

How brain rhythms form memories

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Abstract

The wake human brain constantly samples perceptual information from the environment and integrates them into existing neuronal networks. Neuronal oscillations have been ascribed a key role in the formation of novel memories. The theta rhythm (3-8 Hz) reflects a central executive mechanism, which integrates novel information, reflected in theta-coupled gamma oscillations (> 30 Hz). Alpha oscillations (8-14 Hz) reflect an attentional gating mechanism, which inhibit task irrelevant neuronal processes. In my dissertation I further scrutinized the oscillatory dynamics of memory formation. Study 1 demonstrated that theta-gamma coupling reflects a specific mechanism for associative memory formation. In study 2, I experimentally entrained memory encoding by visual evoked theta-gamma coupling processes, to underline its functional relevance. In two developmental studies, I found that the theta rhythm indexes explicit learning processes in adults and young children (study 3), and that visually entrained theta oscillations are sensitive to the encoding of novel, unexpected events, already in the first year of life (study 4). Throughout these studies alpha oscillations were not sensitive to memory formation processes, but indicated perceptual (study 1) and semantic (study 3) processes. I propose an integrative framework, suggesting that the alpha rhythm reflects activated semantic representations in the neocortex, while theta-gamma coupling reflects an explicit mnemonic control mechanism, which selects, elaborates and integrates activated representations. Specifically, by squeezing real time events onto a faster, neuronal time scale, theta-gamma coding facilitates neuronal plasticity in medio-temporal networks and advances neuronal processes ahead of real time to emulate and guide future behavior.

1. Introduction

„Everything in life is memory, save for the thin edge of the present.“ (Gazzaniga, 2000)

I would like to add to this notion that also the present, at least what we perceive of it, is a mnemonic process. Perception is highly constructive and inextricably linked to the interpretation of sensory inputs, based on former experience. When awake, the human brain constantly attends to, interprets and elaborates novel information from the environment to integrate them into existing knowledge, in order to retain a coherent internal representation of the environment (Buzsáki, 1996). A coherent representation of our environment forms the basis for behavioral navigation, to form experience-based predictions about future events (including behavioral consequences), and to vividly re-experience some episodes even years later. In this tenet, mnemonic processes are here conceptualized as an integral function of human experience and behavior, from re-experiencing the past, making sense of the present, and guiding future behavior.

The basis of human mnemonic functions are associative neuronal networks (Anderson & Bower, 1973; Eichenbaum, 2004), the finely tuned connections between billions of nerve cells in the human brain. Neuronal networks are critically shaped by our learning experiences, from the sensitivity of orientation cells in the primary visual cortex in early development (Blakemore & Cooper, 1970), to highly specialized expert networks in the fusiform face area (Gauthier, Skudlarski, Gore, & Anderson, 2000). Thus, learning experiences shape the neuronal architecture, from a basic perceptual to a conceptual level. Central questions are, how sensory inputs are processed and interpreted within existing neuronal networks and how novel information are integrated, by changing the structure of these networks, forming novel memories.

Behavioral psychological research has a long standing tradition in describing attention and memory processes, from attentional selection (Posner & Petersen, 1990) and the maintenance of perceptual information (Baddeley, 1978), to their integration into existing associative networks (Hebb, 1949). While these processes are often isolated in paradigms from experimental psychology, they are closely interwoven in human basic cognition. One prominent model that integrates these processes is Cowan's model of embedded processes (Cowan, 1997), which will be the basis for the theoretical integration of my work. From a neuroscience perspective, brain structures underlying attentional and mnemonic functions have been identified in patient and neuroimaging studies (Brewer, 1998; Scoville & Milner, 1957). Furthermore, within the last decades, there has been an ever-growing interest in neuronal oscillatory activity, the rhythmic interplay within (Gray, König, Engel, & Singer, 1989) and across (Womelsdorf et al., 2007) nerve cell populations, and their relation to attention and memory processes (Buzsaki, 2004; Engel, Fries, & Singer, 2001; Fell & Axmacher, 2011; Fries, 2015; Varela, Lachaux, Rodriguez, & Martinerie, 2001).

In the first part, I will summarize former findings on brain oscillatory processes that underlie memory formation, which were the starting point for the empirical works of this dissertation. I will then introduce an integrative framework, suggesting that neuronal oscillations implement basic mnemonic functions on the neuroanatomical architecture in the human brain, and thereby bridge the gap between psychology and neurophysiology. Finally I will discuss the findings of the studies of the dissertation in the light of this integrative framework and conclude with implications and directions for future research.

1.1. Theta, alpha, and gamma oscillations orchestrate memory formation

The activity within and across nerve cell populations is coordinated and integrated by the rhythmic synchronization of neuronal activity (Engel et al., 2001; Fries, 2015; Varela et al., 2001). It is assumed that neuronal rhythms are key mechanisms, which facilitate

perceptual processes (VanRullen, 2016) and implement mnemonic mechanisms in neuronal circuits (Juergen Fell & Axmacher, 2011).

To observe memory formation processes in the human brain, in subsequent memory paradigms, the neuronal activity during the encoding phase is contrasted between later remembered and later forgotten items (Paller & Wagner, 2002), see Figure 1. This is, participants are given an incidental encoding task to ensure perceptual processing of the stimulus material. Later on participants report which items they recognize from the encoding phase. The contrast between stimuli which are later remembered and which are later forgotten, the subsequent memory effect (SME) is then interpreted as the critical neuronal substrate for the formation of a novel memory trace.

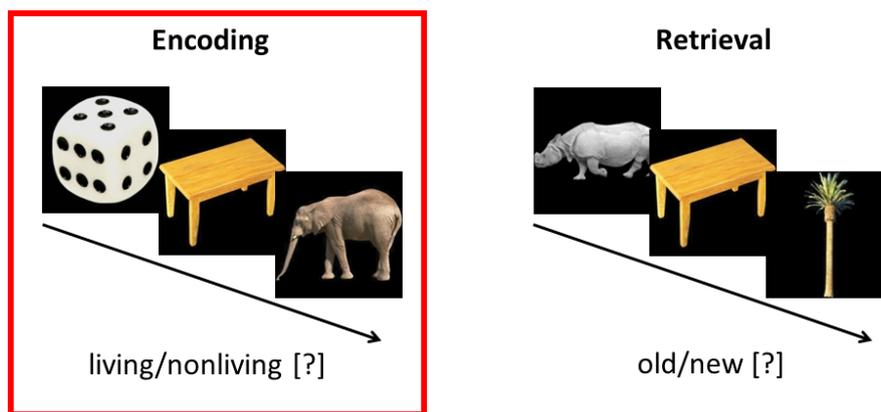


Figure 1. A pictorial subsequent memory task. During encoding participants are confronted with a series of pictorial stimuli and are requested to retrieve them among distractors in the retrieval phase. The critical interest lies on the neuronal activity during encoding, namely the contrast between items that are later on remembered versus items that are later on forgotten (subsequent memory effect, SME).

Previous electro- and magnetoencephalography (EEG and MEG) subsequent memory studies in humans have established that the formation of novel memories is closely associated with neuronal oscillations in the theta (3-8 Hz), alpha (8-14 Hz), and gamma (> 30 Hz) frequency (Friese et al., 2013; Klimesch, Doppelmayr, Schimke, & Ripper, 1997; Osipova et

al., 2006). Successful encoding of visual stimuli was marked by increases in theta and gamma power and a decrease in alpha power (Friese et al., 2013; Osipova et al., 2006). These differences in oscillatory activity for later remembered versus later forgotten stimuli are nicely illustrated in one of our former studies (Friese et al., 2013), where we employed the subsequent memory design described above (see Figure 2A).

