

Oscillatory brain mechanisms for memory formation – Online and offline processes

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Abstract

Brain oscillations refer to rhythmic activity of neural populations, which can be observed in the human brain. The temporal structure of these oscillations can influence neural firing, and in turn affect information processing and synaptic plasticity. In this manner, oscillatory activity could shape the neural mechanisms of memory formation. Here we review how oscillations relate to human memory processes. To this end, we discuss the potential functions of oscillatory activity in different brain regions, such as the neocortex and the hippocampus. Furthermore, we discuss the potential role of neural oscillations during the different stages during memory formation, from encoding processes during wakefulness to offline processes during sleep. Studies which observe oscillations during memory experiments will be discussed alongside studies that manipulate oscillations attempting to behaviourally impact on memory. The reviewed literature suggests that oscillations may hold important answers as to how our brain manages to encode, maintain and consolidate memories.

1. Introduction

Why does the discussion of brain oscillations merit a whole chapter in a book devoted to human memory? Not too long ago, research on human brain oscillations was on the fringes of neuroscience, but this has changed dramatically in the past two decades. With a gradual shift in cognitive neuroscience from describing the role of single brain regions towards trying to understand how coordinated networks in the brain implement complex cognitive functions, it has become paramount to understand how such network coordination comes about. This is especially important for episodic memories, which contain heterogeneous types of information splayed across sensory domains and therefore specialized brain regions (i.e., the smell of salt water or sound of crashing waves can trigger a vivid visual imagery of a holiday experience on the beach).

Brain oscillations are the product of rhythmic neural discharges, which are synchronized across large populations of cells. This large-scale synchrony leads to a signal strong enough to be recorded on the scalp using electrodes attached to the head (as is the case for EEG) or magnetic sensors surrounding the head (as is the case for MEG). But what renders these brain oscillations so important, warranting consideration when trying to understand human memory? One key reason is that a single neuron integrates the input from thousands of other neurons and is more likely to fire if this input is synchronized. Oscillations synchronize neural populations, allowing them to drive down-stream neurons (i.e. neurons they project to) and thus to get their message transmitted within the network (Buzsaki, 2010; Buzsáki, 2006).

Another, and arguably even more important reason to consider brain oscillations to understand memory is that synchronous firing impacts on synaptic plasticity, i.e. the very structure that our memories are made of (Kandel, 2001). As postulated by Donald Hebb, cells that fire in synchrony also strengthen their physical connections at the synapse (Markram, Lubke, Frotscher, & Sakmann, 1997). These two critical functions, i.e., regulating communication in distributed networks and facilitating synaptic plasticity highlight the importance of oscillations for human memory. Excitingly,

beyond their passive recording during memory experiments, oscillations can also be actively induced by various forms of rhythmic stimulation. These oscillatory stimulation studies offer a unique handle on manipulating memory functions, which allows us to determine whether particular brain oscillations are of causal relevance for memory (Hanslmayr, Axmacher, & Inman, 2019).

The aim of this chapter is to summarize the current state of the field of oscillations and human memory and highlight exciting questions for future research. To this end, we will focus on the role of brain oscillations during the different stages of memory formation, and will not discuss in detail the role of oscillations during memory retrieval (see (Staresina & Wimber, 2019) for a recent review of oscillatory dynamics during memory retrieval). This chapter is broadly organized into four parts. In the first part we explain some basic physiological principles and conceptual views of oscillations and their relevance for memory, which are necessary to understand the following sections. Thereafter we will cover the role of brain oscillations as investigated in the three most important stages of memory formation: (i) online processing (i.e. during perception of the event), (ii) maintenance in working memory (processes immediately after perceiving the event), and (iii) consolidation processes during post-encoding rest (offline) periods.

2. Basic physiological principles of oscillations and relevance for memory

Oscillations are generated by rhythmic discharges of large populations of neurons. These discharges arrive at the dendrites of neurons and generate a small voltage change outside the neuron, which is referred to as the Local Field Potential (LFP). If these incoming discharges arrived in an irregular manner, we would record only small irregular electrophysiological signals (see Figure 1). However, if the incoming discharges are synchronized and rhythmic, then their individual potentials sum up and generate a rhythmic signal large enough to be recorded not only outside the cell but even outside the head (Buzsaki, Anastassiou, & Koch, 2012; Lopes da Silva, 2013). These rhythmical brain signals are referred to as brain oscillations and are divided into different frequency bands and named with letters from the Greek alphabet, i.e. delta (~1-3 Hz), theta (~3-8 Hz), alpha (~8-13 Hz), beta (~13-30

Hz) and gamma (~30-80 Hz), which is a non-exhaustive list but mentions the most relevant oscillations for this chapter. Because neurons integrate over incoming spikes they can easily join a network of synchronized and rhythmically discharging neurons and propagate the population rhythm to other regions. Recording these rhythmic population signals is akin to recording the sound in a sports arena with a microphone hanging from the ceiling. A sudden increase in volume, produced by synchronized shouts of spectators, tells us that something important happened (even if we don't have access to other information), and quite often supporters engage in rhythmic clapping, shouting, etc. to cheer their team on.

The powerful nature of this synchronization mechanism, which bears the risk of overpowering other important functions, necessitates the need to balance synchronization with desynchronization. Indeed, uncontrolled hyper-synchronization of neural activity underlies epileptic seizures and prevents controlled movement in Parkinson's disease (to name just two pathological conditions induced by excessive synchronization). The healthy brain strikes a delicate balance between states of more synchronized activity and states of less synchronized activity, both of which are important for memory processes. For instance, neural activity in the hippocampus, a most critical region for memory processes (see), is often highly synchronized, partly because it is clocked by other regions (i.e. the septum) and partly because it is very densely interconnected (Colgin, 2013). According to the Complementary Learning Systems framework (see [Chapter XX](#)), the hippocampus facilitates the formation of cortical connections among neurons coding for a specific event. For episodic memories, these connections have to be formed quickly and efficiently since a particular episode is only experienced once. Animal work has shown that neural firing gated by theta and gamma oscillations in the hippocampus allows for such efficient plasticity mechanisms to take place (Huerta & Lisman, 1995; Hyman, Wyble, Goyal, Rossi, & Hasselmo, 2003; Jutras & Buffalo, 2010; Pavlides, Greenstein, Grudman, & Winson, 1988; Wespapat, Tennigkeit, & Singer, 2004). Indeed, theta and gamma oscillations are two dominant rhythms present in the human hippocampus (see Figure 2).

The hippocampus, however, is believed to only hold a sparse 'index' to an episodic memory (Teyler & DiScenna, 1986), with the cortex holding all the rich sensory and semantic information that makes up the memory's content. Oscillations are also abundantly present in the neocortex, with the most pronounced oscillation being the alpha rhythm (~10 Hz; Figure 2). Alpha oscillations have also been shown to be critically related to memory processing but in a slightly different way than theta and gamma oscillations in the hippocampus. In the human and primate hippocampus gamma oscillations typically show an increase in synchronization measures (i.e. narrow band power, coupling of neural spikes to LFP, etc.) with increasing memory demand/success (Jutras, Fries, & Buffalo, 2009; Sederberg et al., 2007). Concerning theta oscillations, the picture is less clear with both power increases and power decreases being linked to memory demand/success (Herweg, Solomon, & Kahana, 2020). Concerning alpha oscillations, however, a different pattern emerges which is very consistent across studies. Areas which actively hold a representation typically increase in neural activity (i.e. firing rate) which leads to a de-synchronization in alpha oscillations as measured by a decrease in narrow band power. This counterintuitive behaviour of increase in neural activity (i.e. spiking) and decrease in alpha occurs because single units break 'free' from the rhythmic population activity (Parish, Hanslmayr, & Bowman, 2018). This contrasts with areas which are not engaged or actively inhibited and which synchronize in alpha (Hanslmayr, Staresina, & Bowman, 2016; Hanslmayr, Staudigl, & Fellner, 2012; Jensen & Mazaheri, 2010; Klimesch, Sauseng, & Hanslmayr, 2007). How this complex behaviour of alpha oscillations supports memory is a matter of current investigation, and will be discussed in more detail below. However, it demonstrates that different synchronizing and de-synchronizing behaviours are present in different brain regions, each assumed to play a different role in the service of memory. Moreover, the oscillatory profile of the brain depends on our current state. For instance, our brain rhythms look markedly different during sleep compared to being awake. These "offline" states and their accompanying rhythms are particularly relevant for memory formation. That is, when no interfering new information is perceived, the brain can solidify and organize previously acquired knowledge. In the next two sections we will consider

the role of brain oscillations during “online” processing as it first happens during the initial perception of an event (Section 3), and second during the maintenance of that information that has just been perceived (Section 4). We end with a discussion of the role of oscillations during “offline” states, when previously encoded memories are consolidated (Section 5).

3. The gate-keepers: Oscillatory mechanisms during the initial processing of an event

During everyday life we perceive numerous events. Some of these we will remember later, many of them we will forget. Here we review studies investigating oscillatory mechanisms during the initial perception of an event, which are the determinants for whether memory formation takes place. To this end, we will take a close look at those oscillatory mechanisms that give “birth to a memory” (Otten & Rugg, 2002). We use the word mechanism deliberately by which we refer to “... a system of causally interacting [...] processes that produce one or more effects.” ([https://en.wikipedia.org/wiki/Mechanism_\(biology\)](https://en.wikipedia.org/wiki/Mechanism_(biology))). In the case of memory, oscillations would be causally interacting processes, which produce memories via impacting on neural firing and hence on the physical connections between neurons. It should be acknowledged, however, that this rather strong statement describes the aim for future oscillatory memory research, rather than the status-quo of the field. Albeit burgeoning studies begin to suggest a causal role of oscillations for memory (see Hanslmayr et al., 2019), establishing such causal links between entrained/induced oscillations and behaviour is all but trivial (Bergmann & Hartwigsen, 2020). Most of the work to tighten this relationship therefore still lies ahead, which indeed represents a most exciting opportunity for future students.

