-904. doi: 10.1037//0096-
396 1523.20.4.887.
- 397

- 398 Matsui, H., Udaka, F., Tamura, A., Oda, M., Kubori, T., Nishinaka, K., et al. (2005). The relation
399 between visual hallucinations and visual evoked potential in Parkinson disease. *Clin Neuropharmacol*
400 28(2), 79-82. doi: 10.1097/01.wnf.0000157066.50948.65
- 401 McKeith, I.G., Dickson, D.W., Lowe, J., Emre, M., O'Brien, J.T., Feldman, H., et al. (2005).
402 Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium.
403 *Neurology* 65(12), 1863-1872. doi: 10.1212/01.wnl.0000187889.17253.b1.
- 404 Miri, S., Glazman, S., Mylin, L., and Bodis-Wollner, I. (2016). A combination of retinal morphology
405 and visual electrophysiology testing increases diagnostic yield in Parkinson's disease. *Parkinsonism*
406 *Relat Disord* 22 Suppl 1, S134-137. doi: 10.1016/j.parkreldis.2015.09.015.
- 407 Mosimann, U.P., Collerton, D., Dudley, R., Meyer, T.D., Graham, G., Dean, J.L., et al. (2008). A
408 semi-structured interview to assess visual hallucinations in older people. *International journal of*
409 *geriatric psychiatry* 23(7), 712-718. doi: 10.1002/gps.1965.
- 410 Mosimann, U.P., Mather, G., Wesnes, K.A., O'Brien, J.T., Burn, D.J., and McKeith, I.G. (2004).
411 Visual perception in Parkinson disease dementia and dementia with Lewy bodies. *Neurology* 63(11),
412 2091-2096. doi: 10.1212/01.wnl.0000145764.70698.4e.
- 413 Nguyen-Legros, J. (1988). Functional neuroarchitecture of the retina: hypothesis on the dysfunction
414 of retinal dopaminergic circuitry in Parkinson's disease. *Surg Radiol Anat* 10(2), 137-144. doi:
415 10.1007/bf02307822.
- 416 Nowacka, B., Lubinski, W., Honczarenko, K., Potemkowski, A., and Safranow, K. (2015).
417 Bioelectrical function and structural assessment of the retina in patients with early stages of
418 Parkinson's disease (PD). *Doc Ophthalmol* 131(2), 95-104. doi: 10.1007/s10633-015-9503-0.
- 419 Odom, J.V., Bach, M., Brigell, M., Holder, G.E., McCulloch, D.L., Tormene, A.P., et al. (2010).
420 ISCEV standard for clinical visual evoked potentials (2009 update). *Doc Ophthalmol* 120(1), 111-
421 119. doi: 10.1007/s10633-009-9195-4.
- 422 Onofrij, M., Thomas, A., and Bonanni, L. (2007). New approaches to understanding hallucinations in
423 Parkinson's disease: phenomenology and possible origins. *Expert Rev Neurother* 7(12), 1731-1750.
424 doi: 10.1586/14737175.7.12.1731.
- 425 Oostenveld, R., and Praamstra, P. (2001). The five percent electrode system for high-resolution EEG
426 and ERP measurements. *Clin Neurophysiol* 112(4), 713-719. doi: 10.1016/s1388-2457(00)00527-7.
- 427 Perrin, F., Pernier, J., Bertrand, O., and Echallier, J.F. (1989). Spherical splines for scalp potential
428 and current density mapping. *Electroencephalogr Clin Neurophysiol* 72(2), 184-187. doi:
429 10.1016/0013-4694(89)90180-6.
- 430 Pieri, V., Diederich, N.J., Raman, R., and Goetz, C.G. (2000). Decreased color discrimination and
431 contrast sensitivity in Parkinson's disease. *J Neurol Sci* 172(1), 7-11. doi: 10.1016/s0022-
432 510x(99)00204-x.
- 433 Possin, K.L. (2010). Visual spatial cognition in neurodegenerative disease. *Neurocase* 16(6), 466-
434 487. doi: 10.1080/13554791003730600.

