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Executive function but not episodic memory decline associated with visual hallucinations in Parkinson's disease

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Abstract

Introduction: Visual hallucinations (VH) have a significant impact on quality of life for people with Parkinson's disease (PD). A major reason for this is the well-established link with cognitive impairment but there is still a need for more longitudinal studies examining the specific cognitive domains which may be affected. The aim of this study was to profile decline in cognition associated with VH in a cohort of 69 individuals with PD over one year.

Method: VH assessments were done every three months. Executive function and episodic memory were assessed at baseline and 1 year. All evaluations were done via phone interviews. The presence or absence of VH were categorised based on the entirety of the year's data (i.e. no episodes and >0 episodes). We also defined a persistent VH group who had VH present at more than one time point and compared these with a no VH group and a group with transient VH (i.e. only one episode).

Results: Linear mixed-effect models showed that VH were associated with more rapid overall cognitive decline (-0.26 , $t=-2.39$, $p=0.02$), which was driven by executive function (-0.28 , $t=-2.48$, $p=0.02$). Persistent VH were associated with decline in executive function (-0.33 , $t=-2.4$, $p=0.02$), while no relationship was found for non-persistent VH, suggesting that persistent VH be the major driver of this relationship.

Conclusion: This finding brings greater clarity to the relationship between cognitive decline and VH in PD. Future research should examine the robustness of this phenotype for biomarkers studies and treatment interventions.

Introduction

Visual hallucinations (VH) are common in Parkinson's disease (PD), with a cumulative prevalence in excess of 50%, though this varies considerably by disease duration (Fénelon, Mahieux, Huon, & Ziegler, 2000). VH are associated with adverse long-term outcomes - notably progression to dementia (Anang et al., 2014) - while over the shorter term they are associated with impairments in quality of life and other, more subtle, deficits in cognition. VH are progressive with symptoms becoming more frequent and more severe with duration of PD, although minor hallucinations and illusions are more liable to remit than formed hallucinations (de Maindreville, Fenelon, & Mahieux, 2005; Goetz, Leurgans, Pappert, Raman, & Stemer, 2001; Hinkle Jared et al., 2017). In all, these symptoms represent a major source of concern to people affected by the disease and as such the underlying aetiology as well as clinical consequences are an important area for research.

Hallucinations were recently identified as the strongest independent predictor of overall cognitive decline and dementia in PD (Marinus, Zhu, Marras, Aarsland, & van Hilten, 2018). Dementia is one of the most debilitating aspects of PD progression, with around 50% of people developing the condition after 10 years (Dag Aarsland et al., 2017). Early intervention for cognitive decline is especially important and while neuropsychological test batteries show sensitivity to later more severe cognitive changes (Levy et al., 2002; Woods & Troster, 2003) the incorporation of neuropsychiatric predictors may offer more easily accessible measures with additional predictive value, as has been shown in Alzheimer's disease (Ismail et al., 2016).

Numerous cross-sectional studies have shown a link between VH and impaired cognition in PD - see Lenka et al. (Lenka, Hegde, Arumugham, & Pal, 2017) and ffytche et al. (ffytche, Creese, et al., 2017) for extensive reviews. These neuropsychological correlates – largely visuospatial, attentional and

executive in nature - are consistent with neuroimaging findings which show greater atrophy across frontal, occipital and parietal cortices, and hippocampus (ffytche, Creese, et al., 2017). Moreover, different cognitive profiles associated with the phenomenology of VH (specifically, internally and externally driven experiences) have been previously reported, with differences in inhibitory ability (category fluency and Stroop task) being the greatest (Boubert & Barnes, 2015). Broadly, VH have been proposed to arise as a result aberrant integration of top-down and bottom-up processing with dorsal- and ventral-attentional, and default mode networks all being implicated (Onofrj et al., 2013; Shine, Halliday, Naismith, & Lewis, 2011). For the purposes of this study, a distinction needs to be drawn between VH as a result of aberrant frontal or visual cognitive function and VH as a marker of clinically significant cognitive decline and progression to dementia; here, we focus on the latter which would likely encompass a broader range of cognitive deficits.