Most of the below described studies used a paradigm referred to as the “Subsequent Memory” or “Differences in Memory” Paradigm (Paller & Wagner, 2002). In this paradigm neural activity is recorded during the processing of discrete events and then back-sorted based on whether the events are remembered in a later test or not. Although this paradigm is not without limitations (Fellner & Hanslmayr, 2017; Hanslmayr & Staudigl, 2014), it has delivered a quite coherent picture of

how different oscillations in different parts of the brain correlate with the formation of a memory. The main limitation of this paradigm lies in its unspecificity, such that a number of neural mechanisms can correlate with later memory success, regardless of the exact process they reflect (i.e. from basic arousal to attention to binding of an item to its context, etc.). Furthermore, a neural correlate is different from a neural mechanism, because a neural correlate can be epiphenomenally linked to memory, meaning that it does not have to cause memory. The best way to distinguish a mechanism from an epiphenomenon is by conducting studies which manipulate oscillations in some way (e.g. via electrical stimulation) and test whether such manipulation entails a change in the associated behaviour (Hanslmayr et al., 2019).

Finally, a brief discussion of signal processing is warranted here (see (Cohen, 2014) for an in-depth overview of electrophysiological signal processing). Any electrophysiological signal is complex as it contains signals of several different frequencies. In order to arrive at estimates of activity for different brain rhythms some form of frequency decomposition is usually applied (i.e., Wavelet or Fourier transforms). Importantly, changes which are not of oscillatory nature also occur and affect the estimates in different frequency bands, which can then be misinterpreted as a change in oscillatory activity. More specifically, any electrophysiological signal recorded from the brain typically follows a $1/f$ pattern, which refers to the fact that amplitudes decrease as frequency increases. A change in irregular neural activity can also affect this $1/f$ pattern, such that an increase in neural activity leads to a change in the slope of the $1/f$ pattern, which takes the form of a decrease in low frequencies accompanied by an increase in high frequencies. It is therefore important to distinguish between changes of this $1/f$ shape and changes in distinct oscillatory frequency bands (Miller, Sorensen, Ojemann, & den Nijs, 2009; Voytek et al., 2015; Wen & Liu, 2016). Addressing this issue, a recent subsequent memory study (Fellner et al., 2019) found that the formation of memories was accompanied by a complex change in multiple frequencies. These changes included theta, alpha/beta and gamma oscillations. Importantly, the different frequencies could be dissociated in time (gamma oscillations occurred before theta oscillations), space

(alpha/beta oscillations were evident over different areas compared to gamma oscillations), and by experimental conditions (some conditions induced effects in alpha/beta whereas others did not). This study therefore strongly suggests that different oscillations play different roles during the formation of episodic memories. Below we consider each of these frequency bands separately, going from slow to fast oscillations, i.e. from theta (~4 Hz) to alpha/beta (~10 / 15 Hz) to gamma oscillations (~40 Hz).

3.1. Theta oscillations (~4-8 Hz)

The theta rhythm is well described in the rodent hippocampus where its critical role for spatial navigation, but also a role for memory encoding and retrieval has been discussed in various models (Hasselmo, 2005; Ketz, Morkonda, & O'Reilly, 2013). Theta rhythms have been found in the human cortex (Kahana, Sekuler, Caplan, Kirschen, & Madsen, 1999) and hippocampus (Aghajani et al., 2017; Ekstrom et al., 2005; Mormann et al., 2005) where it also has been related to spatial navigation and memory processes. However, while the hippocampal theta rhythm is very clearly observable in rodent recordings, theta rhythms in humans are less clear and appear in 'bouts' rather than being a stationary signal (Kahana et al., 1999; Suthana et al., 2012). Another difference is that human theta rhythms can be slower, fluctuating around 4 Hz rather than 8 Hz as is the case in rodents (Jacobs, 2014).

Given its prominent role and link to the hippocampus, much research has focused on studying the theta rhythm during the initial stages of memory encoding using the subsequent memory paradigm. One of the earliest studies in that regard showed that increased theta power during encoding is indeed beneficial for memory (Klimesch, Doppelmayr, Russegger, & Pachinger, 1996), a finding which has been replicated several times since (Backus, Schoffelen, Szepenyi, Hanslmayr, & Doeller, 2016; Lin et al., 2017; Osipova et al., 2006; Staudigl & Hanslmayr, 2013). However, several studies (some of which have very large sample sizes) found the opposite pattern of decreased theta power during trials that were later remembered compared to later forgotten trials (Burke et al., 2013;

Fellner et al., 2016; Greenberg, Burke, Haque, Kahana, & Zaghoul, 2015; Guderian, Schott, Richardson-Klavehn, & Duzel, 2009; Sederberg et al., 2007). At the moment there is no definitive answer as to how to reconcile these opposing findings, but a few suggestions have been offered. For instance, Lega et al. (B. C. Lega, Jacobs, & Kahana, 2012) showed that there might be two theta rhythms, a slow one at ~3 Hz and a fast one at ~8 Hz. Whereas the slow rhythm increases during successful memory formation, the fast one decreases (see (Pastotter & Bauml, 2014) for a similar finding). Whether to observe decreases or increases might therefore depend on the exact frequency of theta. A study by Staudigl & Hanslmayr (2013) showed that different testing conditions are also a critical factor, with testing conditions which match the encoding conditions producing a positive subsequent memory effect (i.e. theta increase to predict memory), and testing conditions which don't match the encoding condition producing a negative subsequent memory effect (i.e. theta decrease to predict memory). Another reason for the different findings might be differences in signal processing, for instance whether oscillatory signals were separated from a change in the 1/f pattern or not (Miller et al., 2009; Voytek et al., 2015). Additionally, as briefly mentioned in Section 3, the subsequent memory paradigm is quite unspecific and likely subsumes a number of neural processes which relate to successful memory. Consequently, a mix of changes in the 1/f spectrum and theta oscillatory activity can be expected, the balance of which will produce negative or positive theta power effects (Herweg et al., 2020).

All of the above reviewed studies considered theta power as the parameter of interest. Another important parameter, however, is theta phase. The phase of an oscillation refers to the point within a cycle (e.g. peak, zero-crossing, trough). A seminal study by Rutishauser et al. (Rutishauser, Ross, Mamelak, & Schuman, 2010) measured theta oscillations in humans during a memory task together with single neuron firing in the medial temporal lobe (Figure 3A). Their findings showed that trials at which neurons fired at a consistent theta phase were more likely to be remembered compared to trials where neurons fired inconsistently. Theta power, however, did not relate to memory in this study. As described above, oscillations have the ability to synchronize networks distributed in the

brain, which can be measured by phase consistency between brain regions. Accordingly, increased theta phase coherence between brain regions has also been reported to index successful memory formation (Backus et al., 2016; Solomon et al., 2017; Sweeney-Reed et al., 2014). The networks appear to be widespread, involving the MTL and hippocampal subregions (Solomon et al., 2019), the cortex (Solomon et al., 2017), fronto-hippocampal connections (Backus et al., 2016) as well as connections between the anterior thalamus and cortex (Sweeney-Reed et al., 2014). Going beyond correlative approaches, recent studies aimed to manipulate theta phase connectivity in an attempt to change memory performance. Using sensory rhythmic stimulation, which is a technique whereby images or sounds are presented (i.e. flickered or fluttered) at a specific frequency (see Hanslmayr et al., 2019), two studies induced theta oscillations that were either coupled or uncoupled between visual and auditory regions. Both studies found evidence for a causal role of theta phase synchrony for memory formation (Clouter, Shapiro, & Hanslmayr, 2017; Wang, Clouter, Chen, Shapiro, & Hanslmayr, 2018) in showing that higher memory performance was obtained for trials where stimulation was applied in a synchronous rather than an asynchronous manner. Together, these studies draw a consistent picture of the relevance of theta phase as a network communication mechanism to support memory formation.

The findings described above align with the idea that theta phase is particularly important for memory as it may represent time windows for synaptic plasticity (Fell & Axmacher, 2011). It has been demonstrated in animals that the firing of neurons at the peak or at the trough of hippocampal theta has opposing consequences for synaptic plasticity, with the former inducing long-term potentiation and the latter inducing long-term depression (Holscher, Anwyl, & Rowan, 1997; Huerta & Lisman, 1995; Hyman et al., 2003; Pavlides et al., 1988). It thus follows that if cortical input is synchronized in theta it has a higher chance on arriving at the same theta phase in the hippocampus. Since theta oscillations modulate synaptic plasticity, we can expect to see larger changes at the synapses if input is synchronized at theta, compared to asynchronous inputs. Theta oscillations

might therefore reflect binding mechanisms at the hippocampal level, which are necessary to bind information processed in distributed cortical networks (Hanslmayr et al., 2016).

3.2. Alpha (~10 Hz) and Beta (~15 Hz) oscillations

Neuronal oscillations in the alpha (~10 Hz) and beta (~15 Hz) band were first discovered by Hans Berger in the late 1920s by EEG recordings (H. Berger, 1931). For decades it was believed that alpha oscillations reflect a state of relaxation or idling (Pfurtscheller, Stancak, & Neuper, 1996); however, it is now clear that they play a much more active role in for cognitive functions. Alpha and beta oscillations have both been found to track memory formation in a number of subsequent memory studies. Although being two different frequency bands, which show dissociable behaviours in the motor domain (Brinkman et al., 2016), alpha and beta oscillations appear to be strongly correlated in subsequent memory studies, which is why we consider them as unitary here. The hallmark of alpha/beta oscillations is that they typically decrease their amplitude in a cortical region that is engaged in a task. It therefore is not surprising that a first study observed stronger alpha power decreases during encoding for items which were later remembered compared to items that were later not remembered (Klimesch, Schimke, et al., 1996). This finding has been replicated many times since, often showing concurrent beta power decreases alongside alpha decreases during successful encoding (Fellner, Bauml, & Hanslmayr, 2013; Hanslmayr, Spitzer, & Bauml, 2009; Hanslmayr et al., 2011; Sederberg et al., 2007). Decreases of alpha/beta power are considered one of the most robust markers for successful episodic memory encoding (Hanslmayr & Staudigl, 2014). We are only aware of two exceptions of this finding, where alpha power increases rather than decreases have been reported to predict memory formation (Fellner et al., 2016; Meeuwissen, Takashima, Fernandez, & Jensen, 2011). Of note, these alpha power increases were observed over posterior regions. These two studies used special encoding instructions which put a strong emphasis on mental imagery, which likely led to active inhibition of posterior (visual) regions and hence alpha power increases as

seen during working memory maintenance task (Jensen & Mazaheri, 2010; Klimesch et al., 2007), as discussed in section 4.

