The Dual Effect of Cholesterol on Cognitive Functions in REM Sleep Behavior Disorder: a Pilot Study

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INTRODUCTION

Isolated REM sleep behavior disorder (iRBD) is widely recognized as a prodromal stage of α-synucleinopathies [1]. Cholesterol metabolism has been implicated in several neurodegenerative mechanisms [2], and recently linked to α-synuclein aggregation [3]. **No study so far has examined the role of cholesterol in iRBD.**

AIMS

To perform the first analysis to explore the relationship between cholesterol levels and cognitive performance in individuals with iRBD.

METHODS

Seventyseven (77) video-polysomnography-confirmed iRBD patients. Measurement of **total cholesterol (TC) levels**. A **comprehensive neuropsychological assessment** across the following domains: Global Cognition, Short-term Memory, Verbal Long-term Memory, Language,, Visuospatial Function, Visuospatial Long-term Memory, and Executive/Attentive Functions.

Cognitive status (**CS**) was defined as: "**cognitively impaired**" (**CI**), if they exhibited a deficit in at least one test; "**cognitively unimpaired**" (**CU**) if they exhibited no deficits in any neuropsychological test.

RESULTS

Table 1. Individuals in the cognitively unimpaired group were significantly younger and had a significantly higher level of education compared to those in the cognitively impaired group. Cognitively impaired individuals performed significantly worse on all neuropsychological tests, except for digit span forward (after FDR correction) and attentional matrices. No significant differences were observed between the groups in terms of gender distribution, cholesterol levels, or use of lipid-lowering therapy.

Table 1	CU (n=44)	CI (n=30)	p
Sex (female)	8 (18.18%)	7 (23.33%)	1.000
Age	66.45 (59.60; 71.60)	71.60 (68.05; 76.20)	0.002
Education (years)	13.00 (8.00; 13.00)	8.00 (5.25; 13.00)	< 0.001
Dominance (left)	4 (9.09%)	1 (3.33%)	0.588
Cholesterol	174.00 (145.75; 213.50)	177.50 (159.50; 221.50)	0.408
Triglycerides	102.50 (76.75; 150.50)	120.00 (90.75; 150.25)	0.460
Glucose	91.00 (79.00; 104.50)	85.50 (75.25; 91.75)	0.205
High cholesterol	15 (34.09%)	9 (30.00%)	0.907
LLT	13 (29.54%)	11 (36.66%)	0.793
MMSE	27.99 (27.48; 28.92)	26.28 (25.20; 27.96)	0.006
Token test	32.75 (32.00; 33.62)	30.38 (28.38; 32.12)	< 0.001
Semantic fluency	46.00 (42.75; 52.00)	39.50 (33.25; 43.00)	< 0.001
Phonemic fluency	36.50 (29.75; 43.00)	27.50 (20.25; 37.50)	0.002
Naming	48.00 (48.00; 48.00)	47.21 (46.00; 48.00)	< 0.001
Digit span forward	5.85 (5.35; 6.40)	5.54 (4.65; 6.26)	0.038*
Digit span backward	4.39 (3.74; 4.98)	3.71 (3.23; 4.28)	0.004
Corsi test	5.30 (4.81; 5.81)	4.58 (4.17; 5.25)	< 0.001
RAVLT immediate	45.80 (36.57; 51.55)	37.20 (29.00; 45.00)	0.002
RAVLT recall	9.25 (6.60; 11.50)	7.80 (5.00; 9.40)	0.007
RAVLT recognition	14.00 (13.00; 15.00)	13.00 (11.00; 15.00)	0.019
ROCF recall	19.12 (15.81; 24.19)	10.75 (8.06; 13.31)	<0.001
RPM	31.00 (28.50; 33.50)	24.50 (21.00; 28.88)	< 0.001
Attention matrices	49.00 (45.44; 51.31)	44.88 (41.25; 50.25)	0.108
ROCF copy	33.50 (31.94; 35.00)	25.00 (22.31; 27.12)	<0.001

Abbreviations: LLT = Lipid-lowering treatment, MMSE = Mini-Mental State Examination, RAVL = Rey Auditory Verbal Learning Test, ROCF = Rey-Osterrieth Complex Figure, RPM = Raven's Progressive Matrices. Values quoted in the table are medians (IQR) for continuous variables, and frequencies (percentage) for categorical variables. * = significance lost after FDR correction.

Figure 1. Linear models revealed a significant interaction between cholesterol and cognitive status on language, verbal long-term memory, and visuospatial long-term memory. Cholesterol levels were positively associated with performance on language (p = 0.047) and visuospatial long-term memory (p = 0.041) in cognitively unimpaired participants. A trend for a negative effect of cholesterol levels on verbal long-term memory (p = 0.089) appeared in cognitively impaired patients (Fig 1).