Given the abundant evidence of a link between VH and later development of dementia, it is striking that only a small minority of existing studies of more subtle cognitive changes are longitudinal – of the 16 studies cited in the Lenka review for example, only two examined decline in cognitive domains. It is nevertheless a hugely important area for the identification of early markers of clinically significant cognitive decline and for uncovering the full phenomenological profile of VH in PD.

Ramirez-Ruiz et al. tested decline in 11 cognitive tasks in 45 PD patients, broadly covering language, verbal memory, frontal function, visuospatial function and visual memory. Overall, visual memory, visuospatial function and frontal function-related tasks were associated with the highest rates of decline (Ramirez-Ruiz, Junque, Marti, Valldeoriola, & Tolosa, 2007). A related study of extended follow up to 30 months in 26 these patients showed a similarly widespread decline across a number of domains (Ibarretxe-Bilbao et al., 2010). The average disease duration for the patient groups in

both of these studies was >10 years. Given that half of PD patients are expected to develop dementia by 10 years of disease it is not surprising to see such broad cognitive decline; more work needs to be done to elucidate the more subtle deficits likely to be present earlier in the disease. A small number of studies in earlier PD have been conducted showing a less strong relationship with cognitive decline. In one study of early PD (median disease duration 3.4 years) MMSE score was lower in the hallucinations group at cross sectional comparisons at 12 and 24 months, suggesting a greater decline but time was not modelled in the analysis so it is not possible to draw firm conclusions (Morgante et al., 2011). Similarly, Santangelo et al. found no relationship between hallucinations and decline across a range of domains over two years in a cohort with an average disease duration of around 8 years (Santangelo et al., 2007). However, hallucinations were associated with significant impairments at baseline. Furthermore, impairments in phonological fluency and the presence of hallucinations were both associated with mild cognitive impairment at the end of the two year follow up. While the balance of evidence supports a link between cognition and VH across the duration of PD, there is still a notable lack of longitudinal studies addressing this relationship, particularly with respect to specific cognitive domains and in cohorts with a shorter disease duration.

The link between VH, cognition and later dementia highlights the importance of integration of neuropsychiatric and cognitive testing and thus raises the question of how to operationalise VH for this purpose. In all stages of PD there are differences in the frequencies of VH even when they are mild in nature and phenomenologically similar in early disease (ffytche, Pereira, et al., 2017; Gibson et al., 2012) but one aspect of the clinical presentation of VH which has yet to be investigated is the frequency of the symptoms. Recurrent VH have been shown to be associated with a faster rate of decline in AD (Creese et al., 2017) and the elucidation of this relationship in PD will be important for

full understanding of the VH phenotype and could have important implications for the design of biomarker studies of cognitive decline.

In a novel study design with frequent assessments of VH over one year we present an analysis of a longitudinal decline in cognition with two objectives. Firstly, we aimed to examine the relationship between visual hallucinations and decline over one year in global cognition, episodic memory and executive function in a PD cohort with a relative short disease duration. Here we hypothesise that VH would be associated with overall global cognitive decline and that this would be driven by executive function, which prior evidence suggests is a more robust correlate of VH than episodic memory. Secondly, for the first time, we sought to elucidate differences in cognitive decline between participants with persistent versus transient hallucinations, hypothesising that persistent symptoms would be associated with a more rapid decline than transient symptoms.

Methods

A total of 74 participants were recruited through the Parkinson's UK Research Support Network and the South London and the Maudsley NIHR Biomedical Research Centre. All participants were given the option to nominate a project partner to contribute to assessments of VH (see below); fifty-four chose to. Written informed consent was obtained and all contact with participants was carried out by telephone. UK Research Ethics Committee approval was granted by East Midlands - Leicester Central (reference 15/EM/0510).

Participants were required to have a 1) clinical diagnosis of Parkinson's disease, 2) be proficient in English, 3) able to undertake the assessments over the phone (i.e. no hearing impairment or physical impairment which would make that impossible), and 4) have mental capacity to provide informed consent. Exclusion criteria were 1) no formal diagnosis of PD 2) diagnosis not conclusive 3) unable to

provide informed consent 4) a diagnosis of dementia. All participants were under regular outpatient care of a PD medical team with at least 6 monthly reviews by a nurse specialist or neurologist.