- 435 Price, M.J., Feldman, R.G., Adelberg, D., and Kayne, H. (1992). Abnormalities in color vision and
436 contrast sensitivity in Parkinson's disease. *Neurology* 42(4), 887-890. doi: 10.1212/wnl.42.4.887.
- 437 Regan, D., and Neima, D. (1984). Low-contrast letter charts in early diabetic retinopathy, ocular
438 hypertension, glaucoma, and Parkinson's disease. *Br J Ophthalmol* 68(12), 885-889. doi:
439 10.1136/bjo.68.12.885.
- 440 Roth, M., Huppert, F.A., Tym, E., and Mountjoy, C.Q. (1988). *CAMDEX: The Cambridge*
441 *Examination for Mental Disorders of the Elderly*. Cambridge: Cambridge University Press
- 442 Roth, M., Tym, E., Mountjoy, C.Q., Huppert, F.A., Hendrie, H., Verma, S., et al. (1986). *CAMDEX.*
443 *A standardised instrument for the diagnosis of mental disorder in the elderly with special reference to*
444 *the early detection of dementia*. *Br J Psychiatry* 149, 698-709. doi: 10.1192/bjp.149.6.698.
- 445 Sanchez-Castaneda, C., Rene, R., Ramirez-Ruiz, B., Campdelacreu, J., Gascon, J., Falcon, C., et al.
446 (2010). Frontal and associative visual areas related to visual hallucinations in dementia with Lewy
447 bodies and Parkinson's disease with dementia. *Mov Disord* 25(5), 615-622. doi: 10.1002/mds.22873.
- 448 Shine, J.M., Halliday, G.M., Naismith, S.L., and Lewis, S.J. (2011). Visual misperceptions and
449 hallucinations in Parkinson's disease: dysfunction of attentional control networks? *Mov Disord*
450 26(12), 2154-2159. doi: 10.1002/mds.23896.
- 451 Talebi, M., A., Meshkinghalam & Andalib, S. (2014). Association between Visual Evoked Potential
452 and Disease Severity, Disease Duration and Visual Hallucination in Patients with Idiopathic
453 Parkinsonism. *Novel Biomed.* 2, 120-125.
- 454 Taylor, J.P., Firbank, M., Barnett, N., Pearce, S., Livingstone, A., Mosimann, U., et al. (2011). Visual
455 hallucinations in dementia with Lewy bodies: transcranial magnetic stimulation study. *Br J*
456 *Psychiatry* 199(6), 492-500. doi: 10.1192/bjp.bp.110.090373.
- 457 Uchiyama, M., Nishio, Y., Yokoi, K., Hirayama, K., Imamura, T., Shimomura, T., et al. (2012).
458 Pareidolias: complex visual illusions in dementia with Lewy bodies. *Brain* 135, 2458-2469. doi:
459 10.1093/brain/aww126.
- 460 Urwyler, P., Nef, T., Killen, A., Collerton, D., Thomas, A., Burn, D., et al. (2014). Visual complaints
461 and visual hallucinations in Parkinson's disease. *Parkinsonism & related disorders* 20(3), 318-322.
462 doi: 10.1016/j.parkreldis.2013.12.009.
- 463 Urwyler, P., Nef, T., Muri, R.M., Killen, A., Collerton, D., Burn, D., et al. (2015). Patient and
464 Informant Views on Visual Hallucinations in Parkinson Disease. *Am J Geriatr Psychiatry* 23(9), 970-
465 976. doi: 10.1016/j.jagp.2014.12.190.
- 466 Van Voorhis, S.T., and Hillyard, S.A. (1977). Visual evoked potentials and selective attention to
467 points in space. *Perception & Psychophysics* 22, 54-62.
- 468 Weil, R.S., Schrag, A.E., Warren, J.D., Crutch, S.J., Lees, A.J., and Morris, H.R. (2016). Visual
469 dysfunction in Parkinson's disease. *Brain* 139(11), 2827-2843. doi: 10.1093/brain/aww175.

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470 Wood, J.S., Firbank, M.J., Mosimann, U.P., Watson, R., Barber, R., Blamire, A.M., et al. (2013).
471 Testing visual perception in dementia with Lewy bodies and Alzheimer disease. *Am J Geriatr*
472 *Psychiatry* 21(6), 501-508. doi: 10.1016/j.jagp.2012.11.015.

