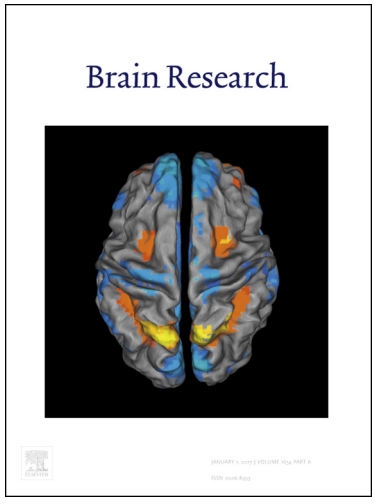

Research report

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Parkinson's patients can rely on perspective cues to perceive 3D space

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Abstract

3D perception, which is necessary for an optimal navigation in our environment, relies on 2 complementary kinds of cues; binocular cues allowing precise depth localization near the point of visual interest and monocular ones that are necessary for correct global perception of visual space. Recent studies described deficient binocular 3D vision in PD patients; here we tested 3D vision in PD patients when based on monocular cues (m3D). Sixteen PD patients and 16 controls had to categorize visual stimuli as perceived in 2D (flat) or 3D (with depth). Both performance and response times were measured. EEGs were recorded to extract Visual Evoked Potentials. Effects of PD were tested by comparing psychometric and electrophysiological data obtained in controls and PD patients evaluated without dopaminergic treatment. Effects of Levodopa were tested by comparing data in PD patients with and without dopaminergic treatment.

We didn't find statistical differences between PD patients and controls' performance. Severity of PD (UPDRS III) in OFF condition is positively correlated with P1 amplitudes and latencies for both 2D and m3D stimuli. Levodopa administration didn't modify either PD patients' performances although it increases principal visual components latencies for both 2D and m3D stimuli.

Unlike binocular 3D vision, monocular 3D vision does not seem to get affected by PD. However given the correlation between severity of PD and VEPs' modifications, alteration of visual cortical processing might have nonetheless begun. PD patients reporting trouble in perceiving space must rely more on m3D cues present in the environment.

Keywords: Parkinson disease; Vision; 3D perception; Psychophysics; VEP

1. Introduction

Although there is a wide variety of visual impairments in Parkinson's disease (PD) (Armstrong, 2011, Bodis-Wollner and Paulus, 1999, Sauerbier and Chaudhuri, 2013), three-dimensional (3D) visual perception of space roused some interest only recently in PD patients (Kim et al., 2011, Kwon et al., 2014, Lee et al., 2015, Sun et al., 2014). Yet, a decent 3D spatial vision is essential for optimal navigation and interaction with our environment. Objects project onto the two retinae images that are in 2 dimensions (2D) but the brain is able to process those images in order to reconstruct their 3D properties. To

achieve that, the brain uses two types of visual indices; on one hand, binocular cues that require both eyes, allow a quantitative and precise 3D perception close to the fixation point (stereopsis), and principally in near space. On the other hand, monocular cues, such as perspective, shading, relative size of objects… give rise to the same 3D perception whether they are viewed by one or both eyes, and allow a more qualitative assessment of 3D position and shape of objects located further away. Both kinds of 3D indices are integrated together in the brain to give rise to a coherent 3D perception (Howard and Rogers, 2002). Deficits in the cortical processing of 3D indices would result in a flat 2D perception of the world. Recently it has been shown that a high proportion of PD patients present impaired binocular stereopsis (Kim et al., 2011, Kwon et al., 2014, Lee et al., 2015, Sun et al., 2014) which raises the possibility that this trouble might have consequence for the interaction of PD patients with their environment. In this study, we addressed the question of whether monocular 3D (m3d) vision was also impaired in PD. We compared m3D vision in PD patients and control subjects with psychophysical methods as well as the underlying electrophysiological activities. The effect of Dopamine on m3D vision was also addressed.

2. Results

The demographic, clinical characteristics and principal statistical effects are shown respectively in Table 1 and 2.

