NEURON REACTIVITY DYNAMICS DURING PROLONGED WAKEFULNESS IS LINKED TO COGNITIVE FITNESS IN HEALTHY OLDER INDIVIDUALS

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BACKGROUND

Neuron reactivity is a basic aspect of brain function that sets neuron selectivity to a given stimulation.

In young individuals, neuron reactivity is influenced by both sleep homeostasis and the circadian timing system, and is related to cognitive performance.

Age-related degradation of sleep and wakefulness regulation is related to cognitive abilities (cognitive fitness)

Here, we sought to investigate the relationship between the dynamics of neuron reactivity during prolonged wakefulness and cognitive fitness in healthy older individuals.

METHODS

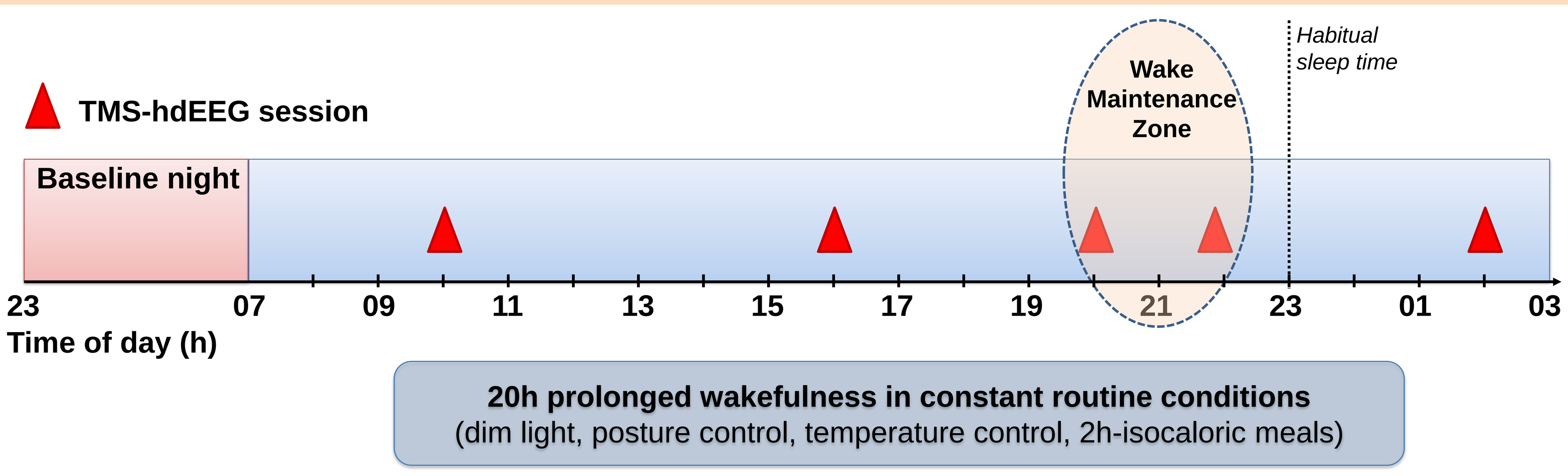


FIGURE 1. EXPERIMENTAL PROTOCOL.

Forty-seven healthy older individuals (30 females, 17 males; aged 59.3 + 5.2 years) underwent 5 TMS-EEG recording sessions during 20 hours of sustained wakefulness under strictly controlled constant routine conditions. Frequency of TMS sessions was increased around the theoretical wake-maintenance zone. Hourly saliva samples were collected for subsequent melatonin assays.

