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Revisiting the role of persistent neural activity during working memory

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Abstract

What are the neural mechanisms underlying working memory (WM)? One influential theory posits that neurons in lateral prefrontal cortex (IPFC) store WM information via persistent activity. In this review, we critically evaluate recent findings that together indicate that this model of WM needs revision. We argue that sensory cortex, not IPFC, maintains high-fidelity representations of WM content. In contrast, IPFC simultaneously maintains representations of multiple goal-related variables that serve to bias stimulus-specific activity in sensory regions. This work highlights multiple neural mechanisms supporting WM, including temporally dynamic population coding in addition to persistent activity. These new insights focus the question on understanding how the mechanisms that underlie WM are related, interact, and are coordinated in IPFC and sensory cortices.

Keywords

Working memory; prefrontal cortex; top-down; decoding; forward encoding; MVPA; fMRI

Working memory (WM) comprises the set of operations that support the active retention of behaviorally relevant information over brief intervals. Given the central role of WM in goal-directed behavior, establishing the neural basis of WM has been a priority of neuroscience research. Early WM studies observed that selective increases in neural activity during the presentation of a to-be-maintained sample item persisted throughout the blank 'delay' interval of a WM delay task, bridging the temporal gap between the sample and the subsequent contingent response [1,2]. This work inspired the theoretical framework that has predominated the field: neurons or neuronal populations that are selectively tuned to the to-be-remembered information hold this information in an active state through persistent activation [3]. We refer to this model, which emphasizes stable persistent neural activity

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(See Glossary) in selective neurons, as the *fixed selectivity model*. Motivated by this model, fMRI studies in humans and electrophysiological studies in monkeys have consistently identified persistent neural activity in lateral prefrontal cortex (IPFC), leading many to conclude that IPFC stores representations of WM memoranda.

A decade ago, we provided a critique of the literature on persistent activity in the context of contemporary models of prefrontal cortical function [4]. We hypothesized that, in contrast to existing theories of WM, persistent IPFC activity signifies attention directed to internal representations maintained in sensory cortices. Viewed through the lens of the fixed selectivity model, evidence for this proposal is limited. Studies of sensory and motor function, however, suggest that information is likely to be represented through the combined activity of neural populations with diverse tuning properties rather than individual highly-tuned neurons [5,6]. This notion offers a promising framework for understanding WM.

In recent years, analytic and methodological advances (see Box 1) have expanded researchers' ability to capture the multivariate nature of population coding and the causal relationships between neural activity and behavior. The findings generated using these approaches underscore the need for a revision of existing views of WM. In light of these results, we revisit the issue of how information remains active during WM. The studies we discuss here focus on visual WM, but the general principles discussed herein apply to WM in other modalities.

Box 1

Methodological advances

Here we briefly describe analytic and methodological advances that have furthered our understanding of the neural basis of WM. The reader is encouraged to seek out some of the excellent reviews on these approaches (referenced below) for more details.

Decoding analysis

Unlike standard univariate analyses, which independently examine data from individual neurons or voxels for differences across conditions, multivariate decoding methods consider data from several neurons or voxels at once to identify patterns of activity that encode task-related information [10–13]. This technique uses machine learning algorithms to decode, or categorize, unlabeled test data using labeled training data. Successful (above-chance) decoding signifies that the activity pattern entered into the algorithm differs between the categories of interest, implying that the underlying neural activity encoded information about these categories. The chief advantage of this approach is potentially increased sensitivity [78]. However, patterns of neural activity may reliably distinguish between conditions for a variety of reasons, some of which are not anticipated by the experimental design [18,79]. Caution is therefore required when interpreting the nature of the information identified via decoding analysis [80].

Forwarding encoding models

Conversely, encoding models predict fMRI activity from task conditions [81–83]. These models rely on *a priori* assumptions about the features of task conditions that will result in changes in the hemodynamic response. In WM studies, forward encoding models of visual cortex have been constructed using knowledge about tuning for visual features [17]. Neural activity in hypothetical populations of neurons (channels) tuned to different values in feature space can be reconstructed from training data by estimating the degree to which each voxel's response contributes to a given channel. The critical advantage over decoding analyses is that this approach can predict fMRI responses to novel stimuli [14]. Encoding approaches are potentially more powerful for identifying information

encoded in neural activity, but are constrained by the validity of the underlying assumptions of the model.

