

Working memory and neural oscillations: alpha–gamma versus theta–gamma codes for distinct WM information?

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Neural oscillations at different frequencies have recently been related to a wide range of basic and higher cognitive processes. One possible role of oscillatory activity is to assure the maintenance of information in working memory (WM). Here we review the possibility that rhythmic activity at theta, alpha, and gamma frequencies serve distinct functional roles during WM maintenance. Specifically, we propose that gamma-band oscillations are generically involved in the maintenance of WM information. By contrast, alpha-band activity reflects the active inhibition of task-irrelevant information, whereas theta-band oscillations underlie the organization of sequentially ordered WM items. Finally, we address the role of cross-frequency coupling (CFC) in enabling alpha–gamma and theta–gamma codes for distinct WM information.

Neuronal oscillations and working memory

Working memory (WM) involves the ability to maintain and manipulate information over short periods of time and can be subdivided into the initial encoding of information and maintenance and retrieval of WM items (Figure 1A) [1]. Because WM is centrally involved in many aspects of higher cognitive functions, a substantial amount of work has been dedicated to identifying the neuronal substrates of different WM processes [2,3].

A central question in WM research is how groups of neurons represent and sustain items in the absence of sensory inputs. One possibility is that reverberating neuronal activity in distributed cell assemblies underlies WM maintenance, as originally proposed by Hebb (Figure 1B)

[4]. This proposal has recently received support through observations that rhythmic activity at low (theta, alpha) and high (beta, gamma) frequencies facilitates the formation of coherently organized groups of neurons via the establishment of transient temporal correlations [5–9].

Although rhythmic patterns of activity were first demonstrated by investigators at the beginning of the 20th century, a relationship with behavior was only established 50 years later in seminal work by Singer and colleagues [10]. Specifically, these findings revealed that action potentials generated by cortical cells in the primary visual cortex (V1) are phase-locked to the gamma rhythm in response to a visual stimulus, thereby providing evidence of a relationship between the phase of neuronal oscillations (see Glossary) and the temporal organization of neuronal activity (for a different perspective on phase-coding through gamma-band oscillations see [11]). This finding is supported by several studies that have demonstrated that neuronal oscillations enable efficient transmission and coding of information in distributed neuronal populations [7,12]. In relation to WM, several groups have demonstrated a

Glossary

Electrocorticography (ECOG): measurement of electrical brain signals using electrodes that are implanted subdurally on the surface of the brain.

Electro/magnetoencephalography (EEG/MEG): non-invasive methods for studying brain function that reflect the electrical activity of neuronal populations with millisecond temporal resolution.

Local field potential (LFP): electric potential in the extracellular space around neurons. LFP is a widely available signal in many recording configurations, ranging from single-electrode recordings to multi-electrode arrays.

Long-range synchrony: synchronizations between widely separated brain regions (> 2 cm) as reflected, for example, in phase synchrony.

Neuronal oscillations: prominent feature of spontaneous and task-related brain activity that occur at the level of single units, local field potentials (LFPs), and EEG/MEG recordings. The traditional view is that neuronal oscillations reflect inhibition-based fluctuations of neuronal activity that emerge from the synchronous activation of large neuronal ensembles.

Phase: way of quantifying the difference between two oscillations according to some feature (peak or trough) of one of the oscillation with respect to the other.

Spectral power: reflects the amplitude of neural oscillations computed through a time–frequency transformation (TFT).

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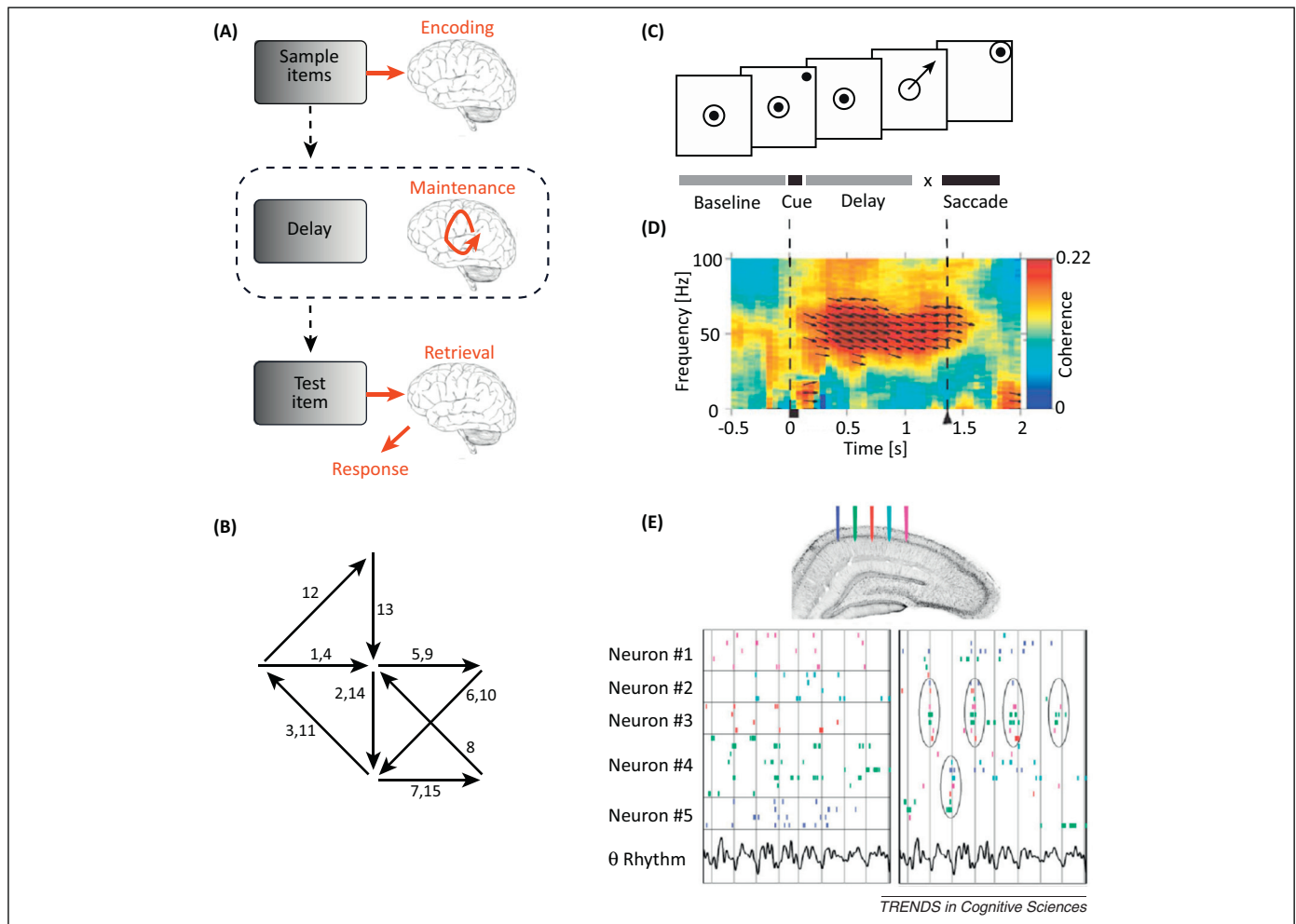