Alpha/beta power decreases during memory formation are regionally specific, that is they occur over posterior/occipital cortex during perception and encoding of visual information (Fellner et al., 2019; Noh, Herzmann, Curran, & de Sa, 2014) but over left prefrontal and temporal regions during encoding of verbal information (Fellner et al., 2019; Hanslmayr et al., 2011). This suggests that alpha/beta power decreases in the cortex are a marker for the engagement of domain specific modules, whereby stronger alpha/beta power decreases indicate stronger levels of information processing and a higher likelihood of memorizing that information. If this hypothesis is correct we can make two predictions. The first is that externally inducing synchronized oscillations at alpha/beta during encoding should impair memory formation, because such stimulation would make information processing less effective. This prediction was confirmed in a study using repetitive transcranial magnetic stimulation (rTMS), which is a technique that uses rhythmic magnetic pulses in order to entrain a specific brain region. An rTMS study stimulated the left prefrontal cortex at various frequencies and showed that only stimulation at the beta frequency (~18.5 Hz), but not at other frequencies, caused memory impairment (Hanslmayr, Matuschek, & Fellner, 2014). By showing that synchronization at beta impairs memory formation, this study suggests that a desynchronization of left prefrontal beta oscillations is causally relevant for memory formation.

A second prediction is that alpha/beta power decreases should relate to information processing. More specifically, alpha/beta power decreases should benefit information processing because they increase the potential for information coding in a neural population (Hanslmayr et al., 2012). This idea is referred to as the Information via Desynchronization Hypothesis, which simply argues that neural desynchronization increases the amount of information that can be neurally encoded because it allows the individual neurons to transmit individual messages as opposed to all of them transmitting the same message (Schneidman et al., 2011). If this is true then the ability of decoding

information from neural patterns should be inversely related to alpha/beta power. This prediction was confirmed in several recent memory studies which showed that (i) information can be specifically decoded from desynchronized alpha oscillations (see Figure 3B) (Michelmann, Bowman, & Hanslmayr, 2016; Michelmann, Staresina, Bowman, & Hanslmayr, 2019) and (ii) that the fidelity of represented information negatively correlates with alpha/beta power (B. J. Griffiths et al., 2019).

Together the above reviewed studies consistently demonstrate a central role of alpha/beta power decreases in memory formation. First, we can say that a decrease in alpha/beta indicates cortical processes which are beneficial for later memory during the processing of an event. Second, alpha/beta power decreases are causally relevant for memory encoding. And third, alpha/beta power decreases allow for the representation of information-rich content. This latter aspect may explain why alpha/beta power is so tightly related to memory encoding. For instance, one influential theory in memory posited that memories are but a by-product of the processes occurring during perception of the event (Craik & Lockhart, 1972). In allowing this information to be more faithfully represented during perception, decreases in alpha/beta oscillations therefore are a strong predictor for later memory retrieval. A reader familiar with the rich literature on attention and oscillations will note that alpha/beta power decreases have been linked also with increased levels of attention (Poeppel, Mangun, & Gazzaniga, 2020). Some theories regard attention as the gate-keeper to episodic memory (Moscovitch, 2008), therefore the strong links between alpha/beta power decreases and memory are not too surprising.

3.3. Gamma (~40 – 80 Hz) oscillations

Oscillations in the gamma frequency appear in a range between 40 and 80 Hz in the human brain and therefore describe rather fast rhythmic neural discharges compared to alpha/beta or theta. Because of their relatively narrow time window gamma oscillations have the ability to precisely synchronize neural events, with neural spikes co-occurring in a time window between 8 to 12 milliseconds. This precise synchronization may be particularly relevant for memory because a

synaptic plasticity mechanism known as Spike Time Dependent Plasticity (STDP) (Bi & Poo, 2001) relies on such precise temporal coordination between pre- and post-synaptic spikes. Simply put, STDP dictates that synaptic modification between a sending and a receiving neuron decreases exponentially with increasing time intervals between sending an output and receiving the input. Gamma oscillations may provide such precise temporal coordination and affect memory via impacting on STDP (Jutras & Buffalo, 2010; Wespatat et al., 2004).

A first demonstration for the role of gamma oscillations for human memory formation comes from a study by Fell et al. (2001) who recorded intracranial EEG from the rhinal cortex and the hippocampus in patients with epilepsy performing a memory task. Using the subsequent memory procedure Fell et al. demonstrated that items which were later successfully retrieved were characterized by higher gamma synchronization (i.e. phase coupling) between rhinal cortex and hippocampus. Since the rhinal cortex is a critical input region into the hippocampus this finding suggests that gamma oscillations play a critical role in routing information from the cortex to the hippocampus. It should be noted, however, that a recent study did not replicate this result (Solomon et al., 2019).

Further subsequent memory studies confirmed a critical role of gamma oscillations in the primate (Jutras et al., 2009) and human hippocampus (B. Griffiths et al., 2019; Lin, Umbach, Rugg, & Lega, 2019; Park et al., 2014; Sederberg et al., 2007) showing that increased synchronization, in most cases measured with increases in power, indicates successful memory formation. In the rodent literature, at least two gamma oscillations have been shown to co-exist in the hippocampus, whereby a slow gamma around 40 Hz indicates memory retrieval processes and a fast gamma oscillation around 60 Hz indicating memory encoding processes. A first hint for a dissociation between high and low gamma oscillations in the human hippocampus comes from Park et al. (Park et al., 2014), who demonstrated that high and low gamma power is differentially related to memory performance in a spatial navigation task. A recent intracranial EEG study was able to more tightly link fast and slow gamma oscillations (as measured with power) to specific encoding and retrieval operations (B.

Griffiths et al., 2019), showing that an increase in fast gamma specifically indicated successful encoding whereas an increase in slow gamma specifically indicated successful retrieval (Figure 4A). Distinct slow and fast gamma oscillations might therefore reflect the balance of activity between different hippocampal subfields (see [Chapter XX](#)), with fast gamma reflecting entorhinal input into CA1 during encoding, and slow gamma reflecting CA3 output during retrieval (Colgin et al., 2009).

Memory relevant gamma oscillations have also been demonstrated in cortical regions (Kucewicz et al., 2019). In the human and primate cortex gamma oscillations are best described in the visual system where they play a crucial role in forming transient networks to allow feed-forward routing of information (Bastos et al., 2015). Using the subsequent memory procedure, two studies demonstrated increased gamma power in the visual cortex for later remembered compared to later not-remembered items (Fellner et al., 2019; Osipova et al., 2006). These effects were found with MEG recordings as well as with intracranial EEG recordings. Both studies used visually presented material and interpreted the gamma effect to reflect early perceptual processes, which support memory formation at an initial level. Whether similar effects are present for acoustically presented material remains to be seen.

The fact that gamma oscillations (i.e. gamma power) are often positively correlated with memory formation across studies raises the question of whether gamma oscillations play a mechanistic, i.e. causal role for memory formation. Unfortunately, not many stimulation studies have been conducted targeting gamma oscillations to test whether manipulating gamma oscillations during encoding impacts on memory. One study, which stimulated the entorhinal cortex with 50 Hz found enhanced memory performance following stimulation (Suthana et al., 2012), however, this effect was not replicated in a larger sample which even found a small decrease in memory performance after stimulation (Jacobs et al., 2016). Another study examined in-phase vs anti-phase stimulation between rhinal cortex and hippocampus, thus mimicking a condition found to benefit memory in an

earlier study (Fell et al., 2001), however, only a trend towards better memory performance for in-phase vs. anti-phase stimulation was obtained (Fell et al., 2013).

3.4. Interacting oscillations: Putting the pieces of the puzzle together

The above findings suggest that all brain oscillations, from theta to alpha/beta to gamma, play a role for memory formation in one way or another. The above reviewed literature also suggests that different oscillations seem to play different roles in the service of memory, as opposed to reflecting one monolithic memory building process (Burke et al., 2013; Fellner et al., 2019). Like players in a football team, these individual processes must cooperate in a specific manner to perform the required complex functions for building memories during the initial stages of encoding. Although we are just at the beginning of putting together the oscillating pieces of the puzzle that make up memories, two ways of how the different oscillations interact in the service of memory have been described. The first way is cross-frequency coupling (Canolty & Knight, 2010; Jensen & Colgin, 2007; Siebenhuhner, Wang, Palva, & Palva, 2016), which refers to a phenomenon whereby a faster oscillation is nested within a slower oscillation. This phenomenon is well described in the rodent hippocampus where the amplitude of gamma oscillations has been found to be modulated by the phase of a slower theta oscillation (Bragin et al., 1995), and to be correlated with spatial memory performance (Tort, Komorowski, Manns, Kopell, & Eichenbaum, 2009). Similar theta-to-gamma cross-frequency coupling has been reported in the human hippocampus (Axmacher et al., 2010; B. Lega, Burke, Jacobs, & Kahana, 2016; Staudigl & Hanslmayr, 2013). Increased theta-to-gamma coupling in the human hippocampus has been reported during successful memory formation (B. Lega et al., 2016). A non-invasive EEG study replicated this result with enhanced frontal theta to posterior gamma coupling predicting successful memory formation (Friese et al., 2013). Animal studies suggest that gamma oscillations nested within theta oscillations are particularly suited for inducing synaptic plasticity in the hippocampus. This suggests that theta-to-gamma coupling is a specific mechanism via which the hippocampus binds the individual elements of a memory together.

