RETROGRADE PROCEDURAL MEMORY IN PARKINSON'S DISEASE AND REM-SLEEP BEHAVIOR DISORDER

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INTRODUCTION

The **procedural memory,** a long-term and implicit memory, is in charge of the encoding, storage, and retrieval of the unconscious procedures that underlie motor or cognitive skills. Its analysis is particularly relevant in neurodegenerative diseases like Parkinson's disease (PD), due to the central role of the basal ganglia in procedural memory. Procedural memory can be separated into an anterograde and a retrograde component[1] (Fig 1).

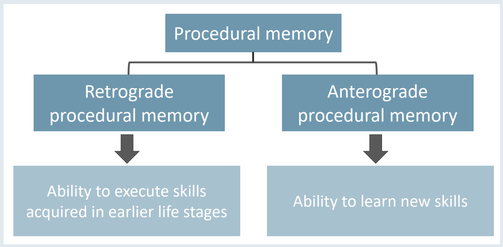


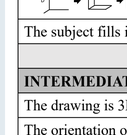
Figure 1. Procedural memory

It has been established that the anterograde procedural memory is affected in PD[2]. Observations on retrograde procedural memory have been done indirectly in form of case-reports[3] and studies on musical memory or overlearned language[1,4].

To our knowledge, validated protocols are missing to evaluate the retrograde part of this memory concept. Therefore, we developed the CUPRO, a brief assessment tool that allows to evaluate the functioning of retrograde procedural memory.

OBJECTIVES

The main objectives of our study were to:



Develop the CUPRO evaluation system to assess functioning of retrograde procedural memory[5]

H_1 **PD** Test the hypothesis (H_1) of a deficit of retrograde procedural memory in **people with PD** compared to control subjects (CS)[5]

H_2 **FOG** Test the hypothesis (H_2) of a deficit of retrograde procedural memory in **people with PD and freezing of gait** (FOG)

H_3 **RBD** Test the hypothesis (H_3) of a deficit of retrograde procedural memory in **people with REM-Sleep Behavior Disorder** (RBD) (at-risk cohort for PD)

+ Validation of our observations in an independent PD/RBD Cohort.

METHODS

Based on the Necker's Cube[6], we established an extended evaluation system, the CUPRO. It assesses both the:

- copying procedure, representing retrograde procedural memory
- final result, representing visuo-constructive functions (Fig. 2).

	YES	NO	
INTERMEDIATE SCORE 1 - IS_1			
The subject starts with one of the squares / surfaces / with the 3 axes	1	0	Retrograde procedural memory
A → The subject drew the inside sides B → The subject drew a second square (superposition) C → The subject drew a second face D → The subject drew the 3 axes and continued by drawing any other surface	1	0	
The subject fills in the connection lines correctly	1	0	
INTERMEDIATE SCORE 1 IS_1 /3			
INTERMEDIATE SCORE 2 – IS_2			Visuo-constructive abilities
The drawing is 3D, the proportions are correct	1	0	
The orientation of the drawing is correct (mirror image)	1	0	
The final result is correct	1	0	
INTERMEDIATE SCORE 2 IS_2 /3			
TOTAL SCORE /6			

Figure 2. Representation of the extended evaluation system for the Cube Copying Test, the CUPRO evaluation system. The first intermediate score (IS_1) evaluates the copying procedure, the second intermediate score (IS_2) the visuo-constructive functions. (A-D) Representation of the four copying procedures.

The Cube Copying Test meets the conditions of assessing retrograde procedural memory ➔ by copying the cube, a (i) previously learned procedure is (ii) unconsciously applied.

Global cognition was evaluated with the MoCA[7]. Given that a wide range of cognitive & neural processing capabilities are required for cube copying, additional testing for discriminant validity by investigating associations of cube copying performance with several related constructs was done with a subgroup of participants for which relevant tests were available (34≤N≤73) (Table 3).

RESULTS - I

For H_1, people with typical PD were compared with age and gender matched controls (CS) (Table 1). We observed significantly worse functioning of retrograde procedural memory in PD compared to the CS (Table 2). Higher MoCA scores and education correlated significantly with higher scores for retrograde procedural memory. No significant correlation for disease duration, MDS-UPDRS-III score, LEDD and depressive symptoms were found.