473

474 **Table 1, Participant demographics and clinical scores. *Denotes significant at $p < 0.05$**

Measurement	Controls (n=21)	PDD NVH (n=17)	PDD VH (n=17)	Posthoc	Statistics Test Val, p, Effect Size
Age (years)	74.90 ± 5.16	72.94 ± 5.19	73.88 ± 5.36		0.756, 0.524, 0.026
MMSE score*	29.10 ± 1.81	24.59 ± 5.0	22.76 ± 4.99	HC>VH, HC>NVH	12.307, <0.001, 0.321
CAMCOG total score*	95.14 ± 6.79	80.94 ± 15.53	73.18 ± 15.91	HC>VH, HC>NVH, VH<NVH	14.003, <0.001, 0.350
CAMCOG Memory score*	23.52 ± 1.5	19.94 ± 4.93	17 ± 4.1	HC>VH, HC>NVH	15.32, <0.001, .36
CAMCOG Executive score*	22.28 ± 3.16	14.53 ± 3.93	12.44 ± 4.04	HC>VH, HC>NVH	38.67, <.001, .59
UPDRS III score*	2.10 ± 2.47	38.65 ± 21.93	57.88 ± 20.47	HC<VH, HC<NVH, VH>NVH	55.147, <0.001, 0.680
Acuity (decimal)*	0.58 ± 0.31	0.29 ± 0.21	0.31 ± 0.19	HC>VH, HC>NVH	7.783, 0.01, 0.234
Acuity (logmar)*	0.31 ± 0.26	0.65 ± 0.32	0.57 ± 0.27	HC>VH, HC>NVH	7.823, 0.001, 0.235
Minimum Angle Perception (degrees)*	8.63 ± 3.25	28.42 ± 23.51	32.68 ± 30.07	HC<VH	7.059, 0.002, 0.214
Motion Perception*	-2.72 ± 0.72	1.80 ± 3.15	2.68 ± 2.88	HC<VH	26.746, <0.001, 0.522
Number of Pareidolia*	1.0 ± 1.46	3.18 ± 4.54	6.82 ± 5.58	HC<VH, VH>NVH	8.188, 0.001, 0.254
Levodopa Dose (24 hours, mg)		569.12 ± 303.05	710.59 ± 363.10		-1.04, 0.31, 0.35
Age at Onset of PD symptoms (years)		64.65 ± 7.08	60.88 ± 7.62		1.06, 0.29, 0.36
PD Duration (years)		7.18 ± 4.51	10.82 ± 7.46		-1.47, 0.15, 0.5
NPI total score*		0.29 ± 0.58	3.11 ± 2.05	NVH<VH	-5.44, <.001, 3.23

475 *Data are mean ± standard deviation. Statistical tests: : Univariate analysis of variance (ANOVA), p-value 2 sided <0.05 significant; PD = Parkinson's disease, PDD =*
 476 *Parkinson's disease dementia, MMSE = Mini-Mental State Examination, CAMCOG = Cambridge Cognitive Assessment, UPDRS = Unified Parkinson's Disease Rating*
 477 *Scale, HC = Healthy Controls, VH = Visual Hallucination, NVH= No Visual Hallucination; Tests reported used univariate ANOVA with partial eta squared effect size,*
 478 *except for Levodopa, age at onset, duration of PD, and NPI Hal total which used independent samples t-tests and Cohen's D effect sizes.*

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482 **Table 2, Comparison of the visual evoked potential component (N1, P1 and N2) amplitude and latency**

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Component		Controls (n=21)	PDD NVH (n=17)	PDD VH (n=17)	Statistics F, p-value, η^2
N1	Amplitude	-1.27 ± 0.93	-0.85 ± 0.82	-0.84 ± 0.51	1.63, 0.21, 0.06
	Latency	88.28 ± 8.62	90.23 ± 08.68	93.35 ± 10.47	0.46, 0.63, 0.02
P1	Amplitude	3.61 ± 2.55	2.32 ± 1.82	2.36 ± 1.33	2.16, 0.13, 0.08
	Latency	124.50 ±	127.59 ± 7.73	126.84 ± 6.33	1.47, 0.24, 0.06
N2	Amplitude	-1.64 ± 1.44	-0.97 ± 0.84	-1.26 ± 1.19	1.7, 0.19, 0.06
	Latency (ms)	162.27 ± 8.97	176.93 ± 14.69	174.15 ± 15.30	7.44, 0.001* , 0.23

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*Data are mean ± standard deviation. Statistical tests: Univariate analysis of variance (ANOVA), $df=52$, p -value 2 sided <0.05 significant; PDD = Parkinson's disease dementia; HC = Healthy Controls; VH = Visual Hallucination; NVH= No Visual Hallucination; * Posthoc = $VH>HC$, $NVH>HC$;*

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