Figure 1. Working memory (WM), neuronal oscillations, and cell assemblies. **(A)** The three stages of WM comprise encoding, maintenance, and retrieval phases. **(B)** Schematic representation of a Hebbian cell assembly. Arrows represent a sequence of neural cell assemblies in which each cell assembly fires according to the numbers on top of each arrow. Once each cell assembly in the loop has fired, the sequence begins again with the first cell assembly. Thus, sequential reactivation of cell assemblies creates a loop (reverberating circuit) that could support sustained neuronal spiking activity during WM maintenance. Modified from [4]. **(C,D)** Example of a delayed oculomotor response task. The cue indicates the spatial position on the screen that has to be memorized. After the delay period, the monkey has to perform a saccade towards the memorized location. The enhancement of spike-field coherence during the delay period reflects the temporal alignment of anatomically distributed neurons with the phase of local field potential (LFP) gamma-band activity. This relationship could underlie the formation of reverberating cell assemblies in parietal cortex during WM retention. Modified from [13]. **(E)** Theta-based activation of cell assemblies in the hippocampus: electrode positions (upper panel) and raster plots (lower left and right panels) of spiking activity for five neurons in the hippocampus. Vertical lines indicate troughs of theta activity (bottom trace). After reordering of the data via a stochastic search for precise temporal relationships, individual cell assemblies become visible around the troughs of theta activity (right lower panel). Modified from [81].

correlation between the timing of neuronal spiking, the phase of oscillatory activity in local field potentials (LFPs), and WM delay activity (Figure 1C–E) [13,14].

Evidence of a relationship between neuronal oscillations and the maintenance of WM items in humans has been provided by electro-/magnetoencephalographic (EEG/MEG) and electrocorticographic (ECOG) recordings. These studies have reported enhanced amplitude and synchrony of oscillatory activity and WM load-specific modulations at different frequencies, in particular in theta (4–7 Hz), alpha (8–13 Hz), and gamma (30–200 Hz) ranges (Table 1). However, the functional role of these different frequencies, as well as their relationship to distinct WM processes, has remained unclear.

Here we propose a framework for integrating the different findings on neuronal oscillations during WM maintenance. Specifically, we suggest that gamma-band oscillations reflect a generic mechanism for active maintenance of WM information, whereas theta-band activity is

specifically involved in the temporal organization of WM items. By contrast, oscillatory activity at alpha frequencies is not relevant for WM information *per se*, but has a critical role in protecting WM items from non-relevant information. As a result, distinct forms of WM information rely on different oscillatory networks that are grouped through cross-frequency coupling (CFC) into different WM codes.

WM delay activity and gamma-band oscillations

Initial research focused on the relationship between gamma-band activity and perceptual processes [15]. However, it soon became clear that high-frequency oscillations are not restricted to visual responses but also occur during a wide range of cognitive and executive processes, including WM. Indeed, gamma-band oscillations occur in all cortical areas and most subcortical structures and are particularly prominent in superficial layers [16].

Experimental and theoretical studies suggest that gamma-band oscillations in the range 30–100 Hz emerge from

