



Riding the slow wave: Exploring the role of entrained low-frequency oscillations in memory formation

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ABSTRACT

Neural oscillations are proposed to support a variety of behaviors, including long-term memory, yet their functional significance remains an active area of research. Here, we explore a potential functional role of low-frequency cortical oscillations in episodic memory formation. Recent theories suggest that low-frequency oscillations orchestrate rhythmic attentional sampling of the environment by dynamically modulating neural excitability across time. When these oscillations entrain to low-frequency rhythms present in the environment, such as speech or music, the brain can build temporal predictions about the onset of relevant events so that these events can be more efficiently processed. Building upon this literature, we propose that entrained low-frequency oscillations may similarly influence the temporal dynamics of episodic memory by rhythmically modulating encoding across time (mnemonic sampling). Central to this proposal is the phenomenon of cross-frequency phase-amplitude coupling, whereby the amplitudes of faster (higher frequency) rhythms, such as gamma oscillations, couple to the phase of slower (lower-frequency) rhythms entrained to environmental stimuli. By imposing temporal structure on higher-frequency oscillatory activity previously linked to memory formation, entrained low-frequency oscillations could dynamically orchestrate memory formation and optimize encoding at specific moments in time. We discuss prior experimental and theoretical work relevant to this proposal.

1. Introduction

Neural oscillations are synchronized rhythmic patterns of electrical activity produced by neurons in the brain that can be readily detected by implanted electrodes or scalp recordings, such as electroencephalography (EEG) or magnetoencephalography (MEG). Neural oscillations naturally occur over a wide range of frequencies, including slow oscillations in the traditional delta (1–4 Hz) and theta (4–8 Hz) range, as well as faster oscillations in the alpha (8–12 Hz), beta (12–30 Hz), and gamma (>30 Hz) range. For decades, researchers and clinicians have been intrigued by neural oscillations and their potential role in a variety of behaviors, ranging from movement (Combrisson et al., 2017; Mirzaei et al., 2017) and sensory processing (Iemi et al., 2017; Landau, 2018; Frühholz et al., 2020) to higher-order cognitive processes such as language (Arnal and Giraud, 2012; Meyer and Gumbert, 2018) and attention (Gross, 2006; Clayton et al., 2015; Helfrich et al., 2018). In the domain of long-term memory, prior work has largely focused on the importance of theta oscillations, including 1–4 Hz “slow theta” oscillations recently identified in the human hippocampus, and their role in

episodic memory (Nyhus and Curran, 2010; Lisman and Jensen, 2013; Jacobs, 2014). Of particular interest has been the role of these oscillations in coordinating neural activity across the brain to bind distinct event features in episodic memory (Sederberg et al., 2003; Jacobs et al., 2006; Klimesch et al., 2010; Lega et al., 2012; Buzsáki et al., 2013; Zhang and Jacobs, 2015; Crespo-Garcia et al., 2016; Lin et al., 2017; Goyal et al., 2020; Kota et al., 2020). Here, we review recent evidence suggesting an additional functional role of low-frequency delta-theta oscillations in episodic memory. Specifically, we propose that by synchronizing to external rhythms, low-frequency oscillations adaptively organize neural activity across time and orchestrate the temporal dynamics of memory formation.

It is well established that low-frequency oscillations in the brain modulate neural excitability in a periodic fashion over time. Interestingly, the phase of these oscillations can shift in the presence of environmental rhythms, such as speech or music, creating windows of heightened neural excitability that occur at predictable moments (i.e., in synchrony with the rhythm) (for review, Schroeder and Lakatos, 2009; Harmony, 2013; Calderone et al., 2014; Haegens and Zion Golumbic,

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2018). The temporal alignment of low-frequency activity in the brain to external rhythms, or ‘neural entrainment’, has been proposed to act as a key mechanism of attentional selection and sensory prediction which enables the brain to exploit temporal regularities in the environment and to optimize processing of relevant events (perceptual sampling) (Lakatos et al., 2008; Schroeder and Lakatos, 2009; Arnal and Giraud, 2012; Calderone et al., 2014; Henry and Herrmann, 2014; Lakatos et al., 2019). In a similar fashion, entrained low-frequency oscillations may dynamically modulate memory formation by providing distinct temporal windows optimized for memory encoding (mnemonic sampling) (Köster et al., 2019). Here, we review recent literature relevant to this proposal. First, we describe the process of neural entrainment and the proposed role of entrained low-frequency oscillations in dynamically modulating attention and perception. Next, we review recent work extending this role of entrained low-frequency oscillations to the memory domain and discuss a potential mechanism (cross-frequency phase-amplitude coupling) by which the dynamic modulation of memory may occur. Specifically, we propose that entrained low-frequency oscillations could adaptively orchestrate episodic memory formation across time by imposing temporal structure on higher-frequency neural activity, such as gamma oscillations. Finally, we discuss important outstanding questions and opportunities for future work to further test this proposal.