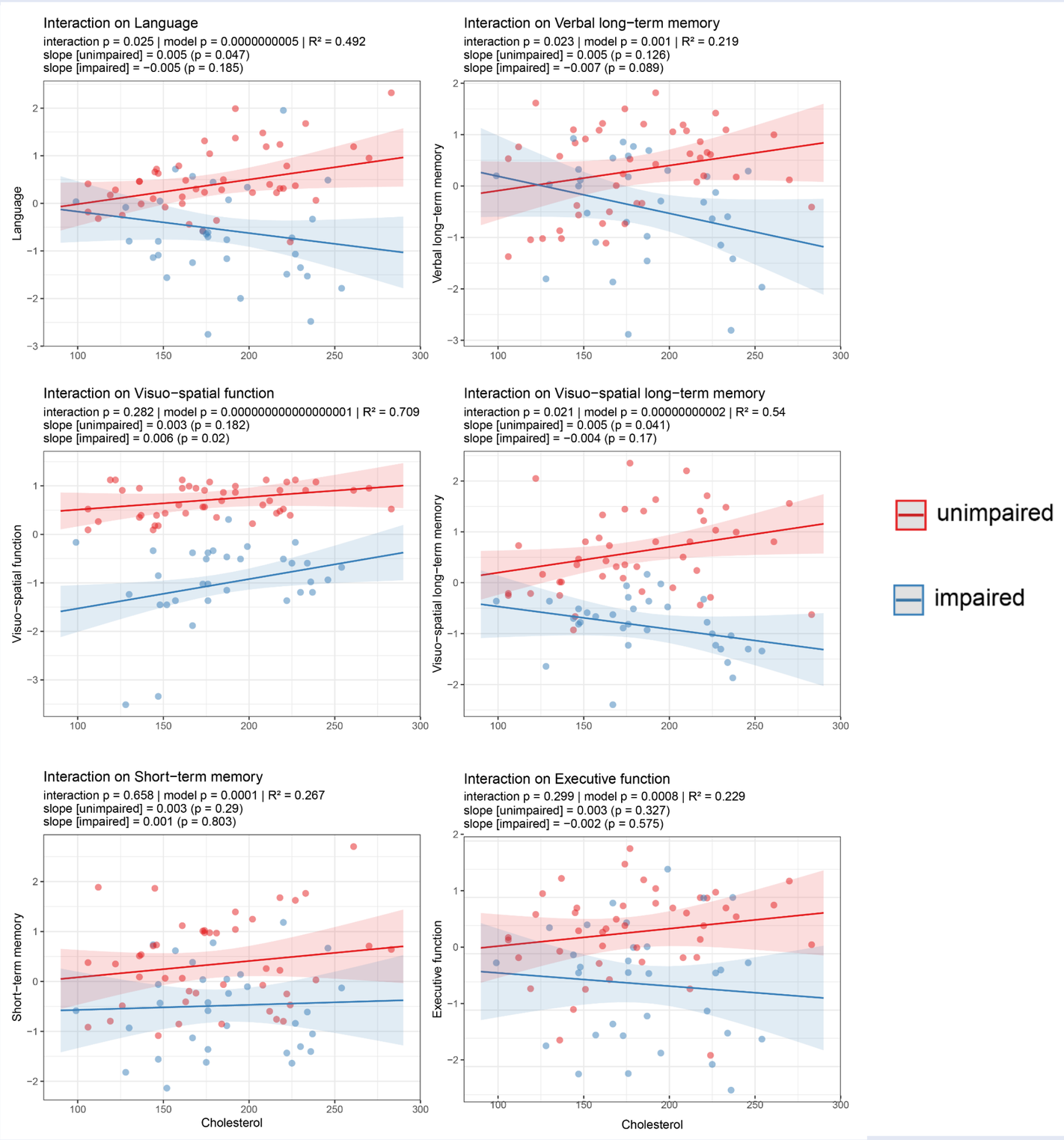

Figure 1. Scatter plots of cholesterol and cognitive domains, with slopes for cognitively unimpaired (**red**) and cognitively impaired (**blue**) subjects.

CONCLUSION

- A bidirectional associations between TC levels and CS suggest that cholesterol may have a differential impact on cognitive function depending on cognitive status in iRBD, highlighting its role in early neurodegenerative processes.
- From a pathological perspective, it could shed light on a modifiable factor involved in the development of α-synucleinopathies.
- From a clinical standpoint, future studies might explore the therapeutic potential of cholesterol modulation as a strategy to mitigate cognitive decline in at-risk populations.

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