Although perceptual and mnemonic mechanisms are inextricably linked in memory formation processes (Cowan, 1988), oscillatory dynamics at different frequency ranges are assumed to index distinct functional mechanisms during encoding. Theta oscillations are proposed to facilitate associative binding, the integration of novel perceptual information into existing memory traces (Clouter, Shapiro, & Hanslmayr, 2017), while increased gamma oscillations may reflect the promotion of perceptual signals along the visual hierarchy (Bosman et al., 2012; Tallon-Baudry & Bertrand, 1999), and the sustained activation of recent perceptual inputs in working memory (WM; Daume, Gruber, Engel, & Friese, 2017; Kaiser, Ripper, Birbaumer, & Lutzenberger, 2003).

Recently, a specific role for mnemonic processing in the human brain has been ascribed to theta-gamma phase-amplitude coupling (PAC), see Figure 2B. The frontal theta rhythm may act as a mnemonic control mechanism, working on perceptual information, which are reflected in gamma activity (Friese et al., 2013; Köster, Friese, Schöne, Trujillo-Barreto, & Gruber, 2014). This is, theta-gamma PAC may reflect the maintenance, ordering and binding of perceptual information within neuronal networks, forming a theta-gamma neuronal code (Lisman & Jensen, 2013). This is substantiated by theta-gamma PAC pattern in the human neocortex (Canolty et al., 2006), and an increase in theta-gamma PAC in neocortical and medio-temporal networks accompanying successful episodic encoding (Friese et al., 2013; Heusser, Poeppel, Ezzyat, & Davachi, 2016; Staudigl & Hanslmayr, 2013) and WM processes (Daume et al., 2017). A classical finding of theta-gamma PAC during successful encoding comes from one of our former studies (Friese et al., 2013) and is

illustrated in Figure 2C. The theta-gamma code is assumed to support long-term potentiation processes in the hippocampus (Pavlidis, Greenstein, Grudman, & Winson, 1988), the core system of human associative memory formation (Eichenbaum, 2004).

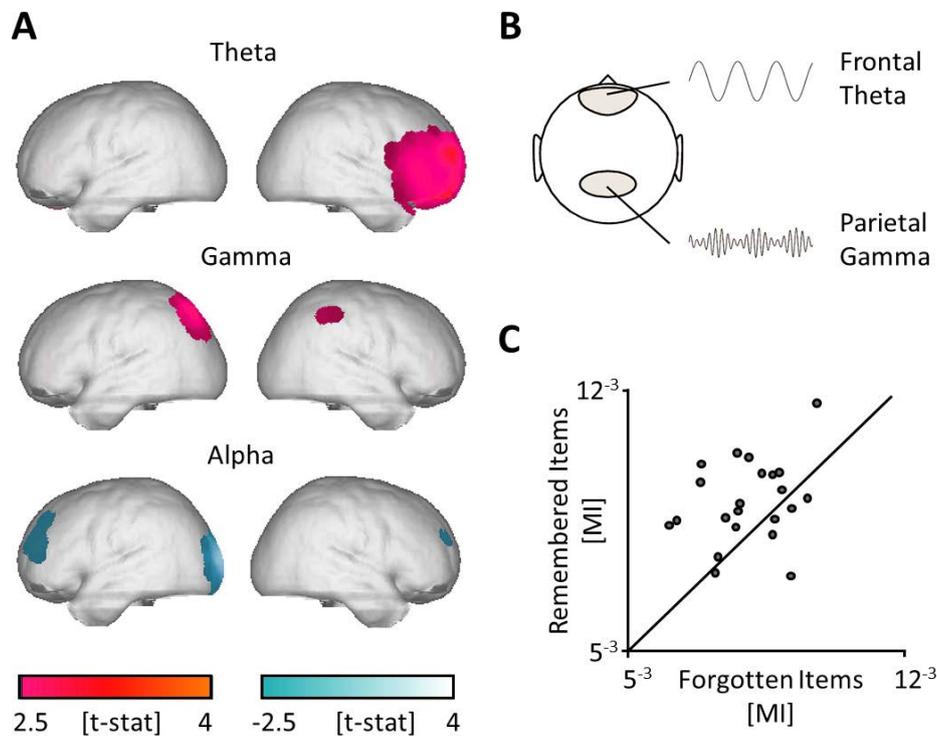


Figure 2. Exemplary results from a pictorial subsequent memory design (adapted from Friese et al., 2013). (A) Source space SMEs are illustrated as t-values (thresholded at $p < .01$) projected onto the surface of an average MRI template brain. (B) The cartoon head illustrates fronto-parietal theta-gamma phase-amplitude coupling. (C) Modulation indices for remember and forgotten items. For participants above the diagonal line, MIs are larger for remembered versus forgotten items ($SR > SF$).

Suppressed alpha activity is assumed to facilitate visual cortical processes during encoding (Friese et al., 2013; Hanslmayr, Spitzer, & Bäuml, 2009; Klimesch et al., 1997). This is, alpha oscillations may suppress task-irrelevant networks, while routing perceptual processes to task-relevant regions (Jensen & Mazaheri, 2010). In a former study, alpha suppression was specifically high for memory formation processes in a semantic encoding tasks (Hanslmayr et al., 2009), and it has been proposed that reduced alpha oscillation reflects

the activation of semantic cortical networks (Klimesch, 2012), a may form a functional architecture on which explicit mnemonic mechanisms operate (Jensen & Mazaheri, 2010).

1.2. Objectives of this dissertation

Although rather specific mnemonic functions have been proposed for theta, alpha and gamma oscillations in the memory formation process, several critical questions regarding their role during the encoding of novel events remain unanswered, specifically in the human brain. In my dissertation, using scalp-recorded EEG, I addressed several critical aspects of memory formation processes in adults, and early and middle childhood. This is critical, since early development is a period of intense brain maturation, and this critical period of human brain development has been largely neglected by cognitive neuroscientists looking at neuronal oscillations, thus far.

Study 1. In a first study, we aimed to disentangle the neuronal oscillatory activity for associative binding and semantic, perceptual processes during memory formation. To pinpoint the encoding of novel associations, we used an associative encoding and retrieval task (i.e., forming item-color associations). Furthermore, to separate mnemonic processes from visual perceptual processes, the encoding of picture stimuli was contrasted to the encoding of word stimuli (i.e., high and low visual perceptual information). We hypothesized that high theta power and fronto-parietal theta-gamma PAC reflect the formation of associative memories (i.e., a subsequent memory effect), while alpha suppression and gamma oscillations *per se* would primarily reflect perceptual processes (i.e., being pronounced for pictures versus words).

Study 2. In a second study, we experimentally manipulated the memory encoding process by a visual stimulation at a theta rhythm, in contrast to the alpha rhythm. This was to selectively enhance the memory encoding process, in contrast to an individual alpha frequency, which may disrupt encoding, and would provide first evidence for a functional role of the theta rhythm for mnemonic encoding in the human brain. A scalp recorded EEG was

applied to test the oscillatory dynamics, elicited by the visual entrainment procedure.

Specifically, we were interested if gamma oscillations would couple to the entrained theta rhythm, and enhance subsequent memory performance.

Study 3. In study 3, we looked at alpha and theta oscillations to investigate the processes underlying intentional encoding in young adults, 10-year-olds, and 7-year-olds, by contrasting an intentional and an incidental encoding condition. A semantic encoding task with pictorial stimuli was used and the memory for the stimuli and their perceptual features was tested during subsequent retrieval. As an intentional encoding, we predicted higher levels of theta power, indicating mnemonic control processes, namely the mental elaboration of perceptual features, which were relevant for subsequent retrieval. Furthermore, as the first study looking at neuronal oscillatory dynamics during encoding, we tested intentional and encoding processes in two groups of school children (10-year-olds and 7-year-olds). Specifically, while the theta rhythm may index an intentional learning mechanism throughout development, alpha suppression may increase with age, indexing the refinement of semantic networks with ongoing development.