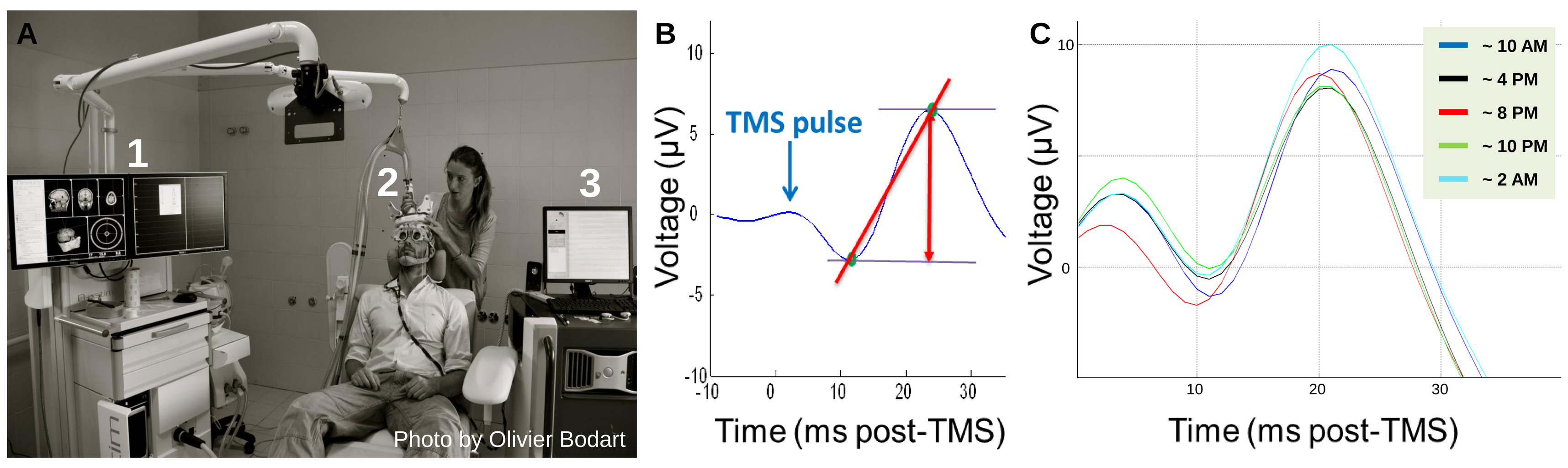


FIGURE 2. TMS-EEG APPARATUS AND EARLY TMS-EVOKED RESPONSES.

A. **1.** Neuronavigation system – target: superior frontal gyrus, sensitive to sleep need and allowing artefact free recording. **2.** Magnetic perturbation of neuronal activity with TMS coil – **3.** Neuronal response recording with 60-channel TMS-compatible EEG amplifier.

B. Neuron reactivity is defined as the *slope* of the early (0-35ms) TMS-evoked responses at the electrode closest to the maximum TMS-evoked electric field.

C. Early response across the 5 sessions in a representative subject.

Circadian phase of each TMS recording was estimated based on dim-light melatonin onset (DLMO).

MEMORY FUNCTION	EXECUTIVE FUNCTION	ATTENTIONAL FUNCTION
Mnemonic Similarity Task	Visual 3-Back	Visual 1-Back
Free and Cued Selective Reminding Test	Verbal Fluency (Letter and Category)	Digit Symbol Substitution Task
	Stroop Colour and Word Test	D2 Test of Attention
	Trail Making Test (part B)	Trail Making Test (part A)
	Reverse-Order Digit Span	

FIGURE 3. EXTENSIVE NEUROPSYCHOLOGICAL ASSESSMENT.

Cognitive fitness was estimated using a comprehensive battery of neuropsychological tasks assessing memory, executive, and attentional functions. The battery was administered outside the prolonged wakefulness protocol, in two sessions, while well-rested. For each domain, a composite score was computed to estimate domain-specific cognitive performance.