This specific binding function of theta-to-gamma coupling was tested in a MEG study, which revealed that theta-to-gamma coupling in the left hippocampus supported the binding of an item to its surrounding context (Staudigl & Hanslmayr, 2013). Intriguingly, a recent direct electric stimulation study used a stimulation protocol whereby bursts of high frequency pulses (50 Hz) were timed at a slower frequency (8 Hz), thus inducing theta-to-gamma cross frequency coupling in the medial temporal lobe during encoding of visual images (Inman et al., 2018). This theta-to-gamma stimulation protocol increased memory retention tested on the following day compared to a non-stimulation condition, suggesting a causal role of theta-to-gamma coupling in the formation of memories. However, one limitation of the study is that no other stimulation conditions were carried out, making it difficult to assess whether the effects on memory were due the specific theta-to-gamma stimulation protocol or due to the fact that electrical stimulation was applied in general. Another important caveat to consider when analysing theta to gamma cross-frequency coupling are methodological challenges, which could render spurious results (Aru et al., 2015). For instance, an evoked response generated by presentation of a stimulus might trigger a phase-reset in theta oscillations together with a gamma power increase. In this scenario, gamma power increase and theta phase are two unrelated phenomena that are both triggered by a third event (i.e. stimulus). Another important caveat are asymmetric waveforms, which can also give rise to spurious cross-frequency coupling (Belluscio, Mizuseki, Schmidt, Kempter, & Buzsaki, 2012).

The second form of interactions are power-to-power correlations between frequency bands, which we briefly describe here. If theta and gamma oscillations in the human hippocampus act to efficiently bind together the different elements that make up an episodic memory, then how do these putative binding mechanisms interact with the alpha/beta power decreases observed during encoding in the cortex? The so-called sync/desync (SDS) model offers an answer to this question (Hanslmayr et al., 2016; Parish et al., 2018). Specifically, the SDS model builds on the complementary learning systems model (McClelland, McNaughton, & O'Reilly, 1995)(see [Chapter XX](#)) in suggesting that there is a division of labour between the hippocampus and neocortex which is visible in

opposing synchronising and desynchronising behaviour. The synchronizing theta-gamma oscillations in the hippocampus are required to efficiently form synaptic connections that turn a transient experience into a lasting memory, while the desynchronizing alpha/beta oscillations in the neocortex are required to represent the information that this episode contains. Simply put, theta-gamma oscillations are the glue that hold the different elements represented in alpha/beta oscillations together. A recent intracranial EEG study confirmed a number of predictions that follow from this model (B. Griffiths et al., 2019). This study showed that neocortical alpha/beta power decreases were coupled with hippocampal gamma power increases in a directionally specific way (see Figure 4B); during memory encoding alpha/beta power decreases preceded the hippocampal gamma power increases; during retrieval alpha/beta power decreases followed the hippocampal gamma power increases. These results not only suggest that alpha/beta power decreases in the cortex correlate with hippocampal gamma power increases, but moreover shows that this correlation maps the input and output dynamics between cortex and hippocampus that occur during memory encoding and retrieval. Although more studies are needed to better understand the interaction between the different hippocampal and neocortical oscillations during memory formation, these models and empirical results suggest how we can understand memory encoding as a complex, well-coordinated process during which different oscillations play different roles.

4. The organizers: Oscillatory correlates of working memory maintenance

This section addresses the oscillatory mechanisms supporting the 'online' maintenance of items in memory (e.g. keeping in mind items to buy whilst shopping for groceries). Such mechanisms are typically studied in the context of working memory tasks in which a set of items have to be held in memory for a few seconds (Addis, Barense, & Duarte, 2015; Sternberg, 2016). Numerous studies in animals and humans have tried to uncover the mechanisms supporting working memory maintenance and it has emerged that brain oscillations support the coordinating of neuronal activity

necessary for the act of keeping information in mind. Broadly speaking, oscillations in lower frequency bands, e.g. theta (5 – 8 Hz) and alpha oscillations (8 – 13 Hz) have been associated with the temporal organization of working memory operations on larger spatial scales, whereas faster activity in the gamma band is associated with maintenance of local neuronal representations. In the light of human electrophysiological research, we will discuss the specific functional roles of these different oscillations and how they interact in order to support multi-item working memory.

4.1. Protecting working memory: inhibition by alpha oscillations

The current tenet in cognitive neuroscience is that alpha oscillations reflect regional specific inhibition. This idea is supported by a number of studies finding alpha power increases with cognitive load. Using EEG, it was shown that alpha power increases during working memory load (Klimesch, Doppelmayr, Schwaiger, Auinger, & Winkler, 1999). Another study in which different numbers of items had to be maintained, demonstrated that alpha oscillations indeed increase in power with working memory load (Jensen, Gelfand, Kounios, & Lisman, 2002) and that the alpha oscillations were generated in early visual cortex (Tuladhar et al., 2007). These findings resulted in the proposal that alpha oscillations serve to functionally inhibit early visual regions in order to reduce interference that could disturb the working memory trace (Foxe & Snyder, 2011; Jensen & Mazaheri, 2010; Klimesch et al., 2007). This hypothesis was supported by EEG and MEG memory studies in which the alpha power was shown to increase in anticipation of visual distraction (Bonnefond & Jensen, 2012; Payne, Guillory, & Sekuler, 2013). In sum, the above correlational studies support the idea that an increase in posterior alpha oscillations serves to inhibit incoming visual information during working memory maintenance.

If the above is true then increasing alpha oscillations at areas that are not involved in maintaining the information at hand should increase working memory performance. This question was addressed in an rTMS study, which found causal evidence in support for a protective role of alpha oscillations. That study showed that stimulating parietal regions ipsilateral to the to-be-maintained

information at 10 Hz indeed increased WM performance, whereas the same stimulation of contralateral regions decreased WM performance (Sauseng et al., 2009). Similar evidence comes from a tACS study showing that WM performance improves in elderly subjects during parietal 10 Hz stimulation (Borghini et al., 2018).

4.2. Multi-item working memory: theta oscillations

Brain oscillations in the theta band have been proposed to play a vital role in working memory maintenance. This notion is partly inspired by oscillations measured in the rat hippocampus during spatial navigation as mentioned above. Spatial navigation relies on keeping recent information active while integrating new information with existing memories. Such memory processes are associated with theta oscillations in the rat hippocampus and neocortical regions (Colgin, 2011). Indeed, working memory maintenance in primates requires the coordination of brain dynamics between multiple regions. For instance, a recent study in primates showed that theta synchronization between prefrontal and parietal neural assemblies predicted task performance in a WM task (Jacob, Hahnke, & Nieder, 2018). In humans, similar cross-regional connectivity patterns during WM maintenance have been found (Sarnthein, Petsche, Rappelsberger, Shaw, & von Stein, 1998). These ideas have resulted in electrophysiological research in humans linking working memory to theta oscillations. EEG and MEG studies in humans have demonstrated increased theta band activity during working memory maintenance over frontal midline areas (Gevins, Smith, McEvoy, & Yu, 1997; Jensen et al., 2002) as well as in parieto-occipital regions (Sauseng et al., 2009). Likewise, intracranial recordings have demonstrated sustained theta during working memory retention in various regions including temporal lobe structures (Axmacher et al., 2010; Howard et al., 2003; Raghavachari et al., 2001; van Vugt, Schulze-Bonhage, Litt, Brandt, & Kahana, 2010; van Vugt, Sekuler, Wilson, & Kahana, 2013).

It seems logical to posit that entraining theta oscillations in parietal and prefrontal regions should benefit WM performance. Indeed, evidence in support of this hypothesis was provided by Albouy

and colleagues (Albouy, Weiss, Baillet, & Zatorre, 2017) who stimulated the left intraparietal sulcus (IPS) using rTMS at 5 Hz, and showed that such theta stimulation increases WM performance specifically in a task that requires maintenance of the serial order of the items. Simultaneous EEG recordings additionally showed that 5 Hz rTMS not only enhances theta oscillations during stimulation but also that these induced oscillations persisted after stimulation ended, which is particularly firm evidence that rTMS indeed affected an internal oscillating network (Hanslmayr et al., 2014). The authors also demonstrated that 5 Hz stimulation of parietal regions increased theta-frequency functional connectivity to the prefrontal cortex, thus showing effects of local stimulation on a fronto-parietal theta network. In summary, the above studies suggest that theta oscillations are crucial for coordinating activity in frontal and parietal areas in order to maintain information in working memory.

Recent transcranial alternating current stimulation (tACS) studies attempted to directly test the causal relevance of such prefrontal to parietal theta connectivity by stimulating prefrontal and parietal areas such that theta phases are aligned (i.e., zero-phase locked) or continuously opposing (i.e., 180° apart). Indeed two studies (Polania, Nitsche, Korman, Batsikadze, & Paulus, 2012; Violante et al., 2017) found that WM performance was enhanced during the ‘synchronizing’ (i.e., zero phase lag) stimulation compared with the ‘asynchronous’ (i.e., 180° phase lag) stimulation. In addition, it was reported that synchronous (zero phase lag) stimulation increased functional connectivity between parietal and frontal regions as measured with functional magnetic resonance imaging (fMRI; (Violante et al., 2017)).