Study 4. In the fourth study, we applied rhythmic visual brain stimulation in 9-month-old infants, to experimentally test for a functional dissociation between the theta and the alpha rhythm in infants, when encoding novel, unexpected events. Specifically, we presented physical, numerical, and human action events at a 4 Hz theta rhythm and a 6 Hz alpha rhythm (corresponding to the infant alpha frequency). Notably, 6 Hz corresponds to 9-month-old infants' alpha rhythm, which we identified for the processing of the stimuli presented here. Our main hypothesis was that visually entrained theta oscillations in the EEG would respond to the presentation of unexpected compared to expected outcomes, indexing learning. Based on the results from study 2, the alpha rhythm was not expected to be sensitive to the encoding condition.

2. Empirical Studies: Overview

At this point, I will provide an overview and a short summary of the main findings of the four empirical studies of my dissertation. The full empirical articles are attached to this synopsis. They will be referred to by their number, studies 1 to 4, throughout this synopsis.

2.1. Overview of the empirical studies

Study 1: Fronto-parietal theta-gamma coupling binds visual perceptual features in an associative memory task. (Köster, Finger, Graetz, Kater, & Gruber, under review).

Study 2: Memory entrainment by visually evoked theta-gamma coupling. (Köster, Martens, & Gruber, under review).

Study 3: Neuronal oscillations reveal the processes underlying intentional compared to incidental learning in children and young adults. (Köster, Haese, & Czernochowski, 2017).

Study 4: Infants encode unexpected events at the 4 Hz theta rhythm. (Köster, Langeloh, & Höhl, submitted).

2.5 Summary of the empirical studies

Across all 4 four empirical studies we could substantiate and further elucidate the specific roles of the theta, alpha, and gamma oscillations for the formation of novel memories. This is, we specified their contribution to associative binding and perceptual processes (study 1), we could proof their distinct causal roles in memory formation by an experimentally

manipulation of neuronal oscillations by visual entrainment (study 2, and also study 4), and we made important first steps in understanding the functions of the theta and the alpha rhythm in the maturing brain of children (study 3) and infants (study 4). While the complete results can be found in the original articles at the end of this synopsis, I will here summarize the main findings.

Study 1. We used an associative memory task (item-color combinations) and picture versus word stimuli (high versus low perceptual information) to separate associative memory functions and visual perceptual processes in a subsequent memory paradigm. In support of our hypotheses, we found increased theta and gamma power for later remembered versus later forgotten items (SME, independent of the color judgement), but no SME for alpha oscillations. We also found an increase in fronto-parietal theta-gamma PAC, specific for the formation of picture-color associations. This is, no SME in theta-gamma PAC was found for pictures remembered without color or words, remembered with or without color. Parietal alpha suppression, as well as theta and gamma power were higher for pictures compared to words. These findings support the idea of a fronto-parietal theta-gamma PAC mechanism for the associative binding of visual perceptual features during encoding. Namely, interpreting and integrating novel information in existing neuronal networks. Alpha suppression likely reflects an attentional gating mechanism in semantic networks, less specific for explicit memory encoding. Gamma activation may index the promotion of visual perceptual information along the visual cortical hierarchy, which may then be organized and bound by the frontal theta rhythm.

Study 2. Supporting our hypothesis, we could experimentally enhance memory formation by a visual stimulation at an individual theta frequency, in contrast to the stimulation at an individual alpha frequency. This memory entrainment effect was not explained by theta power *per se*, which showed an inverse SME, but was driven by visually evoked theta-gamma PAC pattern. Entrained alpha oscillations, as well as alpha-gamma PAC,

were less specific and did not strongly effect later encoding processes. This underlines the functional role of the theta rhythm and the theta-gamma neuronal code in human episodic memory. Strikingly, we could entrain complex mnemonic network mechanisms by a simple external pacemaker, namely a visual stimulation technique. This provides a proof of concept that visual pacemakers can entrain complex cognitive processes in the wake human brain.

Study 3. We investigated the neuronal dynamics during encoding in the EEG of young adults and two groups of children aged 10 and 7 years. Theta (3-8 Hz) and alpha (10-16 Hz) oscillations were analyzed to compare encoding processes during an intentional and an incidental encoding task. Theta activity was increased for the incidental in contrast to the intentional encoding phase, in a task where perceptual details were relevant for later retrieval. No differences between encoding conditions were found for alpha oscillations. Encoding-related alpha suppression increased with age and was associated with age differences in reaction times for the semantic encoding task. This further substantiates the functional dissociation between theta and alpha oscillations. The theta rhythm marks explicit mnemonic control processes, when attending to perceptual features, which is present in the early school years already. The age trend in alpha suppression may reflect the emergence of increasingly differentiated semantic networks through early and middle childhood.

Study 4. While the first year of life is a period of intense brain maturation and learning, very little is known about the neuronal mechanisms that underpin the formation of infants' basic representations. Specifically, novel, unexpected events provide infants with unique opportunities to learn. Using rhythmic visual brain stimulation in 9-month-olds, we provide first evidence for the functional relevance of the theta rhythm for the encoding of novel, unexpected events in the infant brain. Specifically, the visually entrained theta rhythm (4 Hz steady-state visually evoked potentials; SSVEPs) increased for the encoding of unexpected in contrast to expected outcomes. Entrained alpha oscillations (6 Hz SSVEPs, corresponding to infants' alpha frequency) were insensitive to unexpected outcomes. This

provides first experimental evidence for the theta rhythm as an encoding mechanism in the developing infant brain and substantiates the primacy role of the theta rhythm in learning processes, in the first year, when critical brain structures are still immature.

3. Theoretical Integration

At this point, I will broaden the theoretical perspective. I will point out, how neuronal oscillation might bridge the gap between psychological accounts and the neurophysiology of mnemonic processes. This is, neuronal oscillations implement mnemonic functions on the neuroanatomic architecture of the human brain. In cognitive neuroscience, experimental paradigms isolate specific mnemonic functions, for example, attentional selection, object perception, memory formation, working memory, or retrieval. However, in order to understand the functional relevance of neuronal oscillations for human brain functions, it is critical to understand, that these processes are embedded in human attention and memory processes. At the end of this integration, I will discuss how the empirical works of this dissertation substantiate and can be interpreted in the light of this integrative framework.

3.1. Theoretical accounts of attention and memory

The formation of novel memories accompanies perceptual processes (Cowan, 1988; Craik & Lockhart, 1972). Constantly, sensory information is interpreted and integrated into existing neuronal networks to maintain a coherent representation of time and space (Eichenbaum, 2017). A principle assumption of Craik and Lockhart (1972) is that the mental elaboration of novel information is crucial for memory formation (levels of processing account). Perceptual information that is expected (i.e., habituated) or has low relevance for current actions and goals is likewise processed but may not be subject to an in depth mental elaboration and thus not remembered explicitly later on (Cowan, 1988). Critically, the idea that attention and memory are embedded processes has put in question earlier modular theories, which assumed a distinction between attentional selection processes and different

memory storage systems, for example, the modal model of memory (Atkinson & Shiffrin, 1968) or the multicomponent model of WM (Baddeley, 2003).