RESULTS

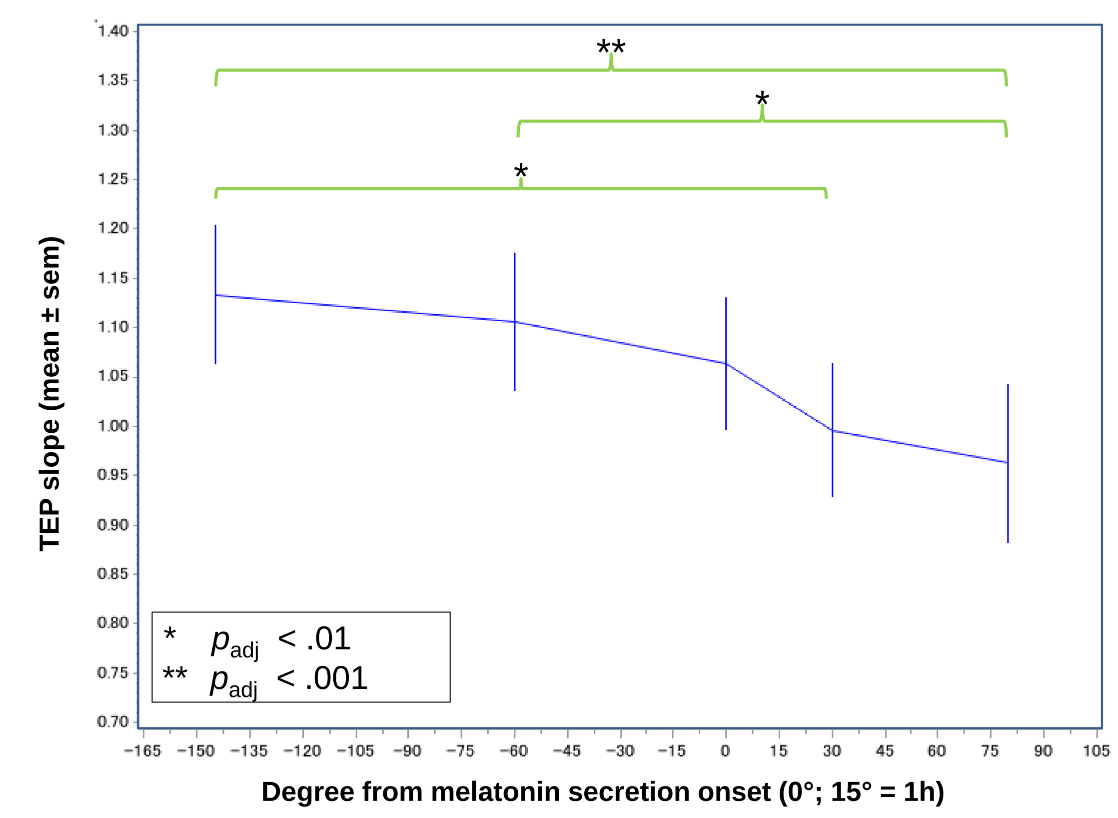
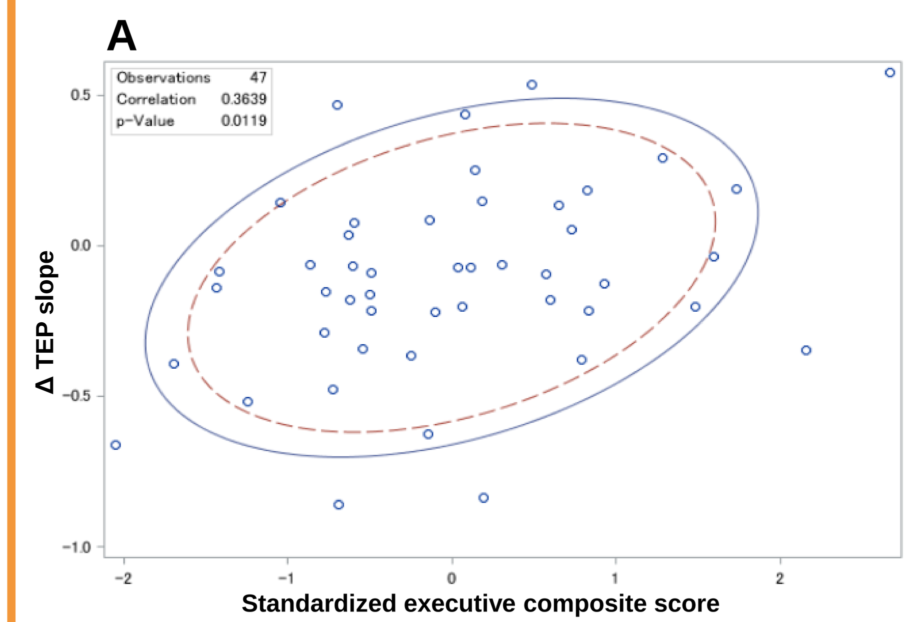


