Chapter 2

Visual object recognition and attention in Parkinson’s disease patients with visual hallucinations

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Accepted for publication in Movement Disorders
CHAPTER 2. VISUAL RECOGNITION IN PD WITH VH

2.1 Abstract

Visual hallucinations (VH) are common in Parkinson’s disease (PD) and are hypothesized to be due to impaired visual perception and attention deficits. We investigated whether PD patients with VH showed attention deficits, a more specific impairment of higher order visual perception, or both. Forty-two volunteers participated in this study, including 14 PD patients with VH, 14 PD patients without VH, and 14 healthy controls (HC), matched for age, gender, education level, and level of executive function. We created movies with images of animals, people, and objects dynamically appearing out of random noise. Time until recognition of the image was recorded. Sustained attention was tested using the Test of Attentional Performance. PD patients with VH recognized all images but were significantly slower in image recognition than both PD patients without VH and HC. PD patients with VH showed decreased sustained attention compared to PD patients without VH who again performed worse than HC. In conclusion, the recognition of objects is intact in PD patients with VH, however, these patients were significantly slower in image recognition than patients without VH and HC, which was not explained by executive dysfunction. Both image recognition speed and sustained attention decline in PD, in a more progressive way if VH start to occur.
2.2 Introduction

Visual hallucinations (VH) are common in Parkinson’s disease (PD) with a prevalence of approximately 30 percent (Barnes and David, 2001). VH are defined as involuntary visual perceptions in the waking state without external visual stimulation (Collerton et al., 2005). Minor forms of hallucinations consist of sensation of presence, a sideways passage or illusions, in which an external stimulus is perceived but misinterpreted (Fenelon et al., 2000, 2008; Barnes and David, 2001). VH can be simple, characterized by the absence of form, or complex, with a clearly defined specific form. All above mentioned categories of hallucinations can occur in PD and often overlap, making it likely that they are related. VH in PD typically comprise complex visual, commonly moving images lasting for seconds to minutes. Animals, people and objects define the categories of images that are often perceived by hallucinating PD patients (Fenelon et al., 2000; Mosimann et al., 2006).

The exact etiology of VH in PD is unknown, however a combination of impaired visual processing and attention may be involved (Diederich et al., 2005). While reduced visual acuity is a risk factor for the occurrence of VH (Matsui et al., 2006b), it was shown that PD patients with VH have additional impairments on facial recognition and object perception compared to PD patients without VH (Ramirez-Ruiz et al., 2006; Barnes et al., 2003). Other studies have shown attentional deficits in non-demented PD patients experiencing VH (Barnes and Boubert, 2008). In a recently described model on VH, it was hypothesized that a combination of impaired visual processing and attention is required for VH to occur (Collerton et al., 2005).

VH in PD tend to occur in dim, suboptimal visual circumstances (Sanchez-Ramos et al., 1996). Several techniques have been used to mimic suboptimal visual situations, such as backward masking, in which briefly presented images are immediately followed by a masking stimulus, and gradual revelation of objects using panels and noise (Bar et al., 2001; James et al., 2000; Grill-Spector et al., 2000). By creating movies in which an image slowly and dynamically appears out of random noise, the speed and content of conscious perception of images can be assessed (James et al., 2000; Reinders et al., 2006; Kleinschmidt et al., 2002). In this study movies were created of pictures of animals, objects and people gradually appearing out of noise.

The aim was to investigate visual perception of gradually revealed images in PD patients with VH compared to PD patients without VH and healthy controls. Additionally, it was investigated whether PD patients with VH showed
CHAPTER 2. VISUAL RECOGNITION IN PD WITH VH

Figure 2.1: Images revealed out of noise. The images Queen (A), Dog (B), Telephone (C), and Rabbit (D) that were dynamically revealed out of noise.

decreased sustained attention and whether this was associated with the visual perception of gradually revealed objects.