Transcranial magnetic stimulation (TMS)

TMS uses magnetic fields to focally modulate cortical excitability [84]. In WM studies, TMS is used either offline to modulate cortical function for the duration of the experiment, or online to modulate activity during specific epochs of a task. TMS effects on behavior or neural activity in distal regions can support strong causal inferences about the functional role of the regions targeted with TMS. Attenuation of TMS effects as a function of distance from the coil imposes restrictions on which brain regions can be targeted with TMS.

Evidence for persistent working memory representations in visual cortex

Neurons in visual cortex are selectively tuned to visual stimulus features, and are consequently well-suited for maintaining high-fidelity representations of visual information in the service of WM [7]. Yet, from the perspective of the fixed selectivity model, evidence for sustained WM representations in visual cortex has been equivocal. While sustained responses have been observed in temporal cortex [8], studies typically describe transient neural responses to sample stimuli without any subsequent sustained activation. Studies of early visual regions routinely note an absence of persistent activity [9].

Contemporary multivariate encoding and decoding statistical analyses (see Box 1), however, consistently demonstrate that visual cortex does in fact retain sensory WM representations. Decoding analysis applied to fMRI or electrophysiological data can identify activity distributed across neurons or neural populations that codes for task-relevant information [10–13]. In contrast, forward encoding models take advantage of assumptions about neural population tuning to reconstruct the response of hypothetical channels from fMRI voxels that represent the weighted sum of subpopulations of neurons tuned to these channels [14]. Both approaches can test whether feature or item information is encoded in the multivariate patterns of persistent activity during WM, regardless of whether this activity exhibits sustained stimulus-selective responses during sample presentation that persist across the blank delay interval of the WM task. Studies incorporating these methods find that patterns of delay period activity in early visual cortex contain information about simple visual features held in WM [15–19] (see Figure 1a & b). Similarly, delay patterns in occipital and temporal regions specialized for object representation code for actively maintained visual objects [20–24], consistent with studies that inferred a role for temporal cortices in WM storage on the basis of persistent neural activity in these regions [8].

Moreover, this work establishes four key properties of population coding of WM information in visual cortex. First, decoding and forward encoding analyses have extracted information specific to the contents of WM from visual cortex activity across multiple timepoints during the delay period [15,17,24,25], indicating that visual cortical WM representations persist throughout the period separating the visual stimulus and contingent behavioral response. Second, given the limited capacity of WM [26], neural coding of sensory representations should prioritize task-relevant over task-irrelevant information [27]. Selectivity for task-relevant information was illustrated in a study where decoding based on the multivoxel pattern of delay period activity in early visual cortex was successful only for the task-relevant feature (orientation or color) of the memoranda [16]. Similarly, other work has shown that multivoxel patterns of delay period activity encodes only items cued in the sample display as task-relevant [15,24]. Third, and in contrast to the fixed selectivity model, information about items maintained in WM can be encoded by neural populations that are not highly selective for the maintained stimuli. A recent fMRI study examined the degree to

which decoding information about items maintained in WM was dependent on voxels that were highly selective for the WM items. The key finding was that removing highly selective voxels from the analysis did not substantially reduce the ability to decode information about the WM items [24]. These results are in line with studies demonstrating that perceptual [28] and motor [5] information is distributed across neural populations with diverse tuning preferences.

Fourth, and perhaps most importantly, fMRI measures of sensory representations in visual cortex are tied to the precision of WM representations. For example, one study found decreases in the ability to decode maintained directions of motion from multivoxel delay period activity as the number of to-be-maintained motion directions increased, possibly due to interference between spatially overlapping representations [29]. Reductions in the ability to decode the contents of WM predicted decrements in the precision of memorized motion direction in individual subjects. Forward encoding estimates of WM representations also correspond to memory precision. Ester and colleagues [17] estimated population tuning curves for maintained orientations from visual cortical activity, and used the width of these tuning curves as an inverse proxy for tuning for the maintained orientation. Tuning precision was correlated with subjects' behavioral precision in reconstructing the remembered orientation (Figure 1c). Although compelling, these studies do not indicate whether the observed modulation of memory precision is a direct or indirect consequence of neural activity in sensory cortex. Fortunately, transcranial magnetic stimulation (TMS; see Box 1) experiments can provide causal evidence for the role of sensory activity in maintaining high-fidelity WM representations. TMS applied to early visual cortex during short-term retention of visual stimuli results in a reduction in behavioral measures of WM precision [30–32]. Together, this work supports the notion that visual cortex stores precise representations of visual WM contents.