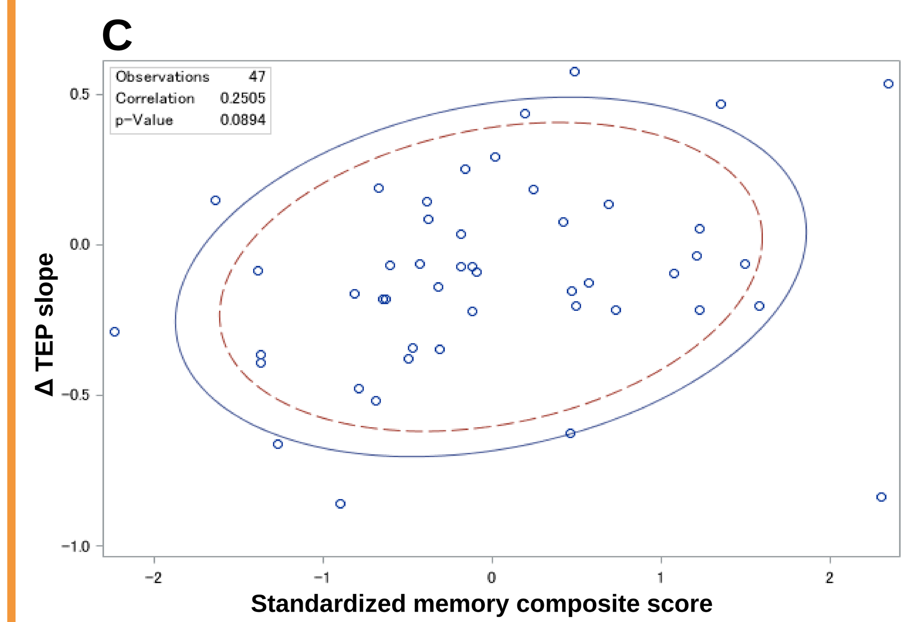
FIGURE 4. POPULATION AVERAGE NEURON REACTIVITY DECREASES WITH TIME AWAKE

Time course of average neuron reactivity during 20 hours of sustained wakefulness (mean ± sem). Time in degrees (15° = 1h) relative to the onset of melatonin secretion (0°). Generalized linear mixed model analyses (PROC GLIMMIX) reveal a main effect of circadian phase ($F_{4,55}$ = 7.26, p < .0001), after controlling for age, sex, and education. Post-hoc analyses show a gradual decrease of TEP slope during prolonged wakefulness, with the strongest significant difference between circadian phase -145° and 80° (p_{adj} = .0003)



