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## Visual hallucinations in Parkinson's disease

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## Chapter 3

# Attentional and perceptual impairments in Parkinson's disease with visual hallucinations

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### 3.1 Abstract

VISUAL HALLUCINATIONS (VH) are common in Parkinson's Disease (PD). Both deficits of perception and attention seem to play a role in the pathogenesis of VH in PD. However, the possible coexistence of impairments in attention and visual perception in PD with VH is not known. This study investigated both attention and visual perception in non-demented PD patients with VH, compared to PD patients without VH and healthy controls. Fourteen participants were included in each group. All patients were assessed with sustained visual attention and object and space perception tests. Only PD patients with VH showed impairments on object and space perception. In addition, PD patients with and without VH showed impairments on sustained visual attention, being more severely affected in PD patients with VH. Only in PD patients with VH sustained visual attention was associated with a decreased object and space perception. The results of our study thus suggest that in PD patients with VH an impairment of object and space perception, possibly in association with a decreased sustained visual attention, might play a role in the pathogenesis of VH.

## 3.2 Introduction

VISUAL HALLUCINATIONS (VH) are common in Parkinson's Disease (PD) and often occur in dim, suboptimal visual surroundings. VH in Parkinson's disease have been commonly viewed as an adverse effect of dopaminergic treatment for PD, causing a relative over-stimulation of the limbocortical dopaminergic receptors (Bosboom et al., 2004). However, VH have already been reported in the pre-levodopa era and may not be associated with the dose or duration of treatment of dopaminergic drugs (Fenelon et al., 2006; Goetz et al., 1998; Holroyd et al., 2001). In addition, cognitive and visual impairments and a dysregulation of the sleep-wake cycle are suggested to be contributing factors to the pathophysiology of VH in PD (Diederich et al., 2009).

Perception normally consists of a combination of bottom-up and top-down processing. Bottom-up processing involves data-driven processing, i.e. the incoming visual stimuli in the occipital cortex and the perception of spaces and objects in the occipito-parietal and inferior temporal lobe, respectively. Top-down processing, on the other hand, involves the process that contributes to perception, but which does not originate in the external world, e.g. perceptual expectations and attentional modulation (Aleman et al., 2008). Several models have been introduced to explain (visual) hallucinations (Aleman et al., 2008; Collerton et al., 2005; Diederich et al., 2005). Although these models are different, all models suggest that hallucinations are due to impairments in both bottom-up and top-down information processing. In patients with PD and VH several studies have shown object and space perception impairments, as compared to PD patients without VH (Barnes et al., 2003; Ramirez-Ruiz et al., 2007a). Secondly, several studies reported PD patients with VH showing a decreased ability to focus attention and fluctuating levels of attention, relative to PD patients without VH (Ballard et al., 2002; Barnes and Boubert, 2008).

Studies on PD patients with VH so far were solely focused on visual perception or on attention. However, both perception and attention play a role in perceiving the external world and the possible coexistence of impairments in visual perception and attention in PD with VH should be investigated. We previously investigated object perception in PD patients with VH, mimicking suboptimal visual situations by creating movies with objects dynamically appearing out of random noise, with no direct manipulations on the objects themselves. In addition, the associations between visual sustained attention and object perception were determined (Meppelink et al., 2008). It was concluded that the

recognition of objects in that way is not impaired in PD patients with VH, however these patients were significantly slower in image recognition than PD patients without VH and healthy controls, which was associated with a decreased sustained visual attention. When perceiving objects it is assumed that we make use of all objects' properties for optimal recognition (Newell et al., 2004). The present study focuses on the recognition and identification of differentially manipulated objects, not taking into account the background environment. Also, the associations between visual sustained attention and object perception will be determined. In addition, space perception will be investigated in the present study.

Previous studies on visual perception in PD patients with and without VH, had matched groups on MMSE scores and level of intelligence (Barnes et al., 2003). However, PD patients with VH show decreased levels of executive functioning, as compared to PD patients without VH (Barnes and Boubert, 2008). The influence of executive dysfunctions is widespread and may have altered previously described results of PD with VH. The present study therefore investigated matched patient groups for their level of executive functioning (assessed with the Frontal Assessment Battery (FAB)) (Dubois et al., 2000), in addition to age, sex and level of education.