The role of lateral prefrontal cortex in working memory

The most pervasive observation in the WM literature is that IPFC activity persists throughout WM maintenance. This finding has been interpreted as evidence that the IPFC delay activity encodes sensory features of WM items [3]. However, in addition to displaying coarse selectivity for WM items and features [33], IPFC activity exhibits selectivity for a broad range of task variables during the delay period of WM tasks. For example, IPFC neurons show differential preferences for task rules [34], contingent motor responses [35], and stimulus-response mappings [36]. Studies examining population coding of IPFC delay activity have similarly found information about stimuli [37], rules [25], and object categories [38] throughout the delay.

Not so selective selectivity

How is IPFC simultaneously selective for multiple task variables? An increasing number of studies find that, rather than utilizing distinct populations to encode each task variable, activity in IPFC encodes multiple task variables within a single population of neurons [37,39,40]. For example, Machens and colleagues demonstrated that individual IPFC neurons responded to combinations of two task variables (maintained stimulus identity and elapsed time), but that information about each task variable could be independently extracted from the population code [41]. This finding suggests that IPFC representations can be high-dimensional, since they simultaneously encode multiple pieces of information that can be interpreted by neural populations in hierarchically lower regions according to their functional relevance.

Recent work by Rigotti and colleagues further characterized high-dimensional representations of multiple task variables in IPFC [42,43]. They demonstrated that activity in

a population of IPFC neurons simultaneously coded for information about all task variables (task, object 1, and object 2) during the delay period of a complex object sequence WM task. In order to examine the degree to which these high-dimensional representations arose from neurons' selectivity for individual task variables (e.g., task A vs. task B), the authors artificially abolished classical neuronal selectivity. This was accomplished by adding noise to each neuron's response to equate the average response across single task variables (e.g., such that the average response to tasks A and B were equivalent), while preserving differences in firing as a result of different combinations of task variables. Strikingly, and counter to the predictions of the fixed selectivity model, population selectivity for task variables persisted even when selectivity for individual task variables was abolished. Most critically, this work highlights two conditions that give rise to high-dimensional IPFC representations. The first condition is nonlinear mixed selectivity, or nonlinear neural responses to combinations of task variables. Artificially abolishing nonlinear mixed selectivity reduced the dimensionality of the representations, limiting the information that was available for readout by other regions, and error trials were associated with reduced nonlinear mixed selectivity. The second condition is randomly connected networks of neurons, which can support complex and diverse input-output mappings [44]. The perspective presented in this intriguing study has the potential to demystify the seemingly limitless ability of IPFC to represent task information; however, an important future direction will be to specify the constraints (such as anatomical input from sensorimotor regions [45]) that limit the dimensionality of information encoded by IPFC activity.

Interpreting stimulus selectivity

How do we interpret evidence that IPFC activity is selective for maintained stimuli? Does this imply that IPFC maintains sensory properties of the WM stimulus [33], analogous to sensory cortices? Duplicating the sustained sensory information in sensory cortices seems unnecessary and metabolically costly [46]. Furthermore, from the perspective of the fixed selectivity model, the maintenance of sensory representations in IPFC would seem to require that IPFC neurons exhibit a comparable degree of tuning for sensory features as neurons in sensory cortex. This does not appear to be the case. For example, neurons in dorsal IPFC exhibit preferences for task-relevant directions of motion, but are markedly less motion-selective than neurons in motion-sensitive visual area MT [47].