2. Entrained low-frequency oscillations act as a mechanism of temporal selection

Many temporal cues commonly found in the environment, such as biological motion, speech, and music, contain slow (<5 Hz) periodic temporal structures that unfold rhythmically over time. Neural oscillations in the brain spontaneously synchronize to these low-frequency rhythms through a process of neural entrainment¹ whereby the phase of the neural oscillation aligns to the timing of the external rhythm (Calderone et al., 2014; Haegens and Zion Golumbic, 2018; Lakatos et al., 2019). For example, when listening to rhythmic music with a steady 1.25 Hz beat, neural oscillations in the 1.25 Hz range will synchronize with the underlying beat structure, evident in increased electrophysiological power (as measured by steady state evoked potentials; SSEPs) and phase coherence (as measured by inter-trial phase coherence; ITPC) at the same frequency as the external rhythm (i.e., 1.25 Hz) (Fig. 1A). Importantly, this orchestration of neural activity by external rhythmic cues results in fluctuations in cortical excitability at predictable moments in time that align with the temporal pattern of the rhythmic stream. This alignment of internal and external rhythms has been proposed to enable the brain to operate in a more efficient manner, or “rhythmic mode,” in which computational resources are directed to specific moments in time when relevant events are likely to occur (Schroeder and Lakatos, 2009). In this way, the entrainment of low-frequency oscillations can act as a key mechanism of selective attention and sensory prediction that coordinates perception and action

¹ Earlier studies, especially those in the memory literature, typically refer to this process as “entrainment” or “neural entrainment.” However, the process by which neural activity increases at the same frequency as external rhythms is widely debated and has been attributed to oscillatory phase resetting (Capilla et al., 2011), oscillatory entrainment (Notbohm et al., 2016), or a combination (Doelling et al., 2019; Lakatos et al., 2019). Although previous work has used “entrainment” as a catch-all term for the brain’s response to rhythm, several recent reviews in the language literature have highlighted the problems with that terminology (Meyer et al., 2019; Obleser and Kayser, 2019; Haegens, 2020). For example, “entrainment” is suggestive of a completely rhythmic stimulus, whereas many rhythms in the environment, such as speech, are actually pseudorhythmic. While terms like “neural tracking” or “entrainment in the broad sense” have been suggested to more accurately capture the process of alignment between neural oscillations and environmental rhythms, in this review we use the term “entrainment” for simplicity.

in an adaptive manner across time (Large and Jones, 1999; Schroeder and Lakatos, 2009; Arnal and Giraud, 2012; Harmony, 2013).

Support for the proposal that entrained low-frequency oscillations act as a mechanism of temporal selection has primarily come from research in the perceptual domain. A large body of prior work has shown that performance on perceptual discrimination and target detection tasks depends on the phase of entrained low-frequency oscillations at the time of stimulus presentation (Lakatos et al., 2008; Stefanics et al., 2010; Henry and Obleser, 2012; Mathewson et al., 2012; Escoffier et al., 2015; for review see Haegens and Zion Golumbic, 2018). In one of the first studies demonstrating this link, low-frequency delta oscillations within sensory cortices (V1 and A1) of macaque monkeys were entrained by rhythmic auditory and visual stimulation during a target detection task (Lakatos et al., 2008). Importantly, the detection of auditory or visual deviant targets embedded within the rhythmic streams was enhanced for targets occurring at specific phases of the entrained delta oscillations. These results suggest that entrained low-frequency oscillations can act as a mechanism of attentional selection by providing periodic temporal windows optimized for sensory-perceptual processing.

In addition, a growing body of work has linked the entrainment of low-frequency oscillations in sensory cortices, measured by either SSEPs or ITPC at the rhythmic frequency, to improved behavioral performance for targets that appear in-phase compared to out-of-phase with the entraining rhythm. For example, entrained low-frequency oscillations have been associated with enhanced perceptual discrimination during pitch detection (Doelling and Poeppel, 2015; Hickok et al., 2015) and detection of tempo changes (Nozaradan et al., 2016), as well as faster reaction speeds on perceptual tasks for events occurring in phase with the rhythm (Lakatos et al., 2008; Stefanics et al., 2010; Soltész et al., 2013). Rhythmic cues can also influence neural processing and behavior across modalities (i.e., auditory entrainment influences visual responses) (Lakatos et al., 2008; ten Oever et al., 2014; Escoffier et al., 2015), indicating that rhythm can have broader, cross-modal effects on neural activity. Together, this research indicates that entrained low-frequency oscillations orchestrate information processing across time and provide periodic windows optimized for information processing.

3. Entrained low-frequency oscillations influence episodic memory

In addition to influencing perception and action, recent evidence suggests that entrained low-frequency oscillations can also influence higher-order cognitive processes, such as episodic memory. To date, the majority of this work has focused on the effect of exogenously boosting theta (~4 Hz) oscillations by methods such as repetitive transcranial magnetic stimulation (TMS) or sensory flicker (Clouter et al., 2017; Wang et al., 2018; Hermiller et al., 2019; Köster et al., 2019). For example, Köster et al. (2019) entrained neural oscillations in the brain by flickering visual stimuli (luminance modulation) at the theta or alpha frequency. Stimulation at the theta frequency increased subsequent memory performance compared to alpha stimulation, and participants’ responsiveness to theta stimulation predicted this ‘memory entrainment’ effect. In another set of studies, both visual and auditory stimuli were presented during a memory paradigm and were flickered (via amplitude or luminance modulation) at 4 Hz theta rhythm either synchronously (i.e., 0° phase offset) or asynchronously (i.e., 90°, 180°, or 270° phase offset) during encoding (Clouter et al., 2017; Wang et al., 2018). When memory for the stimuli was later probed, participants’ associative memory was enhanced for synchronously presented audio-visual information compared to asynchronously presented audio-visual information. Furthermore, this associative memory benefit for synchronously flickered stimuli was related to enhanced phase alignment of entrained theta oscillations across the auditory and visual cortices. This suggests that theta oscillations can enhance cross-regional communication in the brain to bind event features in episodic memory.

