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RESEARCH HIGHLIGHT

Economic "Activity-Silent" Synaptic Mechanisms of Working Memory

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Working memory (WM) allows humans to hold necessary information in temporary storage and manipulate such information online for higher-order cognitive functions, such as language understanding, decision making, and problem solving. Since its first appearance in the science of psychology in the 1960s, many theories have sought to elucidate the nature of WM. The most accepted model is the multicomponent model, which was first introduced by Baddeley and Hitch [1]. However, a state-based model is becoming more promising with the development of neuroscience [2]. Despite a variety of versions of the model, both theories propose that memory representations of information that is held in WM are maintained in an elevated state of activation until the information is no longer relevant to the current target. The state-based model has been extensively investigated in neuroimaging studies. Postle and colleagues isolated the state of attention from WM and proposed a new theory—"activity-silent" synaptic mechanisms—for maintaining information in WM, which is more economical and fine-tuned [3]. These authors applied transcranial magnetic stimulation (TMS) to reactivate neural representations and illustrated a mechanism of short-term plasticity in a recent paper in *Science* [4].

In the study by Postle *et al.*, localizer tasks were performed using multivariate pattern analysis (MVPA) to identify category-selective regions for face, motion, and word processing. Multivariate pattern classifiers that were trained on part of the functional magnetic resonance imaging data predicted later information processing in the same brain. The ability of MVPA to dissociate overlapping representations of items has been well documented [5]. Postle *et al.* also adapted a multistep task from their previous studies, in which two items were presented as memoranda for each trial [6]. The task created a situation in which the items could be put into different states by manipulating the presentation of cues. After the first cue, the cued item (i.e., an attended memory item [AMI]) was the focus of attention, and the uncued item (i.e., unattended memory item [UMI]) was in an intermediate state and held for a later test rather than the immediate test. The results showed that the UMI could be maintained in a latent state *via* a drop-to-baseline pattern rather than maintained in a state of sustained, elevated activity. If the remembered item was needed in a later test, then the neural representation could be returned to a state of activation within seconds when it was needed. If the UMI became irrelevant to the task, then the representation remained in the silent pattern. This process was shown to be more economical than the conventional "persistent activity" theory would suggest.

The authors then sought to activate the neural representations for the UMI using TMS. When TMS was applied after the first cue, a transient period of above-chance decoding performance occurred for both the UMI and AMI. In contrast, for the time-point that immediately

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followed the second TMS pulse (when the UMI was no longer relevant), the UMI classification did not differ from chance. These results indicated that TMS only activated the neural representations for the items that were still maintained in a privileged state rather than items that had lost potential relevance to the task. Furthermore, the participants were instructed to correctly identify the AMI and reject probes that did not match the AMI. A higher rate of false-alarms for the UMI occurred in the TMS condition than in the non-TMS condition, and this effect was found only in the first probe. Once the items fell out of WM, the reactive effect of TMS disappeared, indicating that the neural representations that were reactivated by TMS led to higher recognition for the corresponding items.

The findings of Postle *et al.* challenge the previous long-standing view that holding information in WM involves sustained and elevated neural activation [7–9]. These authors were able to isolate the role of attention from WM and provided empirical evidence of the more economic "activity-silent" theory. The "activity-silent" theory proposes that there are at least two levels of WM (AMI and UMI), and items from different levels have specific neural activation patterns, which is a derivative of the traditional state-based model. The mechanism of short-term plasticity in WM challenges conventional theories and may shed light on a wide range of cognitive functions.

From the perspective of the multicomponent model, numerous studies have focused on the executive component and found that sustained activation of the prefrontal cortex (PFC) is essential for the maintenance of information [10]. The study by Postle *et al.* only investigated the neural systems that are involved in memory storage. The involvement and activation patterns of higher-function regions, such as the PFC, during WM require further investigation. For specific information that is stored in the cortex, sustained activation may be unnecessary, even when the information has a priority status. However, the executive component of WM, which is associated with vigilance and keeps the brain in a state of readiness, would require sustained elevation of activity in corresponding neural representations to function. Fuster and colleague examined the role of the PFC in WM in monkeys, and found that disruption of the PFC caused low specificity and selectivity of spiking activity in response to different stimuli [11]. Because of the heterogeneity of the PFC, specific subregions are crucial. Researchers may use a "localization-intervention" experimental approach to explore the neural mechanisms of the executive component of WM, in which a simple task is first used to determine the regions that are involved in executive control, and then brain stimulation is applied to block the activation of regions that are related to executive function.