Here, I use the term neuronal representations (synonymously with representations in semantic or associative networks) to refer to cell assemblies that encode specific perceptual units (i.e., informational chunks). However, the present account should not be confused with a representational view on cognition: Neuronal representations do not serve as an exact copy of the environment, but ultimately serve the generation of behavior, or, more precisely, the prediction of behavioral outcomes (O'Regan & Noë, 2001). Nonetheless, complex behaviors like communication and prospective planning, require the representation of abstract concepts that closely match real world entities, over and above simple action-perception associations. Thus, although the primary focus of this theoretic integration lies on mnemonic processes, it should be emphasized, that mnemonic processes of sensory information ultimately serve the optimization of generative models (Friston, 2010). This is, the optimization of behavioral predictions in the light of former experiences, the present context and future goals. Thus, a neuronal representation may be the specific cell assembly (associative network) which represents an object, such as a specific cup. This would include perceptual features, but also the knowledge how to grasp it, what to do with it or how to refer to it in a conversation.

The embedded-process-model of memory integrates information processing theories with memory accounts and has received much attention since its formulation in 1988 (Cowan, 1988), Figure 3A. The basic assumption of this model is that attention and explicit memory processes are guided by a central executive, which controls attentional processes. This is, the central executive operates on activated representations (memory items) in long-term memory, activated by sensory information or current cognitive processes, in the light of current behavior and goals. Thus, Cowan highlights in his model the relevance of mnemonic processes for current behavior. To demystify central executive processes, Cowan accentuates that in psychological experiments central executive processes are implemented by the

instructions of the current orienting task. Like former theoretical models, Cowan assumes a sensory buffer for all incoming sensory information, which automatically activate items of the long-term storage. These information may decay rapidly, get in to the current focus of attention, or also contribute to implicit memory processes.

According to Cowan, items can enter the current focus of attention via several routes. First, the central executive can voluntarily shift the attention to task relevant items which are activated by sensory inputs (route *a* in Figure 3A). Second, the central executive can shift the attentional focus to long-term memory entries that are not currently activated by sensory input (route *d* in Figure 3A). This could be the reactivation of episodic and semantic knowledge that are needed for an interpretation of current sensory information or those relevant for current goals. This clarifies that Cowan describes an internal, mental focus of attention. Thereby retrieved information from long-term memory (LTM), not activated by sensory information, can be in the focus of attention and considered in mental elaboration processes. Third, novel sensory inputs can enter the focus of attention without voluntary control, if they are unexpected (route *c* in Figure 3A), what Cowan describes as a dishabituation response and what may be called prediction error in the contemporary debate in neuroscience (Friston, 2010). Finally, sensory inputs may activate long-term memory inputs without being attended and elaborated, which is specifically the case for expected, habituated items (route *b* in Figure 3A). Thereby, Cowan does not only account for explicit mnemonic processes, which are in the focus of the present work, but also for implicit processes, which are activated and can guide behavior, but require less attentional resources.

Cowan's model has received much attention, because it is compatible with principle findings from experimental psychology. First, activated items in LTM are conceptualized as informational chunks and thus the model account for chunking processes (Cowan, 2001). This is, memory items are closely associated network nodes, based on former experiences. For example, the three letters F B I are represented as FBI, a single memory item. Furthermore,

WM processes are conceptualized as memory items in the attentional focus of the central executive. The number of items that can be in the focus of attention at the same time may then correspond to the capacity of the WM. While some models proposed 7 ± 2 items as the “magical number” for WM capacity (Miller, 1956), Cowan assumes a WM capacity of 4 items (i.e., chunks; Cowan, 2001). If sensory information are not elaborated or rehearsed their activation is assumed to decay after a few seconds. Like traditional models (Atkinson & Shiffrin, 1968), Cowan also assumes a sensory buffer, namely that sensory inputs may decay very rapidly if they do not enter the focus of attention. This activation of memory items without explicit elaboration accounts for perceptual priming processes (Tulving & Schacter, 1987). Like Craik and Lockhart’s depth of processing account (Craik & Lockhart, 1972), Cowan assumes that novel, long lasting associations between elements can be formed between items which are elaborated by the central executive.

In contrast to other modal models of memory (Atkinson & Shiffrin, 1968; Baddeley, 1978), Cowan’s model does not postulate different memory systems, but conceptualizes memory as a continuous process that accompanies perception, the attentional selection and mental elaboration of novel information. Furthermore, different from common concepts of WM (Baddeley, 1978), Cowan does not postulate different computational mechanisms for different sensory modalities. Note also that Cowan’s concept of attention unifies exogenous and endogenous attentional processes, since the central executive acts on endogenous representations, which may be activated by both sensory and internal processes. However, Cowan’s model remains imprecise regarding the neurophysiological implementation of these processes (attentional selection, mental elaboration in WM, memory formation, changes in LTM over time). Before I posit that neuronal oscillations are the key mechanisms, which implement the critical elements of the Cowan model (see section 3.3.), I will briefly outline the brain structures which form the neuroanatomic basis for human mnemonic functions.

3.2. Neuroanatomy of attention and memory

Findings from neurophysiology add critical aspects to the understanding of LTM formation. Famous patient H.M. suffered from anterograde amnesia following the bilateral removal of the MTL (Scoville & Milner, 1957), while further cognitive and perceptual abilities, for example, his working memory abilities, remained intact. H.M. also retained the ability to retrieve events that occurred sometime before the surgery. Subsequent neuroimaging and animal research has established a central role of the MTL in the formation of novel associative memories (Squire & Alvarez, 1995) that underpin a coherent representation of time and space (Eichenbaum, 2017). Lesion studies in animals (Kim & Fanselow, 1992), in which the MTL was removed with different delays to an initial spatial learning task, revealed that novel memories are initially fully dependent on the MTL, before they become gradually independent of the MTL (Squire & Alvarez, 1995). This led researchers to assume that the MTL is an intermediate storage, where novel associations can be formed rapidly before they are transferred into lasting semantic networks in the neocortex, the dual memory systems account (Squire & Alvarez, 1995). Computational models substantiate the theoretical relevance for a division of labor between a fast, medio-temporal and a slow, neocortical learning system (McClelland, McNaughton, & O'Reilly, 1995). Namely, this avoids interference between fast updates of contextual information (realized in associative networks in the MTL) and more stable information, stored in the neocortex (NC), which are transferred from MTL into neocortical networks (Squire & Alvarez, 1995) in the process of memory consolidation. To conclude, it is assumed that associative networks in the MTL update fast and provide an internal representation of current context (time and space). Sensory information activates lasting associative networks that represent LTM entries and promotes highly preprocessed, semantic information to MTL networks, where novel associations between LTM elements can be formed (Buzsáki, 1996).

Perceptual information is initially processed in primary sensory regions, such as the primary visual areas, and then promoted along the visual hierarchy (Felleman & Van Essen, 1991), converging on increasingly abstract representations, such as the inferior temporal (IT) cortex (Tanaka, 1993). For the visual system, patient studies revealed that object information are processed along a ventral processing stream in temporal networks, while context information is rather processed along a dorsal processing stream in parietal networks (Goodale & Milner, 1992). Specifically, neuronal populations in the IT encode relatively complex visual features (Tanaka, 1993), which are spatially invariant. It has been proposed that neuronal populations in the parietal cortex act on lower-level object features to spatially integrate them into coherent objects or scenes (Corbetta, Shulman, Miezin, & Petersen, 1995). Importantly, besides these well-defined regions, semantic information were found to be represented in associative networks distributed widely throughout the neocortex (Binder & Desai, 2011). Both mnemonic and attentional control mechanisms are here assumed to act on these basic representations.