2.3 Patients and Methods

2.3.1 Subjects

Forty-two volunteers participated in this study, including 14 PD patients who experienced VH at least weekly during the last month, 14 PD patients without VH and 14 healthy controls. PD was diagnosed according to the criteria of the UK Parkinson’s Disease Society Brain Bank. These three groups were matched 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). The latter was 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 Frontal Assessment Battery (FAB; t-test: t=-0.44 p=0.67). All PD patients were ‘on’ during the assessment. The levodopa-equivalent daily dose (LEDD) was calculated for all patients, according to the formula: LEDD= levodopa dose (mg) + ( 0.3 *levodopa dose if using entacapone with each dose) + (slow release levodopa *0.7) + (bromocriptine *10) + (ropinirole *20) + (pergolide *100) + (pramipexole *100) + (apomorphine *10). In the PD with VH group three patients used stable medication against their VH (one patient used clozapine, one patient used reminyl and one used clozapine and reminyl), while none of the subjects used anticholinergics. Demographic and illness characteristics are described in table 2.1. Exclusion criteria were dementia (Mini Mental State Examination (MMSE) score < 24), neurological disorders other than PD, psychiatric disorders, visual acuity less than 50 percent (Snellen chart) and visual field defects.
2.3. PATIENTS AND METHODS

<table>
<thead>
<tr>
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<th>PD + VH</th>
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<th>PD - VH</th>
<th></th>
<th>HC</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>69.0 (5.0)</td>
<td>range</td>
<td>67.1 (6.8)</td>
<td>range</td>
<td>66.0 (5.9)</td>
<td>range</td>
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<tr>
<td>Education</td>
<td>4.4 (1.7)</td>
<td>1-7</td>
<td>4.2 (1.9)</td>
<td>1-7</td>
<td>4.6 (1.7)</td>
<td>2-7</td>
</tr>
<tr>
<td>Disease duration</td>
<td>10.7 (4.9)</td>
<td>3-19</td>
<td>6.0 (5.7)</td>
<td>1-23</td>
<td></td>
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<tr>
<td>LEDD</td>
<td>944 (509)</td>
<td>220-2150</td>
<td>693 (446)</td>
<td>150-1650</td>
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<tr>
<td>SPES</td>
<td>9.4 (4.3)</td>
<td>4-20</td>
<td>8.0 (5.2)</td>
<td>1-18</td>
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<tr>
<td>MMSE</td>
<td>26.2 (1.3)</td>
<td>25-29</td>
<td>26.4 (1.6)</td>
<td>24-28</td>
<td>27.5 (1.5)</td>
<td>24-29</td>
</tr>
<tr>
<td>FAB</td>
<td>14.3 (1.7)</td>
<td>12-17</td>
<td>14.6 (2.6)</td>
<td>10-18</td>
<td>16.5 (1.0)</td>
<td>15-18</td>
</tr>
<tr>
<td>Males: n (%)</td>
<td>9 (64 %)</td>
<td></td>
<td>10 (71 %)</td>
<td></td>
<td>8 (57 %)</td>
<td></td>
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<tr>
<td>Females: n (%)</td>
<td>5 (36 %)</td>
<td></td>
<td>4 (29 %)</td>
<td></td>
<td>6 (43 %)</td>
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Table 2.1: 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)

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.

2.3.2 Stimulus Material

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 of PD patients was assessed with part B ‘Hallucinations’ of the Neuropsychiatric Inventory and a questionnaire based on the characteristics of visual hallucinations in PD patients as described by Barnes and David (Barnes and David, 2001).

All groups were presented with the following tests:

**Image recognition movies**

Four newly developed movies, in which images gradually and dynamically appeared out of random noise, were shown on a computer screen. The movies contained pictures of animals (dog, rabbit), a well-known person (Dutch queen) and an object (telephone, see figure 2.1). Movies were presented in the same order (Queen, Dog, Rabbit, Telephone) to all participants. Subjects had to verbally name the image when recognized, while time until recognition of the image was recorded by stopwatch. The movie was stopped when the image was recognized. The session duration varied between 91 and 248 seconds.

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

The subtest ‘Optical vigilance’ of this battery was used to assess the ability to focus attention for 10 minutes. Participants had to push a button when recognizing irregularities in a normally regular movement pattern of an object.
on a computer screen. The test contained twelve irregularities. The number of times the participant did not recognize an irregularity was rated. Mean reaction times were also measured, by calculating the time between the irregularity presentation and the button press.

2.3.3 Statistical Analysis

Not all variables were normally distributed in all three groups. Also, concerning the variable ‘number omitted’ of the optical vigilance test of the TAP the assumption of equality of variance was violated. Therefore, the non-parametric Welch test, which is very 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.

