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Short communication

# Spatial learning deficits in Parkinson's disease with and without mild cognitive impairment

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ABSTRACT

*Background:* Several MRI studies have demonstrated hippocampal atrophy in Parkinson's disease (PD), a structure considered a key element in spatial learning. Despite this, no study has been undertaken to investigate spatial navigation in PD using a virtual version of the Morris water maze, which is the gold standard for testing hippocampal function in rodents.
*Methods:* We studied 17 cognitively unimpaired PD patients, 12 PD patients with mild cognitive impairment (MCI) and 15 controls in a virtual water maze procedure.
*Results:* Measured by the main outcome parameters latency to locate the target and heading error (average difference between direction of movement toward anticipated target and real direction toward the target), controls performed significantly better on the virtual water maze task than cognitively unimpaired PD patients or PD patients with MCI, while there was no significant difference between latter two groups.
*Conclusions:* The virtual water maze test differentiates PD patients from controls, but does not distinguish between cognitively normal and cognitively impaired PD patients, indicating a possible dopamine dependent component in spatial learning. Spatial performance deficits might thus constitute very early signs of dopamine depletion independent of the presence of MCI in Parkinson's disease.


## 1. Introduction

Even though spatial disorientation has been described as an early non-motor symptom in Parkinson's disease (PD) more than 25 years ago [1], it has been investigated only sporadically. Spatial performance deficits constitute very early signs of dopamine depletion independent of the presence of MCI in Parkinson's disease. Consistently, the hippocampal formation has been identified as a key element in establishing a spatial map [2], and in the last years several MRI studies have demonstrated hippocampal atrophy in PD patients with greater atrophy in patients with mild cognitive impairment (MCI) compared to PD patients without MCI [3]. The Morris Water Maze is commonly regarded as the gold standard for testing hippocampal spatial cognition [4]. Recently, impaired spatial learning and decision making process of navigation was demonstrated in dopamine depleted rats using a Y-maze [5], but so far, a virtual version of the Morris water maze (vMWM) has not been used to study spatial learning in PD patients. The aim of this study was to test spatial learning in Parkinson's disease with a standardized vMWM paradigm, which was shown to be sensitive for focal hippocampal changes in humans [6]. To measure decision making processes in a spatial context the paradigm was extended to a spatial reversal learning task. We hypothesized that we could identify distinct spatial deficits in PD patients with MCI compared to PD patients and healthy controls.

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## 2. Subjects and methods

### 2.1. Subjects

Subjects across all ages and disease severities meeting the criteria for PD according to the UK PD Brain Bank criteria [7], or the diagnosis "PD with MCI" (PD-MCI) according to the consensus guidelines developed by Litvan and co-workers [8] were recruited as part of the larger ongoing DEMPARK/LANDSCAPE study [9]. Cognitively unimpaired healthy subjects served as controls. Subjects were excluded if they had an identifiable cause of parkinsonism or signs for atypical parkinsonian disorders, psychosis, signs of dementia (Mini Mental Status Examination [MMSE] $\leq$26 points), "PD dementia" according to Emre and co-workers [10], or other relevant conditions interfering with the study protocol. PD and PD-MCI patients were assessed during best motor On state. All participants provided written informed consent and the study was approved by institutional review board.

### 2.2. Assessments

We assessed demographic and clinical data including educational level and computer experience. All participants completed the Modified Card Sorting Test (MCST) to test executive functions, the word list memory, word list recall and constructional praxis parts of the **Consortium to Establish a Registry for Alzheimer's Disease** (CERAD) test battery to assess memory and visuospatial function. In addition, PD and PD-MCI patients completed the extensive neuropsychological test battery of the DEMPARK/LANDSCAPE study protocol [9].

### 2.3. Virtual water maze

We employed a computerized virtual version of the Morris water maze that has been used previously to analyze spatial memory in humans [6,11].