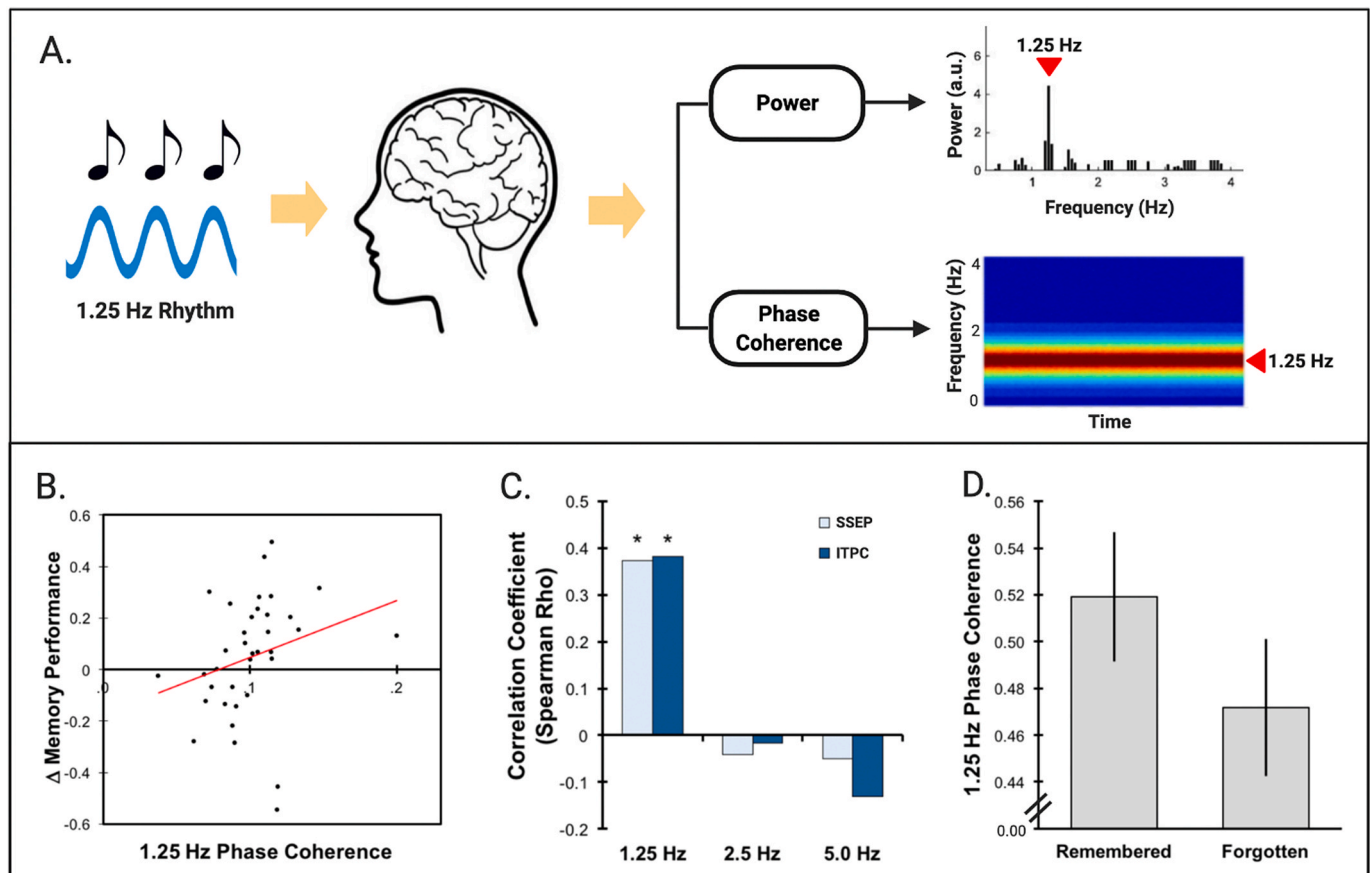


Fig. 1. Entrainment of neural oscillations and their effect on memory formation (Figures adapted from Hickey et al., 2020a,b). (A) Low-frequency neural oscillations synchronize to the temporal dynamics of external rhythms in a process of neural entrainment, evident in increases in electrophysiological power (steady state evoked potentials) and phase coherence at the same frequency as the external rhythm (i.e., 1.25 Hz). (B–D) Relationship between low-frequency neural entrainment and memory formation. (B) Stronger low-frequency neural entrainment (measured by either 1.25 Hz phase coherence or power) during encoding is associated with superior subsequent memory (d') for information presented in-synchrony compared to out-of-synchrony with the entraining rhythm. Y axis represents difference in memory performance between in-synchrony and out-of-synchrony stimuli. (C) The association between neural entrainment and effects of rhythm on subsequent memory is specific to neural entrainment at the frequency of the external rhythm (1.25 Hz) and is not present for other (harmonic) frequencies (i.e., 2.5 Hz, 5 Hz). (D) Low-frequency neural entrainment also predicts subsequent memory for individual trials within participants, with greater electrophysiological measures of entrainment (1.25 Hz phase coherence) for trials that are subsequently remembered compared to those that are subsequently forgotten.

Interestingly, this associative memory effect was not present for rhythmic stimulation at lower frequencies (1.7 Hz).