The three groups were compared concerning their time until correct image recognition using MANOVA. MANOVA was also used to compare the scores of all groups on the optical vigilance test of the TAP. Subsequently, a Helmert contrast, only applied to variables on which groups significantly differed according to the MANOVA, was used to determine firstly, if the group of PD patients with VH differed significantly from both PD patients without VH and healthy controls and secondly, if PD patients without VH differed from healthy controls. To investigate if the 3 PD patients using medication for their VH biased the PD patients with VH group results, we performed a second MANOVA with Helmert contrast, now excluding these subjects. Because much of our data was not normally distributed we calculated within subject variability and made scatter plots to investigate if our results were biased by outliers. Image recognition times on the 4 movies were converted to z-scores and the difference between the highest and lowest z-score was used to calculate within subject variability. This variability was compared between groups using ANOVA.

Mean reaction times (see TAP) of the three groups were compared using ANOVA. A Difference contrast was applied to further differentiate differences between groups. Spearman correlations within groups were calculated to investigate associations between visual acuity, mean reaction times and disease severity on the one side and image recognition time and number omitted on the TAP on the other side.

Additionally, Spearman correlations were calculated between sustained attention and the time until image recognition within each group.
2.4. RESULTS

In the group of PD patients with VH, 7 percent (n=1) reported having VH about once a week, 50 percent had VH several times per week and 43 percent reported having VH several times a day. Twenty-nine percent of the hallucinating PD patients reported that they became upset during their VH and 21 percent considered their VH as a moderate to severe emotional burden. None of the PD patients with VH experienced VH during the testing. Twenty-one percent of hallucinating PD patients associated their VH with the use of dopaminergic medication. LEDD scores were not significantly different in PD patients with VH, compared to PD patients without VH (t=1.38, p=0.18). The motor severity of all PD patients was assessed using the SPES-SCOPA (table 2.1).

All subjects were able to correctly name all images that were gradually revealed out of noise and considered the test as non-fatiguing. The MANOVA showed significant differences between groups for the time until recognition of the images ‘Dog’ and ‘Rabbit’. Moreover, the Helmert contrast showed that PD patients with VH recognized the images significantly slower than both PD patients without VH and healthy controls, while no significant differences between PD patients without VH and healthy controls were found. For the images ‘Queen’ and ‘Telephone’, a trend to similar results was seen, but these differences were not significant (see table 2.2). Excluding the PD patients that used medication for their VH did not alter the results (Helmert contrast com-

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<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>F</td>
<td></td>
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<tr>
<td>Queen</td>
<td>42.6 (16.3)</td>
<td>35.7 (7.9)</td>
<td>34.1 (6.6)</td>
<td>2.3</td>
<td>0.11</td>
</tr>
<tr>
<td>Dog*</td>
<td>23.2 (5.3)</td>
<td>20.2 (3.3)</td>
<td>18.9 (3.9)</td>
<td>3.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Rabbit**</td>
<td>50.2 (19.4)</td>
<td>41.6 (6.6)</td>
<td>37.6 (5.6)</td>
<td>3.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Telephone</td>
<td>23.9 (5.2)</td>
<td>21.7 (6.1)</td>
<td>19.3 (5.3)</td>
<td>2.4</td>
<td>0.10</td>
</tr>
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Table 2.2: Comparison of time until recognition of movies in PD patients with visual hallucinations (PD+VH; n=14), PD patients without VH (PD-VH; n=14) and healthy controls (HC; n=14) using MANOVA (two-tailed). *Helmert contrast: PD+VH are slower in recognition than PD-VH and HC (p=0.01); no differences between PD-VH and HC (p=0.42). **Helmert contrast: PD+VH are slower in recognition than PD-VH and HC (p=0.01); no differences between PD-VH en HC (p=0.39)
Figure 2.2: Relative increase of recognition time in Parkinson’s disease patients. Bar diagram showing the mean percentage of extra time until recognition for PD patients with and without VH (PD+VH, respectively PD-VH), relative to healthy controls.

* group differs significantly from both other groups, shown by MANOVA and Helmert contrast (see table 2.2).

paring PD patients with VH with both PD patients without VH and healthy controls: Queen: p=0.03, Dog: p=0.04, Rabbit: p=0.02, Telephone: p=0.07). Within subject variability did not differ between groups (p=0.59).