### **3.3 Methods**

#### **3.3.1 Subjects**

Forty-two volunteers participated in this study, including 14 PD patients with VH, 14 PD patients without VH and 14 healthy controls. These subjects were included in a larger study focused on perception and attention in PD patients with and without VH and healthy controls, of which part of our results are already described (Meppelink et al., 2008). The groups of PD patients without VH and healthy controls were matched to the group of PD patients with VH in such a way that no group differences existed for age (ANOVA:  $F= 0.91$ ;  $p= 0.41$ ), gender (Chi-Square test  $p= 0.73$ ) and level of education (Kruskal-Wallis Test  $p= 0.86$ ; rated with a Dutch education scale ranging from 1 (elementary school not finished) to 7 (university degree)). Both PD groups were also matched for their level of executive functioning (i.e. score on FAB (Dubois et al., 2000), t-test:  $t= -0.44$ ;  $p= 0.67$ ).

PD was diagnosed according to the criteria of the UK Parkinson's Disease Society Brain Bank by experienced neurologists (K.L. Leenders and T. Van

	PD + VH		PD - VH		HC	
	M (SD)	range	M (SD)	range	M (SD)	range
Age (years)	69.0 (5.0)	60-75	67.1 (6.8)	55-78	66.0 (5.9)	57-74
Education	4.4 (1.7)	1-7	4.2 (1.9)	1-7	4.6 (1.7)	2-7
Disease duration	10.7 (4.9)	3-19	6.0 (5.7)	1-23		
LEDD	944 (509)	220-2150	693 (446)	150-1650		
SPES	9.4 (4.3)	4-20	8.0 (5.2)	1-18		
MMSE	26.2 (1.3)	25-29	26.4 (1.6)	24-28	27.6 (1.5)	24-29
FAB	14.3 (1.7)	12-17	14.6 (2.6)	10-18	16.5 (1.0)	15-18
Visual acuity	0.6 (0.2)	0.5-1.0	0.8 (0.2)	0.5-1.0	0.8 (0.2)	0.5-1.0
Males: n (%)	9 (64 %)		10 (71 %)		8 (57 %)	
Females: n (%)	5 (36 %)		4 (29 %)		6 (43 %)	

**Table 3.1:** Demographic and illness characteristics of PD patients with visual hallucinations (PD + VH; n=14), PD patients without VH (PD - VH; n=14) and healthy controls (HC; n=14)

Laar). Exclusion criteria were patients with moderate to severe cognitive impairments (Mini Mental State Examination score < 24), neurologic disorders other than PD, psychiatric disorders, visual acuity less than 50 percent (Snellen chart) and visual field defects (Donders technique). All PD patients were ‘on’ during the assessment. A levodopa-equivalent daily dose score (LEDD) was calculated for all patients (Esselink et al., 2004). In the PD with VH group three patients used stable medication for their VH (one used clozapine, one used galantamine and one used clozapine and galantamine), while none of the subjects used anticholinergics.

The motor severity of PD patients was rated with the Shortened Parkinson Evaluation Scale (SPES) of the Scales for Outcomes in Parkinson’s disease (SCOPA) (Marinus et al., 2004). The severity of VH was assessed with part B “Hallucinations” of the Neuropsychiatric Inventory and a questionnaire based on the characteristics of VH in PD patients (see Barnes and David (2001)).

All demographic and clinical characteristics are described in Table 3.1. PD patients with VH showed higher LEDD scores than PD patients without VH, however this difference was not significant ( $t= 1.38$ ;  $p= 0.18$ ). PD patients with VH did however show a significantly longer disease duration ( $t= 2.03$ ;  $p= 0.05$ ) and a decreased visual acuity ( $F= 4.3$ ;  $p= 0.02$ ) compared to PD patients without VH. Patient groups did not differ concerning the severity of their motor symptoms ( $t= 0.75$ ;  $p= 0.46$ ).

This study was approved by the Medical Ethical Committee of the University Medical Center Groningen. All participants signed an informed consent prior to study inclusion.

### 3.3.2 Stimulus material

All three groups were presented with the following neuropsychological tests:

#### *Visual Object and Space Perception battery (VOSP, (Warrington, 1991))*

This battery comprises four tests for object perception and four tests for space perception. The tests for object perception include identifying incomplete letters ('Incomplete letters'), identifying silhouettes of objects and animals ('Silhouettes'), identifying a silhouette of a real object out of four silhouettes of which three were silhouettes of non-sense objects ('Object decision') and identifying rotated silhouettes of objects ('Progressive silhouettes'). The tests for space perception include counting dots ('Dot counting'), determining whether dots are placed in the middle of a square or not ('Position discrimination'), determining with which number of at randomly placed numbers in a square the location of a dot in an other square corresponded ('Number location') and counting the number of bricks of a structure of bricks ('Cube analysis'). The subtests of the VOSP were presented in an at random order.