Assessment of cognition

At baseline all participants completed the Modified Telephone Interview for Cognitive Status (TICS-M), a global cognitive screening tool, and the Brief Test of Adult Cognition by Telephone (BTACT) (Lachman, Agrigoroaei, Tun, & Weaver, 2014). The BTACT was repeated at one year using an alternate version to avoid practice effects. The BTACT is a validated tool which incorporates six short cognitive tests assessing the following (the description and cognitive construct tested are in parentheses): immediate word list recall (15 words: episodic memory), backward digit span (recalling increasingly long strings of digits in reverse order: working memory), category fluency (number of words generated in one minute belonging to a particular category, e.g. food: executive function, verbal fluency, semantic memory), number series (identifying the sixth number in a sequence after hearing the first five; five trials: inductive reasoning, fluid intelligence), 30 seconds and counting task (30-SACT, total number of digits produced in 30 seconds by counting backwards from 100; errors and skipping tallied and deducted from total: processing speed) and delayed word list recall (recalling the 15 words from immediate word list recall after completing the rest of the tasks: episodic memory). For each test, z scores were calculated and three composite scores reflecting cognitive constructs from previous principal components analysis of the BTACT were generated by calculating the average of the standardised score for each sub scale: 1) total cognition: all six tests; 2) executive function: backward digit span, category fluency, number series, 30-SACT tasks; and 3) episodic memory: immediate and delayed recall. This battery does not include any visuospatial tests, it nonetheless provides good coverage of executive domains which are associated with VH in earlier PD while the inclusion of episodic memory tests allows us to examine the specificity of these deficits.

The BTACT has good convergent validity with the Boston Cognitive Battery, which used in PD and comprises in person measures of the same cognitive domains as the BTACT. The 30-SACT is a novel task but correlates highly with the Digit Symbol Substitution Test and Letter Comparison Task, which both require visual presentation of stimuli and motor responses. All of these tests to which the BTACT is validated are widely used in PD. Moreover, BTACT score is sensitive to differences in overall physical health in the general adult population, supporting its utility in cohorts with low levels of cognitive impairment (Lachman et al., 2014).

Assessment of visual hallucinations and other neuropsychiatric symptoms

VH assessments were done at three month intervals using the Neuropsychiatric Inventory Clinical Rating Scale (NPI-C) (de Medeiros et al., 2010), which is based on the original NPI but allows the incorporation of additional information deemed necessary by the rater. This is important in PD where VH can be influenced by changes in PD medication. Here, any positive answers relating to VH were additionally screened to evaluate whether the VH was due to recent changes in medication. Classification of VH was based on question 3 of the NPI-C although all questions were asked. Delusion ratings were also taken every three months but there was only one positive score across the whole cohort.

Participants were classified as having any VH if they scored >0 on question three of the NPI-C hallucinations scale at any point during the one year follow up; having persistent VH (VH1+) if symptoms were present on >1 occasion during the year; having transient hallucinations (VH1) if symptoms were only present on one occasion; not having hallucinations (VH-) if a score of 0 was present at every time point.

At baseline a fuller battery comprising of these two symptoms plus dysphoria, apathy, anxiety and sleep disorders was conducted.

Statistical analysis

Our primary analysis focused on the association between VH at any time point and decline cognition while our secondary analysis examined the effect of persistent vs transient symptoms.

Baseline cognitive (TICS-M and BTACT), neuropsychiatric, clinical and demographic data were analysed using parametric or non-parametric statistics (t-test, Wilcoxon rank sum test, Pearson correlation, spearman correlation, or chi-square for frequency data).

Principal analysis

We hypothesised that VH would be associated with a faster rate of total cognitive decline which would be driven by decline in executive function, while there would be a weaker relationship with episodic memory decline. The episodic and executive domain constructs were derived from a large population study of over 4,000 adults (Lachman et al., 2014). Cognitive decline over one year was evaluated in a linear mixed-effect model. Fixed effects entered were symptom (VH, present/absent), gender, age, education level and duration of PD (log 10 transformed) and time (baseline and one year). A symptom*time interaction term was included to evaluate decline. Random intercepts were included for participants.

