**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**

![TMS-tfEEG session](image)

![20h prolonged wakefulness in constant routine conditions (dim light, posture control, temperature control, 2h isotonic meals)](image)

**FIGURE 1. EXPERIMENTAL PROTOCOL.**

Forty-seven healthy older individuals (30 females, 17 males; aged 59.3 ± 5.2 years) underwent 5 TMS-tfEEG 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. Healthy saliva samples were collected for subsequent melanotropin assays.

**FIGURE 2. TMS-tfEEG APPARATUS AND EARLY TMS-EVOKED RESPONSES.**


**MEMORY 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, well-rested. For each domain, a composite score was computed to estimate domain-specific cognitive performance.

**RESULTS**

![Degree from baseline to sleep TMS](image)

**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 (PROCO GLIMMIX) reveal a main effect of circadian phase (F = 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 90° (p < .0003).

![Degree from baseline to sleep TMS](image)

**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’s r = 0.289, p < 0.019). B. Generalized linear mixed model analyses (PICO GLIMMIX) reveal that neuron reactivity dynamics is significantly associated with executive performance, after controlling for age, sex, and education (p = 0.019). C. No significant correlation was found with memory performance (Pearson’s r = 0.205, p > 0.05). D. Generalized linear mixed model analyses (PICO GLIMMIX) show no statistically significant association with memory performance after controlling for age, sex, and education (p = 0.019). E. No significant correlation was found with attentional performance (Pearson’s r = 0.692, p = 0.642). F. Generalized linear mixed model analyses (PICO GLIMMIX) show no significant association with attentional performance after controlling for age, sex, and education (p = 0.832).

**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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