A MANOVA showed that both PD patients with and without VH had longer reaction times than healthy controls (p=0.01). Furthermore, there was no difference in reaction times between PD patients with VH and PD patients without VH (p=0.64).

There was no correlation between the recognition performance and mean reaction times within groups (data not shown). Image recognition times were not associated with visual acuity or disease severity (data not shown). The relative increase of image recognition time in PD patients with and without VH, both compared to healthy controls, is depicted in figure 2.2.

Sustained attention was measured by rating the number of non-recognized ir-
2.5 Discussion

The aim of this study was to investigate visual perception of gradually revealed images, mimicking suboptimal situations in which VH often occur, in PD patients with VH compared to PD patients without VH and healthy controls. Additionally, it was investigated whether PD patients with VH showed decreased sustained attention and whether this was associated with the time until correct recognition of gradually revealed objects. We suggest that our movies with pictures of animals, people and objects gradually appearing out of random noise mimic suboptimal visual perceptual circumstances. In contrast to static images, which are generally characterized by a large degree of regularities on the optical vigilance test of the TAP. On average PD patients with VH did not recognize 4.3 irregularities (SD=3.4), PD without VH 2.5 (SD=2.1) and healthy controls 0.3 irregularities (SD=0.5). The MANOVA showed that the groups differed significantly from each other on sustained attention (F=10.7, p=0.00). Additionally, the Helmert contrast showed that PD patients with VH showed a significantly decreased sustained attention as compared to both PD patients without VH and healthy controls (p=0.00). PD patients without VH showed a significantly decreased sustained attention as compared to healthy controls (p=0.00). The Spearman correlation did not show an association between sustained attention and visual acuity or disease severity (data not shown). Spearman correlations were also calculated between sustained attention and image recognition times within each group. PD patients without VH showed an association between sustained attention and the movie ‘Dog’, while no other associations were found between the time until recognition of images gradually revealed out of noise and sustained attention (table 2.3). Scatter plots of these associations are shown in figure 2.3.

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<th>PD + VH</th>
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<tbody>
<tr>
<td><strong>r (p)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Queen</td>
<td>-0.14 (0.66)</td>
<td>0.19 (0.50)</td>
<td>0.04 (0.90)</td>
</tr>
<tr>
<td>Dog</td>
<td>0.22 (0.48)</td>
<td>0.56 (0.04)</td>
<td>0.47 (0.08)</td>
</tr>
<tr>
<td>Rabbit</td>
<td>0.39 (0.18)</td>
<td>0.33 (0.26)</td>
<td>0.20 (0.50)</td>
</tr>
<tr>
<td>Telephone</td>
<td>0.09 (0.78)</td>
<td>0.00 (1.00)</td>
<td>0.30 (0.30)</td>
</tr>
</tbody>
</table>

Table 2.3: Spearman correlations (two-tailed) between sustained attention and time until recognition of movies in PD patients with visual hallucinations (PD+VH; n=13), PD patients without VH (PD-VH; n=14) and healthy controls (HC; n=14).
perceptual clarity and constancy, a dynamic presentation of stimuli like in our movies probably provides a more natural visual perceptual situation. Regarding the gradual appearance of the images, conscious perception is postponed, creating an additional temporal dimension in the assessment of visual perception. These movies are applied here to measure differences in visual perception associated with the occurrence of VH in PD.

Cognitive impairment is often found in PD patients, if compared to healthy controls. A dysexecutive syndrome is one of the core features of cognitive dysfunction in PD and is usually one of the earliest cognitive symptoms in PD (Dubois and Pillon, 1997; Bosboom et al., 2004). The unique feature of this study is the cognitively matched set-up of the PD patient groups with special focus on executive functioning, which makes it unlikely to explain our findings by a difference in executive functioning. While others used the MMSE to match groups of PD patients with and without VH, we used the FAB, which is a useful screening test to assess executive functioning in PD (Dubois et al., 2000).

PD patients with VH were slower in recognizing images gradually revealed out of random noise than both PD patients without VH and healthy controls. These results were independent of visual acuity, disease severity or reaction
times. Although recognition of these images in PD patients with VH was slower, our data show that the final recognition and naming of the image was unimpaired. It is unclear why only ‘Dog’ and ‘Rabbit’ were recognized significantly slower. It is likely that ‘Queen’ and ‘Telephone’ become significant if group sizes are increased (also see figure 2.2). Other factors might have influenced the results. Firstly the fixed order of presentation of the movies. However, the ‘Telephone’ movie, which was the final movie in all sessions, was not recognized significantly slower, which makes this influence very unlikely. Secondly, as PD patients are generally more fatigued later during the day, when VH also tend to be worse, it is important to consider the time of day at which the assessment was done, because this could have influenced the performance. We tested our subjects arbitrarily over the day, making it difficult to estimate the possible effect of this factor on our results.