Secondary analysis

We hypothesised that persistent VH would be associated with a faster rate of decline compared with no VH and the relationship between transient VH and no VH would be weaker. A symptom status factor with three levels was created: no VH (VH-), 1 VH episode (VH1), >1 VH episodes (VH1+), with the model otherwise being specified in the same way as for the principal analysis. Because our primary interest was the impact of VH status on cognition - rather than domain-specific impairment addressed by the principal analysis - this analysis was restricted to the cognitive domain showing the strongest association with VH in the principal analysis.

Inspection of residual plots did not indicate any deviations from normality or any evidence of heteroscedasticity for any model. Likelihood ratio tests of the full model against the null model (i.e. without the VH*time interaction terms) were used to generate p-values. Due to the high correlation and non-independence between the three BTACT constructs we considered a Bonferroni correction too stringent so the significant threshold was left at $p < 0.05$. All analyses were carried out in the R statistical environment, using the lme4 package to perform the linear mixed-effects analysis.

Results

Of the 74 participants to start the study, 4 withdrew (one lost to follow up, one due to a reversal of PD diagnosis and two elected to withdraw themselves). Baseline clinical, demographic and cognitive characteristics for the 69 participants to complete the year, by presence or absence of hallucinations (including our secondary split of VH1 and VH1+), are shown in *Table 1*. Among baseline characteristics, disease duration (Welch two sample t-test: $t = -2.5$, $df = 53.85$, $p = 0.015$) and NPI-C dysphoria score (Wilcoxon rank sum test: $w = 377.5$, $p = 0.036$) were higher in the VH group. Dosage data for Parkinson's disease medication was only available for 63 out of 69 participants but no differences were found between levodopa equivalent daily dose and VH among these. No

participants were taking antipsychotics and one participant (with VH) was started on a cholinesterase inhibitor during the study. Of the 69 participants, none had received a diagnosis of dementia at 1 year and one had a diagnosis of mild cognitive impairment.

[TABLE 1]

At baseline 13 participants (18.8%) had hallucinations and eight of these also had hallucinations at follow up. Another 11 exhibited hallucinations on at least one other occasion, taking the hallucinations group for the primary analysis to 24 (34.8%). Of these 11, six had hallucinations at multiple follow up time points with the remaining five only having hallucinations at one follow up time point.

Thus, ten participants (14.5%) experienced only one VH episode (VH1) over the course of the year while 14 (20.1%) had more than one episode (VH1+). Taking into account only those time points where VH were present, these two groups did not differ with respect to the severity of VH experienced (mean scores for both groups were mild: 1 on the NPI-C scale), indicating that our measure of persistence was not confounded by more severe symptoms being more persistent. The NPI-C does not contain questions pertaining to the specific content to VH but inspection of case notes made during the NPI-C showed a broad spectrum of mostly externally driven hallucinatory experiences of unknown animals and people as well as illusions of passage and presence. There was no evidence of hallucinations without insight in any participants.

[TABLE 3]

Table 2 shows the raw neuropsychological test scores at baseline and one year by VH status and for the cohort overall. Table 3 shows the results of the mixed-effect models analysis for the total BACT score and the executive and episodic cognitive domains derived from the raw data. There was no main effect of time or VH status in any of the three tests. A significant symptom*time interaction

for total cognition was found (-0.26 , $t=-2.39$, $p=0.02$). Analysis of the two constituent domains shows that this association is driven by executive function (-0.28 , $t=-2.48$, $p=0.02$), with no significant differences in decline in episodic memory between VH groups (-0.22 , $t=-1.03$, $p=0.31$). The secondary analysis of the impact of frequency of symptoms was therefore restricted to executive function decline. Here we found that VH1+ were associated with a significantly increased rate of decline compared with no VH (-0.33 , $t=-2.4$, $p=0.02$). The VH1 group did not decline significantly faster than the no VH group (0.08 , $t=0.33$, $p=0.74$) (Table 3). There were no significant main effects of time or VH status in this analysis. Figures 1A and 1B show decline in adjusted means on the BTACT executive function composite score over one year for both the primary analysis and secondary analysis.