Variable	PD (n = 201) Mean	PD SD	CS (n = 201) Mean	CS SD	P-Values PD vs. CS
Gender, M / F	111 / 90		109 / 92		p = 0.920
Handedness , R / L / A	170 / 14 / 7 $^{+10\ na}$		180 / 6 / 10 $^{+5\ na}$		p = 0.139
Age, in years	64.84	10.20	64.71	10.18	p = 0.943
Education, in years	13.60	3.80	14.25	3.96	p = 0.128
MOCA total score (/30)	26.58	2.68	26.97	2.29	p = 0.246
MDS-UPDRS-III (/132)	32.80	13.40	4.59	5.10	p < 0.001 *,**
Hoehn and Yahr	2.06	0.53	0.00	0.00	p < 0.001 *,**
Stage 1 / 1.5 / 2 / 2.5 / 3 / 4 / 5	19 / 13 / 119 / 29 / 18 / 2 / 1 $^{+1\ na}$				
BDI-I (/63)	8.32	6.36	4.95	4.72	p < 0.001*,**
SAS (/42)	13.63	5.49	9.84	4.75	p < 0.001 *,**
Languages spoken	2.81	1.10	3.56	0.78	p < 0.001 *,**
Disease duration, in years	5.37	4.39	-	-	-
LEDD	596.35	391.30	-	-	-

Table 1. Demographic and clinical data for PD and CS

Variable		PD (n = 201) Mean	PD SD	CS (n = 201) Mean	CS SD	P-Values PD vs. CS
Extended evaluation system of the Cube Copying Test	IS_1 (/3)	2.05	1.13	2.43	0.90	p = 0.008 *,**
	IS_2 (/3)	2.26	1.10	2.59	0.84	p = 0.013 *,**

Table 2. CUPRO Cube scoring system

		N	Spearman – Correlation coefficient R	p
Visuo-constructive abilities	**Qualitative Scoring MMSE Pentagone Test**	54	- 0.103	p = 0.462
Visuo-spatial abilities	**Judgment of Ligne Orientation Benton**	56	+ 0.058	p = 0.249
Executive functions	**Frontal Assessment Battery**	73	+ 0.102	p = 0.392
Visuo-constructive abilities	**Rey-Osterrieth Complex Figure - Copy**	34	+ 0.169	p = 0.338
Planning functions	**Rey-Osterrieth Complex Figure - Type**	34	- 0.381	p = 0.831

Table 3. Discriminant validity - correlations for the IS1 and possible interfering factors

Neither visuo-constructive, visuo-spatial, planning nor executive functions significantly interfered with the score representing retrograde procedural memory (Table 3).

Retrograde Procedural Memory in Parkinson's disease

RESULTS - II

For H_2, people with typical PD and FOG (FOG^+) were compared with their age, gender, education and disease duration matched control group patients without FOG (FOG^-) (Table 4).

Variable	FOG^+ Mean	FOG^+ SD	FOG^- Mean	FOG^- SD	P-Values FOG^+ vs. FOG^-
N Total	127		127		
N GBA+ / GBA-	15/105 $^{+7NA}$		12/92 $^{+23NA}$		p = 0.988
Gender, M / F	87 / 40		83 / 44		p = 0.689
Age, in years	67.26	9.97	66.85	9.49	p = 0.417
Disease duration, in years	4.66	3.94	4.60	3.92	p = 0.962
Education, in years	13.35	3.93	13.10	3.63	p = 0.818
MDS-UPDRS I (/52)	10.81	6.34	7.67	4.94	p < 0.001**
MDS-UPDRS II (/52)	11.93	6.50	7.49	5.15	p < 0.001**
MDS-UPDRS III (/132)	36.60	12.62	33.05	12.78	p = 0.042*
Modified Hoehn and Yahr	2.24	0.54	1.99	0.43	p = 0.001 **
Stage 1 / 1.5 / 2 / 2.5 / 3 / 4 / 5	3/4/78/22/14/5/0		9/14/82/15/7/0/0		
LEDD	612.10	419.10	523.90	315.30	p = 0.204
BDI-I (/63)	9.61	7.37	6.21	5.42	p < 0.001**
SAS (/42)	14.22	5.21	12.52	5.68	p = 0.005*
FAQ (/30)	2.82	4.45	1.35	2.32	p = 0.009*
PDQ-39 (/156)	25.94	17.60	15.51	11.89	p < 0.001**
IQCode (/5)	3.09	0.47	3.09	0.31	p = 0.217
Languages spoken	2.81	1.07	2.73	1.14	p = 0.672