Recently, Jones and Ward (2019) found that more naturalistic rhythms within the traditional delta band (~ 1 Hz) can impact oscillatory activity and memory formation. In this study, images of everyday objects were presented in either a regular, rhythmic temporal structure (i.e., consistent interstimulus interval) with a frequency of 1.67 Hz or an irregular, arrhythmic temporal structure (i.e., variable interstimulus interval). Neural entrainment, as measured by low-frequency (1.67 Hz) phase consistency, was greater in the context of the rhythmic temporal structure. In addition, objects presented rhythmically at encoding were better remembered in a subsequent test of episodic memory compared to objects presented arrhythmically (for related results, see Thavabala-singam, O'Neil, Zeng and Lee, 2016). These results suggest that the brain can exploit low-frequency temporal regularities in the environment to enhance memory encoding and that rhythmic effects on memory formation may not be limited to frequencies within the traditional theta range.

In addition to impacting global memory performance across the entirety of a task, recent evidence suggests that neural entrainment, particularly entrainment to more naturalistic low-frequency rhythms in environment, impacts the encoding of events at particular moments in time. In one set of behavioral studies, the timing of to-be-encoded stimuli was manipulated *within* a rhythmic temporal stream

(background music with a regular 1.25 Hz beat) such that stimuli either appeared in-synchrony or out-of-synchrony with the beat (Johndro et al., 2019). In a subsequent test of memory, participants demonstrated greater memory performance for visual images that had appeared in-synchrony compared to out-of-synchrony with the beat at encoding. These results reveal that like the effect of rhythm on perception (Jones et al., 2002; Escoffier et al., 2010; Barnhart et al., 2018), the effect of rhythm on episodic memory depends on the timing of events within the rhythmic temporal stream. In a follow-up EEG study, this dynamic effect of rhythm on memory formation was linked to entrained low-frequency oscillations in the brain (Fig. 1B and C) (Hickey et al., 2020). Participants in this study again encoded visual images in the context of background, auditory rhythms with a steady 1.25 Hz beat. Oscillatory entrainment was evident in increased steady state evoked potentials and inter-trial phase coherence at the beat frequency (1.25 Hz). Importantly, the effect of stimulus timing on memory performance (better subsequent memory for images presented in-synchrony versus out-of-synchrony with the background beat) positively scaled with the strength of neural entrainment, and this association was specific to entrainment at the beat frequency (1.25 Hz). In addition, neural entrainment at the beat frequency also predicted subsequent memory for individual trials within participants, with greater neural entrainment at the time of stimulus presentation for images that were subsequently remembered compared to images that were subsequently forgotten (Fig. 1D). Together, these

results suggest that entrained low-frequency oscillations create distinct temporal windows optimized for encoding (mnemonic sampling).

4. How do entrained low-frequency oscillations modulate memory encoding?

Although recent evidence suggests that entrained low-frequency oscillations can influence the temporal dynamics of memory encoding, an important outstanding question is the mechanism by which this occurs. One possibility is that the mnemonic effects of rhythm are a downstream consequence of changes in the local excitability and response gain in sensory cortices ('sensory gating'; Lakatos et al., 2008; Schroeder and Lakatos, 2009; O'Connell et al., 2015). Indeed, entrained low-frequency oscillations in primary sensory cortices have been shown to tune cortical responses and enhance perceptual selection of stimuli that fall at specific phases of the oscillation (Lakatos et al., 2008; O'Connell et al., 2015). However, in addition to synchronizing neural activity in the same sensory cortices as the entraining stimulus (e.g., auditory cortex for auditory rhythms), external rhythmic cues can also influence neural activity in a distributed network of brain regions beyond the sensory cortices (Besle et al., 2011). For example, auditory cortical entrainment in the delta band has been shown to modulate oscillatory power in regions such as the frontal and parietal cortex (Keitel et al., 2017). This suggests that low-frequency oscillations orchestrated by sensory stimuli can have broader effects on information processing beyond their effect on early sensory processing. In support of this proposal, a recent event-related potential (ERP) study found that low-frequency environmental rhythms orchestrate neural activity at multiple stages of processing during memory encoding (Hickey et al., 2020). This study manipulated the timing of stimulus presentation within a low-frequency rhythmic temporal stream such that to-be-remembered information appeared either in-synchrony or out-of-synchrony with the rhythmic beat. In addition to influencing response times and later memory performance, both of which were improved for stimuli appearing in-synchrony with the beat, stimulus timing influenced evoked responses relatively late in the information processing stream. Specifically, the amplitude of the N2 and P3 components (traditionally associated with higher-order attentional and cognitive processing) differed for stimuli appearing in-versus out-of-synchrony with the beat. These results reveal that in addition to acting as a mechanism of early attentional selection, rhythm can influence later, post-perceptual cognitive processes as events are transformed into memory.

