RESEARCH HIGHLIGHT

“Transient” or “Persistent” Coding for Working Memory

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Working memory (WM) maintains information temporarily for subsequent goal-directed behaviors, such as remembering a telephone number to dial. WM serves as a supporting mental workspace for many cognitive functions such as mental calculation, reading, and learning new skills. The critical role of persistent activity in the prefrontal cortex in WM, originally proposed to bridge sensory information and motor responses [1], has been severely debated recently [2, 3]. A new study by Zhu *et al.* [4] highlights that transient, rather than persistent, activities in the anterior agranular insular cortex (aAIC) serve as building blocks for the learning phase of WM.

A report from the same laboratory previously suggested the importance of delay-period activity in the medial prefrontal cortex (mPFC) during the learning of new WM tasks [5]. Yet the temporal characteristics of the delay-period activity associated with WM, as well as the neural networks related to this activity pattern were largely unknown. In the new study, mice were trained to perform olfactory delayed-matching/non-matching-to-sample WM

tasks, while an optogenetically-based silencing strategy was adopted to screen the potential involvement of different brain regions in WM learning phases using a high-throughput automatic training system [6]. Out of 12 brain regions of interest, the authors identified the aAIC as the predominant region involved in the learning of new WM tasks. Direct optogenetic suppression of the aAIC during WM learning slowed the learning curve, but had no effect on the WM performance in well-trained animals.

The authors then recorded neuronal spikes from the aAIC of awake mice during WM task training to explore the underlying information processes in this region. Unlike the persistent and differential patterns for different samples reported in the PFC in non-human primates [1], aAIC neurons that selectively responded to different task contents predominantly fired in a transient manner (~35%). In contrast, a low percentage of persistently-firing neurons (~1%) were recorded. The latter activity did not contribute significantly to the decoding accuracy for WM information, while the former transient population did. These results suggested that the aAIC encodes WM content preferentially as transient rather than persistent firing.

Further pathway-specific optogenetic manipulation confirmed that the mPFC-to-aAIC projection biphasically controls WM learning performance, in line with the “hub” function of the PFC in WM initiation and maintenance. Notably, specific manipulation of the mPFC–aAIC pathway altered the proportion of transient firing neurons in the aAIC, indicating a potential causal relationship with direct synaptic connectivity. The proportion of transient firing neurons was also modulated by external distraction, implying that the resilience of WM execution can be attributed to the balance of excitation/inhibition within this neural circuit. However, the detailed synaptic structure and distribution of transiently-firing neurons are yet to be

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mapped in the mPFC–aAIC circuit. It is unclear if aAIC neurons send connections back to the mPFC and form recurrent excitatory inputs, and whether the strength of these synapses is modified during WM learning processes such as long-term potentiation-like changes.

The findings of Zhu *et al.* (2020) add strong evidence to the “persistent” debates about WM coding [2, 3]. This study for the first time highlights the roles of transient aAIC neuronal activity in WM learning, with temporal precision distributed over the “waiting” period. The changes of transient activity correlated with increased task difficulty (e.g. distracted condition) and were associated with behavioral performance. Considering the importance of mPFC–aAIC synaptic inputs, it is likely that the activity pattern in the aAIC is well synchronized with the mPFC, which could be mediated by coordination based on neural oscillation during the learning of a new WM task. For instance, neuronal firing when gamma (40–100 Hz) band oscillation bursts, which happen at the trough of beta/alpha (12–30 Hz) band oscillations, might serve as the gating mechanism in WM [7], and contribute to the mPFC–aAIC coordination (Fig. 1). It will be interesting to analyze the temporal relationships of neuronal spikes and local field potentials between the mPFC and aAIC at different stages of WM learning.

Although the neural substrate for WM is better known as persistent activity during the delay period [1], recent evidence suggests that WM information may also be stored in synaptic weights as hidden states [8] to save the energy from continuous spiking. The transient time-window reported in Zhu *et al.*'s study may offer a temporal window in which to re-activate or strengthen certain WM representations with neuromodulation. For instance, it has been reported that delay-period pulses of transcranial magnetic stimulation can re-activate latent WM representations and influence WM performance [9]. As the contents of WM could be decoded from widely-distributed brain areas [10] and WM sub-components could be attributed to dissociable neural substrates [11], in future it will be interesting to

develop content-specific neuromodulation approaches for WM manipulation.

The study has a few limitations. First, the anterior insula cortex is associated with interoception and self-awareness [12], and has been proposed as an important hub for the salience network in humans [13]. The transient activity in the aAIC could also be attentional signals indicating salience-coding for odors (natural preference or by training). In addition, insula activation is also associated with risk-prediction error during reinforcement learning [14]. Whether the transient activity in the aAIC represents a signal of reinforcement learning is yet to be elucidated. Last but not least, it will be important to test the current findings in non-human primates and potentially human subjects as well.

In conclusion, Zhu *et al.* propose the aAIC as an extended family member of the neural substrates underlying WM, and strengthen the importance of previously-unappreciated transient neuronal activity in the acquisition phase of WM. These characteristics greatly enrich the information-processing theory during WM maintenance, and might contribute to the expansion of WM capacity by forming distinct temporal domains.

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Conflict of interest The authors claim that there are no conflicts of interest.

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Fig. 1 Coordination between mPFC and aAIC through neural oscillations.

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