Table 1. Overview of EEG/MEG and ECG studies of WM maintenance^a

Study	Method	WM paradigm	Frequency	Localization of WM effects
[44]	EEG	Sternberg task	θ (4–7.5 Hz)	ACC
			α (7.5–14 Hz)	Occipito-parietal cortex
[20]	EEG	Visual DMS	α (9–12 Hz)	Occipital channels
			β (15–20 Hz)	Occipital and frontal channels
			γ (20–80 Hz)	Occipital and temporal channels
[55]	ECOG	Sternberg task	θ (5–9 Hz)	Frontal and temporal cortex
[56]	MEG	Sternberg task	θ (7–8.5 Hz)	Frontal channels
[40]	EEG	Sternberg task	α (9–12 Hz)	Posterior and central channels
[26]	MEG	Auditory spatial	γ (50–70 Hz)	Frontal, parietal, and temporal sensors
[25]	MEG	Auditory spatial	γ (55–80 Hz)	Temporal and prefrontal sensors
[28]	ECOG	Sternberg task	θ (6.73 Hz)	OTC, parietal cortex, and frontal cortex
			γ (38 Hz)	
[41]	EEG	Visual DMS	α (8–12 Hz)	Posterior electrodes
[43]	MEG	Auditory Sternberg task	θ/α (6–12 Hz)	Posterior, central, and left anterior electrodes
[45]	MEG	Visual DMS task	α (8–13 Hz)	Occipital lobe
			γ (30–100 Hz)	Occipital lobe
[42]	MEG	Auditory DMS	α (9–12 Hz)	Superior temporal cortex
[22]	MEG	Memory saccade task	α (8–12 Hz)	Posterior parietal and occipital sensors
			β (13–25 Hz)	Posterior channels
			γ (60–90 Hz)	Posterior channels
[23]	MEG	Auditory DMS	γ (50–90 Hz)	Parieto-occipital sensors
[24]	MEG	Auditory DMS	γ (55–85 Hz)	Frontal, occipital, and central sensors
[46]	EEG	Visual DMS	θ (4–8 Hz)	Parieto-occipital sensors
			α (8–12 Hz)	
			γ (50–70 Hz)	
[82]	EEG	Sternberg task	θ (3.7–7.5 Hz)	Frontal electrodes
			α (7.5–13.7 Hz)	Posterior electrodes
[69]	ECOG	Sternberg task	θ (4–8 Hz)	Hippocampus
			γ (25–100 Hz)	Hippocampus
[27]	MEG	Somatosensory DMS	α (8–14 Hz)	Parietal cortex and right SII
			γ (65–150 Hz)	SII and frontal cortex
[29]	ECOG	Sternberg task	γ (48–90 Hz)	Hippocampus
[72]	EEG	Temporal order/DMS	θ (5–7 Hz)	Prefrontal electrodes
			α (9–12 Hz)	Parietal/occipital electrodes
[33]	MEG	Visual DMS	γ (80–100 Hz)	Parietal cortex
[31]	MEG	Visual DMS	θ (5–9 Hz)	Distributed network of regions including
			α (10–14 Hz)	occipital, parietal, temporal, and frontal
			β (15–30 Hz)	cortex
			γ (30–150 Hz)	
[21]	MEG	Visual DMS task	α (10–14 Hz)	Premotor cortex, left PFC, IPL
			γ (60–80 Hz)	
[65]	MEG	Sternberg task	α (8–12 Hz)	Parieto-occipital sensors
[71]	EEG	Sternberg task	θ (5–8 Hz)	Left frontal electrodes
			α (9–12 Hz)	Posterior
			β (14–28 Hz)	Left posterior
		Visual DMS	γ (30–50 Hz)	Right frontal electrodes

^aAbbreviations: ACC, anterior cingulate cortex; DMS, delayed match to sample task; IPL, intraparietal lobe; OTC, occipito-temporal cortex; PFC, prefrontal cortex; PPC, posterior parietal cortex; SII, somatosensory cortex.

the interplay between GABAergic interneurons and glutamatergic inputs mediated by NMDA and AMPA receptors [17]. GABAergic interneurons, especially those expressing the calcium-binding protein parvalbumin (PV), play a particularly important role in the generation of high-frequency oscillations because of their fast-spiking characteristics and the short time constants of synaptic interactions mediated by these cells [18]. Gamma-band oscillations above 100 Hz are likely to be mediated by different generating mechanisms, such as gap-junction-mediated transmission [17]. Moreover, broad gamma-

band activity may not reflect an oscillatory process but instead could be more closely related to multi-unit activity [19].

First evidence of a link between the maintenance of WM items and gamma-band oscillations was reported by Talon-Baudry and colleagues [20], who observed a sustained increase in oscillatory activity in the 24–60-Hz frequency range in EEG recordings during a visual delayed-match-to-sample (DMS) task. Subsequently, a large body of evidence has supported these findings for visuospatial [21,22], auditory [23–26], and somatosensory WM maintenance [27].

Importantly, several studies demonstrated a parametric relationship between the number of items to be memorized (WM load) and the amplitude of gamma-band oscillations [21,28–31].

In addition, recent advances in source localization of EEG/MEG data [32] have allowed insights into the spatial layout of the underlying generators during WM. WM-load-related gamma-band activity has been localized to key nodes of the WM network, including parietal and prefrontal cortices [21,30,31,33]. This evidence is complemented by ECOG data highlighting the WM-load-dependent modulation of gamma-band oscillations in frontal [28] and hippocampal regions [29].

Finally, a functional relationship between gamma-band activity and maintenance of WM items is supported by the fact that (i) different gamma-band frequencies underlie the maintenance of distinct WM items [23], (ii) gamma-band activity correlates with behavioral indexes of WM performance [21,24], and (iii) single-trial fluctuations of gamma-band activity predict the number of WM items [21,34].

WM delay activity and alpha-band oscillations

Alpha oscillations (8–13 Hz) were the first rhythm to be discovered by Berger in 1924 [35]. One brain region that is crucially involved in the generation of alpha-band oscillations is the thalamus [36]. In addition, alpha oscillations have been recorded in subcortical areas, such as the hippocampus and the reticular formation, and are particularly prominent in the deeper layers (layer V) [16].

It is well established that alpha rhythms result from reciprocal interactions between excitatory and inhibitory neurons whereby the synchronization is also stabilized by gap junctions among inhibitory interneurons. The susceptibility of these networks to engagement in alpha rhythms is in turn modulated by cholinergic and serotonergic mechanisms and by glutamatergic afferents acting via metabotropic receptors [37].

Although initially thought to reflect cortical idling, a growing body of evidence critically implicates rhythmic activity in the alpha band in cortical communication and cognition [38,39]. According to the inhibition timing hypothesis [39], alpha oscillations may play an active role during cognitive processes through the inhibition of task-irrelevant brain regions, for example.

In agreement with this perspective, alpha-band activity has also been prominently observed during WM tasks. Jensen *et al.* examined EEG data during the retention interval for a modified Sternberg task and found pronounced activity at 9–12 Hz [40]. Similar to gamma-band activity, alpha-band oscillations have been observed in several sensory modalities during WM maintenance [27,41,42]. Moreover a load-dependent increase has been demonstrated [43], although evidence of an opposite relationship has been reported as well [44].