4.3. Maintaining working memory: Gamma band activity

Oscillations in the gamma band (30 – 80 Hz) have been proposed to coordinate the timing of neuronal ensembles in a fine-grained manner. Accordingly, slower narrow-band gamma oscillations (30 – 50 Hz) might segment processing in time windows of about 20 – 30 ms. Distributed neuronal

firing within each gamma cycle then constitutes a representation. This grouping by gamma oscillations might be maintained during online processing as required in working memory (Jensen, Kaiser, & Lachaux, 2007). Broad-band high frequency activity in higher frequency ranges (>80 Hz) is likely not oscillatory per se (because an oscillation presupposes a narrow frequency band) and might instead reflect a mixture of population firing and/or randomly distributed postsynaptic potentials contributing to the code (Buzsaki et al., 2012; Miller et al., 2009). A number of studies describe sustained gamma band activity during working memory maintenance in humans. Both EEG and MEG studies have reported gamma band activity over posterior regions during the maintenance of both visual (Jokisch & Jensen, 2007; Roux, Wibral, Mohr, Singer, & Uhlhaas, 2012; Tallon-Baudry, Bertrand, Peronnet, & Pernier, 1998); and auditory working memory (Lutzenberger, Ripper, Busse, Birbaumer, & Kaiser, 2002). Also, intracranial studies have reported gamma band activity during working memory maintenance (Kambara et al., 2017; Noy et al., 2015; van Vugt et al., 2010). In sum, these studies suggest gamma band activity being present during working memory maintenance and the findings are consistent with the idea that this high-frequency activity contributes to the neuronal code sustaining the memory trace.

4.4. Juggling multiple items: Coupled oscillations

The previous sections provide evidence for the involvement of specific oscillations in the theta, alpha and gamma band for working memory maintenance. How might these oscillations interact? One mechanism that has been described already in section 3 is cross-frequency coupling, or more specifically gamma oscillations nested within theta oscillations (see Chapter XX by Helfrich et al.). Indeed, Lisman and Idiart proposed a computational model in which coupled theta and gamma oscillations serve to maintain multiple working memory items (Lisman & Idiart, 1995). In this model, up to seven memory representations were activated sequentially within one theta cycle (Figure 5A). That is, different items were activated at different phases of theta. The faster gamma oscillations served to segment the items in time. This scheme could explain why the upper limit of working

memory capacity is about 7 items (+/- 2). This is because the number of gamma cycles that fit into a theta cycle is also about 7. Likewise, the model could account for the 'Sternberg slope': Sternberg (Sternberg, 1966) found that memory retrieval increases linearly with the number of items in working memory. This linear increase is consistent with the period of a gamma cycle, i.e. the scanning through multiple working memory items, which is clocked by the gamma oscillations. This framework has received empirical support from several lines of investigation (Lisman & Jensen, 2013; Roux & Uhlhaas, 2014). First, a number of correlative studies found evidence for gamma oscillations nested within theta oscillations during working memory tasks. For instance, intracranial recordings in the medial-temporal lobe in patients performing a working memory task, revealed gamma band activity coupled to the phase of theta oscillations. This coupling as well as the frequency of the theta oscillations were shown to be dependent on the memory load (Axmacher et al., 2010). Similar findings were obtained with MEG (Heusser, Poeppel, Ezzyat, & Davachi, 2016) where the measure of theta-gamma coupling decreased with memory load and the theta phase of the gamma activity was load-dependent as well. Another important piece of evidence comes from an electrocorticography (ECoG) study (Bahramisharif, Jensen, Jacobs, & Lisman, 2018), which made use of the fact that certain electrodes display selective broadband high frequency (80 – 120 Hz) activity in response to a specific letter (e.g. 'Q' but not 'P'). An analysis of the phase-amplitude coupling of the data during the retention interval revealed that both gamma activity ~40 Hz and high frequency broad-band activity (80-120 Hz; Figure 5B) were coupled to the phase of ongoing ~8 Hz oscillations. As predicted by Lisman's model, this allowed the researchers to demonstrate that letter specific high frequency activity (80-120 Hz) for different letters were present at different phase of the ~8 Hz oscillations (Figure 5C). Consistent with the theoretical framework, the gamma oscillation (~40 Hz) would segment the representations in time, whereas the high frequency activity represents the individual items. Intriguingly, the ~8 Hz oscillations in this study displayed the same temporal dynamics as alpha oscillations recorded by EEG and MEG: the power was suppressed during item presentation, and it increased during memory retention. This observation hints at the possibility that

both, theta and alpha oscillations may perform a similar function, which is to temporally coordinate item-specific codes.

If theta to gamma coupling indeed supports working memory, then are we able to increase/decrease working memory capacity by externally manipulating this theta-gamma interaction? Alekseichuk and colleagues (Alekseichuk, Turi, Amador de Lara, Antal, & Paulus, 2016) tested this hypothesis by stimulating the left prefrontal cortex (PFC) with complex theta-gamma waveforms during a spatial WM task. Stimulating with gamma oscillations nested in the theta peak improved WM performance, whereas stimulating with gamma oscillations nested in the theta trough did not. Similar evidence comes from another study (Reinhart & Nguyen, 2019), which was able to improve working memory performance in elderly subjects by stimulating the brain with a theta-gamma cross-frequency protocol. Another prediction that follows from Lisman and Idiart's (1995) model is that slowing down the frequency of theta allows more gamma cycles to be nested, which should then increase WM capacity. Conversely, speeding up theta frequency should decrease the number of gamma cycles and consequently decrease WM capacity. This prediction was confirmed by two recent tACS studies showing that stimulating at lower theta frequencies increases WM capacity (Vosskuhl, Huster, & Herrmann, 2015; Wolinski, Cooper, Sauseng, & Romei, 2018). Wolinski and colleagues further demonstrated that stimulation at faster theta frequencies reduced WM capacity (Figure 5D). A recent study combined EEG and TMS to investigate fronto-posterior interactions during working memory maintenance (B. Berger et al., 2019). They found that posterior gamma power was phase-locked to frontal theta oscillations and that the theta phase of the coupling depended on cognitive demands. Importantly, performances could be manipulated by perturbing frontal regions with TMS. Performance was reduced when stimulation was done at the trough of the theta oscillations. Together, there is ample correlational and causal evidence for a mechanistic role of gamma oscillations nested within alpha/theta cycles, which determines the number of items one can maintain in WM.

4.5. Working Memory and Oscillations: Conclusions

Over the past decade numerous human studies using correlational approaches like EEG, MEG and intracranial recordings have demonstrated that brain oscillations in the theta, alpha and gamma band play a role in working memory tasks (Roux & Uhlhaas, 2014). Brain stimulation studies provide evidence that these different oscillations implement specific mechanisms necessary for the maintenance of information in WM. In particular, the slower theta and alpha oscillations seem to be involved in temporally coordinating large scale neuronal dynamics required for working memory maintenance. Gamma oscillations and broad-band high frequency activity seems to reflect the activation of local neural ensembles which hold the actual memory representation and which are timed by the slower theta and alpha oscillations. Consistent with theoretical ideas, gamma oscillations coupled to the phase theta/alpha oscillations therefore likely serve to coordinate multi-item working memory.

5. The consolidators: Oscillatory correlates of offline processing

In this section we consider oscillations supporting memory processes during offline periods. By offline periods we refer to intervals occurring after learning during which the individual either sleeps or rests quietly. The importance of these offline periods has traditionally been somewhat neglected in main-stream cognitive neuroscience of memory. However, it has been known for almost 100 years that sleep benefits memory performance compared to the same time spent awake (Jenkins & Dallenbach, 1924). Specifically, sleep seems to solidify recently acquired memories and slows down forgetting, a phenomenon termed memory consolidation (Muller & Pilzecker, 1900). For a long time sleep has only been ascribed a passive role, i.e., protecting memories from interference by blocking new incoming information (McGeoch, 1932). In contrast, recent frameworks postulate that the sleeping brain engages in active and specific processes dedicated to preserving the most relevant experiences (Tononi & Cirelli, 2006) and to transferring representations from short- to long-term

storage sites (Diekelmann & Born, 2010). The question of how these postulated processes are implemented in the absence of external input will be discussed in this final section.

5.1. Oscillations during offline states: Slow oscillations, spindles and sharp wave ripples

Consolidation of episodic memories is thought to mostly occur during non-rapid-eye-movement (NREM) sleep (Diekelmann & Born, 2010). During this stage three main oscillatory signatures are observable: First, Slow Oscillations (SOs), which are cortically-generated high-amplitude oscillations with a spectral maximum at .75 Hz. SOs reflect fluctuations in cellular excitability, which results from alternating phases of depolarization ('up-states') and hyperpolarization ('down-states'). Up- and down-states are linked to synchronous neuronal firing of large neuron populations and to widespread neuronal silence, respectively (Achermann & Borbely, 1997; Nir et al., 2011; Steriade, Nunez, & Amzica, 1993). Second, sleep spindles, which are transient (0.5-3 s) oscillatory events of waxing and waning amplitude. Spindles are generated by intra-thalamic feedback loops between excitatory thalamo-cortical (TC) neurons in the thalamic core and inhibitory neurons in the reticular thalamic nucleus (TRN) (Luthi, 2014; Steriade, 2003). The frequency range of spindles spans 9-16 Hz, with a distinction between slow (9-12 Hz) and fast (12-16 Hz) spindles. Notably, only fast spindles have been found in the hippocampus (Andrillon et al., 2011; Sarasso et al., 2014; Schabus et al., 2007; Staresina et al., 2015) and we focus on this subclass of spindles henceforth. Finally, sharp wave-ripple (SW-R) complexes are high-frequency oscillations (ripples) superimposed on a low-frequency (~3 Hz) sharp wave. Ripples are generated within the hippocampal circuitry (Buzsaki, 2015) and - in humans - represent 80-100 Hz oscillations of 30-150 ms duration (Axmacher, Elger, & Fell, 2008; Bragin, Engel, Wilson, Fried, & Buzsaki, 1999; Staresina et al., 2015).