[TABLE 3]

[FIGURE]

Conclusion

Our data present new evidence to add greater clarity to the relationship between cognitive decline and VH in PD. We show that decline in overall cognition is driven by executive function rather than episodic memory in this cohort, which has an average disease duration of 5.5 years. In addition, for the first time we show that a higher frequency of symptoms is associated with a more rapid cognitive decline than symptoms occurring less frequently, which suggests that persistent symptoms are the major driver of the more rapid cognitive decline observed in the principal analysis.

Disease duration is an important factor to consider when interpreting these findings. VH frequency increases with disease duration (Fénelon et al., 2000) and it is noteworthy that the strongest associations with cognitive decline to date have been in studies of cohorts with longer disease duration (those with disease duration around 10 years). The median disease duration of the present

study was 5.5 years and thus perhaps episodic memory impairments were not pronounced enough to be detected. In the cohort overall we did not observe any significant decline in cognition across the year which is expected given the disease duration but our findings suggest that there are cognitive changes present at these early to middle disease stages which are associated with hallucinations. This is an informative finding with respect to how the cognitive profile associated with hallucinations may differ as a function of disease duration and suggests a focus on executive function in earlier disease stages may yield greater power for studies examining the cognitive correlates of hallucinations. At the other end of spectrum, Morgante et al., in a cohort with disease duration 3.4 years, found no evidence of a relationship between hallucinations frontal assessment battery (FAB) decline, though there was evidence of MMSE decline (which is memory and language orientated) indicating deficits even in early PD (Morgante et al., 2011). Although both measuring some aspects of frontal function there is only a modest overlap between the tasks which comprise the FAB and those on the BTACT executive function score, which may go some way to explaining the difference here.

Our split of VH into those experiencing them at just one point and those at more than one point fits in with the diagnostic criteria for psychosis in PD which requires the presence of symptoms for 1 month or more (Ravina et al., 2007). It is therefore not surprising that we found a sharper decline in cognition in this group. This new finding suggests that that more rapid decline not only accompanies more severe VH but also more frequent VH and that this decline is tied to concurrent clinical presentation of VH. Supporting this view, cognition does not appear to decline more rapidly prior to the onset of hallucinations (ffytche, Pereira, et al., 2017), but VH are known to predict more rapid cognitive decline (D. Aarsland, Andersen, Larsen, & et al., 2004). It is notable that we found no association between VH and cross-sectional measurements of cognition. This is on the whole contrary to the majority of other studies but there are studies with cohorts of shorter disease

duration which have also failed to find associations (ffytche, Pereira, et al., 2017; Morgante et al., 2011). This raises interesting questions as to the distinction between VH as a marker of aberrant frontal and visual cognitive function, which fit in to explanatory models, and VH as a marker of clinically significant cognitive decline which one would expect to encompass a broader range of deficits as VH given the increased risk of dementia among this group. One important area of research will be closer comparison of individuals with VH but who don't develop clinically significant cognitive decline with those who do; the findings here suggest frequency of symptoms may be an important indicator.

Notably, most VH in this study, irrespective of persistence, were mild, causing minimal disruptions to participants. We also note the small effect sizes in this study however, very early neuropsychiatric indicators of problematic cognitive decline are by definition unlikely to manifest as clinically significant problems and our data suggest that in spite of their mild nature, recurrent VH may have important clinical consequences. As it stands the long-term effects of these deficits are not known so further long-term outcome research is needed to investigate this. The more immediate implications of these findings are that it is not just the type of VH that is important but also the frequency. This could represent a more robust phenotype for biomarker studies. More broadly, the fact that there was no main effect of VH on cognition (i.e. at when measured at baseline or 1 year) emphasises the importance of longitudinal monitoring. Our results suggest one year is a sufficient period to see an effect although the long term significance of this is still to be determined.

