

Associations between hypothalamic volume, sleep architecture, and memory performance according to *APOE-ε4* status in Alzheimer’s disease

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BACKGROUND

APOE-ε4 is the strongest genetic risk factor in sporadic Alzheimer’s Disease (AD), and its status may exacerbate neurodegeneration and modulate sleep. The hypothalamus plays a key role in cognition, particularly in memory given its connection with the hippocampus and the regulation of physiological states such as sleep and arousal. This role may be affected by *APOE-ε4*-related neurodegeneration.

We aimed to compare **hypothalamic volume** and **polysomnography parameters**, and to explore **their relationship with neuropsychological performance** between *APOE-ε4* carriers and non-carriers in AD.

METHODS

Seventy-nine AD biomarker confirmed individuals were classified into two groups:



Participants underwent:

- **MRI T1** sequences to quantify the volumes of the **whole hypothalamus and its subunits**
- **Subjective** (Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale) and **objective** (overnight polysomnography) **sleep measures**
- **Neuropsychological assessment**

Statistical analyses:

- **Hypothalamus volumes** and **polysomnography variables** differences between *APOE* carriers and non-carriers were compared using ANCOVAs, adjusting for age and for age and sleep medication, respectively
- **Linear regression models** were used to explore the **association** between **hypothalamic volume** and **polysomnography with neuropsychological performance**, adjusting for age, education, sex and sleep medication, when appropriate

RESULTS

- **No between-group differences were found** in demographic characteristics, CSF biomarkers, clinical variables, global cognition or subjective sleep measures (*Table 1*).
- ***APOE-ε4* carriers** showed **reduced volume** in the **whole hypothalamus** ($F(1,54)=4.932$, $p<0.05$) and the **anterior-superior subunit** ($F(1,55)=4.626$, $p<0.05$) than non-carriers (*Figure 1A*).
- ***APOE-ε4* carriers** spent **more time in REM vs. Non-REM** ($F(1,44)=4.676$, $p<0.05$), **REM Total Sleep Time (TST) (%)** ($F(1,44)=5.550$, $p<0.05$), and **N3 TST (%)** ($F(1,44)=4.278$, $p<0.05$) than non-carriers (*Figure 1B*).
- Linear regression models showed an **association** between the **whole hypothalamus volume** and **verbal learning** ($\beta=0.53$, $sd=0.025$, $p<0.05$) and **encoding** ($\beta=0.112$, $sd=0.047$, $p<0.05$), **only in carriers** (*Figure 2*).
- The **percentages of REM and N3 sleep** were associated with **higher performance across multiple cognitive domains** ($\beta=0.068-5.614$; all $p<0.05$), **only in non-carriers** (*Figure 3*).