How might neural responses to rhythmic sensory cues translate into such changes in post-perceptual cognitive processing? One possibility is that entrained low-frequency oscillations modulate higher-order cognitive processes important for memory formation in an indirect manner by coordinating higher-frequency oscillatory activity (e.g., ~40 Hz gamma oscillations). It is well established that low-frequency neural oscillations modulate the amplitude/power of higher-frequency oscillations (Lakatos et al., 2005; Canolty and Knight, 2010; Thut et al., 2012, for review, Sadeh et al., 2014). This process of cross-frequency phase-amplitude coupling (PAC) has been observed in a variety of brain regions (Tort et al., 2008; Tort et al., 2009; van Wingerden, van der Meij, Kalenschier, Maris and Pennartz, 2014; Esghaei et al., 2015; Jaime et al., 2019; Jiang et al., 2020) and is thought to be a central mechanism by which the brain coordinates network activity and transfers information at multiple temporal scales to support sensory, perceptual, and cognitive processes (Lakatos et al., 2008; Händel & Haarmeier, 2009; Fries et al., 2013; Köster et al., 2014; Szczepanski et al., 2014; Esghaei et al., 2015; Landau et al., 2015; O'Connell et al., 2015; Lega et al., 2016; Bonnefond et al., 2017; Chacko et al., 2018; Lizarazu, Lallier and Molinaro, 2019). For example, in the language domain Keitel et al. (2017) found that low-frequency neural activity tracks the natural rhythms present in speech and couples with higher-frequency activity to support speech perception. In this way, cross-frequency PAC to entrained oscillations

could provide a potential mechanism by which external sensory cues could dynamically organize neural activity and influence more complex cognitive processing and behavior (Canolty and Knight, 2010).

The effect of entrained low-frequency oscillations on higher-frequency neural activity may be particularly important in the context of episodic memory (Hanslmayr et al., 2016). Cross-frequency coupling, particularly between theta and gamma oscillations, has been widely observed in memory tasks and plays a central role in theories of episodic memory (Hasselmo et al., 2002; Lega et al., 2016; Lisman and Jensen, 2013; Staudigl and Hanslmayr, 2013; for review see Hanslmayr et al., 2019). These theories propose that cross-frequency theta-gamma coupling provides a temporal coding scheme that organizes information in memory and optimizes synaptic plasticity. For example, in the hippocampus, slow-theta (2.5–5 Hz) activity has been shown to modulate gamma activity during the formation of new episodic memories in a phase-dependent manner (Lega et al., 2016). Here, we propose that similar cross-frequency interactions may be utilized to construct temporal predictions that adaptively guide memory performance (Fig. 2). Specifically, entrained low-frequency oscillations could adaptively modulate the timing of higher-frequency gamma band activity to enhance encoding at relevant moments in time. This dynamic adjustment of gamma oscillations need not be mediated by low-frequency oscillations in a specific frequency band (e.g., theta vs. delta); instead, the frequency of the entrained oscillation could simply reflect the frequency of the environmental rhythm. Importantly, PAC orchestrated by entrained oscillations may have unique functional role in memory formation by providing periodic "windows" of optimal memory formation. In this way, the current proposal builds upon and extends existing theories of PAC in memory formation to incorporate the dynamic entrainment of low-frequency oscillations (Canolty and Knight, 2010; Lisman and Jensen, 2013; Sadeh et al., 2014). In the next section, we review prior work relevant to this proposal, with a particular focus on the coupling of higher-frequency oscillations in the gamma range given the extensive body of work implicating the theta-gamma neural code in memory formation.

5. Evidence for the role of cross-frequency phase-amplitude coupling in memory

Prior work emphasizing the importance of cross-frequency PAC for memory performance has primarily focused on how the phase of lower-frequency oscillations in the theta range influences the power of higher-frequency oscillations in the gamma range. Theta-gamma PAC has been detected using recordings from the scalp as well as intracranially, and has been observed in a variety of brain regions known to support learning and memory, such as the hippocampus (Tort et al., 2008, 2009; Lega et al., 2016; Jiang et al., 2020), prefrontal cortex (Vaz et al., 2016), and striatal circuit (von Nicolai et al., 2014). Additionally, PAC has been associated with dopamine release after learning (Andino-Pavlovsky et al., 2017), coordinated neuronal spiking across brain regions (Canolty and Knight, 2010; Sadeh et al., 2014), and synaptic plasticity (Bergmann and Born, 2018), further suggesting a potential role in episodic long-term memory. From this work it is proposed that low-frequency oscillations provide an organizational structure by which encoding can occur (likely by coordinating higher-frequency gamma activity in regions important for memory).

5.1. Theta-gamma coupling during long-term memory encoding

One common way that researchers have studied PAC in human episodic memory is by looking at neural activity that predicts subsequent memory (i.e., subsequent memory effects; SMEs). SMEs reflect differences in brain activity during the encoding of information that will be subsequently remembered compared to information that will be subsequently forgotten in later tests of memory (Paller and Wagner, 2002). In one study, Fries et al. (2013) made use of a classic subsequent

