MEMORY AND AGING

Reversing working memory decline in the elderly

Noninvasive delivery of alternating electrical currents to temporal and prefrontal brain regions improves working memory and reverses age-related changes in brain dynamics in the elderly, report Reinhart and Nguyen in this issue of *Nature Neuroscience*. They also report a similar effect in young adults with poor working memory performance.

Romain Quentin and Leonardo G. Cohen

Thanks to advances in medicine and public health, we're all now more likely to reach old age[1]. If this improvement in life expectancy keeps the same pace, most people born in developed countries in the 21st century will celebrate their 100th birthday by the 22nd century[2]. However, an unanswered question remains: how do we remain socially productive, intellectually fit, and physically active and healthy in our twilight years? Research over the last two decades has attempted to address these problems through different strategies. However, substantial controversy surrounds claims of 'effective' anti-aging treatments in humans made in the absence of rigorous, reproducible, and well-controlled clinical trials[3]. As Reinhart and Nguyen[4] point out, any prospect of finding effective interventions to improve age-related cognitive decline relies on a deeper understanding of the mechanisms underlying the cohort of symptoms loosely grouped under the word 'aging'.

Working memory, the ability to store behaviorally useful information for a few seconds, declines with age and is considered a core component of cognitive deficits associated with aging[5]. Recent research has improved our understanding of the systems-level neural substrates of working memory[6]. However, most of this work has provided correlational but not causal evidence of the role of brain oscillatory dynamics in cognition. In their paper, Reinhart and Nguyen[4] identify a causal link between reduced frontotemporal brain oscillatory dynamics and working memory deficits in the elderly. In doing so, they also demonstrate that it is possible to improve reduced working memory in the elderly using transcranial alternating current stimulation.

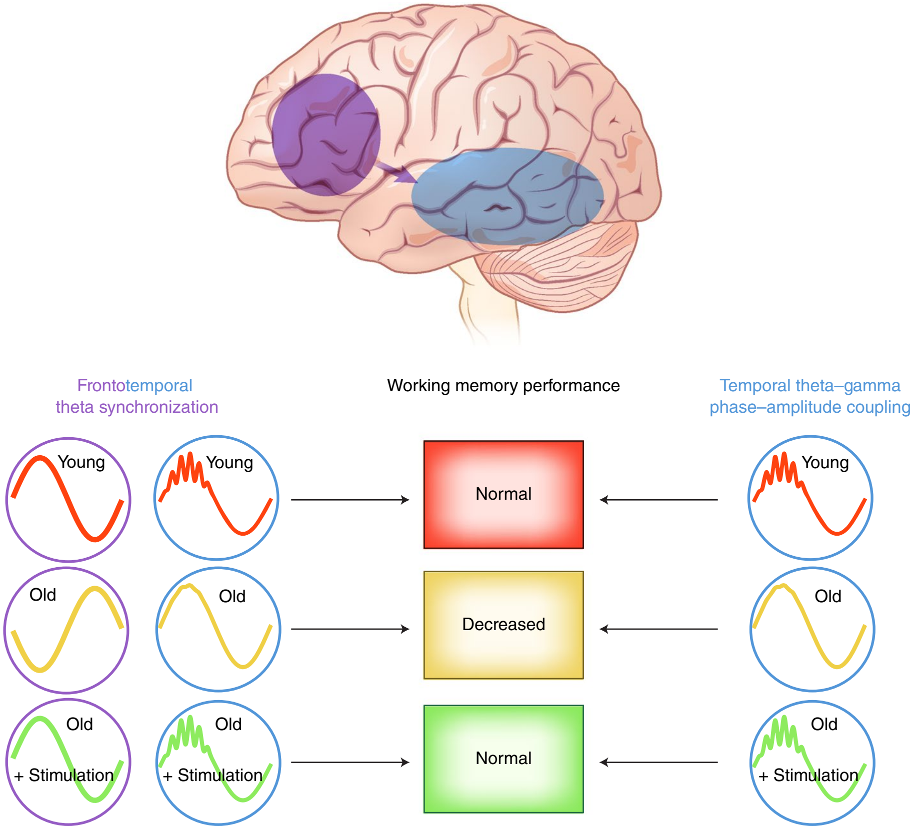

Fig. 1 | Causal role of frontotemporal dynamics in working memory. Working memory in the elderly (yellow row) was associated with loss of theta-gamma phase–amplitude coupling in left temporal regions (blue brain region) and frontotemporal theta-phase synchronization (purple brain region and purple arrow) relative to young subjects (red row). HD-tACS reversed the age-related changes in brain dynamics in the elderly (green row).