Despite the consistent involvement of alpha-band oscillations in WM maintenance, the functional interpretation is conflicting. Although some studies have related delay activity in the alpha band to the functional inhibition of task-irrelevant brain areas [22,40,45,46], others have linked alpha-band activity directly to processes underlying WM maintenance [31,41,43,47]. The former hypothe-

sis is supported by studies involving source localization of EEG/MEG data that have demonstrated an increase in alpha-band oscillations outside core regions of the WM network [21,27]. Haegens *et al.* observed an increase in alpha band activity over task-irrelevant regions during a somatosensory WM task that was strongest during successful WM performance [27]. Moreover, Roux *et al.* observed a positive correlation between 10–14-Hz delay activity and reaction times, suggesting that increased alpha-band activity does not support efficient WM performance [21].

Distinct roles for gamma- versus alpha-band oscillations during WM?

Manipulation of WM load alone may not be sufficient to disentangle the relationship between alpha/gamma-band oscillations and WM maintenance because an increase in the number of WM items is also associated with increases in attentional demands [48], which can influence oscillatory activity [49]. Therefore, experimental designs may be required that allow differentiation between the manipulation of attentional resources and WM load, for example through paradigms in which distracting information is introduced while the number of task-relevant WM items is kept constant.

In a study by Sauseng and colleagues, task-relevant and task-irrelevant items were indicated by a cue that pointed towards either the right or the left side of a visual array, thus making information in either the left or the right hemifield task-irrelevant (Figure 2A) [46]. The results showed that alpha-band activity was modulated by the number of irrelevant items (distractors) and lateralized to the task-irrelevant hemifield (Figure 2B). Crucially, repetitive transcranial magnetic stimulation (rTMS) at alpha frequencies (10 Hz) over the task-irrelevant hemisphere was associated with an improvement in WM capacity (Figure 2C), thereby supporting the possibility of a causal relationship between alpha oscillations and the inhibition of task-irrelevant information.

Similarly, Roux *et al.* tested whether the amplitude of oscillatory activity in a particular frequency band reflects the maintenance of task-relevant WM items by comparing the amplitude of oscillatory activity in response to three relevant items, three relevant and three irrelevant items (distractor condition), and six relevant items in a DMS paradigm (Figure 2C) [21]. The results showed a specific relationship between the amplitude of 60–80-Hz activity and the number of relevant WM items (Figure 2D–G), which was not observed for alpha-band oscillations. The distinct relationship between alpha/gamma-band oscillations and maintenance of relevant WM items was further supported by source localization results, which indicated that 60–80-Hz activity occurred in parietal and prefrontal cortices and covaried with WM load, whereas 10–14-Hz activity was localized to the premotor cortex, suggesting a role for alpha-band oscillations in the inhibition of motor plans during the delay period.

Theta-band oscillations during WM maintenance

An additional important observation from our study [21] and previous work [27,31,45] is the absence of theta-band