Table 1 about here
Table 2 about here

2.1. Effect of PD

No differences were found between PD patients and controls in terms of performances ($p=0.7$) or response times ($p=0.7$) (figure 1, table 2a). 3D perception based on monocular cues is not affected in our population of patients, which means that images with an imbedded perspective are correctly interpreted as being in 3D and are not perceived flat. We didn't find either any relationship between the severity of disease expressed by UPDRS III measured in OFF condition and performances ($p=0.26$, table 2b) or response times

(p=0.9, table 2c). Although PD patients displayed normal performances and did not have cognitive impairment, PD patients had on average lower Mattis scores (p>0.05, see table 1) and we observed a correlation between the Mattis global score and performances (table 2b, p=0.04). This relationship was mainly driven by the attention subdomain scores (table 2c, p=0.02).

Figure 1 about here

Consistently with psychophysical data, we observed no differences in the underlying electrophysiological signals between PD patients and controls whether in 2D (p=0.91, 0.39, 0.53, 0.89 for P1 and N1 amplitude, P1 and N1 latency respectively) or 3D conditions (p=0.87, 0.89, 0.7, 0.94 for P1 and N1 amplitude, P1 and N1 latency respectively) (see figure 2a and 2b and table 2d). However, we did find that patients with higher UPDRS scores had, for both kinds of stimuli, higher P1 amplitudes (2D, p=0.052; m3D, p=0.02) and longer P1 latencies (2D, p=0.008; m3D, p=0.002) (table 2e).
Furthermore, patients with higher attention sub-scores had longer P1 and N1 latencies (table 2f) for both kind of stimuli (p=0.05, 0.02, 0.04, 0.02 respectively for P1 latency for 2D and m3D stimuli, N1 latency for 2D and m3D stimuli).

Figure 2 about here

2.2. Effect of treatment on 3D perception

While motor symptoms measured by UPDRS III sub score were greatly reduced with levodopa administration (p>0.001, see table 1), no differences were found between PD patients in OFF and ON conditions in terms of performances (p=0.73) or response times (p=0.62) (figure 1, table 2g).

Although PD patients were as capable as controls to categorize 2D and m3D stimuli, we did observe a general slow-down in recorded cortical activities in patients in ON condition compared to OFF condition (figure 2b right part, table 2h), concerning both responses to 2D and m3D stimuli (p=0.0001, 0.005, 0.03, 0.005 respectively for P1 latency for 2D and m3D stimuli, N1 latency for 2D and m3D stimuli).

3. Discussion

In our study, PD patients preserved a normal depth perception in presence of monocular cues like perspective, although Kim and collaborators showed that PD patients had difficulty to perceive depth produced by binocular stereopsis (Kim et al., 2011). Considering the very small statistical size effects observed, it is unlikely that we missed a potential effect of PD on monocular 3D perception because of an insufficient number of patients.

Rather, our results suggest that PD has a different effect according to the types of visual indices for 3D perception. This result is not surprising because selectivity for retinal disparity, which is responsible for binocular 3D perception, is present as early as primary visual cortex (see (Howard and Rogers, 2002)). PD could affect stereopsis processing there which is not the case for monocular 3D cues as they are processed much later in visual cortex (Howard and Rogers, 2002). Both kinds of cues are then combined in regions within the intra parietal sulcus (Durand et al., 2007) in order to allow the optimal estimation of object's 3D position and shape required for reaching movement and to perform correctly pre-shaping of the hand before grasping that object.

We found that patients with higher Mattis attention sub-scores tend to have better performances and longer components latencies: patients who were able to maintain more steadily their attention focused during the visual discrimination task obtained logically better performances. Coherently, it has been shown that a discrimination task requiring great attention effort was accompanied by increased N1 latencies (Callaway and Halliday, 1982). Our subjects did confirm after the experiments that they indeed found the discrimination task used here quite attention demanding.

We did not observe slower responses in PD patients as often reported in other studies; this is certainly due to the instructions given to the subjects. Because this 2D/m3D discrimination task was quite difficult, we emphasized more on the necessity of precise responses rather than on speed. Time needed to form a firm decision must have exceeded the motor slowdown observed in PD patients. Coherently, we did not observe either a decrease in response time in ON condition.