The authors asked young (20–29 years old) and older (60–76 years old) adults to perform a working memory task while recording their brain activity with electroencephalography. They first reproduced a previously reported decrease in working memory performance in older adults compared to the young group[5]. Subsequently, they characterized brain oscillatory dynamics during performance of the working memory task compared to during a control task that did not require working memory. In the younger group, performance of the working memory task was associated with phase–amplitude coupling of theta (7–9 Hz) and gamma (26–34 Hz) oscillations in left temporal regions, as well as frontotemporal theta rhythm synchronization (Fig. 1). Theta–gamma phase–amplitude coupling, a form of cross-frequency coupling in which the amplitude of gamma rhythms is coupled to the phase of theta rhythms, relates to local processing and storage of information in working memory[7]. Theta-phase synchronization between frontal and temporal regions is thought to reflect the influence of the frontal cortex on content processing and storage in temporal areas[8]. These neural dynamics were absent in the elderly group (Fig. 1), an effect that was not due to differences in theta or gamma spectral power between age groups. Consistently, the phase–amplitude coupling in temporal regions correlated with working memory performance in the younger group but not in the older group. These results suggested the possibility of a causal relationship between these neural signatures and working memory performance, which the authors explored next.

They applied noninvasive high-definition transcranial alternating current stimulation (HD-tACS)[9,10] to strengthen frontotemporal theta-phase synchronization in the older adult group while they were performing the working memory task. HD-tACS led to an improvement of working memory that resembled performance levels seen in younger subjects. These behavioral gains started, on average, 12 min after the onset of stimulation and outlasted the stimulation period by at least 50 min. Importantly, theta–gamma phase–amplitude coupling and frontotemporal theta-phase synchronization, the two neural dynamic signatures reduced in the elderly, were restored at the end of the stimulation (Fig. 1). These effects were present when HD-tACS was applied at each individual's theta-band frequency but not when applied at a fixed 8 Hz, underlining the need to characterize each individual's electrophysiological brain dynamic signatures before defining electrical stimulation protocols.

Causality, a crucial question in many scientific domains, is often difficult to demonstrate. With their within-subject, double-blind and sham-controlled design that combined brain stimulation and electrophysiology, Reinhart and Nguyen[4] checked off different boxes. They first identified correlational neural signatures of working memory performance, in agreement with previous research[7,11], and observed a decrease of these neural dynamics in the elderly. Then, they developed an individualized, noninvasive brain stimulation approach that restored both neural dynamic signatures and cognitive performance in older adults. Following stimulation, the strength of theta–gamma phase–amplitude coupling correlated with restored working memory performance, as observed in younger adults. They further showed that this stimulation protocol improved working memory in poor-performing younger participants. Additionally, out-of-phase theta stimulation of frontotemporal regions (to desynchronize communication between these regions) had a deleterious effect on working memory in younger adults. Altogether, they provide convincing evidence on the causal role of frontotemporal theta-phase synchronization and theta–gamma phase–amplitude coupling in working memory[5].

The authors suggest that these results pave the way for the development of non-pharmacological interventions that could improve cognitive decline. Since working memory correlates with other cognitive functions like problem-solving[12] and fluid intelligence[13], it is conceivable that noninvasive electrical stimulation interventions that enhance related brain dynamics could be generalized to these functions as well. These results, however, are far from demonstrating the efficacy of this approach in the clinic, and future steps should include optimization of stimulation and dose–response protocols to enhance duration, safety, and plasticity induction[14]. Implementation of properly powered, preregistered, hypothesis-driven multicenter protocols, together with data- and code-sharing, will provide crucial information on reproducibility and could confirm and strengthen such proposals[15].

The development of a clinically useful strategy to improve working memory in the elderly will likely require a long and laborious research process. Nevertheless, Reinhart and Nguyen[4] identify a promising first step by successfully modulating frontotemporal neural dynamics to improve working memory performance in the elderly. ❐

Romain Quentin and Leonardo G. Cohen*
Human Cortical Physiology and Neurorehabilitation Section, NINDS, NIH, Bethesda, Maryland, USA.
**e-mail: cohenl@ninds.nih.gov*

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Competing interests

The authors declare no competing interests.