In subsequent memory paradigms, neuroimaging studies consistently found increased blood-oxygen dependent (BOLD) signal within the prefrontal cortex (PFC) and the MTL (Brewer, 1998; Kirchoff, Wagner, Maril, & Stern, 2000; Wagner, 1998). The PFC is ascribed an executive control function (Blumenfeld & Ranganath, 2007): Ventrolateral regions of the PFC are involved in the selection of task relevant information, dorsolateral regions of the PFC are involved in organizing multiple pieces of information in WM. Furthermore, the anterior cingulate cortex (ACC), as part of the prefrontal cognitive control network, with a central role in the evaluation and prediction of behavioral outcomes (Jahn, Nee, Alexander, & Brown, 2014).

Like parietal and temporal networks, MTL networks are assumed to represent highly preprocessed, abstract information about the external world (Buzsáki, 1996). This is supported by findings from the rat MTL, namely single cells that represent a certain position

in space (O’Keefe, & Recce, 1993), or in humans, single MTL cells represent specific people, objects (Quiroga, Reddy, Kreiman, Koch, & Fried, 2005) or places (Jacobs et al., 2013). Presumably, PFC control processes act on memory items, activated representations in neocortical semantic representations (Binder & Desai, 2011), and MTL networks, representing recent contextual information (Miller, Neufang, Solway, & Brandt, 2013) in a temporally ordered way (Lisman & Jensen, 2013).

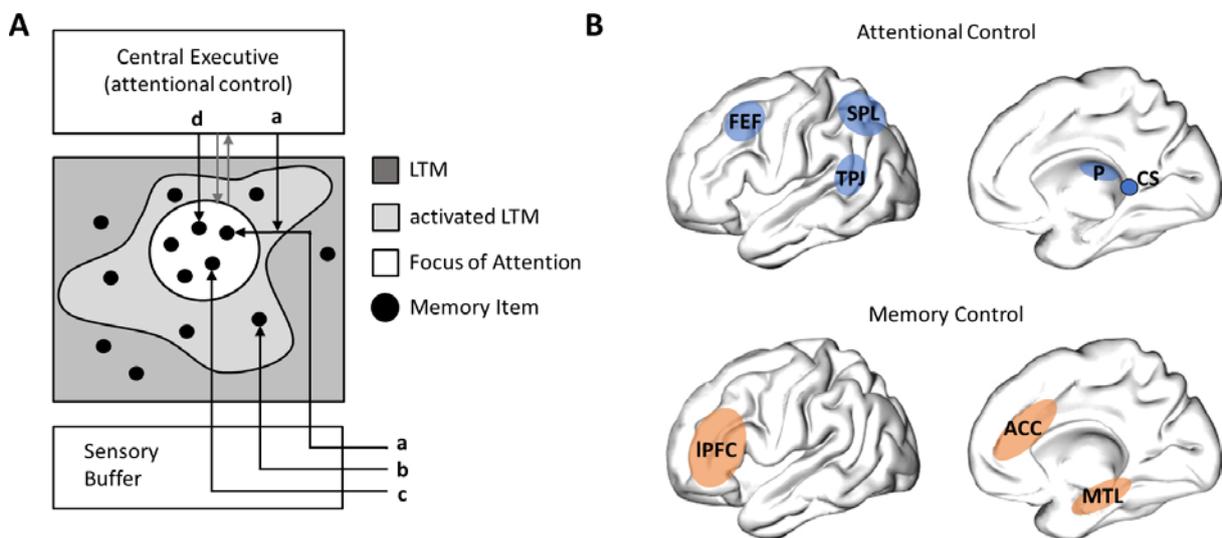


Figure 3. Cowan’s embedded-process-model and neuroanatomical structures involved in attention and memory. (A) Cowan (1988) suggests that memory and attention processes are inseparably linked, acting on activated entries in long term memory (LTM), so called memory items. This internal (mental) focus of attention is mainly controlled by the central executive (gray arrows) and lies on a subset of activated items: Sensory information may be selectively attended (a), but activated LTM items may also guide behavior without being attended (b), if they are highly habituated, accounting for implicit processes. Sensory information may further enter the focus of attention immediately, if they are unexpected and thus dishabituated (c), or may be activated by the central executive without sensory information (d). (B) Memory and attention processes engage semantic networks across the wide cortical networks (Binder & Desai, 2011). A central role for mnemonic control has been ascribed to the lateral prefrontal cortex (IPFC), the anterior cingulate cortex (ACC) and the medial temporal lobe (MTL). A central role for selective attention processes is ascribe to the frontal eye field (FEF) and the colliculi superiores (CS) in eye-movement control, as well as the pulvinar (P), the superior parietal lobe (SPL) and the temporal parietal junction (TPJ) in cortical attentional control, (adapted from Posner & Rothbart, 2007).

Selective attention or orienting is the ability to select specific information among multiple sensory stimuli (Posner & Rothbart, 2007; Raz & Buhle, 2006), and is the most intensely studied attentional network. Selective attention is often differentiated into exogenous orientation, for example, when an unexpected flashing light automatically captures attention to a specific position and endogenous orientation, for example, when a central cue indicates one of two possible position where a target may occur, such as in the classical Posner paradigm (Posner, 1980). These accounts come close to the attention processes that accompany memory formation. Namely external, unexpected information capture attentional processes or expectations are formed about relevant perceptual information. Selective attention leads to a relative increase in neuronal activity in the respective sensory system, for example in anticipation of a target in a cued location in the Posner task. The selective attention system involves thalamic and tempo-parietal regions, amplifying lower sensory regions, as well as the frontal eye-field and the superior colliculi, which control overt attention by directing eye-movement behavior (Posner & Rothbart, 2007).

3.3. Brain rhythms implement mnemonic functions on the neuronal architecture.

As mentioned previously, my central proposal is that rhythmic activity in neuronal networks reflect the critical mechanisms that realize the embedded attention and memory processes, postulated by Cowan (1988). Neuronal oscillations reflect key computational principles, phylogenetically preserved in mammalian species, from rodents to non-human primates and the human brain (Buzsaki, 2004). Across various species, the function of neuronal oscillatory processes is described at the microscopic (e.g. Fell & Axmacher, 2011), the mesoscopic (e.g., Fries, 2015), and the macroscopic (Hanslmayr, Staresina, & Bowman, 2016). The rhythmic interplay within and across cell assemblies renders neuronal communication effective, selective, and precise (Fries, 2015) and form the basis for neuronal learning mechanisms, facilitating structural changes in neuronal networks (Fell & Axmacher, 2011).

Memory items - Gamma oscillations reflect the activation of neuronal

representations. In their seminal works, Singer and colleagues found that neurons in the cat visual cortex synchronize their activation pattern in the gamma frequency (> 30 Hz), if they encode features of the same object (Gray et al., 1989), exemplified by the shape and the color of a red car or a green tree in Figure 4A. According to their binding by synchrony theory, perceptual information, encoded by neurons distributed across the brain, are integrated by synchronizing their firing activity (Engel et al., 2001). This initial proposal is now substantiated by an abundance of research in rodents and monkeys (see Fries, 2015, for a recent review). In particular, the coherency of neuronal firing in the gamma frequency promotes visual processes along the visual cortical hierarchy (Bosman et al., 2012) and synchronizes neuronal activity within (Gray et al., 1989) and across (Womelsdorf et al., 2007) cell assemblies. When sensory information is processed along the visual system, the rhythmic synchronization between presynaptic and postsynaptic neurons allows a precisely timed input of activity from the presynaptic neuron to phases of postsynaptic excitability. It has been proposed that early gamma oscillatory responses reflect the processing of sensory stimulus information within existing representations, which are then further utilized by higher cognitive processes (Herrmann, Munk, & Engel, 2004). For example, gamma oscillations may then reflect recurrent activity within recently activated representations in WM, to maintain these representation in the absence of external input (Pesaran, Pezaris, Sahani, Mitra, & Andersen, 2002).