Importantly, each of these three sleep oscillations has been linked to memory consolidation: Learning a hippocampus-dependent declarative task prior to sleep enhances subsequent SO amplitudes (Molle, Eschenko, Gais, Sara, & Born, 2009), and experimental induction of SOs bolsters post-sleep memory performance (Ngo, Martinetz, Born, & Molle, 2013). Likewise, the amount of

spindles increases after learning of a declarative memory task and correlates with memory performance (Gais, Molle, Helms, & Born, 2002). Importantly, recent evidence has linked the emergence of spindles to reactivation of learning experiences (Antony, Schonauer, Staresina, & Cairney, 2019; Bergmann, Molle, Diedrichs, Born, & Siebner, 2012; Cairney, Guttesen, El Marj, & Staresina, 2018), which is assumed to be pivotal for effective consolidation (Buzsaki, 1996; Diekelmann & Born, 2010). Finally, the amount of ripples during an afternoon nap was found to correlate with post-sleep memory performance across participants (Axmacher et al., 2008). A recent report was able to link ripples to replay of learning experiences in humans (Zhang, Fell, & Axmacher, 2018), analogous to a large body of animal work showing replay of spatial trajectories during ripples in rodents (Joo & Frank, 2018).

Although the studies reviewed thus far are consistent with a role of SOs, spindles and ripples in memory consolidation, the hypothesised information transfer from short- to long-term storage presumably requires some more intricate mechanism. Indeed, it has been speculated that active consolidation requires systematic interactions between these oscillations (Diekelmann & Born, 2010). In particular, it has been argued that under the top-down control of cortical SOs, thalamic spindles are deployed to both the hippocampus (the short-term store) and to cortical target sites (the long-term store). These coincident spindles effectively open communication channels between the hippocampus and cortex, such that reactivated information, linked to ripples, can travel between the two sites. One requirement for the validity of this model is that all three oscillations be observable in the hippocampus. A recent study using intracranial recordings directly from the hippocampus of human epilepsy patients indeed found evidence for this notion (Staresina et al., 2015): Ripples were nested within spindle troughs, and spindles were in turn nested in the up-states of SOs (Figure 6A). These findings have since been replicated in a number of iEEG studies (Helfrich et al., 2019; Jiang, Gonzalez-Martinez, & Halgren, 2019; Ngo, Fell, & Staresina, 2020). Together, these data suggest that during sleep, the brain uses a fine-tuned machinery of oscillations to foster cross-regional interactions.

5.2. Relevance of offline oscillations for consolidation

How important might this fine-tuning really be for memory consolidation? Recently, evidence has begun to accumulate that the exact timing of these oscillations with respect to each other is indeed vital. At least for the coupling of SOs and spindles, data show that the more precise the timing of spindles with respect to the SO up-state, the better an individual's memory performance (Helfrich, Mander, Jagust, Knight, & Walker, 2018; Muehlroth et al., 2019; Niknazar, Krishnan, Bazhenov, & Mednick, 2015) (Figure 6B). Future work will have to establish whether the precise coupling of ripples to spindles is of similar importance for consolidation.

Lastly, what are the oscillatory mechanisms promoting memory consolidation during wake rest periods? Although less pronounced than the beneficial effects of sleep (Stickgold, 2005), quiet rest has been shown to bolster memory performance compared to more active post-learning intervals (Dewar, Alber, Butler, Cowan, & Della Sala, 2012). Is there a qualitative or quantitative difference between consolidation mechanisms deployed during sleep vs. wake rest? For instance, hippocampal ripples have recently been found during active retrieval in human intracranial recordings (Norman et al., 2019; Vaz, Inati, Brunel, & Zaghoul, 2019). Moreover, a recent Magnetoencephalography (MEG) study suggests that replay-related ripples occur during periods of quiet rest in humans (Liu, Dolan, Kurth-Nelson, & Behrens, 2019). One study even reported SO-like activity during quiet rest, predicting later memory performance (Brokaw et al., 2016). These tentative findings would point to potentially quantitatively, but not qualitatively different oscillatory mechanisms of wake vs. sleep consolidation. On the other hand and as reviewed earlier in this chapter, theta rhythms have been strongly linked to hippocampal function during wake periods. In one recent study, participants were trained to voluntarily enhance their theta oscillations via neurofeedback (Rozenfurt, Shtoots, Sheriff, Sadka, & Levy, 2017). Intriguingly, theta power up-regulation during a post-learning rest period boosted later memory performance, compared to beta power up-regulation or passive viewing of a

movie. This would point to qualitatively different mechanisms underlying sleep vs. wake consolidation.

In sum, electrophysiological data strongly implicate an intricate relationship of different oscillatory phenomena for offline consolidation in humans. Accumulating evidence from intracranial recordings in patients, advances in source reconstruction of M/EEG signals and progress in experimental brain stimulation will help pinpoint the exact rules that govern the intriguing means of information processing in the resting brain.

6. Conclusion

In this chapter we discussed what role brain oscillations play for memory formation. A lot has been accomplished in the past two decades and we now know much more about the critical and diverse roles that oscillations play on every step of the life of a memory, from its 'birth' during the initial processing stages, to organizing neural activity during the maintenance phase, and solidifying the memory trace during sleep. From the above reviewed literature we can conclude that first, oscillations play a diverse role in different brain areas and support memory processes in different ways. For instance, synchronization in the alpha frequency band in the cortex likely has the function of silencing regions that might otherwise interfere with processing. Synchronization in the theta and gamma oscillations in the hippocampus, but also in the cortex on the other hand has the function of temporally organizing and binding information together into a coherent memory trace. Therefore, memory formation is not one monolithic process, instead different oscillations in different regions each perform complementary functions. Second, these different oscillations coordinate their activity in the service of memory. The nesting of faster oscillations into slower oscillations can be observed during memory encoding and working memory, where gamma oscillations are nested within theta oscillations. A similar behaviour is observable during sleep, where ripples are nested into spindles, which in turn are nested into slow waves. Decreases of alpha oscillations in the neocortex are correlated with increases in gamma oscillations in the hippocampus. This shows that oscillations

truly are a network phenomenon and orchestrate brain networks on different levels. Third, perturbing these oscillations externally impacts on memory. Brain stimulation studies importantly close the loop from observing oscillations during behaviour on the one hand, to inducing this behaviour when injecting these oscillations from the outside. This is of particular significance because it paves the way for the development of invasive and non-invasive stimulation devices in order to alleviate memory-related problems in healthy and clinical populations. Future students of memory will undoubtedly build on this foundation and use brain oscillations to draw a much more detailed picture of human memory than we can now imagine.

Figure Legends

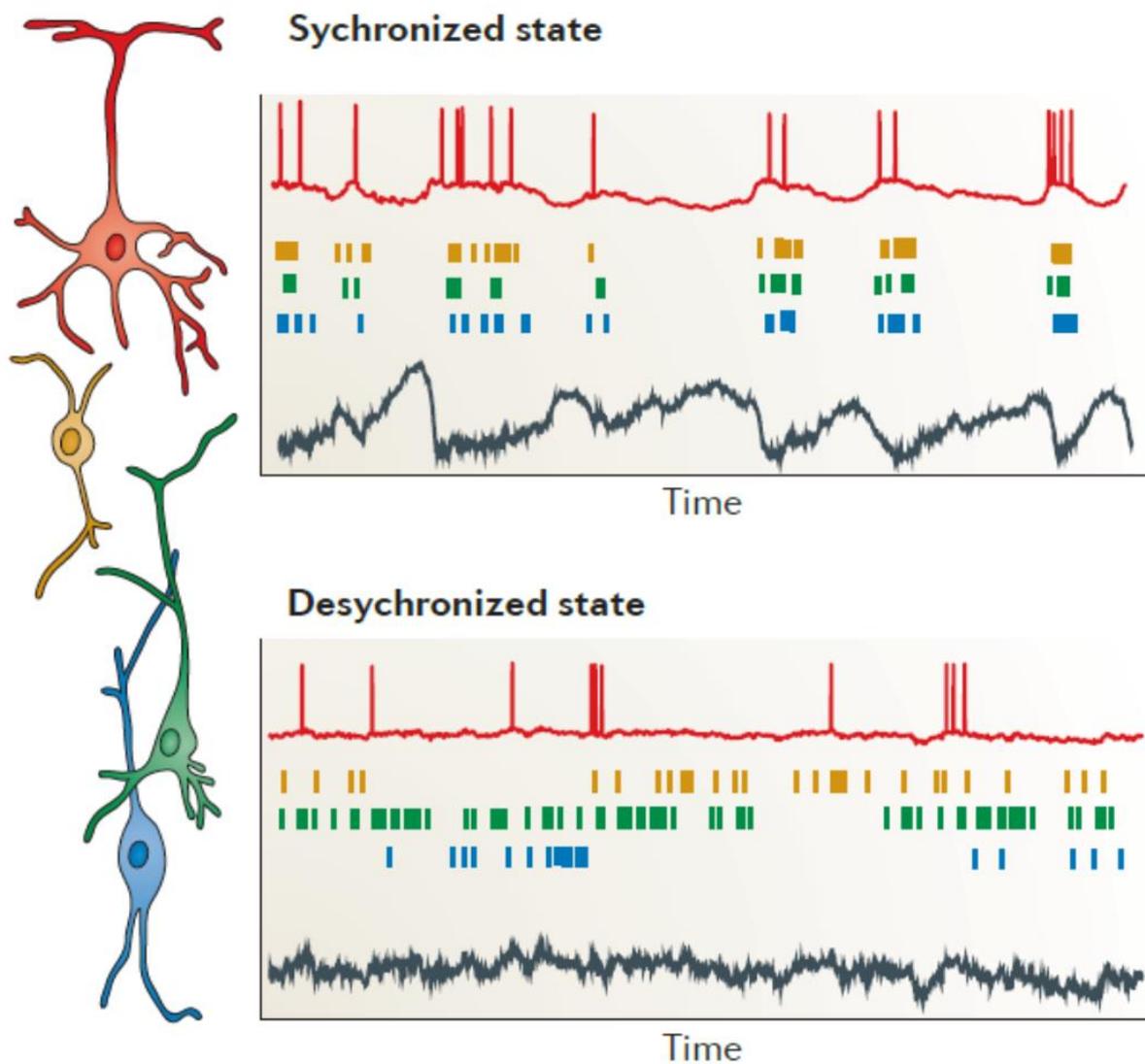


Figure 1. The firing patterns of four neurons are shown (red, yellow, green and blue), together with the local field potential which represents the population activity as would be recorded with EEG (black trace). In a synchronized state, rhythmic fluctuations are observed in the population activity (EEG). In a desynchronized state these rhythmic fluctuations are absent. Figure taken with permission from Harris & Thiele 2011 (Nat Rev Neurosci).