Although no modification in psychophysical results have been observed after Levodopa administration, we detected at the neuronal level a small increase of P1 (3.3ms) and N1

(4.2ms) latencies that was not specific to 3D vision but on the contrary seemed to reflect a general slow-down in visual processing. Other studies have measured VEP latencies in PD before and during Levodopa treatment; results are very variable depending on studies and seem to be dose-dependent, reflecting thus antagonizing effects of dopamine in visual system due to both excitatory and inhibitory influences (Bodis-Wollner et al., 1982, Yaar, 1980).

Patients included in this study were moderately affected by PD. Whereas we did not observe any relationship between psychometric data and severity of disease as measured by UPDRS part III sub score in OFF condition, we can't exclude the existence of a deterioration in m3D perception in patients with more severe motor symptoms. The correlation between both amplitude and latency of P1 components with the severity of disease might reflect the beginning of visual cortical processing alteration, although not yet visible at the behavioral level.

A single monocular depth cue, like the cavalier perspective used in this study, is not sufficient to give rise by itself to a realistic estimation of the 3D environment, especially when binocular cues are not correctly processed; however it is known that combination of several monocular 3D cues helps greatly to approach a veridical depth. Cavalier perspective showed to our subjects is only one among several other monocular cues like texture, contrast, shading… (see (Howard and Rogers, 2002)). These other cues should be tested, using psychophysics, EEG and fMRI, to conclude that 3D perception based on monocular cues as a whole, as opposed to binocular 3D perception, is preserved in PD. In that case, PD patients would compensate more easily the perceptual loss due to binocular 3D processing deficits.

Whether PD patients could be trained to privilege monocular cues in a visual scene to optimize their navigation and interaction with surrounding objects is an open question.

4. Experimental Procedure

4.1. Participants

Sixteen PD patients have been included in the study together with sixteen age- and sex-matched healthy control subjects.

PD patients were recruited in the neurology department of Toulouse University Hospital and fulfilled the UKPDSBB (UK Parkinson's disease society brain bank) criteria. Exclusion criteria were a Hoehn & Yahr stage > IV in "on" state, dementia according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV), Mattis Dementia Rating Scale < 132 (Mattis, 1988), and the inability to read or understand questionnaires. Patients suffering from an atypical Parkinson syndrome were not included. Both patient and controls with poor visual acuity (<7/10) for each eye were excluded. Controls had no medical or neurological history. They were recruited by the clinical investigation center of Toulouse hospital.

The study was approved by the local Ethics Committee "CPPSOOM" and all patients gave their informed consent prior to their inclusion in the study. This trial is registered with ClinicalTrials.gov, number NCT01620164.

4.2. Assessment

In addition to socio-demographic data, Mattis Dementia Rating Scale (Mattis, 1988) was used on both patients and controls.

Severity of disease was assessed by the Unified Parkinson's Disease Rating Scale part III sub score (UPDRS III) (Fahn and Elton, 1987) measured in OFF condition (see below).

Patients and controls, wearing a 64 electrodes EEG cap (BIOSEMI system), performed psychophysical tasks in front of a computer screen placed at 57cm. They had to fixate binocularly a cross on the screen that appeared before the visual stimuli. 2D stimuli were geometrical figures without any depth embedded and thus perceived flat, while 3D ones were cavalier perspective versions of the 2D stimuli (fig 1A). Each stimulus, randomly presented, was flashed for 200ms. The presentation of the next stimulus was triggered by the subject's response. The participants were asked to press a different key to report either a 2D perception or a 3D perception. During these tasks, the VEPs (visual evoked potential) associated with the different stimuli were recorded and collected. EEG processing was done with Cartool software.

For each patient, tests were randomly evaluated in two conditions: medication OFF after 12 hours of dopaminergic treatment withdrawal and medication ON one hour after the administration of a single suprathreshold levodopa dose (150% of their usual levodopa

equivalent morning dose). PD patients performed four blocks, two in ON condition and two in OFF condition, of 204 trials each (fig 1B). Controls performed two blocks.
Figure 3 about here

4.3. Variables and Statistical analysis

Performances were expressed as the percentages of correct 3D answers (hit rate). Although subjects were not explicitly told to respond as quickly as possible but rather to press the keys when they were quite sure of their perception, their response times were also recorded. Anticipatory and delayed answers were discarded.
For the electrophysiological analysis, the latency and amplitude of the P1 and N1 peaks were measured for each subject in each condition.
Statistics were performed on the inverse of response times and VEP components.