Table 4. Demographic and clinical data for FOG^+ and FOG^-

Variable		N FOG+ /FOG-	FOG^+ (n = 127) Mean	FOG^+ SD	FOG^- (n = 127) Mean	FOG^- SD	P-Values FOG+ vs. FOG-
CUPRO Evaluation System	**IS_1 (/3)**	127/127	1.88	1.10	2.23	1.07	p = 0.009*
	IS_2 (/3)	127/127	2.24	1.12	2.32	1.01	p = 0.719
General Cognition	**MOCA total score (/30)**	127/127	25.91	2.67	26.69	2.39	p = 0.022*
Psychomotor speed / Executive functions	**TMT-A (sec)**	123/122	54.72	33.55	47.73	22.59	p = 0.057
	TMT-B (sec)	123/122	141.20	80.63	112.20	58.63	p = 0.006*
	Delta TMT (sec)	123/122	86.46	70.65	64.51	46.75	P = 0.007*

Table 5. Neuropsychological assessments

Besides lower global cognition and executive functions, FOG^+ performed worse in retrograde procedural memory compared to matched control patients (Table 5).

DISCUSSION & OUTLOOK

Despite the importance of procedural memory in our daily life activities and the numerous studies that have investigated this topic, there are still many discrepancies, mainly due to the varying definitions of the memory concept and to the nature of the used tasks[8]. Until now, assessments primarily evaluated the motor, perceptual and cognitive procedural learning, with tasks such as the pursuit rotor task[9], serial reaction time task[10], and arithmetic alphabet test[11]. Only few studies focused on the suggested long-term retention of new skills [12,13,14].

The CUPRO evaluation system has a number of strengths: it is simple to administer and as the Cube Copying test is widely used in clinical and research settings it is already incorporated in standard assessments, i.e. MoCA. Therefore, it can be easily integrated in protocols. It adds valuable information to an already well-established screening tool without increasing the burden for patients. However, we can not verify if all participants learned the drawing of geometric forms . The non-conscious acquiring of skills makes it difficult to gain insights into if and how the strategy of cube drawing has been learned.

Our findings suggest that impaired retrograde procedural memory could be detectable in a prodromal, non-motor stage of the disease. Given that diagnosing PD means identifying an already advanced disorder with progressed neurodegeneration, it is essential to advance in the identification of early marker in order to aim the early diagnosis of PD. Therefore, in an upcoming study we investigate this memory concept in a PD-risk cohort, with people with REM sleep Behavior Disorder (RBD) (H_3). Additionally, future research will validate the CUPRO evaluation system in an independent Parkinson's disease cohort.

CONCLUSION

The integrity of retrograde procedural memory is crucial for a person's ability to conduct routine activities of daily living. This study established a new tool to assess functioning of retrograde procedural memory and showed deficits in retrograde procedural memory in people with PD compared with control subjects. Furthermore, we were able to observe declined procedural memory in PD with FOG. These insights may lead to hypotheses on FOG aetiology and the development of treatment options.

The CUPRO evaluation system will not only fill the gap of techniques for reliably assessing functioning of retrograde procedural memory in clinical settings but may also help to identify valuable perspectives for future research.

Abbreviations SD: Standard Deviation; PD: People with Parkinson's disease; CS: Control subjects; FOG^+: Freezers ; FOG^-: non-Freezers; M: Male; F: Female; R: Right-handed; L: Left-handed; A: Ambidextrous; na = not available; n = sample size; MDS-UPDRS: Movement Disorder Society - Unified Parkinson's Disease Rating Scale; BDI: Beck Depression Inventory; SAS: Starkstein Apathy Scale; PDQ-39: Parkinson's disease questionnaire 39-item MoCA: Montreal Cognitive Assessment; LEDD: Levodopa Equivalent Daily Dose; IS: Intermediate Score. * Significant at the 5% level (2-tailed). ** Significant at the Bonferroni-adjusted 5% level (2-tailed).

References: [1]Crystal et al. (1989); [2]Muslimović et al. (2007); [3]Matthews et al. 2015; [4]Bridges et al. (2013), [5]Pauly et al. (2022), [6]Necker (1832); [7]Nasreddine (2005); [8]Seidler et al. (2007); [9]Heindel et al. (1989), [10]Clark et al. (2019); [11]Thomas et al. (1996); [12]Crystal et al. (1989), [13]Cohen et al. (2007), [14]Mochizuki-Kawai et l. (2004).

[5]Pauly L, Pauly C, Hansen M, Schröder VE, Rauschenberger A, Leist AK - Retrograde Procedural Memory in Parkinson's Disease: A Cross-Sectional, Case-Control Study. J Parkinsons Dis; 2022

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