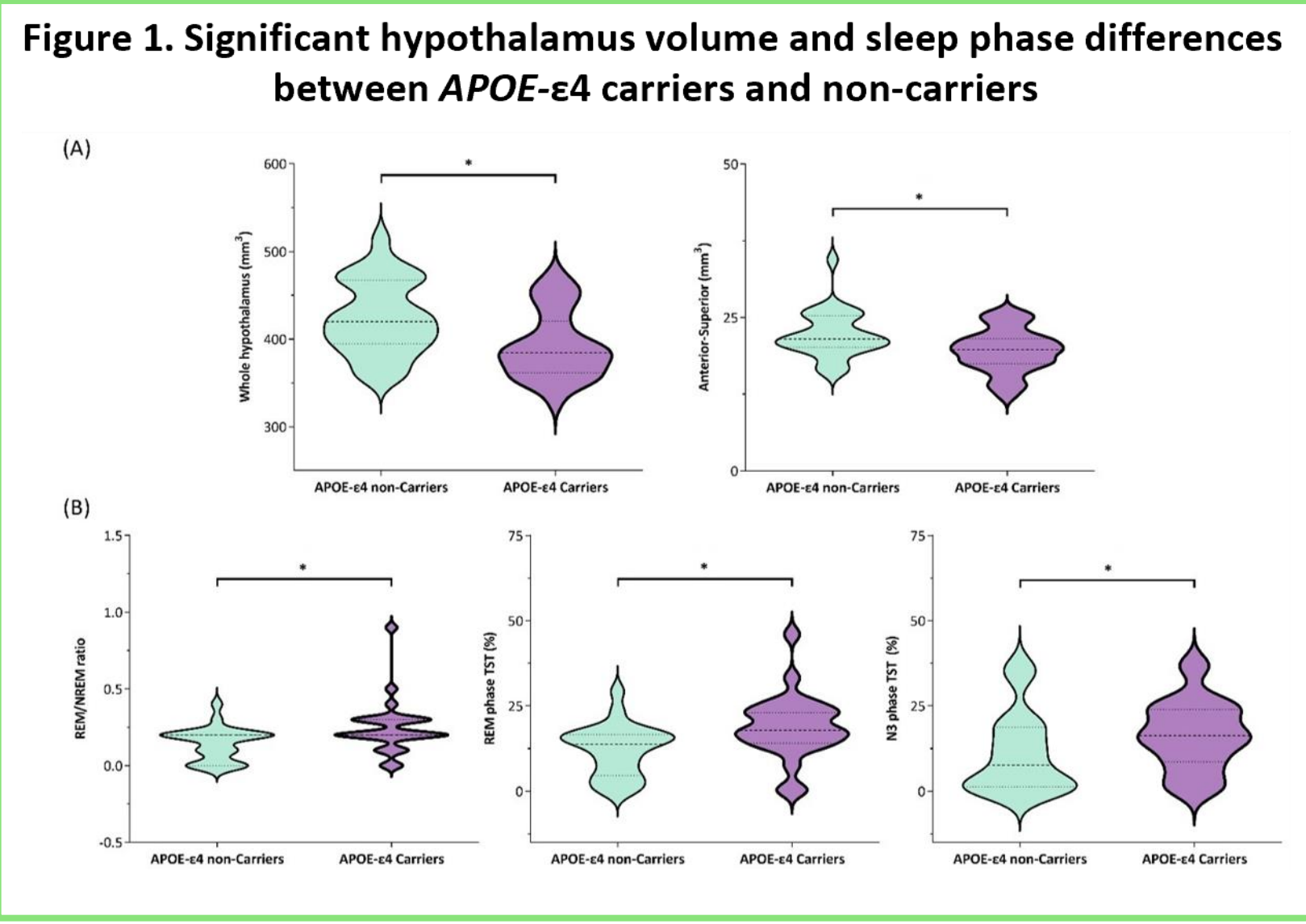
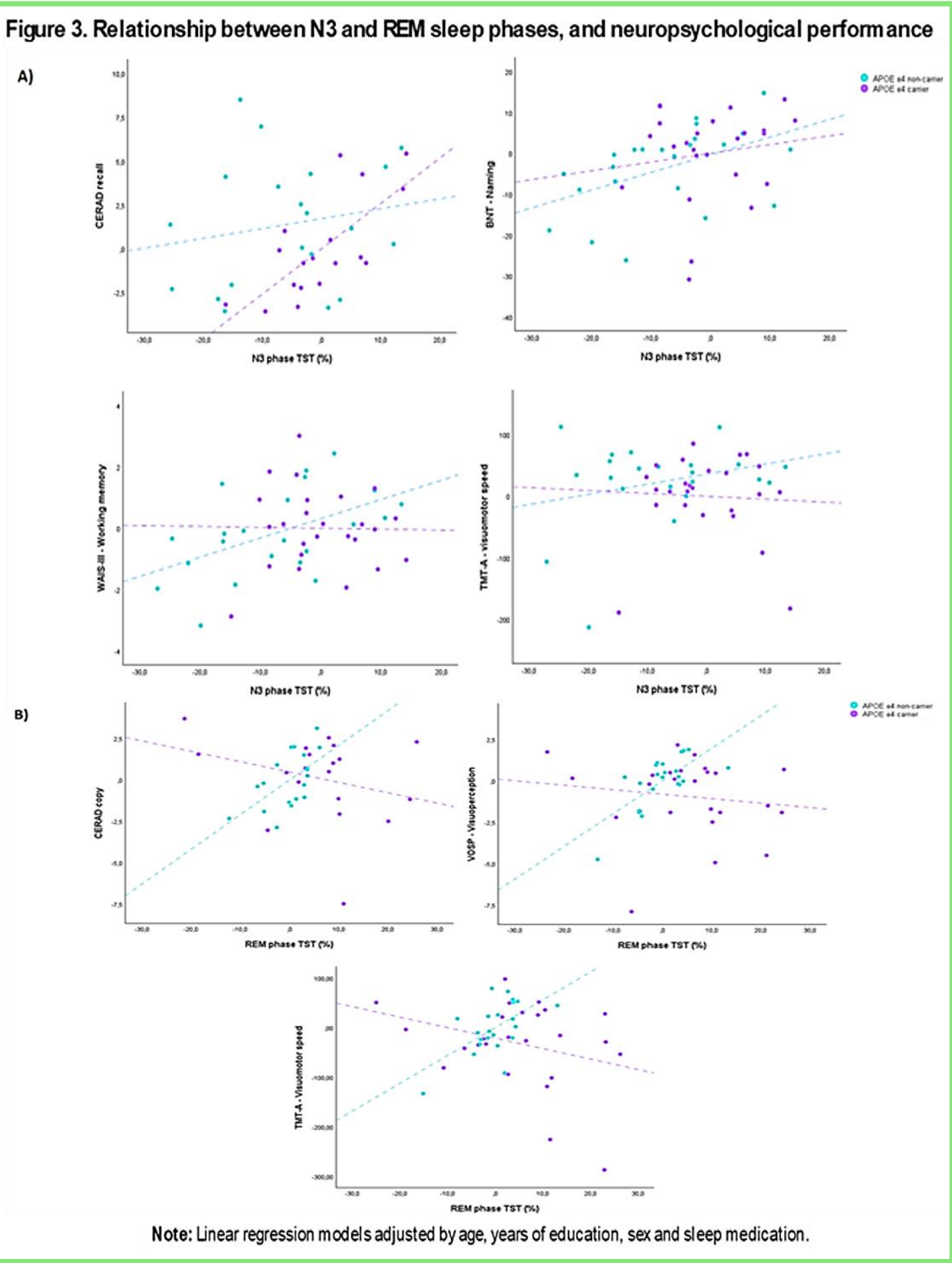