The number of subjects retained for this experiment was based on Kwon's study (2014) that reports that 44% of their PD patients have problems of binocular 3D perception. By considering that about 3% of controls may also have 3D perception, we included 16 PD patients and 16 controls in our study to assess the effect of PD on m3D perception.

Statistics of demographic and clinical data were done with t-test and paired t-test.

To assess the effect of PD on m3D perception, MANOVAs were performed (controls and PD patients in OFF condition: independent variable - performances and response times: dependent variables). Multivariate correlations between performances and (i) Mattis values and subscores, and (ii) severity of disease (UPSRS III in OFF condition) were tested. Bonferroni correction weighted by the mean correlation between outcome variables has been applied (Dubey, 1994) and confidence intervals were corrected accordingly.

To assess the effect of treatment on m3D perception, repeated measures MANOVAs were performed (psychophysical values: dependent variables - OFF and ON conditions: independent variable).

As no effect of electrodes locations could be observed, we averaged the amplitudes and latencies of early VEP components recorded with occipital and parieto-occipital electrodes during 2D and 3D visual stimulations. Manovas and repeated measures Manovas were

performed respectively to assess effects of PD (controls versus patients in OFF condition) and Levodopa treatment (patients in OFF versus ON condition) respectively on 2D and 3D VEP components. Multivariate correlations between principal components and clinical data (Mattis and UPDRS) were tested.

Statistical tests were done with commercial softwares: Statisca and Prism (GraphPad software).

Authors' contributions

A.S.C., F.O.M., C.B.C. and S.C. designed the study.

M.R. developed computer programs for the experiments.

F.O.M and C.B.C. recruited the patients.

M.G. performed the UPDRS III ratings.

V.J., A.S.C. and S.C. collected and analyzed the data.

A.S.C., F.O.M and S.C. wrote the manuscript.

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Conflict of interest

None of the authors have any conflicts of interest associated with this study.

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Figures legends

Fig. 1

Psychophysical data for control subjects (C) and PD patients in OFF and ON conditions: performances on the left and response times on the right. Data are displayed as mean and 95% Confidence Interval.

Fig. 2

Electrophysiological data for control subjects (C) and PD patients in OFF and ON conditions. a. Amplitudes of EEG principal components P1 and N1. b. Left: latencies of principal components P1 and N1 in control and OFF conditions. Right: differences of latencies of principal components P1 and N1 measured in ON and OFF conditions showing an effect of treatment on both components.

Fig. 3

a Example of stimuli used. 2D: flat stimulus. 3D: cavalier perspective of the same stimulus.

b Protocol of the psychophysical task performed by subjects.

Table 1
Demographic and clinical data

Demographic and clinical profiles	Controls		PD patients		Significativity		
Gender (M/F)			11/5		11/5		n.s.
Age (years)			65.1 ± 8.5	65.8 ± 7.8		n.s.	
Duration of disease (years)					7.6 ± 4.3		
UPDRS III							
OFF					22.3 ± 10.8		
ON					14.9 ± 10.6	ON/OFF	***
Mattis total score			142.8 ± 2.3	140.5 ± 3.3		*	
Attention			36.7 ± 0.4	36,4 ± 0.8		n.s.	Construction
	6		6			n.s.	Memory
	24.6 ± 1.3	24,1 ± 1.6			n.s.		
Initiation			36.9 ± 0.5	35,6 ± 2.2		*	
Conceptualization			38.6 ± 0.7	38,4±0.9			n.s.
Mean levodopa dose administrated (mg)					284.4 ± 92.3		

Mean values ± SD. *p <0.05, ***p <0.001.

