The Enigma of Working Memory: Changing Views

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Abstract

Working memory is of great interest because of its importance in cognitive function, its relation to consciousness, and impairments in disease, but the cellular mechanisms remain elusive and controversial. A recent article by Barbosa and colleagues overturns the conclusions of an influential study by Wolff and colleagues, which concluded that working memory can be maintained in a hidden state by transient plasticity of synaptic connections that form dynamic ensembles of neurons encoding information temporarily. A reanalysis of the data reveals that there is a persistent electrically active signature in the EEG recordings that is sustained for the duration of the working memory. This reanalysis adds to a large body of evidence indicating that working memory is encoded by sustained action potential firing. However, several studies show that unconscious (unattended) working memories can be recalled even in the absence of measurable neural activity, suggesting that electrically silent mechanisms may be involved. Testing that hypothesis is problematic, given that it posits no neuronal firing that could be easily measured.

Keywords

working memory, attention, hidden states, subliminal perception, synaptic plasticity, EEG, fMRI, short-term memory

In contrast to other forms of memory that retain past experiences for future recall, working memory sustains information in real time while performing a task. The cellular mechanisms of working memory may also differ from other forms of memory, and this is a matter of ongoing research. Working memory has very limited capacity and a short duration (for review, see Linden 2007), but this capability is essential for diverse cognitive functions and behaviors. It is a major component of intelligence, and working memory is often diminished in impairments from aging, disease, or intoxication.

There are two leading theories for the mechanism of working memory; each one is supported by electrophysiological and functional brain imaging data. A recent study (Barbosa and others 2021) overturns the conclusions of a seminal study (Wolff and others 2017) which supported the theory that working memory is dependent upon activity-dependent synaptic plasticity. This was not accomplished by performing new experiments, but instead by reanalyzing the data from the earlier paper. Using new analytical approaches to reanalyze the original data, the authors find evidence supporting an alternative hypothesis.

Two Theories for Working Memory

Two theories for the mechanism of working memory are “activity-silent neural networks” and “sustained activity.” The first proposes that activity-dependent synaptic plasticity couples neurons functionally into transient neural ensembles that encode the experience (Goldman-Rakic 1995). According to this theory, spike-timing dependent plasticity drives transient biochemical changes at individual synapses that increase or decrease neurotransmitter signaling to form dynamic neural networks that retain the experience. Intracellular calcium dynamics that influence synaptic transmission could be sufficient to form transient neural assemblies that are dynamically modified by new information (Mongillo and others 2008). Quickly these rapid activity-dependent changes in synaptic strength subside; functional coupling of the neural networks dissolves, and the working memory is lost.

Temporary storage of information in working memory by brief changes in synaptic strength would enable rapid encoding of information that can be dynamically updated to maintain new information in memory in real time. Importantly, the synaptically coupled neural networks are electrically silent. That is, information encoded in the neural networks is reactivated during recall, much the

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way short-term and long-term memories are stored and recalled, not by maintained action potential firing in these circuits.

The alternative hypothesis is that working memory is sustained by persistent action potential firing. Continuous firing of action potentials would be an improbable and energetically inefficient way to store information for long periods of time, but since working memory operates in real time and persists for only a few seconds, synaptic plasticity mechanisms of information storage and recall that are responsible for short-term and long-term memory may not be necessary. Instead, persistent action potential firing in neural networks that are responsible for perception and information processing could maintain information for the immediate purpose of carrying out a specific cognitive task. Indeed, if there is conscious awareness of an event while the behavior is being carried out, persistent action potential firing in cortical circuits would be expected.

There is long-standing evidence for sustained firing of action potentials during the delay period before recall in working memory. The prefrontal cortex is the hub of working memory because this is where various aspects of sensory experience are combined to form a coherent schema. Pioneering studies in nonhuman primates established the importance of prefrontal cortex in working memory (Butters and Pandya 1969), and electrophysiological recordings in the 1970s revealed neuronal firing in the prefrontal cortex of monkeys sustained for the duration of a working memory task (Fuster and Alexander 1971). Similarly, increased activity sustained during the delay period in working memory tasks has also been shown by functional magnetic resonance imaging (fMRI; Courtney and others 1997) and electroencephalography (EEG; Foster and others 2016) studies on humans. Sensory cortex and other brain regions can exhibit similar behavior.