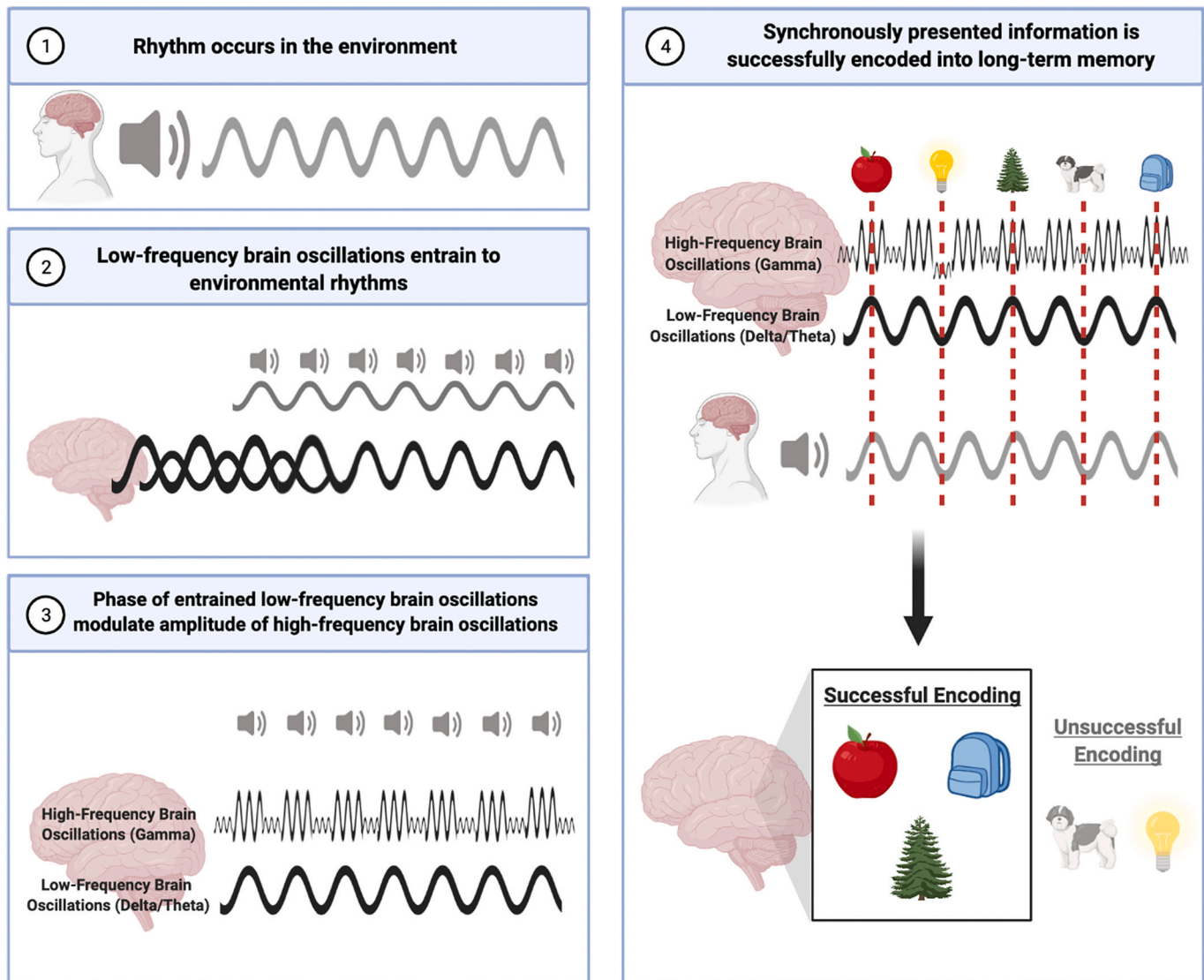


Fig. 2. Proposed framework whereby low-frequency oscillations in the brain entrain to external rhythms and dynamically modulate memory formation. (1) Many temporal cues commonly found in the environment (biological motion, speech, music) contain slow (<5 Hz) periodic temporal structures that unfold rhythmically over time (grey audio symbols indicate underlying beat). (2) Neural oscillations in the brain synchronize to these low-frequency rhythms through a process of neural entrainment whereby the phase of the oscillation aligns to the timing of the rhythm. (3) Through a process of cross-frequency phase-amplitude coupling (PAC), the phase of the entrained low frequency (delta-theta) oscillation determine the amplitude of higher-frequency activity (e.g., gamma oscillations). (4) Temporally structured nested oscillations provide discrete time windows optimized for memory encoding (mnemonic sampling). During these time windows, the brain is in an optimal ‘memory state’ and information (i.e., an object in the environment) is more likely to be successfully encoded into memory.

memory paradigm in which participants incidentally encode a series of images of living and nonliving objects and, after a retention period, are tested on their memory of the previously shown images. Activity during encoding was compared for items that would be later remembered (successful encoding) compared to later forgotten (unsuccessful encoding). During successful encoding, there was increased theta-gamma PAC in frontal (theta) and parietal (gamma) cortices, regions which have been associated with top-down attentional modulation and visual processing, respectively. In a similar study, fronto-parietal theta-gamma coupling was again linked to subsequent memory performance in an associative subsequent memory paradigm (Köster et al., 2018), providing a replication and extension of this finding.

Others have reported PAC in the human hippocampus as well as frontal and temporal cortices during word learning (Lega et al., 2016). Interestingly, in the frontal and temporal cortices coupling was primarily between theta (4.0–9.0 Hz) and gamma oscillations, while in the hippocampus coupling was predominantly between slow-theta (or

delta) (2.5–5.0 Hz) and gamma oscillations. Within the hippocampus, slow-theta – gamma PAC correlated with other subsequent memory effects (e.g., greater theta power during successful encoding). These results provide evidence that low-frequency oscillations can be coupled with higher-frequency amplitudes across a variety of brain regions, and that cross-frequency PAC differs between subsequently remembered and forgotten information, suggesting a role in memory formation.