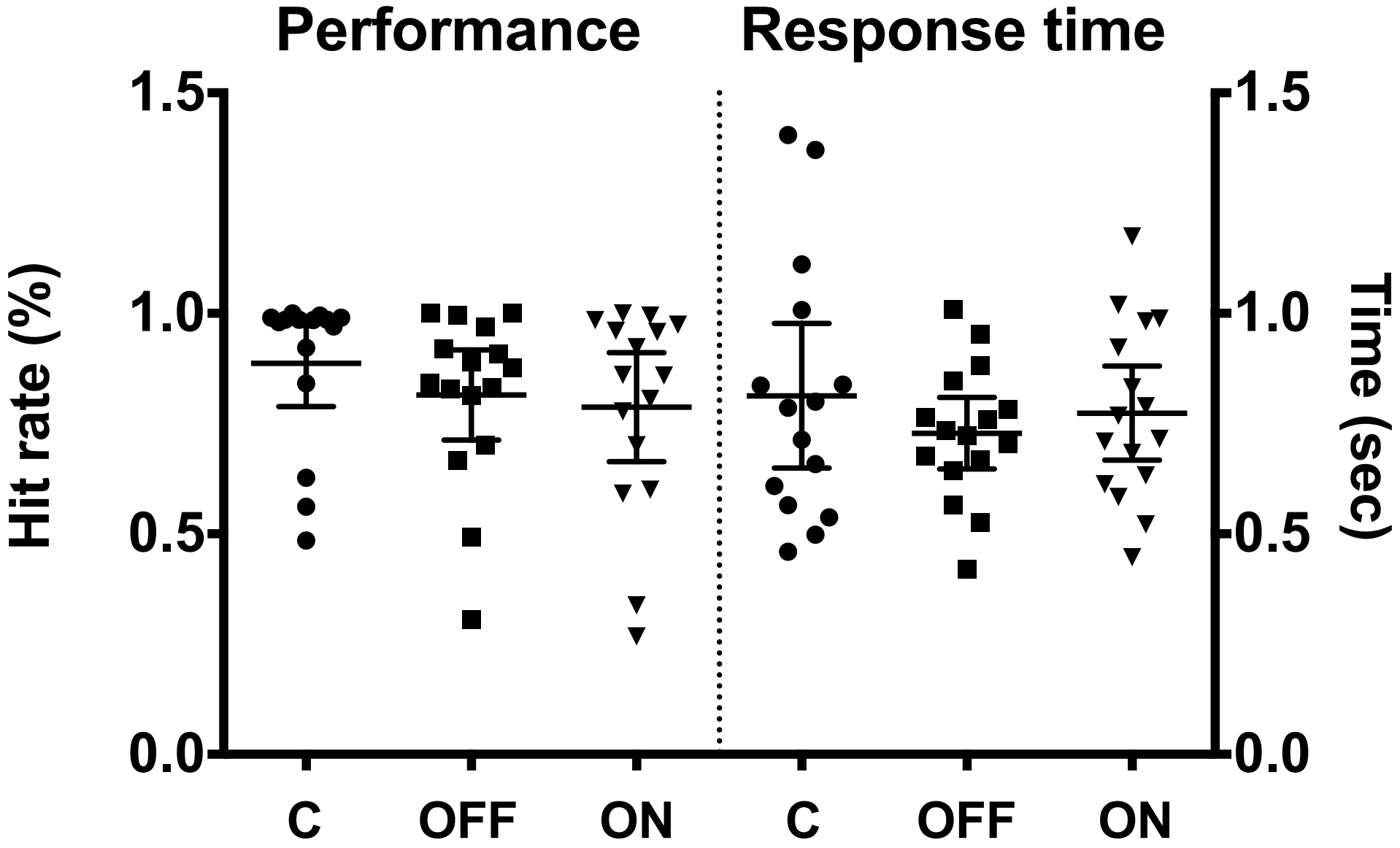
Table 2
Detailed statistics of experimental results