The results from population decoding studies also support a dissociation between stimulus-specific IPFC representations and sensory representations. In one study, researchers were able to decode the identity of the memoranda from delay period activation patterns in visual cortex – but not IPFC – when subjects were required to maintain a visual representation [48]. The pivotal finding was that stimulus-specific activation patterns emerged in IPFC when subjects retained the category of the item, rather than the item itself. This finding accords well with prior work showing that IPFC preferentially encodes and maintains arbitrary and abstract representations of object category over representations of visual similarity [38,49–51]. Further support for the distinction between stimulus-selective IPFC representations and sensory representations comes from a second fMRI study [24]. This study demonstrated that, in contrast to visual cortex, where category-selective patterns of delay period activity were more similar for visually similar categories, category-selective IPFC activity patterns were not sensitive to visual similarity, suggesting that the representations encoded by these patterns were categorical but not sensory in nature.

Source of top-down input

Although the above findings are compatible with the well-described role of IPFC in storing and integrating information, an alternate perspective is that, rather than representing the storage of information, the primary role of IPFC during WM is to influence representations

in other regions [52]. Specifically, patterns of activity in IPFC may serve as top-down signals used to bias the competition of neural representation in hierarchically lower areas, such as sensorimotor [4] and parietal regions [53]. Indeed, the IPFC sits at the apex of the motor hierarchy [54] and possesses diverse anatomical connections capable of directly influencing a variety of regions [45]. We propose that activity in the IPFC is a likely source of top-down input to visual systems during visual WM.

A causal link between prefrontal activity and the properties of visual cortical neurons has been established through electrical microstimulation [55], pharmacological manipulations [56], and intervention with TMS [57]. Until recently, however, there was little direct evidence that IPFC input modulated visual activity during WM. Studies combining TMS and neural measures such as fMRI and EEG provide such a link. TMS administered to focal regions of IPFC causes a significant reduction in the selectivity of fMRI responses in visual cortex, suggesting that IPFC inputs enhance selectivity in visual cortex during WM [58,59]. Comparable results were found in patients with stroke-induced lesions to IPFC: the selectivity of responses was reduced in ipsilesional compared to contralesional visual cortex [58].

While highly informative, these experiments did not establish whether IPFC input physically influenced visual cortical selectivity during a specific stage of the WM task or whether IPFC input operated at multiple stages during WM in order to preserve visual selectivity throughout WM maintenance. Two recent papers described TMS effects on selectivity during stimulus encoding and maintenance. One group found that TMS applied over caudal IPFC caused reduced selectivity for the sample stimuli, as indicated by enhanced EEG responses to task-irrelevant sample stimuli as well as marginally suppressed EEG responses to task-relevant sample stimuli [60]. Another group used concurrent TMS-fMRI [61] to modulate IPFC activity during the delay period of a WM task [62]. They observed enhanced processing in visual cortex of task-relevant information in the presence of distractors, further confirming that IPFC input modulates visual selectivity during WM maintenance.

Taken together, these studies provide direct evidence that top-down IPFC signals modulate sensory activity during WM, and IPFC feedback signals, whether periodic or tonic, may enhance the selectivity of representations in sensory cortex throughout WM maintenance. This idea is in line with results showing that consistent communication between IPFC and visual cortex across stimulus encoding and maintenance is important for WM [63]. It should be noted that although none of the TMS studies described above drew specific links between top-down IPFC input and persistent activity within IPFC, they all targeted subregions of IPFC that typically exhibit sustained activation during WM tasks. Further work is required to explicitly test the relationship between top-down IPFC signals and persistent activity.

Persistent neural activity revisited

Persistent neural activity, particularly in IPFC, has become synonymous with WM. However, this equivalence is misleading. First, IPFC does not appear to be privileged in its ability to generate persistent activity. Particularly when analyses focus on neurons or voxels that are highly stimulus-selective, persistent neural activity can be observed nearly everywhere in the brain [8,64–66]. Second, although persistent neural activity is a key mechanism for forming temporal links between sensation and action [54] in a variety of contexts [67–69], there may be other mechanisms by which WM information is actively retained (Figure 2a).

The evidence we have presented thus far underscores the importance of population coding of WM information [40]. As demonstrated in other domains, information can be represented by dynamic spatiotemporal patterns among populations of neurons [70,71]. That is, information

encoded in a given state – or set of activation levels across the population – at time t , may be encoded in an entirely different state at time $t+1$. Thus, a representation can be sustained via a dynamic trajectory through state space (where the space is defined by the activity of the neurons in the population) [72] (Figure 2b). Surprisingly, this is not antithetical to the notion of a stable representation; theoretical work suggests that in the case where redundant coding of information is present, time-varying population activation can encode a stable representation [73].