#### *Test battery for Attention Performances (TAP)*

PD patients with VH might show fluctuating levels of attention and might consequently obtain a relatively normal score on an attention test with a short duration (Ballard et al., 2002). Therefore a test (the subtest 'Optical vigilance' of the TAP), during which participants had to focus their visual attention for a longer period of time, was applied in this study. During 10 min participants had to push a button if they recognized irregularities in a normally regular movement pattern of an object on a computer screen. The test contained a total of twelve irregularities. The number of omitted irregularities was rated as a measure for sustained visual attention.

### 3.3.3 Statistical analysis

Not all variables were normally distributed within all three groups. Also, some variables violated the assumption of equality of variance. Therefore, the non-parametric Welch test, which is robust when sample sizes are equal and the normality and equality of variance assumptions are violated (Buning, 1997), was used to verify the results of the parametric tests. The results of the non-parametric test supported our parametric findings, therefore only the results of the parametric tests are described.

All three groups were compared on all subtests of the VOSP and on the sus-

tained visual attention test, using MANOVA. Since PD patients with VH showed a higher LEDD score (even though this was not significant), had a longer disease duration and showed a lower visual acuity than PD patients without VH, these variables were entered as covariates (NB. The Welch test does not allow the inclusion of covariates. Therefore, a regression analysis was performed and residual variables, which represent the performances on the VOSP subtests and the sustained visual attention test without the influence of the above described covariates, were saved. These residual variables were entered in the Welch test). Subsequently, a Helmert contrast was used to determine first of all whether PD patients with VH differed significantly from both PD patients without VH and healthy controls and second whether PD patients without VH differed from healthy controls. The achieved effect sizes and power of all comparison between groups were calculated post hoc, using G\*Power (Faul et al., 2007).

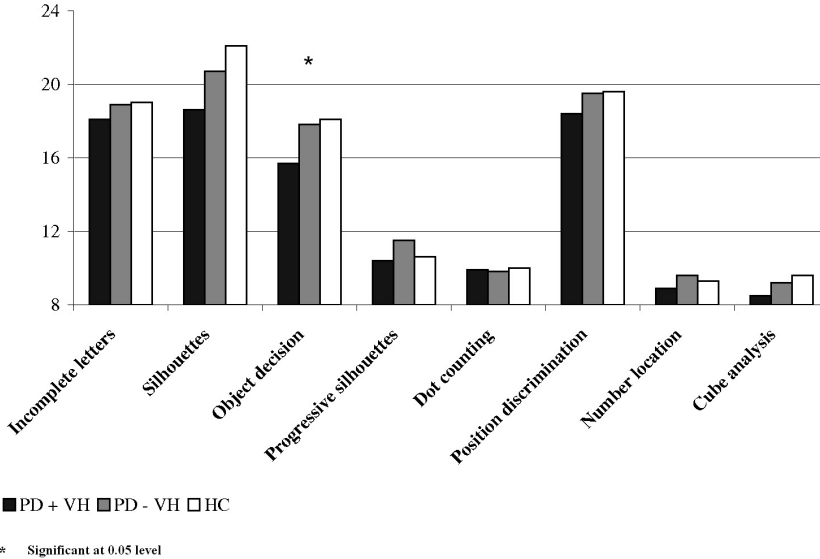
In addition, Spearman correlations were calculated within groups between sustained visual attention and the subtests of the VOSP on which PD patients with VH differed significantly from both other groups.

### 3.4 Results

Of all PD patients with VH, 7 percent reported having VH about once a week, 50 percent had VH several times per week and 43 percent reported to have VH several times a day. In total 29 percent of the hallucinating PD patients became upset during their VH and 21 percent of the hallucinating PD patients considered their VH as a moderately to severely emotional burden.

The performance on the subtests of the VOSP of all three groups is shown in Table 3.2 and Fig. 3.1. The groups showed a statistical significant difference on 'Object decision' and trends towards significant differences between groups were found for 'Dot counting' and 'Number location'. No significant differences were found between the 3 groups on the other VOSP subtests. The differences were further analyzed using the Helmert contrast, which showed that PD patients with VH scored significantly lower on 'Object decision' than both PD patients without VH and healthy controls ( $p=0.02$ ). PD patients without VH and healthy controls scored similarly on 'Object decision' ( $p=0.88$ ). Concerning 'Number location' the same pattern was found; PD patients with VH scored significantly lower than both PD patients without VH and healthy controls ( $p=0.05$ ) and PD patients without VH and healthy controls obtained similar scores ( $p=0.74$ ). On 'Dot counting' PD patients with and without VH obtained similar scores ( $p=0.44$ ), while both PD patient groups showed