Effect of disease (OFF/controls): Manova					
Ref	**Variables**	**r^2**	**Mean diff** (OFF – controls)	**95% CI**	**p**
a	performance	0.039	-0.071	(-0.17, 0.57)	0.7
	response time	0,007	0.063	(-0,46, 0,3)	0.7
d	m3D P1 amp	< 0.001	0,029	(-0.34, 0,40)	0.87
	m3D N1 amp	0.023	0,026	(-0.21, 0.52)	0.89
	m3D P1 lat	0.005	< 0.001	(-0.44, 0.30)	0.7
	m3D N1 lat	< 0.001	< 0.001	(-0.37, 0.37)	0.94
	2D P1 amp	< 0.001	-0.029	(-0.39, 0.35)	0.91
	2D N1 amp	0.024	0.044	(-0.21, 0.52)	0.39
	2D P1 lat	0.009	< -0.001	(-0.46, 0.27)	0.53
	2D N1 lat	< 0.001	< -0.001	(-0.39, 0.34)	0.89

Pearson Correlations (OFF population)				
Ref	**Variables**	**r**	**95% CI**	**p**
b	performance/ Mattis	0.54	(0.06, 0.82)	0.04
	performance/UPDRS III	0.35	(-0.17, 0.72)	0.26
c	response time/Mattis	0.3	(-0.22, 0.75)	0.44
	response time: UPDRS III	-O.17	(-0.65, 0.40)	0.9
	performance/attention	0.62	(0.09, 0.88),	0.02
	performance/memory	0,04	(-0.59, 0.75)	1
	performance/initiation	0,41	(-0.20, 0.79)	0.22
e	UPDRS III/P1 amp 2D	0.56	(0.01, 0.85)	0.052
	UPDRS III/P1 amp m3D	0.61	(0.06, 0.7)	0.02
	UPDRS III/P1 lat 2D	0.71	(0.24, 0.91)	0.008
	UPDRS III/P1 lat m3D	0.73	(0.29, 0.92)	0.002
f	attention/ P1 lat 2D	0.56	(0, 0.86)	0.05
	attention/P1 lat m3D	0.62	(0.08, 0.88)	0.02
	attention/N1 lat 2D	0.59	(0.04, 0.87)	0.04
	attention/N1 lat m3D	0.62	(0.08, 0.88)	0.02

Effect of treatment (ON/OFF): repeated measures Manova					
Ref	**Variables**	**r^2**	**Mean diff** (ON-OFF)	**95% CI**	**p**
g	performance	O.10	0.03	(-0,14, 0,02)	0.73
	response time	0.04	0.06	(-0.19, 0.31)	0.62
h	P1 lat 2D	0.54	< 0.001	(0.0002, 0.0005)	0.0001
	P1 lat m3D	0.37	< 0.001	(0.0001, 0.0004)	0.005
	N1 lat 2D	0.32	< 0.001	(0.0001, 0.0003)	0.03
	P1 lat m3D	0.31	< 0.001	(0.0001, 0.0005)	0.005