Empirical findings confirm that WM information can be sustained through dynamic population coding: by examining data in short time-steps across the delay period, studies have found that the pattern of activation states encoding WM information changes over the course of maintenance. One study decoded electrophysiological data from monkey IPFC during a WM task for object category and showed that decoding was most successful when the decoding algorithm was trained and tested on data from the same point in the trial [38]. Training and testing from temporally distal times resulted in chance-level decoding. The inability to generalize decoding performance over time suggests that the patterns of activity containing information about the relevant category drifted over the course of the trial. Other studies have documented similar temporally dynamic population codes in monkey IPFC [37,39,74], and one fMRI study recently demonstrated dynamic population coding in visual cortex [24]. In contrast to the fixed selectivity model, therefore, WM representations may not critically depend on the persistent activity of a fixed set of selectively tuned neurons.

Although the precise neuronal mechanisms underlying dynamic population coding are yet to be defined, recent computational work suggests that information can be maintained through rapid short-term changes in synaptic plasticity [75,76]. Thus, activity-dependent changes in neural networks trace dynamic trajectories through state space that reliably and efficiently code for task-related variables [72,76]. Future studies must determine the functional relevance of these mechanisms for the neurobiological implementation of WM.

Concluding remarks

An understanding of the neural mechanisms underlying WM is critical for gaining insight into the wide range of goal-directed behaviors supported by WM. In this review, we present a perspective on WM that emphasizes the notion of distributed population activity in encoding WM information. Methodological advances in the last ten years, and in the last few years in particular, have highlighted the sensory nature of sustained WM information in sensory cortices and the high-dimensional nature of information coded for by IPFC activity. Contrary to its imputed role as a storage buffer, we suggest that IPFC activity represents top-down influences to sensory regions. This conceptualization of IPFC echoes models of hippocampal function that propose that the hippocampus stores pointers that can reactivate cortical memory traces rather than storing the memories themselves [77]. Future work must prioritize further efforts to specify the role of IPFC in WM, as well as the functions that arise through interactions between IPFC, sensory regions, as well as other regions involved in WM (see Box 2). An emphasis on sustained representations through multiple neural mechanisms will facilitate the incorporation of these mechanisms into a comprehensive theory of WM.

Box 2

Areas for future research

- A key feature of WM is the ability to maintain task-relevant information in the face of task-irrelevant or distracting information [27,85]. A complete understanding of how WM is implemented in the brain will require new insights

into how sustained representations in sensory cortex are affected by incoming sensory input. One study observed that visual WM recruits populations with spatial receptive fields that are distinct from the receptive fields of the neurons activated by the sample item [86]. Although the authors did not examine interference from irrelevant information, some form of global recruitment could potentially prevent distracting items presented in the same spatial location as the sample item from corrupting the WM representation.

- With the studies we review here, we argue that WM relies in part on encoding that is temporally dynamic and spatially distributed. One proposal is that temporal and spatial coordination arises through brain oscillations [87–89]. Direct intracranial recordings in human epilepsy patients [90] and the use of subdural electrode arrays to directly record neural activity across broad regions of cortex in monkeys [91] offers an opportunity to describe the properties of these oscillations in the context of WM [92], simultaneously marrying temporal precision and spatial coverage. These techniques can provide greater insight into regional specificity and interregional integration that are critical for elucidating the neural basis of WM. Additionally, these techniques can facilitate more direct comparisons across monkey and human studies.
- A logical extension of the notion of distributed coding within a region is the idea that brain function arises from large-scale network coordination [93]. There is evidence to suggest that WM relies on such large-scale interregional communication. Visual WM involves top-down signals from IPFC to parietal cortex [53,94] as well as communication from frontoparietal regions to visual cortex [95]. Additionally, interactions between basal ganglia and IPFC are thought to mediate the filtering of task-irrelevant information and the updating of task-relevant information in WM [96]. Future work must integrate knowledge about the neural computations carried out by these individual regions in the service of WM with an understanding of the functions resulting from interactions between these regions in order to build a complete picture of WM.