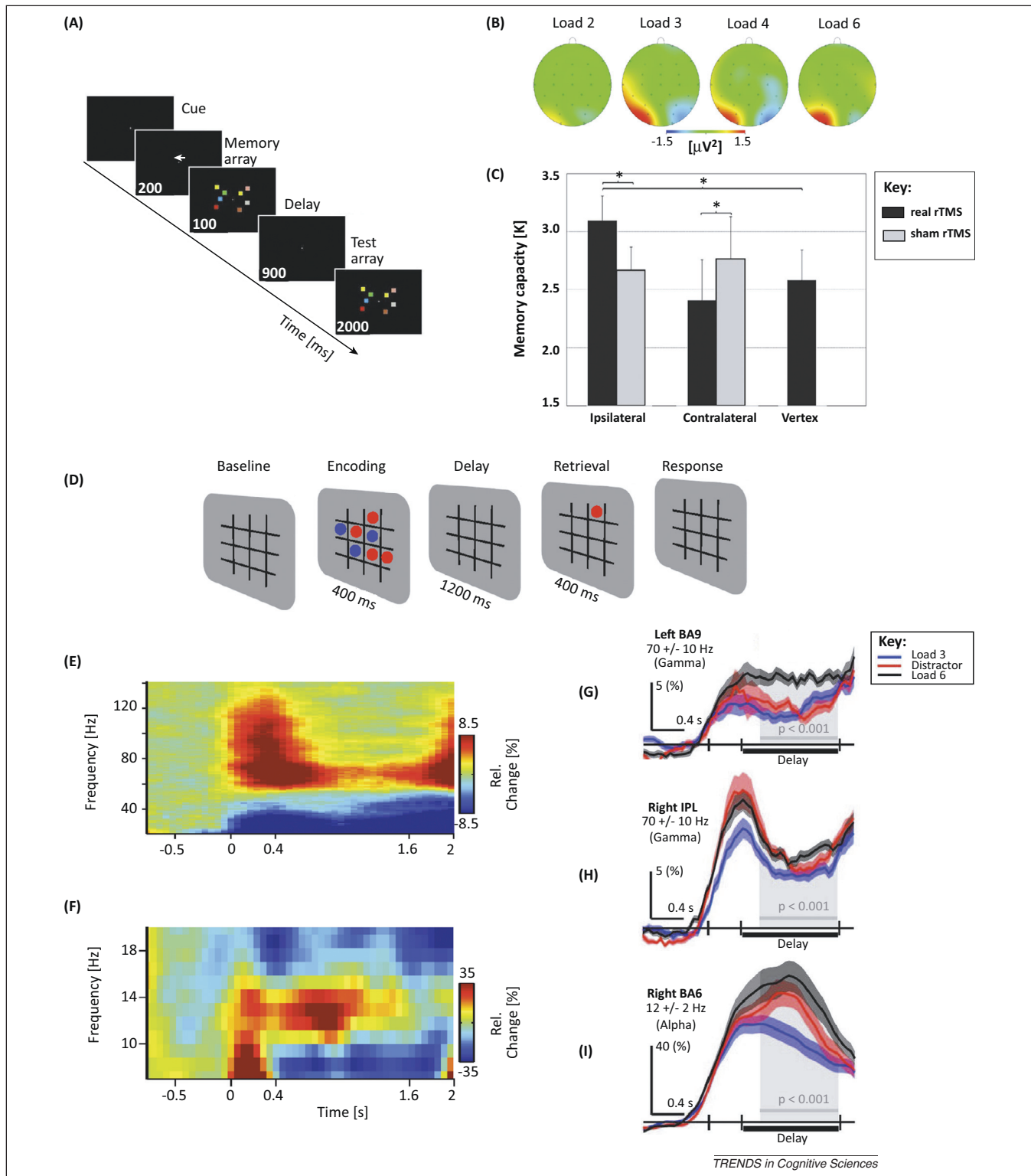


Figure 2. Alpha/gamma-band activity during working memory (WM) maintenance. **(A)** WM task used by Sauseng *et al.* [46]. A cue is presented at the beginning of each trial that indicates in which part of the screen participants have to memorize the presented items. After a delay period, participants are instructed to report whether the items presented in the WM array have changed by pressing a button. **(B)** Topographies of alpha power showing modulation of lateralized (ipsilateral minus contralateral) alpha-band activity with increasing WM load. Alpha-band power is consistently enhanced over electrodes in the ipsilateral hemisphere compared to those contralateral to the attended side. **(C)** Effects of repetitive transcranial magnetic stimulation (rTMS) at alpha frequencies (10 Hz) on WM capacity. rTMS over the ipsilateral hemisphere improves WM capacity compared to sham TMS and the control condition. By contrast, rTMS over the contralateral hemisphere leads to a reduction in WM capacity compared to sham TMS and the control condition. Panels B and C modified from [46]. **(D)** Visual-spatial WM task used by Roux *et al.* [21]. Participants were instructed to memorize the spatial positions of red items only and to ignore the blue items. **(E,F)** Spectrograms of sensor activity for (E) lower and (F) higher frequencies showing enhanced oscillatory activity at alpha (10–14 Hz) and gamma (60–80 Hz) frequencies during the delay period. Pseudo-colors indicate the relative increase in task-related activity compared to baseline activity. **(G,H)** Time courses of 60–80-Hz activity in the prefrontal cortex (BA9) and intraparietal lobe (IPL). The source reconstruction of delay activity suggests the possibility that gamma power in the IPL and PFC reflects different aspects of WM maintenance. This is supported by the fact that gamma-band activity in parietal cortex was modulated by the number of stimuli presented in the memory array but not by the number of relevant items, which suggests that modulation of 60–80-Hz activity reflects scanning and maintenance of the spatial positions of possible WM locations. **(I)** Time courses of 10–14-Hz activity in the premotor cortex (BA6) showing that alpha-band activity was not modulated by the number of task-relevant items. Panels E–I are modified from [21].