One difficulty, however, is that such persistent activity could be ancillary to the fundamental mechanism of working memory; for example, it could reflect neural activity related to attention (Lewis-Peacock and others 2012). Indeed, other studies have shown that neural activity can wax and wane during the delay period before recall. Frequently neural activity drops to baseline and rebuilds in strength near the end of a delay period in anticipation of recall needed to execute a repetitive task (Barak and others 2010). Together these studies suggest that although persistent action potential firing can attend working memory, other electrically silent mechanisms may retain working memory in some cases. One parsimonious explanation is that attended working memories (those retained in conscious awareness) and unattended (nonconscious) working memories may operate through different cellular mechanisms.

**Attended versus Unattended Working Memory**

Working memory can be maintained without conscious awareness, and then recalled after an appropriate cue, as when one forgets their train of thought in a conversation but then recalls it immediately when reminded of what was being said only seconds previously. In support of this, a single TMS (transcranial magnetic stimulation) pulse can restore a lost visual working memory in studies on humans, and boost levels of neural activity detected by fMRI and EEG that are indicative of recalling the memory (Rose and others 2016). This supports the hypothesis that unattended memories are stored by mechanisms other than sustained action potential firing. In these experiments, participants are presented simultaneously with two objects on a computer screen. After a short delay they were told which of the two to remember. Thus, that cued image becomes the focus of attention and is maintained in an attended working memory state. An increased neural response, detected by fMRI and EEG in separate experiments, was identified that corresponded to when the image is recognized.

The neural response associated with the object in unattended memory declined to baseline before recall was tested, but neural activity associated with the object in working memory was sustained. When a single TMS pulse was applied 2 to 3 seconds after the cue to indicate which object to remember, neural activity associated with the object in unattended memory was now elevated. This suggests that latent (electrically silent) unattended memory can be maintained via mechanisms other than by sustained elevated activity and it can become reactivated by TMS. It is not clear how TMS revives latent neural activity that subsides in unattended working memory, however.

**Revealing Hidden Neural Networks in Working Memory**

It is much more challenging to investigate the hypothesis that dynamically coupled, electrically silent neural networks underlie working memory, because physiological techniques, such as EEG, fMRI, and electrophysiology, monitor neuronal activity. Building on the TMS studies by Rose and others (2016), Wolff and others (2017) devised a unique approach to test for the presence of an electrically silent neural network maintaining unattended working memory (Fig. 1A).
The investigators reasoned that if an electrically silent neural network had formed and was retained for the duration of working memory, then the response of the network at a systems level should differ from the response had this silent network not formed. Rather than apply a TMS pulse, the researchers provided an unrelated visual stimulus (target-shaped circles) to reactivate neural networks related to the visual working memory task. If synaptic plasticity had driven dynamic changes in connectivity in the working memory task, then probing these networks with a different stimulus should yield a different neural response than if the network had not been altered. The authors refer to this as “pinging” the neural networks to assess their response. Moreover, the nonspecific visual stimulus could, in theory, reactivate activity in the synaptically coupled silent neural networks encoding the memory, similar to TMS. This would appear as a reactivation of EEG responses that are evoked when the object is recalled from memory.

In preparation for the studies using the unrelated target-shaped image to “ping” the neural networks, participants viewed a screen displaying two objects adjacent to each other, and they were instructed to remember both items. After a short delay, an arrow pointed left or right to cue the observer as to which object should be remembered for a subsequent test. This object would then be retained in attended working memory, while the other object would be forgotten or retained in unattended (nonconscious) memory. The objects to remember were two stripe-filled circles that were rotated so that the stripes on each had different orientations. After a delay, a striped circle was displayed, and participants were required to indicate if that “probe” object had been rotated clockwise or counterclockwise from the striped circle they were keeping in working memory.

The results showed increased activity in the alpha band at appropriate electrode recording sites for objects in visual working memory corresponded to how much the probe object differed in rotation from the object in memory. Obviously, if the orientation of the object in working memory had been forgotten, this discriminating EEG response would not appear, and the accuracy of the subjects’ reported responses would drop to chance. Second, the EEG response indicative of the degree of rotation of the probe image relative to the image in memory would decline with time, as working memory is sustained for only a matter of several seconds. The results showed that this EEG activity increased after the arrow cue and was sustained until the image was presented to test recall, but the activity slowly returned to baseline with time for the object in unattended memory (Fig. 1B). This supports the hypothesis that there are different mechanisms sustaining unattended and attended working memories, with persistent neural activity associated with attended but not unattended memories.

The researchers then used a third unrelated visual stimulus to ping the system for changes in neural network function driven by synaptic plasticity that theoretically records working memory. The unrelated stimulus boosted neural activity for the object in attended memory, but not the object held in unattended memory (Fig. 1C). The authors concluded that in contrast to attended working memories, unattended working memories are stored by synaptic plasticity forming dynamically coupled, but electrically silent neural networks, without the requirement for ongoing increases in neural activity.