The experiment itself consisted of the following parts: 1) A training trial. 2) Twelve acquisition trials, in which participants had to find a hidden virtual target. The start position varied across trials in a block-randomized fashion. 3) After a 25 min delay, four reversal learning trials with the target hidden in a new position. 4) Three control trials with visible target, which served as an assessment of visuo-motor control. Quantitative behavioral measures assessed for each trial were (a) heading error (average difference between the direction of movement toward the anticipated target and the real direction toward the target), (b) path length (total distance moved in proportion to the total pool diameter), and (c) latency to locate the target. Heading errors served as key measure of hippocampal-dependent spatial information processing.

To investigate search strategies the following two methods were used: Eyeballing as the traditional method as defined by Garthe and co-workers [4], and a parameter-based automatic classification method described previously [12]. In both cases, search strategies were grouped into three categories, representing spatial strategies, non-spatial strategies, and miscellaneous movement patterns, which did not represent spatial or non-spatial learning.

### 2.4. Statistical analyses

For statistical comparisons, mean values of quantitative behavioral data from 2nd to 12th acquisition trial and 2nd to 4th reversal learning trials were used. Fisher's exact test, two-sided unpaired *t*-test, or one-way ANOVA were used to compare data as appropriate. Pearson's correlation were used to examine correlations with $|r|>0.5$ considered heuristical a relevant correlation. Data were analyzed using the software programs SPSS 21.0 (SPSS Inc., Chicago, IL) and SAS 9.2 (SAS Institute, Cary, NC). Significance level was set at $P < 0.05$ (two-tailed test). Pairwise deletion was applied to missing data. Finally, generalized linear models (GLM) were calculated using the candidate variables disease group, gender, education, experience with computer games, age. In addition, outcome variables of the control trials (visible target) were chosen as candidate variables for the GLM. They correlated significantly with UPDRS part III scores and, in contrast to the latter, were available for all three groups.

## 3. Results

### 3.1. Study cohort

A total of 17 PD patients (6 women, 11 men, mean age 64.3 ± SD 6.1 years [mean ± SD]), 12 PD-MCI patients (2 women, 10 men, 68.2 ± 5.6 years), and 15 control subjects (4 women, 11 men, 64.8 ± 6.6 years) were enrolled in the study. There were no significant differences between groups concerning age, sex, educational level, and computer experience. All participants were right handed. Disease duration was significantly longer for PD-MCI subjects (8.5 ± 5.5 years) than for PD subjects (4.5 ± 3.0 years, $P = 0.018$). PD-MCI participants also had higher UPDRS part III scores (22 ± 9 vs. 17 ± 4, $P = 0.028$) and Hoehn & Yahr stages ($P = 0.019$) than PD subjects. PANDA and CERAD word list memory scores were significantly higher for PD than PD-MCI subjects. None of the PD-MCI patients showed impairment of the visuospacial cognitive domain. (For extended clinical and neuropsychological data see Tables S1-S3.)

### 3.2. vMWM performance in acquisition trials

The performance data of the 12 acquisition trials are shown in Fig. 1*A-C*. The performance variables heading error, mean path length, and latency of trials 2 to 12 were subjected to GLM analysis using the candidate variables disease group, gender, education, experience with computer games, age, and outcome variable in control condition (visible target; Table 1). Mean *heading error* in the acquisition trials was larger for PD and PD-MCI than controls, while there was no difference between PD and PD-MCI. Education was the only influencing covariate, with participants with higher educational level showing smaller heading errors. Mean *path length* was longer for PD than for controls, while there was no difference between PD and PD-MCI or PD-MCI and controls. There were also effects for education with participants with higher educational level traveling shorter distances. Similar effects of group were found on mean *latency,* which was longer for PD and PD-MCI than controls, while there was no difference between PD and PD-MCI groups. No significant effects of the other candidate variables could be observed.

### 3.3. vMWM performance in reversal learning trials

Fig. 1*D-F* shows the performance data of the 4 reversal learning trials. The three performance variables were subjected to a GLM analysis as described above (Table 1). Significant effect of group were found on *heading error*, indicating larger heading errors for PD and PD-MCI than controls, while there was no significant difference between PD and PD-MCI. Similar effects were found on mean *latency,* which was longer for PD and PD-MCI than controls. Mean *path length* was shorter for controls and PD than PD-MCI with no significant difference between PD and controls. For all three performance variables the patient group was the only significant main effect.

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