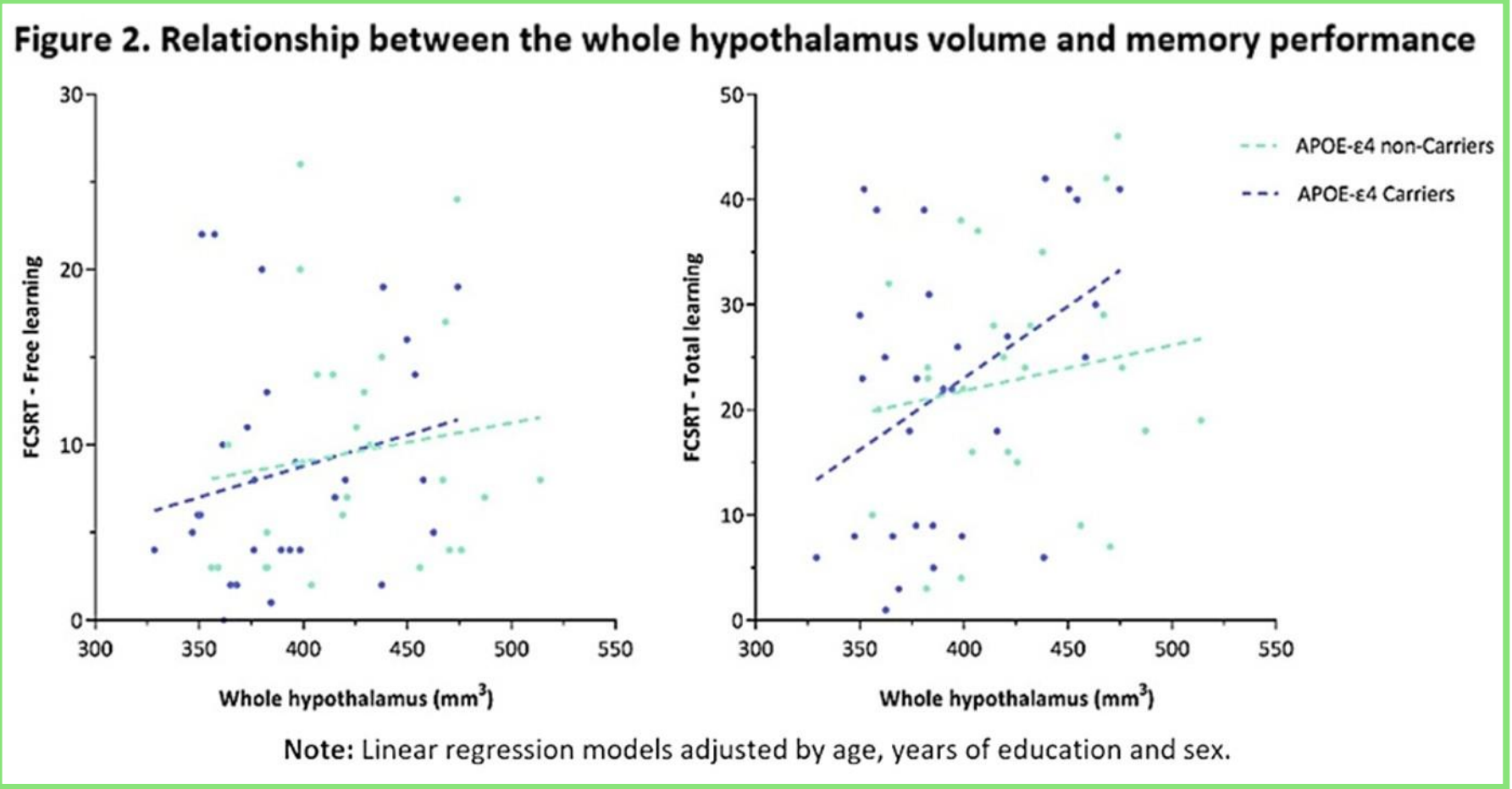