Recently, theta-gamma PAC has also been experimentally induced by rhythmic theta stimulation and linked to memory formation (Köster et al., 2019). In this study, participants encoded a series of images that either flickered at an individual theta frequency or an individual alpha frequency, or did not flicker (static presentation). After a short retention interval, participants completed a subsequent memory test. Robust entrainment at the theta frequency was observed during image encoding and a strong positive correlation was observed between this theta entrainment and subsequent memory performance. Importantly, however, at the individual trial level theta entrainment did not predict

subsequent memory performance (i.e., SSEP measures of theta entrainment were not greater for subsequently remembered versus forgotten images). Instead, subsequent memory was related to the coupling of entrained theta oscillations to higher-frequency gamma oscillations (entrained theta-gamma PAC). These results suggest that entrained low-frequency oscillations may indirectly contribute to memory performance by modulating higher-frequency neural activity.

5.2. Theta-gamma coupling contributes to associative long-term memory

Coupling between theta and gamma oscillations has also been linked to the formation of associative long-term memories. Associative long-term memory involves binding multiple pieces of information together, such as items with the contexts in which they appear. Although this binding process has been previously linked to the phase alignment of theta oscillations across the brain (Kaplan et al., 2014; Sweeney-Reed et al., 2015; Backus et al., 2016; Clouter et al., 2017; Wang et al., 2018), a number of studies have also suggested that theta-gamma PAC may also support this binding function. For example, evidence of theta-gamma PAC has been seen within the hippocampus, a brain region known to bind and integrate information during the learning of new associations (Davachi and Wagner, 2002; for review: Mayes et al., 2007; Staresina and Davachi, 2010; Zeithamova et al., 2012; Preston and Eichenbaum, 2013). Using a rodent model, Tort et al. (2009) found that the strength of PAC in the hippocampus during learning impacted the formation of associations in memory. Mice in this study were first exposed to two different environments during a learning period. In each environment, there were two stimuli, a target and a foil, and the location of these stimuli varied across the two environments. After the learning period, the mice completed a conditional discrimination (memory) task in which they were placed in one of the two environments and had to locate the target stimuli. During learning, theta-gamma PAC gradually became stronger with more exploration, suggesting that PAC may be particularly relevant in binding new pieces of information, such as the spatial location of the target and the environmental context. Furthermore, a positive correlation was found between theta-gamma PAC during learning and associative memory performance at test.

Theta-gamma PAC in other brain regions outside the hippocampus has also been linked to associative memory formation. For example, theta-gamma PAC has been observed in the orbitofrontal cortex in rodents during the formation of odor associations (van Wingerden et al., 2014) and in the striatum during active navigation and decision making in a T-maze (Tort et al., 2008). Using scalp electrodes in humans, Köster et al. (2018) found evidence that increased frontal theta and coupled to posterior gamma activity supports the binding of distinct visual features in episodic memory. Together, these results suggest that cross-frequency PAC may be a general mechanism that operates across species and brain regions to coordinate neural activity and support memory formation (see also Adams et al., 2019).

5.3. Theta-gamma coupling contributes to multi-item working memory

In addition to influencing the encoding of information into episodic memory, theta-gamma PAC is also thought to play a role in the maintenance and organization of sequential information in working memory (defined here as multi-item working memory). Specifically, it has been suggested that a theta-gamma neural code may support working memory by providing an organizational scheme (via theta oscillations) for the online maintenance of individual items (via coupled gamma oscillations) (for review, see Lisman and Jensen, 2013). In support of this idea, work in humans has found that theta-gamma PAC is associated with successful maintenance of individual items and their sequential order in working memory (Rajji et al., 2017; Axmacher et al., 2010). Additionally, increases in theta-gamma PAC between prefrontal and temporal-parietal cortex elicited by transcranial direct current stimulation has been shown to enhance performance in a working memory task

(Jones et al., 2020).

Recent results by Heusser et al. (2016) further suggest that theta-gamma coupling aids in the temporal organization of information in working memory. In this study, participants encoded six-item sequences and then were asked to remember the order in which the items occurred. Theta-gamma coupling was present in numerous temporal and occipital sites and, importantly, varied by serial position when participants correctly recalled the order in which items had been presented. Specifically, items at the beginning of the sequence (1st and 2nd serial positions) were associated with PAC early in the theta cycle, whereas items at the end of the sequence (5th and 6th serial positions) were associated with PAC later in the cycle. These results support the proposal that theta-gamma phase coding supports the temporal ordering of information in episodic memory (Lisman and Jensen, 2013), and suggest that low-frequency oscillations may contribute to memory formation indirectly by organizing higher-frequency gamma oscillations across time.

To date, the majority of the work investigating PAC contributions multi-item working memory has focused on coupling between theta and gamma oscillations. However, PAC between gamma oscillations and lower-frequency oscillations in the traditional delta band has also been observed (Siegel et al., 2009). Such lower-frequency PAC has been proposed to support switching between processing modes within working memory (i.e., a predictive mode for upcoming information and a maintenance mode for recently encountered information) and may also support this function during long-term memory formation (De Almeida, Idiart, Villavicencio and Lisman, 2012; Leszczyński et al., 2015).

6. Outstanding questions and directions for future research

Rhythmic temporal cues abound in our natural environment and provide important information about the onset of relevant events. Here, we have proposed a combination of mechanisms by which the brain might leverage these rhythmic temporal cues to optimize memory formation. Central to our proposal is the ability of low-frequency cortical oscillations to track sensory events in the environment and to modulate higher-frequency activity across the brain. In this way, entrained oscillations could adaptively orchestrate neural processing and memory encoding at specific moments in time. Future research should more directly test this proposal by investigating whether PAC between higher-frequency (gamma) oscillations and entrained low-frequency (delta/theta) oscillations influences memory encoding in a phase-dependent manner. Such evidence would unite prior work from the memory domain, which has traditionally focused on the impact of theta oscillations and theta-gamma PAC on global memory performance, with work from the perception and attention domains, which has highlighted the role of entrained low-frequency oscillations in directing computational resource to relevant moments in time.