Regarding Cowan's embedded process model, sensory information is promoted along the visual hierarchy, where accumulated perceptual evidence converges on and activates increasingly abstract representations in associative cortical networks (Gauthier et al., 2000; Tanaka, 1993), or yet more abstract concepts (Quiroga et al., 2005), and contextual information within medio-temporal networks (Jacobs et al., 2013). A memory item then represents an activated cluster of highly interconnected nodes within the associative network

(each node being a single neuron or highly associated local cell assemblies). Both, the promotion of perceptual information in primary sensory regions, as well as the activation and maintenance of an associative network, may be reflected in the gamma rhythm. In line with the Cowan model, the activation of such a network cluster would correspond to an activated entry in long-term memory, for example the activation or maintenance of the concept of a red car or the green tree in Figure 4. This corresponds to Cowan's idea that memory items represent informational chunks, based on individual learning experiences. I assume that the semantic content, namely the interpretation and meaning of perceptual information, is activated automatically within the associative network, as part of the perceptual process. This is, a red car can hardly be seen without perceiving a red car. In Cowan's model, this would also be the case for activated items in LTM which are not in the focus of attention, but may be involved in implicit processes and automated actions.

In the human brain, gamma oscillations were identified as an object representation mechanism in the visual cortex, in the EEG and MEG (Tallon-Baudry & Bertrand, 1999). Namely, gamma oscillations were found to be higher for familiar object stimuli, compared to unfamiliar or scrambled object stimuli. Critically, micro-saccadic eye-movements are also dependent on the visual information (e.g. familiar versus unfamiliar objects) and cause artifacts in the (30-90 Hz) gamma-band range (Yuval-Greenberg, Tomer, Keren, Nelken, & Deouell, 2008). However, gamma band oscillations have thereafter been reported when micro-saccadic artifacts have been removed from the EEG signal (e.g. Hassler, Barreto, & Gruber, 2011; Keren, Yuval-Greenberg, & Deouell, 2010).

Besides the activation of representations via sensory signals the Cowan model postulates that representations can be maintained, elaborated and bound into novel memories by central executive processes. This brings me directly to the next aspect of my integrative framework.

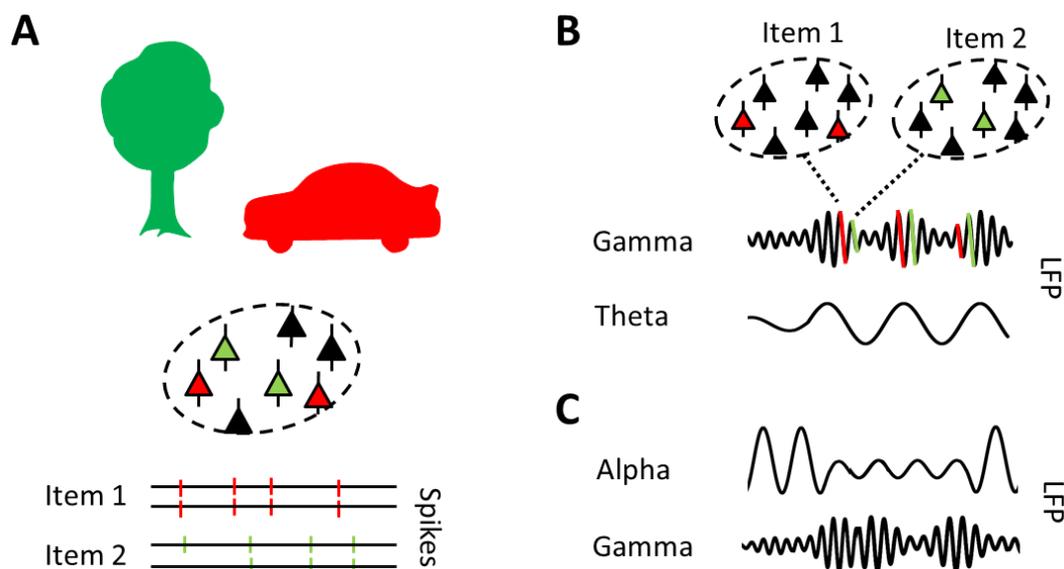


Figure 4. Theta, alpha, and gamma oscillations reflect distinct neuronal mechanisms. (A) Neurons which encode the same object synchronize their firing activity within and across cell assemblies in the gamma rhythm (>30 Hz) (Gray et al., 1989), a phenomenon named binding by synchrony or communication through coherency. This principle may integrated distributed brain processes and underpin the activation and reinstatement of neuronal representations. (B) The theta rhythm (3-8 Hz) orders neuronal representations, reflected in a theta-gamma neuronal code. For example, neurons in the rat MTL that encode a specific place, fire in an ordered manner, nested in the theta cycle. As the rat passed through the labyrinth, the firing of a place cell occurs at earlier phases of the theta rhythm, as the rat proceeds through the labyrinth, a phenomenon called phase precession (O'Keefe et al., 1993). The theta-gamma code has been proposed a more general coding schema for the representation and manipulation of multiple items (Lisman & Jensen, 2013). (B) Alpha (8-14 Hz) oscillations inhibit neuronal processes in task irrelevant networks and thereby gate information processing in task relevant networks, reflected in reduced alpha power (Lisman & Jensen, 2013). Alpha suppression is described a central role in semantic processes in associative networks (Klimesch, 2012).

Central executive functions – theta-gamma coupling reflects attentional selection, mental elaboration and associative binding. The theta rhythm is a prominent marker of cognitive processes in the PFC - ACC control network (Hiroshi Asada, Fukuda, Tsunoda, Yamaguchi, & Tonoike, 1999), and there is good evidence that coherent theta oscillations index the communication between prefrontal and MTL networks in associative memory processes in animals (Jones & Wilson, 2005; Brincat & Miller, 2015) and humans (Kaplan et

al., 2014; Staudigl & Hanslmayr, 2013; Backus, Schoffelen, Szabenyi, Hanslmayr, & Doeller, 2016). It is assumed that the theta rhythm implements a general coding schema to represent multiple items, in an ordered way, each item being activated or reactivated in distinct cycles of the gamma rhythm (Lisman & Jensen, 2013). Specifically, I propose that the prefrontal theta rhythm explicitly selects, maintains, elaborates and binds neuronal representations (i.e., memory items) into novel memories. These assumptions are inspired by the basic research on place cells in rodents (O’Keefe et al., 1993). Place cells are neurons in the MTL that fire at a specific spatial location, for example, in a labyrinth. Place cells fire at a several successive theta cycles as the rat passed through the labyrinth, and the firing of a place cell occurs at earlier phases of the theta rhythm, as the rat proceeds through the labyrinth, a phenomenon called phase precession, see Figure 4B. Later research revealed that theta phase precession occurs at rhythmic gamma bursts, nested in the ongoing theta rhythm of the MTL (Senior, Huxter, Allen, O’Neill, & Csicsvari, 2008). The number of gamma bursts, representing single items, may then determine the number of items that can be processed in WM (Lisman, 2010). More precisely, it is assumed that the sequence coded in MTL networks is linked to neocortical representations, which serve as a multi item buffer (Jensen & Lisman, 2005).