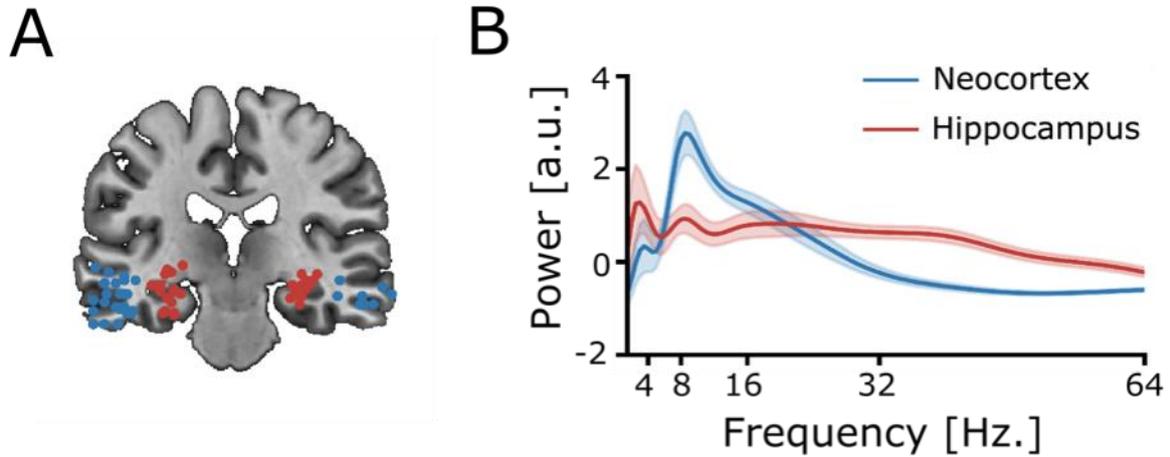


Figure 2. Comparison of frequency spectra in the Neocortex and Hippocampus. A) Electrodes were implanted in 12 epilepsy patients in the anterior temporal lobe of the Neocortex (blue) and the Hippocampus (red). B) The averaged $1/f$ corrected power spectrum is shown for the Neocortex (blue) and Hippocampus (red). The Hippocampus (red line) shows a narrow peak of power in the theta frequency band, and a broader peak in the gamma frequency band, whereas the Neocortex shows the strongest peak in the alpha/beta frequency band. Figure adapted with permission from Griffiths et al. 2019.

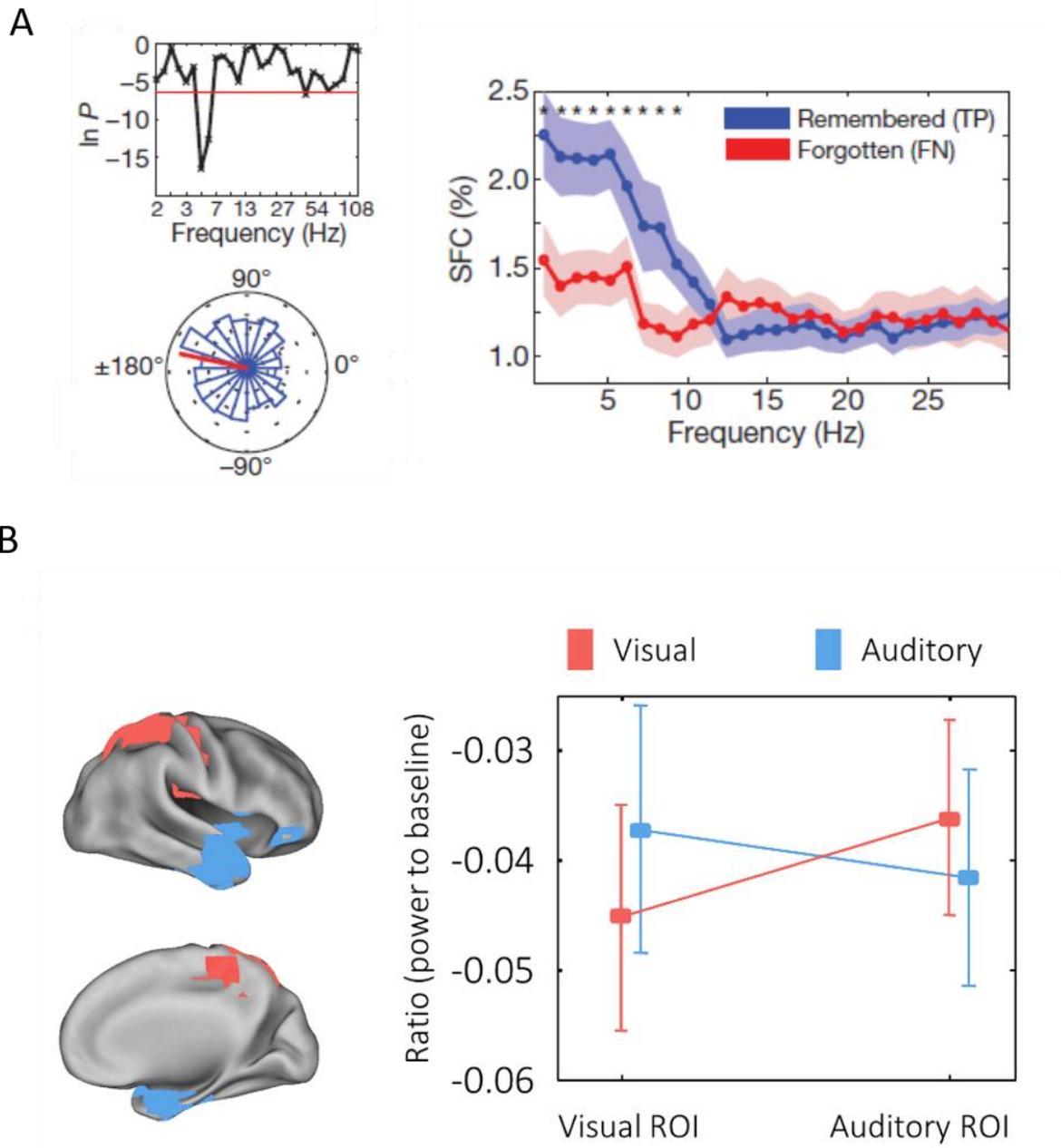


Figure 3. Hippocampal theta oscillations and neocortical alpha oscillations during memory encoding. (A) The diagram on the left shows one exemplary hippocampal neuron that is rhythmically clocked by a theta oscillation (~ 4 Hz). The top plot shows statistical significance in terms of log-transformed p-values, the bottom plot shows a phase histogram. The unit shows a preferred phase angle of ~ 180 degrees which corresponds to the trough of the theta wave. The plot on the right shows the averaged phase locking of all neurons as a

function of later memory. Later remembered items (blue) show higher theta phase locking compared to later forgotten items (red). These results show that theta synchronizes neurons in the hippocampus in order to form memories. (B) Alpha power results from an EEG study are shown during retrieval of visual or auditory stimuli. The regions that represent visual stimuli are shown in red, the regions that represent auditory stimuli are shown in blue. The visual region shows stronger alpha power decreases during reactivation of visual stimuli, compared to auditory stimuli. This pattern is reversed for the auditory region. This result shows that alpha power decreases track the representation of information. Figure in A reproduced with permission from Rutishauser et al. 2010. Figure in B reproduced from Michelmann et al. (2016).