It is important to note that we are not able to separate out different symptoms on the VH spectrum (i.e. illusions and formed VH) and further work focused on the unique contribution to cognitive decline of these will be essential to properly characterise the clinical significance of hallucinations (including non-visual). We also did not have data on motor status so were unable to control for this

in our statistical analysis. A recent major review of risk factors for non-motor symptoms showed that the biggest risk factor for cognitive decline was hallucinations (ffytche, Pereira, et al., 2017; Marinus et al., 2018). Motor severity was the third biggest risk factor for cognitive decline (behind age; disease stage assessed by H&Y was ranked seventh) but was not a risk factor for hallucinations. Thus while not controlling for motor severity would have likely led to more error in our model evidence strongly suggests its effect is spread evenly over the hallucinations groups. Other limitations include the relatively high education level of the sample and the fact that individuals self-selected to take part. These latter two may restrict the generalisation of the findings but our method of telephone recruitment and follow up meant that we were able to reach a much wider participant pool than those routinely attending hospital clinics. We acknowledge that there is a strong role for visuospatial deficits being associated with VH in PD and a limitation of this study is the cognitive battery which did not include any measures of these domains. Strengths of this study include the sample size (there have only been a small number of longitudinal studies examining the relationship between cognitive decline and VH in PD and most are in comparable sample sizes) and the very frequent assessment of VH which we believe has produced a robust characterisation. This high frequency of assessment allowed us to evaluate the frequency of VH and detailed longitudinal cognitive neuropsychological testing – to our knowledge a first. We must acknowledge that this split (persistent vs non-persistent vs no VH) did reduce our sample size; it is particularly important that this relationship is subject to further study in larger cohorts. Finally we note that ‘executive function’ covers many different cognitive domains. It is therefore important to emphasise that in this study this construct refers to those domains covered by the four tasks of the BTACT (verbal fluency, inductive reasoning, fluid intelligence and processing speed). We acknowledge that there are a larger number of cognitive domains which may be important cognitive correlates of VH which should be the subject of further study.

In summary, we present new data highlighting the relative importance of executive function decline over episodic memory relating to VH in PD. We also show that the frequency of VH may be an important neuropsychiatric marker of cognitive decline. Larger long-term follow up studies are needed to explore the consequences of the combination of VH and decline in executive function. Over the short-term this combination of symptoms may represent a more robust and easily testable phenotype for biomarker studies; and emphasises the importance of, and need for more, longitudinal follow up studies.

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Table 1 Baseline cohort characteristics by presence or absence of visual hallucinations

	VH-		P ^A	VH 1 episode (VH1)		VH>1 episode (VH1+)		P ^B
N (%)	45	24	-	10		14		-
Male gender (%)	27 (60)	13 (54)	0.83	5 (50)		8 (57)		0.84
Age (mean, sd)	65.68 (8.46)	67.84 (7.82)	0.3	66.83 8.18		68.56 7.77		0.25
Education Level (median, IQR) ^C	2 (2)	2 (2)	0.55	2 (1.75)		1 (2)		0.78
Disease duration months (median, IQR)	41.36 (38.24)	64.54 (99.03)	0.02	59.68 (56.74)		68.02 (107.26)		0.01 ⁺
Levodopa equivalent daily dose (median, IQR)*	385 (403.5)	522.5 (450.5)	0.25	568.25 (306.75)		500 (629.50)		0.34
TICSM (mean, sd)	28 (2.76)	27 (4.55)	NS	28 (4.38)		27 (4.73)		0.37
BTACT total (mean, sd)	-0.01 0.54	-0.01 0.78	1	0.11 0.81		-0.10 0.78		0.47
BTACT executive function (mean, sd)	-0.03 0.60	-0.01 0.69	0.94	-0.01 0.61		-0.01 0.77		0.95
BTACT episodic memory (mean, sd)	0.02 0.82	-0.01 1.21	0.92	0.34 1.49		-0.22 0.81		0.52
NPI-C Delusions (median, IQR)	0 (0)	0 (0)	-	0 (0)		0 (0)		-
NPI-C Apathy (median, IQR)	0 (1)	1 (2.25)	0.12	1.5 (3.25)		0.5 (2)		0.19
NPI-C Anxiety (median, IQR)	1 (3)	1.5 (3)	0.61	2 (2.75)		1 (3.75)		0.85
NPI-C Dysphoria (median, IQR)	1 (3)	3.5 (5.5)	0.04	3 (6.5)		4 (4.25)		0.11
NPI-C Sleep disturbance (median, IQR)	1 (3)	2 (2.5)	0.13	2.5 (1.75)		2 (3.75)		0.25