Critically, place cells in the MTL of rats are activated prior to the actual place that is represented by the specific place cell (O’Keefe et al., 1993). Thus, associative networks in the MTL circuit seem to generate context dependent predictions, based on a given sensory input processed in parietal networks and an emulation of own behavioral actions. That is, based on its present location in the labyrinth, the rat emulates its behavioral outcomes, by activating spatial representations ahead of real time, forming a generative model for planned behavioral responses (Friston, 2010). At the same time, novel (i.e., unpredicted) information may be integrated into activated representations, in order to retain a coherent representation of time and space. I assume that the prefrontal central executive samples perceptual information at a theta pace and interprets them in the light of known concepts in semantic, associative

networks (e.g., parietal cortex, IT), the present context (in the MTL) and current goals (in the PFC and ACC). Thereby the central executive updates internal representations and emulate behavioral outcomes, in order to optimize behavior.

First evidence from visual attention research supports the idea that the theta rhythm implements an attentional sampling mechanism (Fries, 2015). For example, in the macaque visual cortex, gamma coherence between V1 and V4 resets at a theta pace (Bosman et al., 2012). Furthermore, overt visual attention in humans, namely saccades and micro-saccades occur at a theta rhythmicity (Troncoso, Otero-Millan, Macknik, Serrano-Pedraza, & Martinez-Conde, 2010) and gamma-processes in a visual attention task fluctuate at the theta pace (Landau, Schreyer, Van Pelt, & Fries, 2015). Possibly, the prefrontal theta rhythm implements a perceptual sampling loop, steering eye-movements via the FEF and the colliculi superiors. Thereby the PFC initiates (resets) a neatly ordered processing sequence, sampling and integrating novel information bit by bit, at a theta pace.

I hypothesize that, the theta-gamma code squeezes real time events into a neuronal time scale, in order to solve two critical problems of neurophysiological computation. First, the neatly timed activation within and across cell assemblies implements the Hebbian learning principle, cells that „fire together, wire together“ (Hebb, 1949). Within the MTL the precisely timed neuronal input at a gamma pace to the down phase of the theta rhythm is a precondition for long term potentiation processes (LTP, Pavlides et al., 1988). This is, tetanic inputs at the pre and post synapsis are a prerequisite for LTP processes, and thus the formation of novel associations in MTL networks (Juergen Fell & Axmacher, 2011). Second, regarding the emulation of behavioral outcomes (see above), the theta-gamma code allows neuronal processes to speed up and advance ahead of time and thereby form a generative model to predict future events and behavioral outcomes (Friston, 2010). For example, the green tree disappearing behind the car if the car dives forward, see Figure 4A.

Regarding Cowan's model, the central executive sets the focus of attention on a subset of activated entries in LTM, and mentally elaborates these entries in the light of the current context and goals. Here I conceptualize mental elaboration processes as the explicit selection, manipulation and associative binding of memory items by the PFC. Specifically, I assume that these memory items are activated associative networks within the neocortex, while associative networks in the medio-temporal lobe complement information about the current context, temporal and spatial relations (Eichenbaum, 2017). The prefrontal theta-rhythm reflects the working pace of the central executive, which dynamically selects, maintains and integrates memory items, reflected in the theta-gamma code, to update the internal representations and emulate behavioral outcomes. Associative binding in the MTL can occur at different levels of the perceptual hierarchy, binding together novel object features or forming novel associations between places and people (Hanslmayr et al., 2016). In accordance with the depth of processing account (Craik & Lockhart, 1972; Hanslmayr & Staudigl, 2014), the formation of novel memories accompanies mental elaboration of activated memory items and is a continuous process that accompanies memory encoding.

In the human brain, best evidence for the control function of the theta rhythm and the theta-gamma code come from WM and LTM studies. The PFC, MTL and IT networks closely interact in WM processes (Axmacher, Schmitz, Wagner, Elger, & Fell, 2008). Theta oscillations in the PFC and the anterior cingulate cortex index higher cognitive processes (Asada, Fukuda, Tsunoda, Yamaguchi, & Tonoike, 1999) and have often been reported during WM maintenance (Jensen & Tesche, 2002; Khader, Jost, Ranganath, & Rösler, 2010; Scheeringa et al., 2009). Furthermore, in favor with the view that theta-gamma PAC reflects mental elaboration processes, theta-gamma PAC was reported in a diversity of cognitive tasks in the PFC (Canolty et al., 2006) and during the maintenance of information in WM in intracranial recordings in the MTL (Mormann et al., 2005). In a MEG study, long-range theta-gamma coupling mechanism between the frontal theta rhythm and gamma oscillations in the

IT region during maintenance of information in a visual WM task (Daume et al., 2017). Support for a serial representation of items reflected in the theta-gamma neuronal code during WM maintenance, was obtained from intracranial recordings in human patients (Bahramisharif, Jensen, Jacobs, & Lisman, 2017). In this study, the theta phase of letter sensitive gamma bursts during maintenance reflected the order of letter presentation, in a letter-based Sternberg task. In support of a functional role of the theta rhythm for the maintenance of neuronal representations, WM capacity could be increased experimentally, when the theta rhythm was slowed down by transcranial alternating stimulation (Vosskuhl, Huster, & Herrmann, 2015), possibly due to an increased number of items that could be rehearsed in each theta cycle.

As outline in the introduction, successful encoding is associated with pronounced theta activity over right prefrontal areas (Friese et al., 2013; Osipova et al., 2006). Furthermore, intracranial electrodes in the MTL revealed SMEs in the phase synchronization between neurons in the theta power (Fell et al., 2003; Rutishauser, Ross, Mamelak, & Schuman, 2010; Sederberg, Kahana, Howard, Donner, & Madsen, 2003), two structures which closely interact in LTM processes (Simons & Spiers, 2003). A recent audio-visual entrainment study highlights the importance of the theta phase for encoding (Clouter et al., 2017). The authors found that a synchronous stimulation of visual and auditory information at the theta rhythm facilitated associative memory formation. No such effect was found for the stimulation out of phase or at a slower delta (~ 2 Hz) or an alpha frequency. In humans, pronounced gamma oscillations were correlated with episodic memory processes in the posterior cortex (Friese et al., 2013; Osipova et al., 2006; Sederberg et al., 2003) and MTL regions (Fell et al., 2001; Sederberg et al., 2007).

Furthermore, recent studies provide first evidence for an increase in theta-gamma PAC, accompanying successful episodic encoding, in neocortical (Friese et al., 2013) and medio-temporal networks (Heusser et al., 2016; Staudigl & Hanslmayr, 2013). Further

research also established theta-gamma PAC for successfully retrieved objects (Kaplan et al., 2014; Köster et al., 2014).

Activated long term memory – the alpha rhythm gates attentional processes in semantic networks. The most prominent marker of attentional and perceptual processes in the human EEG is the alpha rhythm (8 -14 Hz), first identified by Berger (1934). He found pronounced alpha activity when his participants had their eyes closed and a sharp decrease in alpha synchronization, when participants opened their eyes. Subsequent research has established that alpha desynchronization is modulated by attention and mnemonic processes (Klimesch, Doppelmayr, Schimke, & Ripper, 1997), with good evidence for both the visual (Fries et al., 2013), and the auditory domain (Obleser, Wostmann, Hellbernd, Wilsch, & Maess, 2012). Specifically, alpha oscillations are assumed to reflect an attentional gating mechanism that inhibits task irrelevant cortical processes and facilitates neuronal processes in task relevant cortical networks, shaping a functional architecture (Jensen & Mazaheri, 2010). Neuronal processing is then reflected in gamma oscillations, Figure 4C. Best evidence for an inverse relation between local field alpha power desynchronization and neuronal firing rates comes from a study by Haegens and colleagues (Haegens, Nacher, Luna, Romo, & Jensen, 2011), measuring sensory cortical regions in monkeys. The alpha rhythm has also been ascribed a top-down facilitatory role for the processing of sensory information (Fries, 2015), acting as a prediction and preparing relevant sensory regions for expected sensory inputs (VanRullen, 2016). For example, pre-stimulus decreases in alpha power over posterior regions facilitate the perception of a cued target in the Posner paradigm (Busch, Dubois, & VanRullen, 2009).