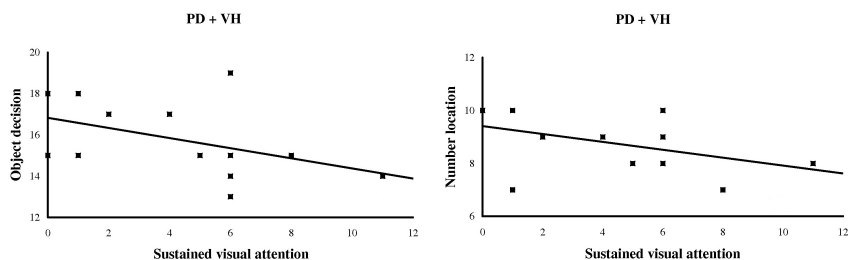




**Figure 3.1:** Mean performance of PD patients with VH (PD + VH;  $n = 14$ ), PD patients without VH (PD - VH;  $n = 14$ ) and healthy controls (HC;  $n = 14$ ) on VOSP subtests.

significantly lower scores than healthy controls ( $p = 0.02$ ).

The MANOVA showed that the three groups differed significantly on sustained visual attention ( $F = 4.1$ ;  $p = 0.03$ ; effect size = 0.74; power = 0.99). On average PD patients with VH did not recognize 4.3 (SD = 3.4) irregularities, PD without VH did not recognize 2.5 (SD = 2.1) irregularities and healthy controls did not recognize 0.3 (SD = 0.5) irregularities. The Helmert contrast showed that PD patients with VH had significantly more difficulties sustaining their visual attention than both PD patients without VH and healthy controls ( $p = 0.02$ ) and PD patients without VH had significant more difficulties sustaining their visual attention than healthy controls ( $p = 0.05$ ). The correlations between sustained visual attention and the subtests of the VOSP on which PD patients with VH obtained significantly lower scores than both PD patients without VH and healthy controls (Object decision and Number location) are shown in Table 3.3. Sustained visual attention was significantly correlated with ‘Object decision’ and ‘Number location’ within PD patients with VH (see Fig. 3.2 and Table 3.3). In both other groups no correlations were found between ‘Ob-



**Figure 3.2:** Correlations between Object decision, Number location and sustained visual attention in PD patients with VH (PD + VH;  $n = 14$ ).

	PD + VH M (SD)	PD - VH M (SD)	HC M (SD)	F	p
Incomplete letters	18.1 (1.7)	18.9 (1.0)	19.0 (0.9)	1.3	0.30
Silhouettes	18.6 (4.7)	20.7 (3.5)	22.1 (4.1)	0.7	0.52
Object decision	15.7 (1.8)	17.8 (1.0)	18.1 (1.6)	3.5	0.04
Progressive silhouettes	10.4 (2.7)	11.5 (2.5)	10.6 (3.4)	2.1	0.14
Dot counting	9.9 (0.3)	9.8 (0.4)	10.0 (0.0)	3.1	0.06
Position discrimination	18.4 (2.8)	19.5 (0.8)	19.6 (0.6)	1.6	0.21
Number location	8.9 (1.1)	9.6 (0.5)	9.3 (0.8)	2.7	0.08
Cube analysis	8.5 (2.2)	9.2 (1.1)	9.6 (0.6)	0.4	0.71

**Table 3.2:** Differences between PD patients with VH (PD + VH;  $n=14$ ), PD patients without VH (PD - VH;  $n=14$ ) and healthy controls (HC;  $n=14$ ) on the different subtests for object and space perception

ject decision', 'Number location' and sustained visual attention (see Table 3.3).