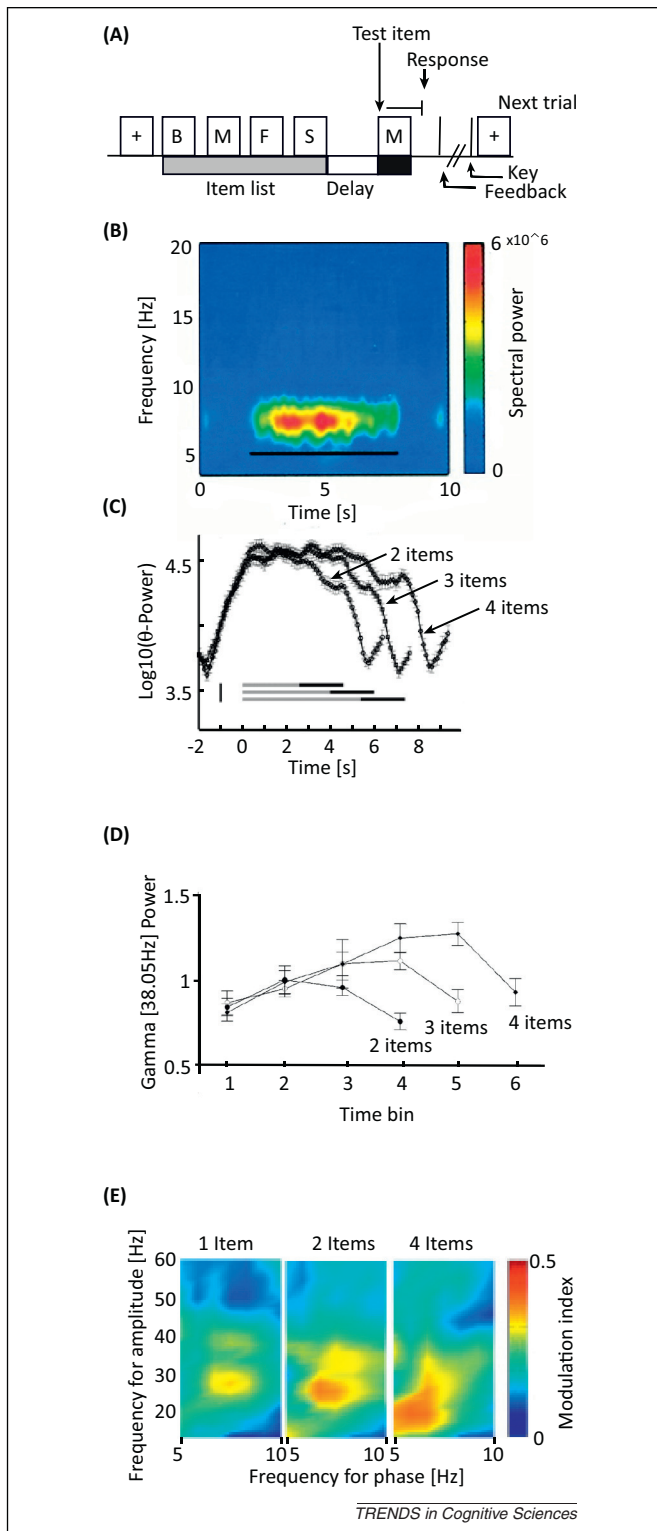


Figure 3. Theta-gamma band activity during working memory (WM) maintenance. **(A)** Schematic representation of a Sternberg paradigm used by Raghavachari *et al.* [55]. Participants have to memorize a list of letters that are presented sequentially. After a brief delay period, a probe item is presented and participants have to indicate whether the probe belongs to the list of memorized items. **(B)** Spectrogram of electrocorticographic (ECOG) signals recorded in human participants showing enhanced oscillatory activity at theta frequencies (6–9 Hz) during the delay period (black bar). **(C)** Time courses of theta power for differing list length. Theta power remains elevated above baseline levels throughout the sequential encoding of individual letters (gray bar) and during the retention phase (black bar). Importantly, a list size effect can be detected from the modulation of theta power during the encoding and delay phases. Panels B and C modified from [55]. **(D)** Time course of gamma-band activity as a function of list size. A similar effect can be observed in the modulation of gamma-band activity for different list

activity, raising the question whether theta-band activity is relevant for WM processes.

Theta oscillations (4–8 Hz) represent one of best-studied rhythms in the mammalian brain [50]. Theta oscillations are particularly prominent in the hippocampus–entorhinal system, but also occur in extrahippocampal regions, such as the prefrontal cortex, amygdala, and visual cortex. In the hippocampus, theta oscillations are generated by an interplay of glutamatergic and GABAergic neurons. In addition, GABAergic inputs are modulated by cholinergic inputs from the septum, which possibly acts as a pacemaker for theta activity [51].

Studies in rodents revealed a close relationship between the occurrence of theta oscillations in the hippocampus, locomotion, and the place-specific firing of hippocampal pyramidal cells (place cells), which have been implicated in the coding of spatial positions through phase precession [52]. In addition, a large body of work indicates that the hippocampus plays a crucial role in the formation and recall of episodic and declarative memory [53]. More specifically, it has been proposed that theta-band oscillations are related to WM capacity limits of approximately seven items [54].

Consistent with this evidence, several studies have revealed pronounced theta-band activity during WM maintenance. Raghavachari *et al.* obtained ECOG data from epileptic patients while they performed a Sternberg task [55]. Time–frequency analysis indicated the occurrence of theta-band activity in several cortical sites throughout the task, including during the delay period, which increased systematically with WM load. These results were supported by a MEG study in which frontal theta activity increased parametrically with the number of items retained in WM (Figure 3A,B) [56], and Moran *et al.* observed a complex relationship between theta-band activity in hippocampal, frontal, and parietal regions and WM capacity [57].

Long-range synchronization during WM maintenance

In addition to amplitude modulation of neural oscillations within local circuits, long-range synchronization between neuronal assemblies, as assessed through phase or coherence measures, has been demonstrated in several studies [30,47,58,59]. Long-range synchronization could support computations during WM maintenance within circumscribed brain regions by establishing transient neural communication to facilitate information transfer within distributed WM networks [60]. Consistent with this hypothesis, there is cumulative evidence of synchronization at theta, alpha, and gamma frequencies during WM maintenance that has been related to top-down control [59], manipulation of WM items [61], integration of WM subprocesses [62], and synaptic plasticity [60].

Neural oscillations and distinct WM memory contents

The current evidence suggests that oscillations at theta-, alpha- and gamma-band frequencies are the dominant

sizes. Panel D modified from [28]. **(E)** Empirical evidence of the occurrence of theta-gamma coupling during the maintenance of multiple sequentially ordered WM items. Co-modulograms of ECOG signals indicate list-length-dependent modulation of theta-gamma phase–amplitude coupling (PAC) during the delay period of a Sternberg task. Pseudo-colors denote the strength of PAC. Panel E modified from [69].

rhythms engaged during WM maintenance, albeit with potentially important differences with regard to their functional role and task-dependent modulation. An overview of recent studies that investigated neural oscillations during WM delay activity (Table 1) suggests that theta activity occurs preferentially in tasks that involve sequential coding of multiple WM items, such as during the Sternberg paradigm (Figure 3A), whereas alpha oscillations tend to occur during tasks that require maintenance of simultaneously presented visual or spatial information.

This distinction may be considered compatible with evidence on the two specialized storage systems for WM information: the phonological loop and the visuospatial sketch pad [1]. The former deals with the rehearsal of verbal/acoustic information and consists of two parts: a short-term phonological store for auditory memory traces that are subject to rapid decay, and a subvocal rehearsal component or articulatory loop that can consolidate memory traces through sequential reactivation. Accordingly, sequential encoding, such as during Sternberg tasks, could activate the phonological loop to support the maintenance of sequenced WM items through subvocal rehearsal, which results in a corresponding increase in theta activity during the delay period. By contrast, it has been proposed that the visuospatial sketchpad is responsible for the storage and rehearsal of visual and spatial WM items. In analogy to its phonological counterpart, the sketchpad contains a storage component, the visual cache, and a rehearsal component, the inner scribe [1].