Ref reference in text, CI confidence interval, amp amplitude, lat latency. Statistics for response times and PEV components are done on inverse values.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ON
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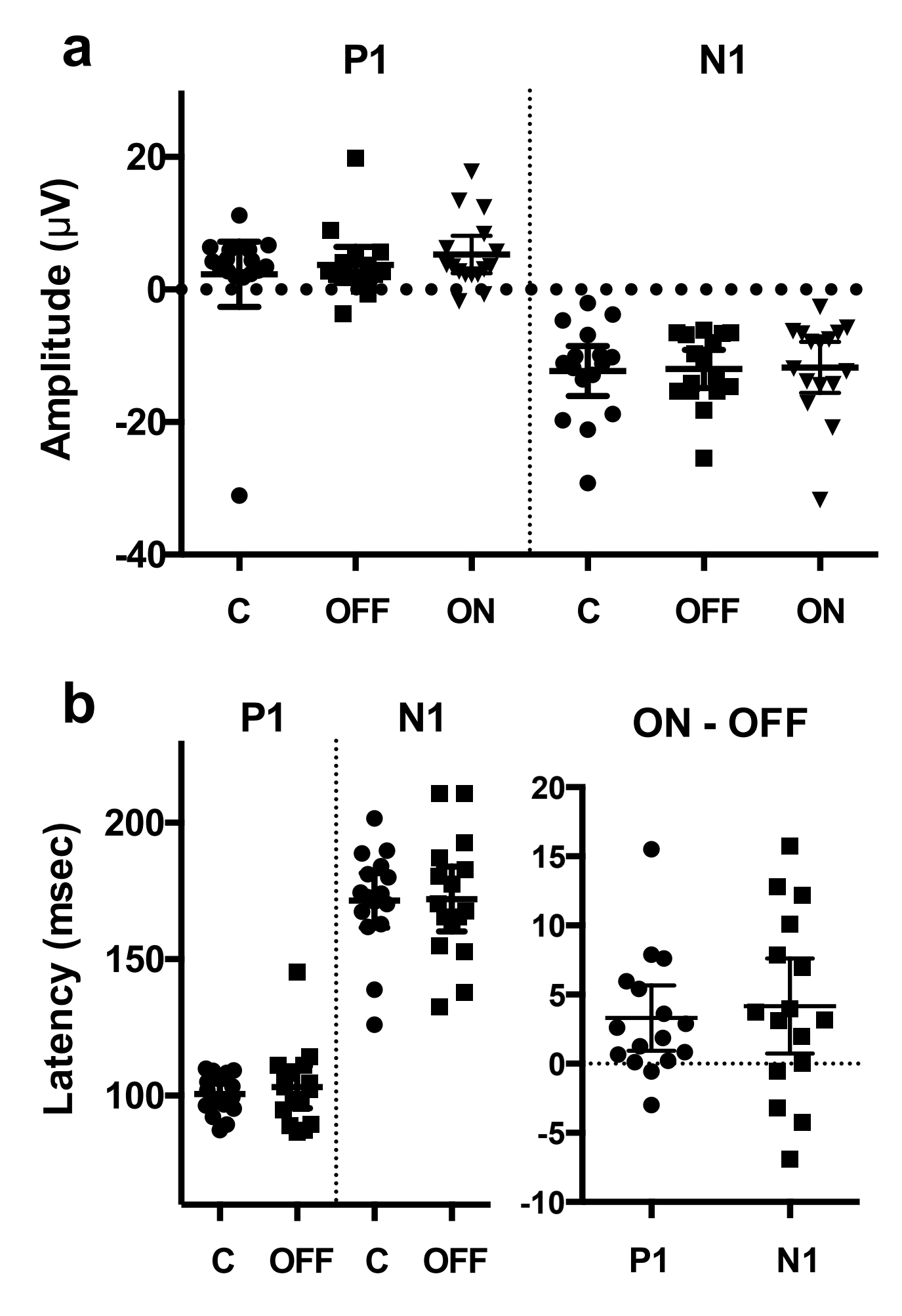
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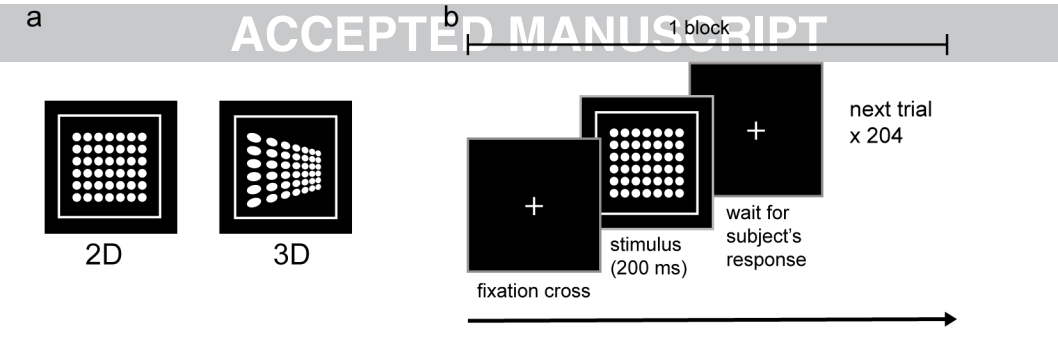

- 3D perception is necessary for navigation and optimal interaction with environment.
- Despite reported stereopsis loss, 3D vision based on monocular cues is intact in PD.
- Levodopa administration has no influence on 3D vision based on monocular cues.
- PD patients should rely more on visual m3D cues present in the environment.