Table 1. Demographics, CSF biomarkers, clinical data, global cognition and sleep measures differences between <i>APOE-ε4</i> carriers and non-carriers.				
	<i>APOE-ε4</i> carriers	<i>APOE-ε4</i> non-carriers	t	p value
Age	71.41 ± 5.85	69.43 ± 7.48	-1.320	0.19
Sex (% female)	56.8%	51.4%	0.228	0.63
Years of education	12.39 ± 3.68	11.85 ± 3.78	-0.627	0.53
CSF Aβ42 (pg/mL)	399.16 ± 113.5	423.84 ± 155.33	0.738	0.46
CSF t-tau (pg/mL)	586.97 ± 172.24	642.74 ± 295.13	0.931	0.35
CSF p-tau (pg/mL)	90.66 ± 34.68	102.19 ± 50.03	1.088	0.28
Sleep medication (%)	22.7%	14.3%	0.903	0.34
MMSE	23.31 ± 3.93	25 ± 3.74	1.781	0.08
ESS	4.7 ± 3.89	5.62 ± 3.6	1.060	0.29
PSQI	5.39 ± 3.9	6.15 ± 4.28	0.818	0.41
Total Sleep Time (min)	316.92 ± 104.99	340.08 ± 101.6	0.776	0.44
Sleep Latency	33.32 ± 50.4	16.15 ± 12.57	-1.644	0.11
WASO	110.8 ± 71.47	120.95 ± 86.45	0.445	0.65
Sleep Efficiency	65.91 ± 20.79	69.05 ± 19.9	0.533	0.59

Note: Data is presented as means ± standard deviation for continuous variables and as percentages for categorical variables. t-values are reported for continuous variables and χ^2 for categorical variables. Abbreviations: MMSE, Mini-Mental State Evaluation; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; WASO, Wake After Sleep Onset; TST, Total Sleep Time.

* $p<0.05$; ** $p<0.01$



CONCLUSIONS

APOE-ε4 genotype could **modulate the relationship** between **hypothalamic atrophy** and **sleep architecture**, and **neuropsychological performance** in AD, with **carriers showing greater vulnerability**.

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