This multicomponent model of WM is consistent with the distinct functional roles and anatomical regions involved in the generation of theta/alpha-band oscillations. Theta activity is prominently involved not only in the hippocampal–entorhinal system but also in cortical regions such as the prefrontal cortex. One of the core functions attributed to theta-band oscillations in the hippocampal system is the temporal integration of cell assemblies [52]. Although first demonstrated for the tracking of spatial positions, the same mechanism may also support the representation and consolidation of sequentially organized memory traces [63].

Alpha-band activity, by contrast, is most frequently observed in sensory regions and the thalamus, and is prominently involved in the discrete sampling and gating of visual scenes [64]. Accordingly, modulation of alpha activity may enable the gating of task-relevant WM items, for example during suppression of distracting information during WM encoding and maintenance. In this context, recruitment of alpha-band oscillations for inhibition of distracting information can also occur during tasks requiring the maintenance of sequential information [65], highlighting that theta/alpha frequencies are closely linked to the task demands during WM and not limited to the format of WM representations.

In this framework, gamma-band oscillations represent a generic mechanism for the representation of individual WM items, irrespective of WM content and format. This is because the synchronization of neuronal discharges at gamma frequencies supports the integration of neurons into cell assemblies in different cortical and subcortical

Box 1. Cross-frequency coupling

WM may constitute a prominent example of a cognitive process in which cross-frequency coupling (CFC) occurs between two frequency ranges, an issue that is attracting increased attention in cognitive neuroscience [66] because it may play a crucial role in neuronal communication. This is supported by numerous observations that slower brain rhythms occur simultaneously with faster oscillations during WM [18,20,21,23], and different forms of CFC may exist between these rhythms [3,71]. One form of CFC is phase–amplitude coupling (PAC), whereby the amplitude of a higher frequency is modulated by the phase of a slower rhythm. Other forms include amplitude–amplitude coupling and n:m phase locking [71], which refer to power and phase co-fluctuations between different frequencies. For the generation of theta–gamma and alpha–gamma codes during WM delay activity, we consider both phase–phase and PAC as possible ways to establish cross-frequency interactions. Importantly, the modulation of local high-frequency activity through the phase of a slower rhythm has been proposed as a putative mechanism for the synchronization of fast oscillations across distant sites [3].

structures [5] and thus could represent an effective representational format for WM information.

Distinct theta/gamma and alpha/gamma codes for WM information?

Importantly, theta/alpha rhythms do not occur in isolation but are frequently accompanied by activity in higher frequency ranges, in particular at gamma frequencies [21,27,31,45]. This observation is consistent with increasing evidence that neural oscillations form a hierarchical system in which different rhythms exhibit CFC [66], suggesting that populations of neurons oscillating at different frequencies interact with each other, forming nested assemblies (Box 1) [63].

Cross-frequency interactions between theta- and gamma-band oscillations are a prominent feature not only of hippocampal circuits [67] but also of other structures [68] and thus could provide a code for representing multiple and sequentially ordered WM items in which cycles of gamma-band oscillations are coordinated through an underlying theta rhythm. Evidence of such a theta–gamma code [63] during WM has been reported by Axmacher *et al.* [69]. The authors examined intracranial EEG recordings in human epilepsy patients to demonstrate that maintenance of multiple items in WM is accompanied by load-dependent theta–gamma coupling in the hippocampus (Figure 3E). Similarly, Holz *et al.* observed enhanced theta–gamma coupling for correctly identified visual WM items in EEG data in a DMS paradigm [70].

In contrast to theta–gamma interactions, evidence of an alpha–gamma code during DMS tasks that involve maintenance of sensory information has not yet been investigated. However, evidence of a differential relationship between WM content and oscillatory activity at theta and alpha frequencies has been provided by recent EEG studies [71,72]. Specifically, these data show that if the content of WM is changed from multiple sequentially ordered items to discrete visual [47] or spatial information [49], theta activity is replaced by alpha activity.

Another important finding from these studies is that theta and alpha activities were localized over distinct EEG recordings sites, thereby supporting the view that WM

Box 2. Outstanding questions

- What is the role of long-range synchronization in WM and how does it relate to CFC?
- Is beta-band activity relevant for WM and what is its function?
- Which oscillation frequencies are important for manipulation of WM items?
- What is the relationship between theta and gamma/alpha codes during WM maintenance and encoding and retrieval stages of WM?
- What is role of subcortical structures, such as the thalamus, in the generation of neural oscillations during WM maintenance?
- Has theta activity in the rodent hippocampus a similar role in human memory processes?

content may also influence the recruitment of distinct WM networks. This hypothesis is supported by evidence from ECOG recordings showing that theta–gamma phase–amplitude coupling (PAC) occurs preferentially in fronto-temporal regions during non-visual tasks, whereas alpha–gamma PAC is most likely observed in parietal–occipital networks during the processing of visual information [73].

The possibility that theta–gamma versus alpha–gamma codes underlie distinct WM contents is also supported by psychological evidence of different capacity limits for sequentially versus simultaneously presented WM material [74]. It is conceivable that this difference is a manifestation of the varying length of the gamma duty cycle, that is, the number of gamma cycles that can occur within a fixed temporal window [38]. In other words, the increased capacity for sequentially presented WM material could be

due to the greater number of gamma cycles that can be accommodated within a theta versus alpha cycle. Indeed, there is preliminary evidence to suggest that WM capacity limitations are directly related to the nesting of theta/gamma-band oscillations [54].

WM and neural oscillations: towards an integrated paradigm

Although a large body of psychophysical studies and investigations with fMRI and event-related potentials (ERPs) of WM processes have been conducted [3,48,75–78], we believe that further inquiries into the involvement of rhythmic activity at different temporal and spatial scales could add an important, complementary perspective on the mechanisms, subprocesses, and brain regions involved in WM (Box 2).