The current study also showed that PD patients with VH had decreased sustained attention, compared to PD patients without VH, who in turn performed worse than healthy controls. Sustained attention refers to the ability to focus on an enduring, monotone task for a longer period of time. Attentional deficits may fluctuate as is seen frequently in PD Dementia and Dementia with Lewy bodies, in which VH are common (Walker et al., 2000). Moreover, reduced sustained attention in PD patients with VH, as compared to PD patients without VH and healthy controls, is consistent with recent data, showing a decreased focused attention in PD patients and an even worse attention in PD patients with VH (Barnes and Boubert, 2008).

Regarding this study and the previous studies on visual processing in PD patients with VH, it is difficult to compare the behavioral data, because all studies used different techniques to investigate visual perception. We used a different time frame as compared to others, taking into account visual object perception as well as time until recognition of the object. The slower image recognition in PD patients with VH might be caused by a reduced bottom-up visual processing. Hypothetically, this may lead to a higher demand on the top-down system, resulting in activation of visual images by a kind of overcompensation, causing VH in PD. Imaging studies have shown that the primary visual cortex (V1) is equally affected in PD patients with VH as compared to PD patients without VH (Boecker et al., 2007; Oishi et al., 2005), while secondary visual cortices, i.e. occipital-temporal and occipital-parietal regions, show hypoperfusion and reduced glucose metabolism in PD patients with VH, as compared to PD patients without VH (Okada et al., 1999; Oishi et al., 2005; Matsui et al., 2006a; Boecker et al., 2007). This may reflect reduced bottom-up visual processing, in which the visual image is processed
ventrally from V1 to the occipital-temporal region, which is involved in object perception, and dorsally to the occipital-parietal region, which is involved in space and movement perception.

In higher visual processing, attentive, i.e. ‘top-down’, processes are considered to play an important role in the identification of objects in suboptimal visual circumstances (Hopfinger and West, 2006). It has been hypothesized that VH and attentional deficits are both due to a degeneration of the cholinergic system and that attentional deficits may play a causative role in the generation of VH in PD (Francis and Perry, 2007). This study has shown that both image recognition and sustained attention are impaired in PD patients with VH, as compared to PD patients without VH, in turn being more impaired than healthy controls. However, the time until recognition did not show significant differences between PD patients without VH and healthy controls. This suggests that in PD sustained attention as well as image recognition both deteriorate, probably in consequence of the same underlying disease process, but with different time intervals. Irrespective of the overall level of executive functioning, attention seems to decline linearly from the beginning in PD patients, while visual perceptual functions remain relatively intact in the course of PD, starting to deteriorate when VH become apparent (figure 2.4).

All movies, except one (‘Dog’), failed to show positive correlations between the time until recognition and sustained attention, in all three groups. Only the ‘Dog’ movie did show a correlation between recognition time and sustained attention in the PD patient group without VH, for reasons we do not understand. These limited correlations suggest that impaired sustained attention does not seem to cause an increased recognition-time of images revealed out of random noise. However, the somewhat ambiguous results make it difficult to draw firm conclusions. Whether sustained or other forms of attention, such as focused, selective or divided attention are involved in the generation of VH, should be determined in future research.

2.6 Conclusions

In conclusion, our dynamic image recognition paradigm provides a natural means to present visual stimuli and creates an additional temporal dimension in the assessment of visual perception. The recognition of these images in PD patients with VH was intact, but significantly slower than in patients without VH and HC. Sustained attention was also shown to be impaired in PD patients with VH, compared to PD patients without VH and HC. This was not explained by a difference in executive functioning. Future research has
to validate the image recognition paradigm described in this article, using a greater number of movies of comparable duration, in order to average data and to investigate test-retest reliability. Currently we use similar movies with images revealed from random noise, in an fMRI paradigm, to elucidate cerebral patterns involved in image recognition and possible higher order deficits in PD patients with VH during this task.