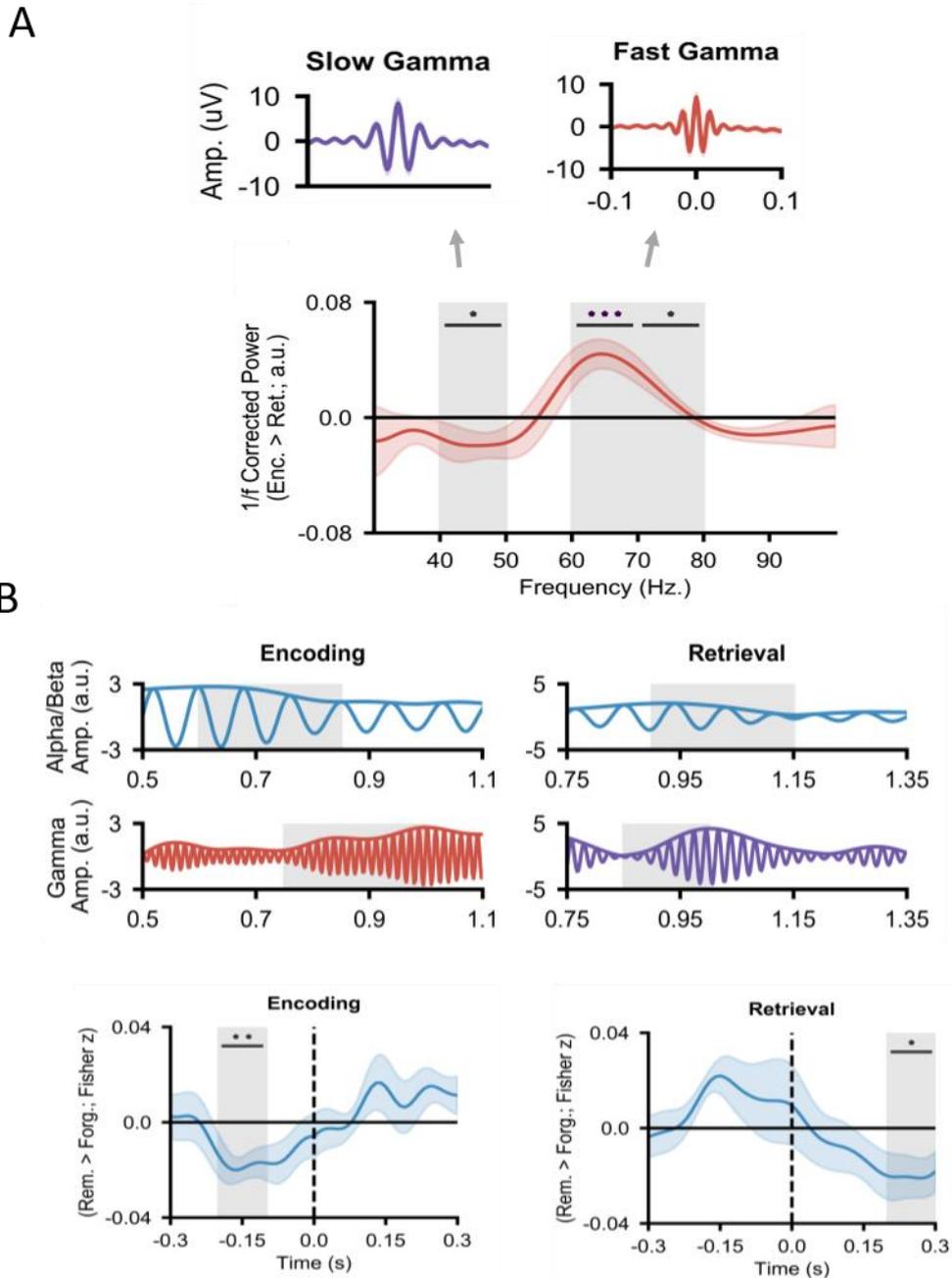


Figure 4. Hippocampal gamma oscillations and interaction with neocortical alpha oscillations. (A) Slow and fast gamma oscillations are present in the human hippocampus (top). A difference plot between encoding and retrieval is shown on the bottom. During encoding fast gamma oscillations dominate, during retrieval slow gamma oscillations dominate. (B) Interaction between neocortical (Anterior Temporal Lobe) alpha oscillations and hippocampal gamma oscillations is shown. During encoding, a decrease in neocortical

alpha oscillations precede an increase in hippocampal fast gamma oscillations. During retrieval, the decrease in neocortical alpha oscillations occurs after an increase in slow gamma oscillations. This is shown for one single trial in the top panel. The bottom panels show the averaged cross-correlations between neocortical alpha and hippocampal gamma oscillations. A negative lag is observed during encoding, indicating that neocortical alpha power decreases before hippocampal gamma increases. During retrieval this pattern reverses, now showing a positive lag (i.e. neocortical alpha follows hippocampal gamma). Figure reproduced from Griffiths et al (2019).

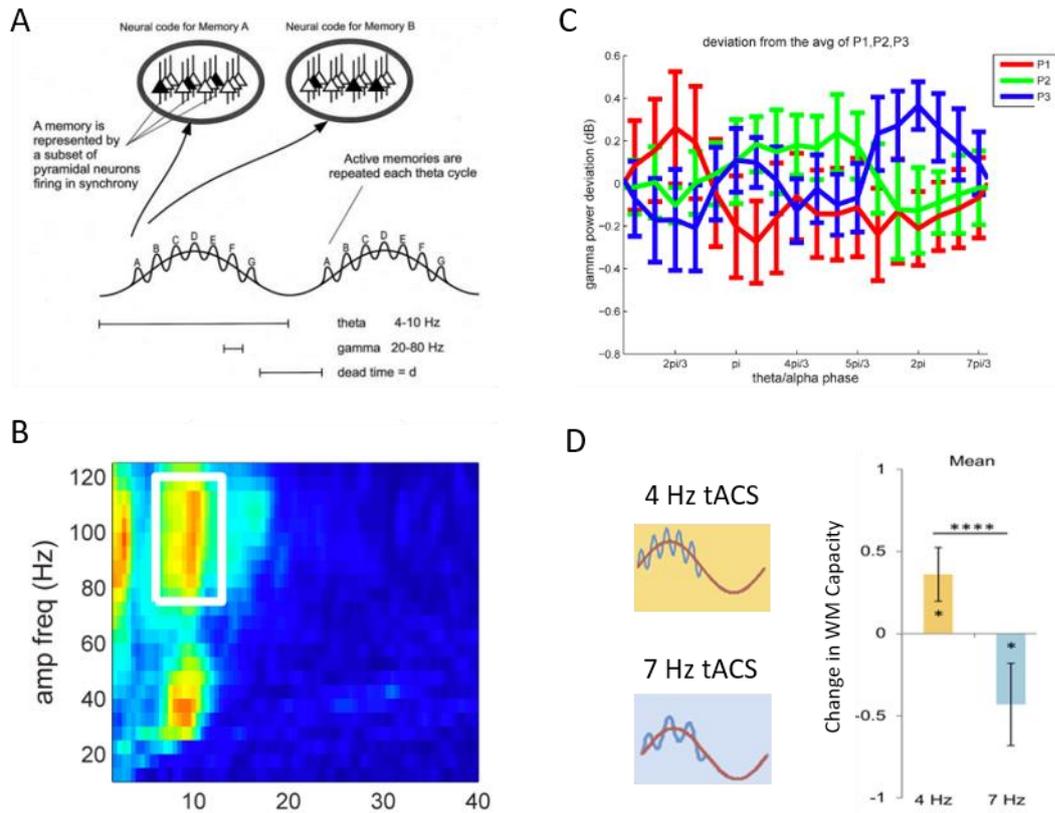


Figure 5. The nesting of gamma oscillations into theta oscillations during working memory. (A) The computational model illustrates how items specific codes are organized into gamma cycles which in turn are coupled to a slower theta oscillation. (B) A frequency-frequency spectrum calculated from human ECoG data during a working memory task. The phase providing frequency is plotted on the x-axis; the amplitude providing frequency is shown on the y-axis. A narrowband gamma oscillation around 40 Hz and broad-band high frequency activity (highlighted) are both coupled to the theta/alpha phase (~8 Hz). (C) The deviation of high frequency broadband power for each position from the average measured as a function of theta/alpha phase (Hilbert phase 7–13 Hz). (D) Results from a tACS study are shown where stimulation was applied either at a slow (orange) or fast (light blue) theta oscillation. More gamma cycles can fit into the slow compared to the fast theta. Stimulating

with slow theta enhances WM capacity, whereas stimulating with slow theta decreases WM capacity.

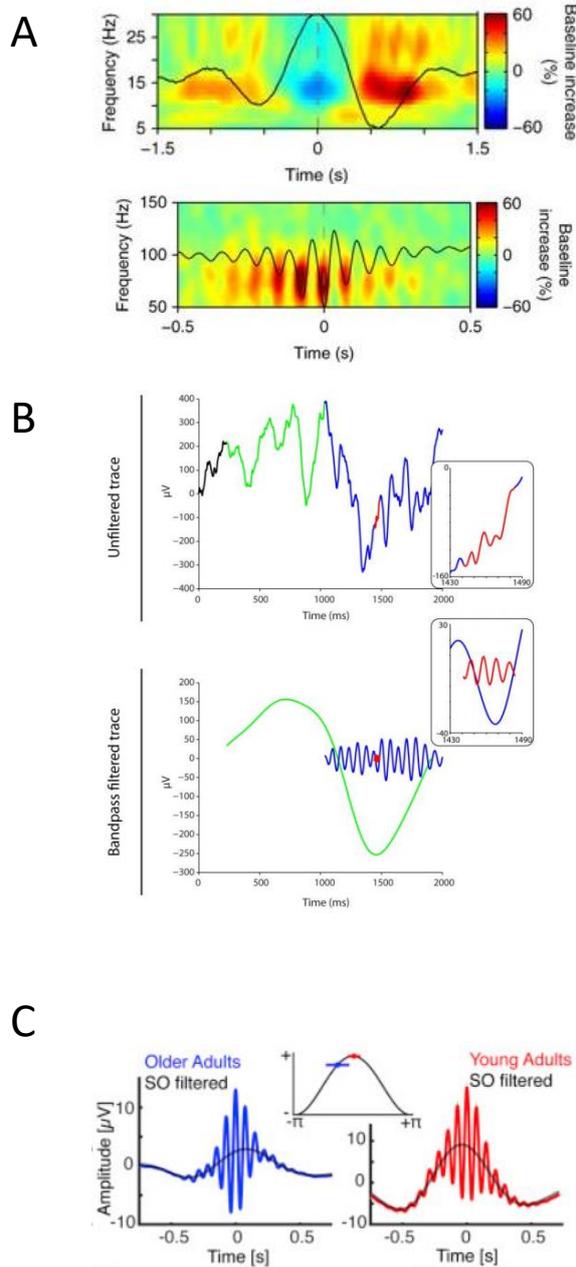


Figure 6. Nesting of oscillations in the during sleep. A. *top*: Single-subject average hippocampal slow oscillation (SO) superimposed on the down-state locked (time 0) time-frequency representation (TFR), revealing a spindle power increase in the SO up-state. *bottom*: Single-subject average hippocampal spindle

superimposed on the spindle-centre locked (time 0) TFR, revealing ripple power increases nested in spindle troughs. **B.** Data sweep (2000 ms) showing the co-occurrence of all three oscillations [SO (green), spindle (blue), ripple (red)] in the human hippocampus during sleep. *Top*: unfiltered EEG. *bottom*: bandpass-filtered signal (SO: 0.5–1.25 Hz, spindle: 12–16 Hz, ripple: 80–100 Hz). Adapted from *Staresina et al. (2015)*. **C.** Different levels of precision in SO-spindle coupling for older (*blue*) and younger (*red*) individuals. Data show peak-locked spindle grand averages with superimposed low-pass filtered signal (black). *Inset*: Mean coupling phase and standard deviation shown on a schematic SO. Adapted from *Helfrich et al. (2018)*.

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