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Glossary

Delay tasks	The experimental paradigm typically used to study the neural basis of WM. A trial in a delay task begins with a brief presentation of a sample item. The subject encodes this item into WM and maintains this item over a blank ‘delay’ period of a few to several seconds. At the end of the delay period, a probe stimulus appears, and the subject initiates a behavioral response contingent on the WM representation of the sample item. A key feature of delay tasks is that they temporally segregate sub-components of WM such as stimulus encoding, storage, and retrieval/response
Persistent neural activity	Above-baseline neural activity that remains stable and elevated during a trial of a delay task. Persistent neural activity begins during the sample presentation and persists throughout the delay period, returning to baseline at the end of the trial. According to the fixed selectivity model of WM (see main text), persistent neural activity in neurons selective for WM

memoranda is the mechanism by which WM information is actively maintained

Voxel	The spatial unit for measuring changes in blood oxygenation dependent signal (BOLD) with fMRI. A voxel is a three-dimensional volumetric pixel, typically on the order of 3 mm ³ , and is an indirect measure of the summed activity of many tens of thousands of neurons. A single whole-brain fMRI image can consist of 60,000–100,000 voxels
Working memory	The set of operations that support the ability to maintain information in an active state, to manipulate that information, and to use that information to guide behavior. Working memory is essential for several aspects of goal-directed behavior, including language, reasoning, and abstract thought

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Highlights

Recent work suggests the standard neural model of working memory is in need of revision

Multivariate analyses find that sensory cortex stores working memory information

Lateral prefrontal cortex simultaneously encodes multiple task variables to bias sensory regions

Working memory is mediated by dynamic population codes in addition to persistent neural activity

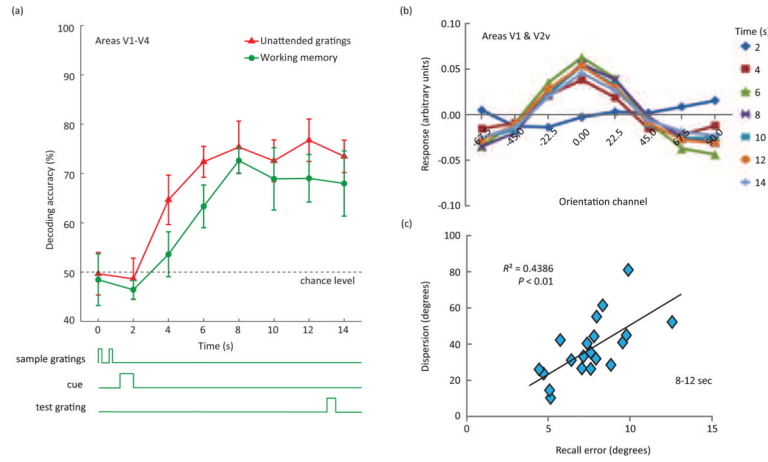


Figure 1.

Evidence for sustained WM representations in early visual cortex. Subjects maintained an orientation of a grating over a delay period. **A**, decoding analysis demonstrated successful decoding of the cued orientation throughout the delay period. Decoding accuracy for maintained orientation (green circles) was comparable to decoding accuracy for the orientation of visually presented gratings (red triangles). Adapted from Ref [15]. **B**, a forward encoding analysis found tuning for maintained orientation, indicating that information about the maintained orientation was present during the delay. As in **A**, this information was preserved throughout the delay period (different color channels response functions represent tuning at different points during the trial; error bars have been omitted for clarity). **C**, the relationship between the degree of tuning of the channel response functions (estimated as dispersion of the best fit Gaussian), which was taken as a proxy for the precision of the WM representation, and behavioral accuracy in reconstructing the maintained orientation. Greater tuning (i.e., less dispersion in the channel response functions) predicted increased accuracy across subjects, establishing a relationship between the quality of WM information stored in visual cortex and memory precision. Adapted from Ref [17].