Postle *et al.* also found that TMS stimulation in specific regions associated with memory traces reactivates memory representations and makes the potentially relevant information easier to retrieve (Fig. 1). This finding will inspire future studies that focus on treating pathological memory-related diseases, such as addiction and post-traumatic stress disorder (PTSD). For people with memory impairments, such as patients with Alzheimer's disease, TMS may enhance memory by activating memory traces and making

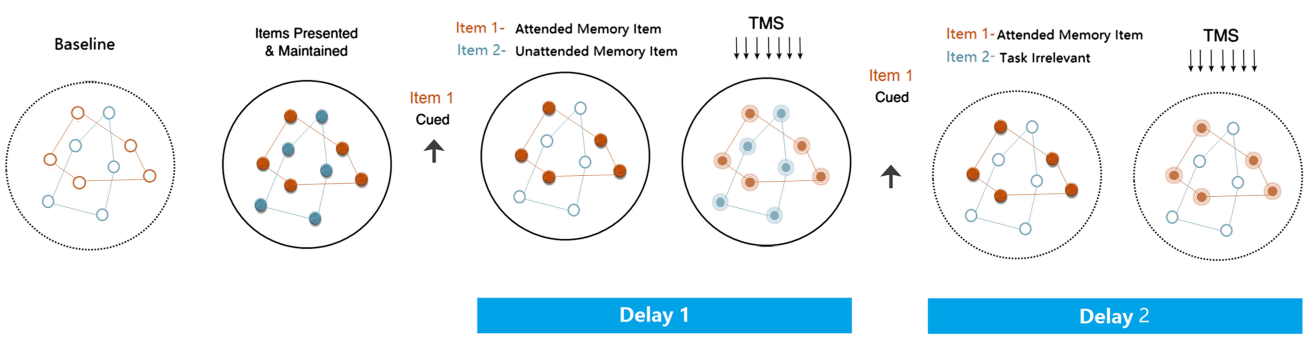

Fig. 1 Illustration of the "Activity-silent" synaptic mechanisms of working memory. Neural representations are activated when the novel "to-be-remembered" items are first encoded. After the first cue, neural representations of the attended memory item (AMI) are sustained, with elevated activation. Neural representations of the unattended memory item (UMI) enter a "drop-to-baseline" pattern. The transcranial magnetic stimulation (TMS) could reactivate the representations of the AMI and UMI, including the elevated and latent representations, suggesting that the UMI is still at a state of "easy to activate" priority, and that information held in working memory (WM) is interconnected (in the *solid circle*). If the same AMI is cued again in the second phase, the representations of the uncued item drop to baseline and maintain there, and TMS is unable to activate them. After the second cue, the uncued item becomes task-irrelevant, and the connectivity between the representations of different items is broken (*solid circle* disappear). Before this model, the traditional state-based model proposes that memory representations of information held in WM are maintained in an elevated state of activation until the information is no longer relevant to the current target. The traditional theory does not isolate the role of attention from WM and suggests that the items held in working memory are at the same priority

memories more accessible. A recent study found that brain stimulation improved human memory performance, and the target areas were highly connected with the hippocampus, which is critical for associative memory [12]. Postle *et al.* identified potential target regions based on a different perspective, and their experiment design may be useful for improving memory in patients with memory impairment. For patients with PTSD, the persistent reappearance of negative memories is both distressing and exhausting. An exciting possibility is that TMS may also be used to target corresponding regions and lessen their activation.

In conclusion, Postle and colleagues provide new evidence supporting a more economic and efficient short-term plasticity mechanism of WM. However, the involvement and activation pattern of the PFC in WM are still unclear, and further studies are needed to verify the regions that are related to higher-order cognition. The application of TMS to elicit memory traces may shed light on the neural representations of other cognitive functions and elucidate the building blocks of memory.

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