This is because neural oscillations represent a physiological signal that reflects the ensemble activity of neurons that have been hypothesized to underlie WM maintenance. In addition, time–frequency analyses allow a decomposition of distinct spectral bands that can be linked to different cognitive processes involved in WM. This is supported by the current review that suggests distinct roles of different oscillation frequencies in WM subprocesses.

Finally, an important advantage of neural oscillations is that comparable indexes of rhythmic activity can be obtained across different species and spatial scales, which allows for direct EEG/MEG and invasive recordings in rodents, for example. This possibility can also facilitate in searching for the mechanisms underlying neural oscillations and associated cognitive processes, and thus in

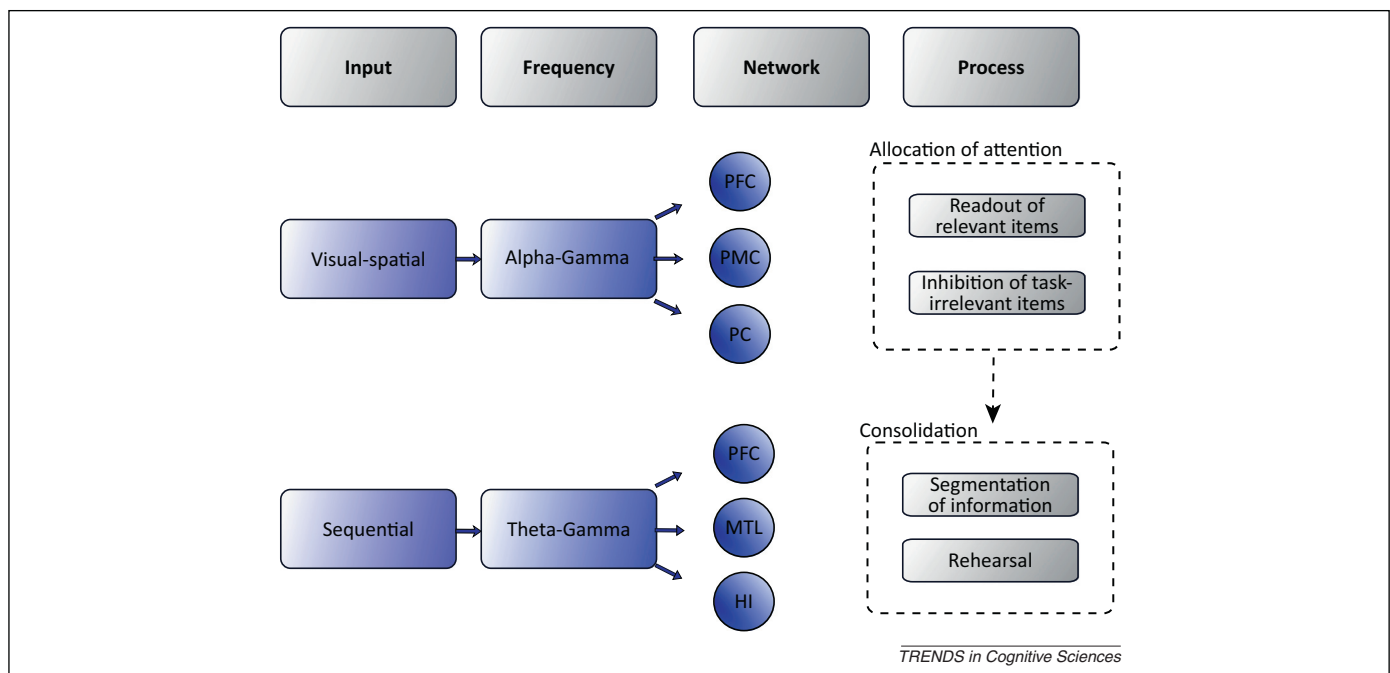


Figure 4. Oscillatory networks for working memory (WM) maintenance. Overview of oscillatory networks for sequential and sensory WM information. For sensory information, alpha–gamma networks occur predominantly in the prefrontal cortex (PFC) and parietal cortex (PC) and subcortical regions such as the thalamus (PMC), which has been prominently implicated in the gating of sensory information and the generation of alpha oscillations [21,36,79]. In this framework, gamma-band activity underlies the active maintenance and read-out of relevant WM items, whereas alpha-band activity is predominantly involved in the inhibition of task-irrelevant WM items. For the coding of sequential information, theta–gamma band oscillations occur predominantly in medial temporal lobe and frontal cortices. It is important to note that these networks can overlap, as in cases in which distracting information is introduced into a sequential WM task.

testing of mechanistic relationships between physiological and behavioral phenomena.

Concluding remarks

We have provided an overview of the potential role of distinct oscillation frequencies in WM information. Overall, there is consistent evidence to suggest that theta-, alpha-, and gamma-band frequencies are functionally relevant for maintenance of WM items, as evidenced by close relations with WM capacity and detection rates. More specifically, the data suggest that different types of WM information require distinct oscillatory codes. Accordingly, maintenance of sensory–spatial WM items involves an alpha–gamma code, whereas sequential WM information relies on theta/gamma-band oscillations, which also emerge from different functional networks (Figure 4). This hypothesis is supported by recent evidence suggesting that alpha–gamma coupling may be related to thalamo–cortical circuits [79], whereas theta–gamma coupling has been associated with fronto–hippocampal networks [63].

Testing of this hypothesis could involve experiments with different types of WM information to demonstrate dynamic switching between theta–gamma and alpha–gamma networks, accompanied by advanced source analysis to identify the underlying generators. Moreover, recent advances in the entrainment of neural oscillations through either transcranial magnetic or transcranial alternating current stimulation (TMS/tACS) stimulation indicate that it is also possible to bias rhythmic activity and associated cognitive processes [80]. Accordingly, differential entrainment at theta/alpha/gamma frequencies can be used to bias specific WM processes and key nodes of the WM network to establish causal relations between neural oscillations and cognition.

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