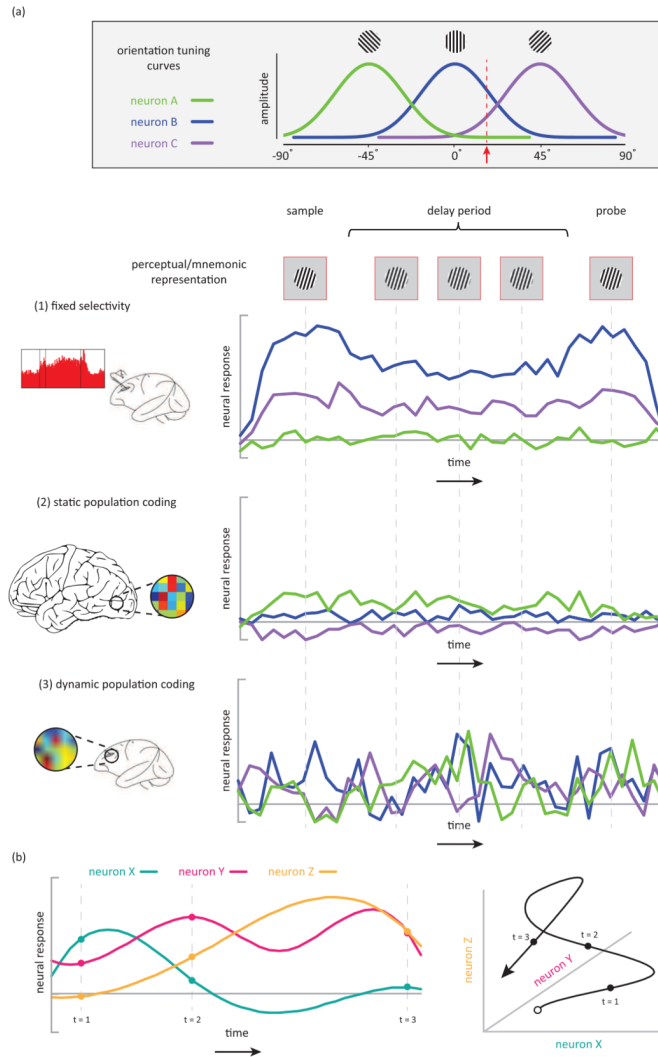


Figure 2.

Multiple neural mechanisms of WM. **A**, a simplified schematic comparing and contrasting the fixed selectivity model with population coding models involving static and dynamic temporal codes. Orientation tuning curves for three hypothetical neurons, A, B, and C, are shown in the top inset; neurons A–C are tuned to -45° , 0° , and 45° , respectively. Neural responses to the to-be-maintained orientation (17°) are indicated by the red arrow and dashed line in the inset. The perceptual and mnemonic representations are depicted below the inset. The visually presented sample orientation (oriented at 17°) elicits a perceptual representation and is followed by a delay period. The mnemonic representation of the sample orientation persists across the delay period and is followed by a probe stimulus that elicits a perceptual representation. Below this are schematics for three different potential neural models of WM. Note that timecourses shown here are for illustrative purposes only and do not depict actual data. *Top row*: the fixed selectivity model, primarily derived from single-unit recordings in monkey LPFC, predicts that neuron B, which is selective for the maintained orientation (refer to the tuning curves in the inset), will exhibit persistent, sustained activity. Neuron C, which is less selective for the maintained orientation, exhibits persistent activity to a lesser degree, while neuron A's activity remains at baseline. *Middle row*: evidence for static population coding comes primarily from fMRI decoding and

forward encoding studies of visual cortex. Here, the pattern of activity across neurons can encode stimulus orientation in the absence of highly selective neural responses. This pattern is sustained throughout maintenance. *Bottom row:* dynamic population coding has been demonstrated largely in monkey IPFC. Despite time-varying activity in all three neurons, the representation of orientation remains stable. The relevant orientation is encoded by a different combination of neural responses at each point in time. Note that each of these models is potentially compatible with the notion of mixed selectivity, where activity within a single neuron or neuronal population can be simultaneously selective for multiple goal-related variables. Portions of this figure are adapted from Ref [2]. **B**, a schematic illustrating dynamic population coding in a hypothetical population comprised of neurons X, Y, and Z. *Left:* the timecourses for neurons X–Z. *Right:* the population response can be depicted as a trajectory through multidimensional state space. The black path represents the combined activity of the three neurons across time. Timepoints $t = 1$, $t = 2$, and $t = 3$ in the trajectory on the right correspond to activity at points $t = 1$, $t = 2$, and $t = 3$ (indicated by the dashed lines) in the timecourses on the left.