### 3.5 Discussion

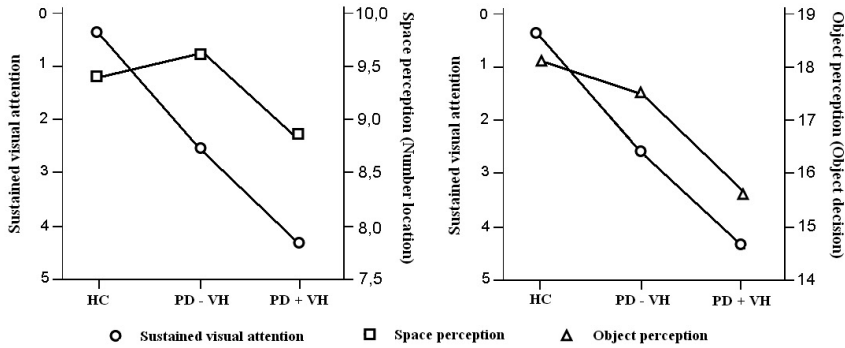
Sustained visual attention and object and space perception were investigated in PD patients with VH, compared to PD patients without VH and healthy controls. PD patients with VH showed decreased sustained visual attention, compared to both other groups, independent of visual acuity or disease severity. These results are consistent with studies reporting a decreased ability to focus attention and fluctuating levels of attention in respectively PD patients with VH (Barnes and Boubert, 2008) and patients with PD dementia, with very frequent VH (Ballard et al., 2002).

Our results also showed that PD patients with VH scored significantly lower on the object perception test 'Object decision' compared to both PD patients without VH and healthy controls, independently of visual acuity and disease severity. Importantly, no differences were found between PD patients without

VH and healthy controls, which confirms previous data (Barnes et al., 2003; Meppelink et al., 2008). The Object decision test used in this study required participants to identify a silhouette of a real object amongst the silhouettes of three nonsense objects. These silhouettes showed a lack of perceptual clarity and a lack of detail. Previously this was explained by suggesting that PD patients with VH can not resolve ambiguities of these stimuli and therefore activate previously stored internal schemata in higher-level visual areas (Barnes et al., 2003). These suggestions are consistent with the models that explain (visual) hallucinations (Aleman et al., 2008; Collerton et al., 2005; Diederich et al., 2005) and suggest that perception in patients with VH is influenced by top-down factors, such as perceptual expectations and visual representations of the exterior world, which are stored in memory. In addition, PD patients with VH showed a decreased performance on a space perception test (Number location), relative to both PD patients without VH and healthy controls. It is not likely that perception during this task was influenced by visual representations stored in memory or perceptual expectations, however this does not exclude the possibility that PD patients with VH also increasingly relied on top-down processes during this task.

Previously we mimicked suboptimal visual situations by creating movies of undegraded objects dynamically appearing out of random noise, with no direct manipulations on the objects themselves and showed that PD patients with VH had no difficulties recognizing objects, they were however significantly slower than PD patients without VH and healthy controls (Meppelink et al., 2008). The present study extends these findings by showing that PD patients with VH do show object perception impairments if objects are manipulated without taking into account the background environment, specifically if the objects that need to be recognized lack perceptual clarity and detail. PD patients with VH thus show impairments if the objects that need to be recognized lack clarity, not if the surroundings of the object (random noise) are unclear.

Decreased levels of sustained visual attention were correlated with a decreased object and space perception in PD patients with VH. Importantly, no correlations were found between sustained visual attention and object and space perception in PD patients without VH, nor in healthy controls. Since sustained visual attention and object and space perception are both processes in which bottom-up and top-down factors interact, these results confirm the models that have been introduced to explain (visual) hallucinations (Aleman et al., 2008; Collerton et al., 2005; Diederich et al., 2005). A possible explanation for



**Figure 3.3:** Course of Object decision, Number location and sustained visual attention. Line diagram showing the performances on the Test battery for Attention Performances (TAP) and the tests Object decision and Number location of the VOSP in healthy controls, PD patients without VH (PD - VH) and PD patients with VH (PD + VH).

this correlation could be that the decreased performance of PD patients with VH on the object and space perception tests was influenced by an impaired sustained visual attention. However, since the object and space perception tests were presented in an at random order, this is not likely. It is more likely that sustained visual attention and the perception of objects and spaces are two cognitive functions that both decline with the progression of PD (see Fig. 3.3) and both play a role in the pathogenesis of VH.

It should be noted that PD patients with VH did not show a decreased performance on all subtests for object and space perception. A first explanation for these findings may be the fact that participants who obtained a score of 24 or lower on the MMSE were excluded. Consequently, the group of cognitively most severely affected PD patients, in which VH are common, were not included in this study. Secondly relatively small groups of participants were included in this study, causing a relatively small distribution of data. The effect sizes and power of our main findings (differences on sustained visual attention and Object decision) were however high, suggesting that the decreased sustained visual attention and object perception are evident in PD patients with VH and can even be detected in small groups. All other results show low to average effect sizes and power and thus need to be confirmed in a larger samples of subjects.

### **3.6 Conclusion**

In conclusion, the results of this study suggest that in PD patients with VH impairment of visual processing of objects, possibly in association with a decreased sustained visual attention, might play a role in the pathogenesis of VH.