An important outstanding question is the precise type of cross-frequency coupling through which entrained oscillations act to influence memory encoding. While the current review has primarily focused on the modulation of high-frequency (gamma) activity by low-frequency (delta-theta) oscillations, cross-frequency coupling could occur at multiple levels to influence memory encoding. Indeed, PAC has been observed across many frequency bands during cognitive processing (Canolty and Knight, 2010; Lega et al., 2016) and dynamic PAC effects orchestrated by external rhythms could occur at multiple levels within the delta, theta, and gamma ranges (Lakatos et al., 2005, 2008). For example, theta-gamma PAC could fluctuate as a function of delta phase, or power in both the gamma and theta ranges could independently lock to the phase of entrained delta oscillations. In support of this possibility, multiple forms of nested coupling between delta, theta, and gamma oscillations have been previously observed in sensory cortices and linked to perceptual processing (Lakatos et al., 2005, 2008). In addition, different frequencies of slow oscillations are proposed to co-modulate

high-frequency activity (Lakatos et al., 2005). Characterizing the types of PAC that are influenced by low frequency entrainment and their potential contributions to episodic memory represents an important area for future research.

The dynamic orchestration of PAC in frequencies outside the delta, theta, and gamma bands could also contribute to the temporal structuring of episodic memory. For example, alpha oscillations are thought to play an important role in gating selective attention and are known to play a role in memory formation (Voytek et al., 2010; Hanslmayr and Staudigl, 2014). Beta oscillations have also been implicated in memory tasks and are thought to control shifts in attention and neural excitability according to temporal expectations (Cravo et al., 2011; Buschman et al., 2012; Hanslmayr and Staudigl, 2014; Fiebelkorn and Kastner, 2019). In the language domain, interactions between the phase and amplitude of nested theta, gamma, delta and beta oscillations have been proposed to provide a dynamic neural code, or “neurocomputational multiplexing,” central for structuring language (Murphy, 2016). Future research should investigate the degree to which nested oscillations across multiple frequency bands adaptively structure memory formation.

Future research should also explore the relationship between entrained cortical oscillations in the delta-theta range and “slow” 1–4 Hz theta oscillations recently discovered in human hippocampus. Like entrained cortical oscillations, slow hippocampal oscillations impose temporal structure on the coordinated firing of neural assemblies and have been proposed to provide a timing signal that supports episodic memory (Hasselmo et al., 2002; Lega et al., 2016). In addition, slow theta oscillations in the hippocampus have been shown to organize the activity of high-frequency gamma oscillations through PAC (Buzsáki et al., 2013; Jacobs, 2014; Zhang and Jacobs, 2015; Crespo-Garcia et al., 2016; Lega et al., 2016; Lin et al., 2017; Goyal et al., 2020). Thus, both slow theta and entrained low-frequency oscillations share characteristics and functional properties relevant for memory formation. However, slow theta is endogenously generated in the hippocampus and reflects synchronized neural activity that occurs over short durations (~2.75 cycles) (Jacobs, 2014) whereas entrained cortical oscillations are driven by external rhythmic cues and are sustained across time. By flexibly adapting to temporal cues in the environment, entrained oscillations may therefore be uniquely situated to optimize information processing at relevant moments in time. In this way, slow hippocampal oscillations and entrained low-frequency cortical oscillations may play distinct, yet complementary, roles in memory formation.

Finally, future work should explore the degree to which dynamic fluctuations in PAC play a similar role in orchestrating memory during sleep. Low-frequency oscillations are highly synchronized and prominent in the brain during periods of slow-wave sleep, and are believed to coordinate activity across brain regions and across different oscillatory frequencies to support memory consolidation (Mölle and Born, 2011). For example, delta activity has been found to synchronize activity between the hippocampus and neocortex during slow wave sleep to support the consolidation of long-term memories (Walker, 2009). Recent work has also found that sleep spindles couple to slow “sub-delta” (0.5–1.5 Hz) oscillations (Bartsch et al., 2019; Cox et al., 2020), suggesting that low-frequency oscillations during sleep may be coordinating higher frequency activity to support memory consolidation. An important outstanding question is the degree to which low-frequency oscillations during sleep temporally structure consolidation, and whether this temporal structuring has implications for the strength and durability of memory.

7. Conclusion

It is well established that low-frequency neural oscillations in the delta-theta range spontaneously entrain to rhythms in the environment. A growing body of work has demonstrated that these entrained low-frequency oscillations serve an important functional role in behavior

by supporting rhythmic sensory sampling and the dynamic allocation of attention across time. The current review places this work in the context of episodic memory and proposes a framework by which entrained low-frequency oscillations influence the temporal dynamics of memory formation. Specifically, we propose that nested oscillations synchronize to the timing of external rhythmic cues and provide discrete time windows optimized for memory encoding (mnemonic sampling). During these time windows, the brain is in an optimal memory ‘state’ and information is most likely to be successfully encoded into memory. While this proposal remains to be tested, it represents an exciting area for future research.

Author statement

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Declaration of competing interest

The authors declare no competing financial interests.

Appendix A. Supplementary data

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