

Journal Club

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The Neural Code of Working Memory Maintenance

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Review of Quentin et al.

The pursuit of the neural mechanism of working memory has been a fundamental topic in neuroscience. The mental function of maintaining information for immediate use is a universal experience, but measuring the specific neural signature of working memory during task has been challenging. To temporally separate the memory signal from signals related to stimulus perception, early researchers introduced a delay between stimulus presentation and behavioral response. Pioneering work in the 1970s using such a design in an oculomotor task demonstrated that individual frontal lobe neurons remain active during the delay period only when the stimulus was shown in a specific location (Goldman and Rosvold, 1970; Fuster and Alexander, 1971; Kubota and Niki, 1971). This work propelled a persistent-firing model of working memory, in which the remembered items are encoded by the activity of a subset of neurons, which is sustained by reciprocal excitatory connections among them (Compte et al., 2000).

Although extensive experimental evidence supports the hypothesis that persistent firing during delay periods is a task-related neural signature, the experimental design described above does not completely rule out the possibility that

this signal contains representations of motor planning, response-rule selection, or reward expectation. For example, in the oculomotor task, the subject indicated the stimulus location with a saccade in the same direction, so the observed persistent activity could represent either the stimulus location or the planned eye movement. One strategy to separate these mental processes is to use a “response cue” during the delay period to specify a response rule, such as indicating whether the subject should saccade in the same or opposite direction of the stimulus. In such a design, the subject cannot form a specific motor plan before receiving the response cue; thus, neural activity before response-cue presentation should be a cleaner representation of memory maintenance, whereas signal after the response cue may be related to planning a motor response. Several studies have used such a behavioral design in combination with unbiased brain activity monitoring techniques to search for the neural signature of working memory maintenance (Rowe et al., 2000; Rowe and Passingham, 2001). These studies revealed two consistent findings: (1) the initial activity triggered by the stimulus rapidly decays; and (2) persistent activity emerges after the response cue. These data suggest that the persistent firing represents memory utilization and/or motor planning, but not memory maintenance.

Quentin et al. (2019) provide additional support for this interpretation. The authors measured brain-wide neural activity using MEG while human subjects

completed a visually guided memory task, with a response cue in the middle of the delay period. Instead of examining bulk activity levels, the study used multivoxel pattern analysis and constructed logistic and ridge regression decoders to analyze the neural activity during each epoch of the task. Consistent with previous findings, a persistent and stable neural pattern emerged only after the appearance of the response cue. Because response rule and stimulus identity were randomly assigned in each trial, the authors were also able to demonstrate that only the response rule, not the stimulus identity, was decodable from this persistent neural pattern (Quentin et al., 2019, their Fig. 2). Importantly, this persistent neural pattern did not exist when subjects' responses did not depend on the response cue (Quentin et al., 2019, their Figs. 4, 5), ruling out that this persistent neural pattern represents the visual memory of the response cue itself. Furthermore, the authors determined that the persistent neural pattern originates from occipital and frontal lobes at the α and theta frequency bands (Quentin et al., 2019, their Figs. 2, 3). While these findings cannot rule out the possibility that the same group of neurons that show heightened persistent activity after the response cue exhibits a low level of persistent activity that escapes detection or that before the response cue the memory is held at a subcortical nucleus, such as thalamus (Bolkan et al., 2017; Guo et al., 2017), which cannot be picked up by MEG, a more par-

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simonious interpretation is that the persistent activity in the frontal area, classically considered to be the memory maintenance signal, is indeed encoding a signal for memory-guided response selection.

Where, then, is the neural signal for memory maintenance? As discussed above, a neural signature of memory maintenance might be a representation of the stimulus during the delay period, but before the response cue occurs. However, Quentin et al. (2019) showed that the decoding accuracy of the stimulus decays rapidly to chance level in the delay period, suggesting that either the memory is maintained in activities that cannot be resolved by MEG or that the maintenance of memory does not require persistent neural activity. These two hypotheses imply two different cellular models of working memory: a dynamic coding model in which serial neural loops maintain the information without heightened activity (Druckmann and Chklovskii, 2012; Rajan et al., 2016) and a silent activity model in which the memory is encoded by the short-term plasticity changes that require no activity to maintain (Mongillo et al., 2008). Previous work with fMRI showed that the visual stimulus can be decoded tens of seconds after its presentation (Harrison and Tong, 2009), favoring the dynamic coding model. However, this is not conclusive because fMRI looks at blood vessel dynamics, which can be much slower than the neural change, and the study did not use a response cue to separate stimulus maintenance from response selection. These two models make two different predictions regarding the neural activity at the moment of memory utilization. While the dynamic coding model suggests no change in the stimulus decodability between memory maintenance and recall, the silent activity model predicts that item-specific activity emerges when the network is reactivated during recall. Quentin et al. (2019) showed that the stimulus identities can again be decoded from the neural data after the response cue, consistent with the silent-activity model. However, the decoding performance the authors observed was relatively poor. This may be partially due to the fact that recall-related activation can be a transient signal whose appearance may be variable in time across trials and/or sub-

jects, so the averaged decoding result may not accurately reflect the existence of item-specific information. Interestingly, the recall-related activity involved the general occipital lobe, overlapping with the brain regions activated by the stimulus. This observation is consistent with previous work showing that the brain regions that perceive certain features may be responsible for memorization (Ungerleider, 1995). Again, this phenomenon is in line with the silent-activity model, in which a subset of neurons activated by the stimulus maintains this information.

Finally, Quentin et al. (2019) showed that the delay-period stimulus-decoding algorithm before and after response cue was different. The authors concluded that the neural representation of item-specific information is transformed after the initial stage, and that the representation of the same information in two epochs of the task were different. However, considering the fact that MEG signal primarily reflects current flow within neurites, not neuronal firing, the dendritic and axonal signal from the same neural ensemble may be registered as different wavelets in MEG recordings. In this case, a shift in decoders may represent a utilization of different signal sources that may or may not be related to the same neural ensemble. Hence, the authors' conclusion that different subsets of neurons are engaged in visual perception and memory maintenance remains speculative.

In conclusion, Quentin et al. (2019) provide important evidence that frontal lobe persistent activity represents a neural process of memory utilization, not memory maintenance. The results are consistent with a silent-activity model for memory maintenance, yet the evidence is not conclusive. In theory, the silent-activity model of working memory dictates that the information is held among transient changes in the synaptic weights, rather than neuronal firing. This idea is very similar to the concept of long-term memory storage by structural changes of synaptic connections (Queenan et al., 2017). If true, this similarity between short- and long-term memory may be a common scheme in the neural circuits of memory, simplifying the neural processing of memories with different time scales. Future studies using modern imaging or

electrophysiological recording techniques and causal manipulations in animals may provide direct evidence regarding the mechanism of working memory.

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