A: VH vs no VH; B: no VH vs VH1 vs VH1+; C: reflects the three main levels of education in the UK: 1= left high school at 16; 2= left high school at 18; 3= undergraduate degree level education or higher. *Dosage data available for 63 out of 69 participants. +One-way anova: $F=6.65(1,67)$, $p=0.01$. Post-hoc pairwise comparison between VH>1 and VH- significant after Bonferroni correction ($p=0.04$), all other pairwise comparisons NS. VH: Visual hallucinations. Abbreviations: VH: visual hallucinations at any point; VH1: one episode of visual hallucinations over the year; VH1+: more than one episode of visual hallucinations over the year; VH-: no visual hallucinations; BTACT: Brief Assessment of Adult Cognition by Telephone; NPI-C: Neuropsychiatric Inventory Clinical Rating Scale; TICSM: Modified Telephone Interview for Cognitive Status; IQR: interquartile range.

Table 2 Raw cognitive test scores at both time points and change in score over the year

		Baseline		1 year		Change
		Mean	SD	Mean	SD	
Immediate recall	VH-	6.44	1.85	7.22	1.91	0.78
	VH	6.38	2.89	6.62	3.1	0.24
	Overall	6.42	2.25	7.01	2.39	0.59
Digits backward	VH-	5.02	1.32	5.42	1.31	0.4
	VH	5.33	1.31	5.04	1.52	-0.29
	Overall	5.13	1.32	5.29	1.38	0.16
Category fluency	VH-	22.49	6.44	24.4	5.37	1.91
	VH	21	5.12	22.58	5.6	1.58
	Overall	21.97	6.02	23.77	5.48	1.8
Number series	VH-	3.33	1.07	3.44	1.22	0.11
	VH	3.33	1.46	3.04	1.6	-0.29
	Overall	3.33	1.21	3.3	1.36	-0.03
Thirty seconds and counting	VH-	37.8	9.5	37.96	9.19	0.16
	VH	38.42	10.4	36.42	9.45	-2
	Overall	38.01	9.75	37.42	9.24	-0.59
Delayed recall	VH-	3.98	2.15	4.98	2.36	1
	VH	3.92	2.87	4.38	2.58	0.46
	Overall	3.96	2.4	4.77	2.44	0.81

Abbreviations: VH: visual hallucinations at any point; VH-: no visual hallucinations.

Table 3 Results of linear mixed-effects model of decline in BTACT cognitive domains by VH status

	Estimate	SE	t	p
Visual Hallucinations^A				
BTACT total:				
VH*time	-0.26	0.11	-2.39	0.02
VH	0.14	0.16	0.88	0.38
Time	0.1	0.06	1.6	0.1
BTACT executive function:				
VH*time	-0.28	0.11	-2.48	0.02
VH	0.14	0.17	0.82	0.42
Time	0.12	0.07	1.78	0.08
BTACT episodic memory:				
VH*time	-0.22	0.21	-1.03	0.31
VH	0.15	0.23	0.64	0.53
Time	0.07	0.13	0.56	0.57
Visual Hallucinations episodes^A				
BTACT executive function:				
VH1*time	-0.21	0.16	-1.35	0.18
VH1+*time	-0.33	0.14	-2.4	0.02
VH1	0.08	0.22	0.33	0.74
VH1+	0.18	0.20	0.89	0.38
Time	0.12	0.07	1.78	0.08

A. Linear mixed-effect models controlling for gender, age, education level and duration of Parkinson's disease. Abbreviations: VH: visual hallucinations at any point; VH1: one episode of visual hallucinations over the year; VH1+: more than one episode of visual hallucinations over the year. Reference category: no visual hallucinations. BTACT: Brief Assessment of Adult Cognition by Telephone.

1A:

1B:

Figure 1 Decline in executive function over one year, adjusted mean BTACT scores. 1A: any visual hallucinations; 1B: persistent, transient and no hallucinations. Abbreviations: VH: visual hallucinations; VH1: one episode of visual hallucinations; VH1+: more than one episode of visual hallucinations. Error bars: standard error