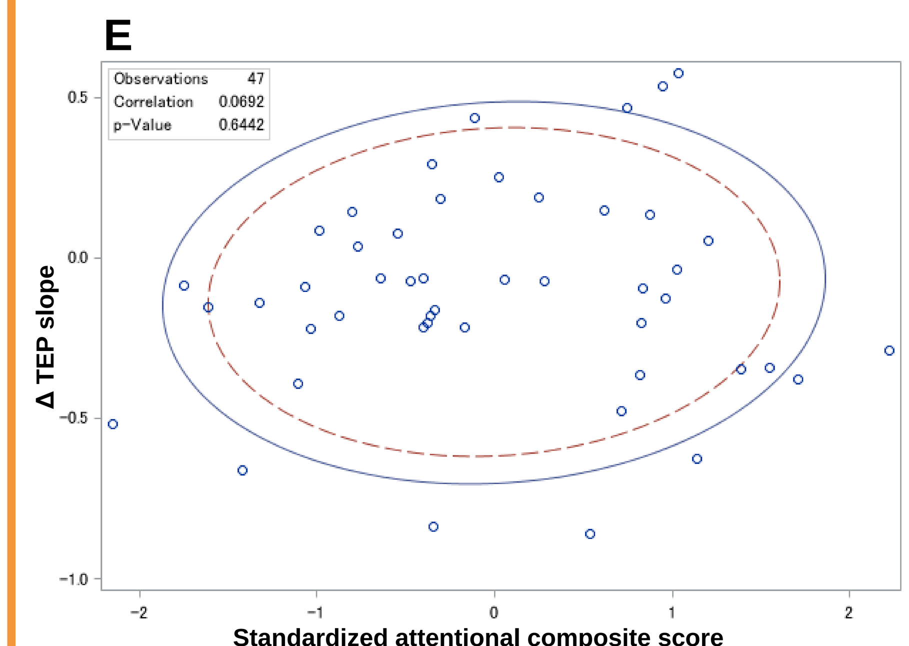
B

Type III Tests of Fixed Effects			
Effect	Beta (std error)	F-value	p-value
Δ TEP slope	1.24 (0.42)	$F_{1,42}$ = 8.73	p = .0051**
Age	-0.02 (0.03)	$F_{1,42}$ = 0.76	p = .3890
Sex	0.12 (0.28)	$F_{1,42}$ = 0.16	p = .6916
Education	0.11 (0.04)	$F_{1,42}$ = 7.10	p = .0109*



D

Type III Tests of Fixed Effects			
Effect	Beta (std error)	F-value	p-value
Δ TEP slope	0.93 (0.46)	$F_{1,42}$ = 3.95	p = .0534
Age	-0.01 (0.03)	$F_{1,42}$ = 0.07	p = .7945
Sex	0.33 (0.30)	$F_{1,42}$ = 1.15	p = .2904
Education	0.07 (0.05)	$F_{1,42}$ = 1.63	p = .2093



F

Type III Tests of Fixed Effects			
Effect	Beta (std error)	F-value	p-value
Δ TEP slope	0.51 (0.44)	$F_{1,42}$ = 1.35	p = .2516
Age	-0.07 (0.03)	$F_{1,42}$ = 6.14	p = .0173*
Sex	0.30 (0.29)	$F_{1,42}$ = 1.06	p = .3080
Education	0.07 (0.04)	$F_{1,42}$ = 2.51	p = .1205

FIGURE 5. DYNAMICS IN NEURON REACTIVITY IS RELATED TO DOMAIN-SPECIFIC COGNITIVE PERFORMANCE.

A. Significant correlation between the *dynamics in neuron reactivity*, **defined as the increase of TEP slope from the first to the last TMS session (Δ TEP slope)**, and executive performance (Pearson, r = .3639, p = .0119).

B. Generalized linear mixed model analyses (PROC GLIMMIX) reveal that neuron reactivity dynamics is significantly associated with executive performance, after controlling for age, sex, and education ($F_{1,42}$ = 8.73, p = .0051).

C. No significant correlation was found with memory performance (Pearson, r = .2505, p = .0894).

D. Generalized linear mixed model analyses (PROC GLIMMIX) show no statistically significant association with memory performance after controlling for age, sex, and education ($F_{1,42}$ = 3.95, p = .0534).

E. No significant correlation was found with attentional performance (Pearson, r = .0692, p = .6442).

F. Generalized linear mixed model analyses (PROC GLIMMIX) show no significant association with attentional performance after controlling for age, sex, and education ($F_{1,42}$ = 1.35, p = .2516).

CONCLUSIONS

- **Healthy older individuals who exhibit temporal pattern of frontal neuron responsiveness similar to younger individuals, also perform better at tasks probing executive functions.**
- **Executive tasks are known to involve brain networks which include the investigated region of stimulation.**
- **This provides new insights into the link between temporal regulation of neuronal function and cognition among older people, as well as a potential use of neuron reactivity measures as a new marker of cognitive fitness in older individuals.**

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