Reexamining the Data

A recent study reexamined the original data by Wolff and others (2017) and found that the neural response to the object in unattended memory was sustained for the entire duration before recall, when the data were analyzed differently. Instead of monitoring the EEG voltage, Barbosa and others (2021) analyzed the power of the alpha band EEG activity. Increased power of EEG activity that was indicative of both the objects in attended and unattended working memory was sustained for the duration prior to recall (Fig. 1D). The responses in terms of alpha power were boosted by the unrelated visual stimulus “pinging” the system, but the fact that an active response was evident for both attended and unattended memories renders somewhat moot the effects of eliciting active responses to visual pinging as a method to reveal hidden states storing memory. Moreover, visual pinging could energize activity in neural networks sustained by action potential firing as well as for putative electrically silent networks, so the visual pinging technique cannot clearly distinguish between these two mechanisms of information storage.

Barbosa and others (2021) reason that voltage measurements are subject to greater variance because of baseline drift and variation in impedance of scalp electrodes, whereas the frequency and power of oscillations are more robust to such technical difficulties. Thus, the ongoing increase in neural activity associated with unattended memory was not detected by Wolff and others (2017) because of signal-to-noise limitations. Moreover, their analysis showed that the power of the statistical analysis of the original data was weak, and that a larger sample size would likely have detected increased sustained activity during the delay period for objects in unattended memory. A closer analysis also showed wide subject-to-subject variation in responses, and that in many instances sustained increases in EEG voltage were
Figure 1. Reanalysis of data from Wolff and others (2017) by Barbosa and others (2021) investigating the hypothesis that working memory can be maintained by electrically silent neural networks. (A) Experimental design by Wolff and others (2017). See text for details. (B) Attended memories are accompanied by elevated EEG activity in the alpha band that is sustained for the duration prior to recall, but activity associated with unattended memory subsides to baseline. (C) An unrelated visual stimulus (three target-shaped circles) can boost activity related to the item in attended memory (cued) but not for memory in unattended memory (uncued). (D) A reanalysis of data shown in B by Barbosa and colleagues using alpha band power instead of voltage reveals an increased active response that is sustained during the delay period before recall regardless of whether the object is in attended or unattended memory. The colored bars at the top of the plots show times where differences are statistically significant. Bars on the x-axis indicate presentation of the visual stimulus. Images in A and C are reprinted from Wolff and others (2017) with permission, and images in B and D are reprinted from Barbosa and others (2021) with permission.
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evident accompanying unattended memory, but in other test subjects this was not evident. The increased variance would have undermined efforts to identify a persistent increase in electrical activity sustaining unattended memory.

Conclusions

A reanalysis of the original data overturns the conclusions of the influential study by Wolff and others (2017) that failed to find a signature of working memory in terms of elevated sustained EEG activity, but it does not invalidate the experiments, nor provide evidence that synaptic plasticity does not form dynamic ensembles of neural networks underlying working memory. The reanalysis only demonstrates the truism that “the absence of evidence is not evidence of absence.” The original experiments and the data are valid, but the conclusions change when analyzed differently.

Importantly, these two papers demonstrate the power of collaboration in scientific research, as Wolff and colleagues provided their raw data to Barbosa and colleagues for reanalysis and they are gratefully acknowledged for their helpful discussions. Both groups recognize that it is far more difficult to obtain experimental evidence in support of the synaptic plasticity mechanism for working memory, since it is by definition electrically silent. This is especially so if such silent mechanisms operate in tandem with active mechanisms that confound their detection. Thus, the axiom regarding “the absence of evidence . . .” pertains even more to dismissing the silent neural network hypothesis on the basis of the current lack of evidence.

Indeed, these two mechanisms may operate together. Studies by Trübutschek and others (2017) show that participants can recall information that they have no conscious awareness of even though there is no active neural response detected by EEG that is sustained during the delay period prior to testing recall. They suggest that, following a transient encoding phase via active neuronal firing, nonconscious stimuli may be maintained by activity-silent short-term changes in synaptic weights without any detectable neural activity, allowing retrieval for several seconds.

How to reveal the existence of a possible electrically silent neural process remains an enigma, but finding ways to explore possible changes in synaptic connectivity that may attend working memory will remain a vigorous endeavor, which will no doubt spark new collaborations and new advances.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by NIH intramural grant no. ZIAHD000713.

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