Regarding the Cowan model, the alpha rhythm may act as an attentional gating mechanism on primary sensory areas, facilitating the promotion of relevant perceptual information (by reduced alpha activity), or by preventing novel sensory information to interfere with internal focus of attention (by increased alpha), for example, when items are

maintained in a WM task (Jensen & Tesche, 2002). Critically, when sensory information is promoted along the perceptual hierarchy, or maintained in WM, these perceptual processes are inextricably tied to their semantic interpretation, which is activated automatically. This is, within existing associative networks, sensory information is automatically interpreted in terms of its meaning. For example, one cannot look at a red car, without perceiving a red car. Thus, I assume that the alpha rhythm reflects the dynamic inhibition and recruitment of task relevant neuronal networks and thereby promotes the neuronal processing in semantic associative networks that underlie implicit as well as explicit cognitive processes. In the Cowan model this conceptual idea closely corresponds to activated LTM storage, the gray cloud in Figure 3A. Thus, the alpha rhythm may also gate automated, implicit neuronal processes and behavior without the explicit mental manipulation by central executive functions.

Noteworthy, Klimesch (2012) uses a very similar concept of the alpha rhythm, namely a continuous semantic interpretation of sensory inputs based on a 'knowledge system' in the wake human brain. Interestingly, he links the processing of perceptual information in semantic networks to an integrated information theory of consciousness (Tononi, 2008). Like in the framework suggested here, Klimesch separates the attentional processes in the alpha rhythm (suppressing task irrelevant neuronal processes) from attentional mechanisms reflected in the theta rhythm (the processing and monitoring of novel perceptual information). Similar to Jensen and Mascheri (2010) this would imply a rather unspecific cross-frequency interaction between alpha as a gating and gamma as a representation mechanism during mnemonic processes, namely a "positive correlation between gamma power in task-relevant regions and alpha power in task-irrelevant regions", but no specific coupling pattern.

In humans pacemakers of the alpha rhythm have been identified in thalamic nuclei, and within the parietal cortex (Roux, Wibral, Singer, Aru, & Uhlhaas, 2013). Source localization in the human EEG revealed alpha suppression in prefrontal and parietal cortical networks during successful encoding, which largely overlapped with the regions of theta and

gamma oscillations (Friese et al., 2013). Furthermore, episodic encoding is marked by a decrease in alpha oscillations in parietal and frontal networks, see Figure 2A. This is, desynchronized alpha power coincided with increased theta power during episodic encoding across several studies (Friese et al., 2013; Klimesch et al., 1997; Mölle, Marshall, Fehm, & Born, 2002). Likewise, alpha oscillations over parietal regions are closely associated with WM maintenance (Jensen & Tesche, 2002; Khader et al., 2010; Scheeringa et al., 2009), which likely index the inhibition of interfering sensory information during WM maintenance (Cooper et al., 2003). For a more comprehensive overview of the interplay of theta, alpha and gamma oscillation in WM processes, see (Roux & Uhlhaas, 2014).

In sum, the integrative framework proposed here, suggests distinct roles for the theta and the alpha rhythm. The alpha rhythm reflects the activation of associative, semantic networks and may thus mainly operate on slow adapting neuronal networks of the neocortex. These activated parts of the LTM storage can be involved in implicit and also in explicit processes. In contrast, the theta-gamma code reflects explicit control processes: The PFC sets the focus of attention on a subset of activated LTM representations and integrates them in existing representations of time and space in MTL networks, where novel memories are formed fast. Thereby neuronal oscillations steer the dialog between MTL and neocortical networks (see Buzsáki, 1996, for a similar proposal), as suggested by the dual memory systems account (Squire & Alvarez, 1995).

3.4. The findings of the dissertation in the light of the integrative framework

The findings of my dissertation are in strong support of the integrative framework proposed here. I could further specify the pivotal role of the theta rhythm and theta-gamma PAC for mnemonic encoding, as well as the less specific role of the alpha rhythm, being involved in perceptual, semantic processing. Furthermore, this dissertation contains two of the first studies that scrutinize the ontogenetic development of neuronal oscillatory dynamics underpinning memory formation.

The primacy role of the theta rhythm and theta-gamma PAC for memory

encoding. All four studies of this dissertation substantiate the distinct role of the theta rhythm for memory formation: In study 1, we found a clear SME in theta power and a somewhat weaker SME in gamma power, when assessed across all scalp electrodes. Like in former studies. Theta power during successful encoding peaked over prefrontal regions and we found a SME in fronto-parietal theta-gamma PAC for the successful associative encoding of pictorial memories. This supports the idea that frontal executive functions act on perceptually activated memory items, in order to bind them into novel memories. In study 3, we found that an intentional encoding instruction, namely the explicit task to remember pictorial stimuli and their perceptual details, increased theta power, compared to an incidental encoding condition. This effect was consistent in adults and two groups of school children, 7 and 10 years old, which substantiates the idea that the prefrontal theta rhythm is involved in explicit memory processes and the binding of associative features.

In both studies we found no evidence for an involvement of the alpha suppression in associative or intentional encoding. Based on this dissociation between the theta and the alpha rhythm, we visually entrained participants at an individual theta frequency (study 2), to experimentally enhance their memory performance, in contrast to a visually entrained alpha rhythm. Indeed, we could improve later memory performance for the theta, compared to the alpha stimulation, providing first causal evidence for the theta rhythm as an encoding mechanism in the human brain. Interestingly, at an individual level, we found an inverse SME in the theta rhythm, trials with lower theta SSVEP being associated with higher memory performance. However, we found a positive SME in theta-gamma PAC pattern, distributed across the scalp. This suggests that successful encoding may not depend on theta power *per se*, but that theta-gamma PAC is the specific mechanism of explicit encoding, likely reflecting the mental elaboration and binding of perceptual features (i.e., Memory items) during encoding.

Taken together there is now very good evidence, including the studies of this dissertation, that the prefrontal theta rhythm reflects executive control processes. These control processes sample, elaborate, and bind activated neuronal representations into novel memories, reflected in theta-coupled gamma oscillations.

The functional dissociation between the theta and the alpha rhythm. Former designs did not separate explicit memory processes from perceptual, semantic processes (Friese et al., 2013; Osipova et al., 2006), and latter may also contribute to later retrieval processes due to semantic priming effects. Both former studies found a contribution of increased theta power, as well as alpha suppression during encoding. Jet another study used a subsequent memory design with a semantic encoding task and a task that focused on perceptual features (Hanslmayr et al., 2009). Successful semantic encoding was associated with alpha suppression, while perceptual feature encoding was associated high theta power. The studies of my dissertation sharpen the differentiation between the theta and the alpha rhythm. In study 1 we dissociated mnemonic from perceptual processes (using pictures vs. words as stimuli). We did not identify any SME in the alpha suppression. However, alpha suppression was pronounced over posterior recording sites and sensitive to the stimulus material, being higher for perceptually rich (i.e., pictures), compared to perceptually poorer stimuli (i.e., words). At the same time we found higher gamma oscillations over parietal recording sites for pictures, compared to words. This is in support of the idea that alpha oscillations inhibit functionally irrelevant brain regions, and thereby gate perceptual processing. Furthermore, in study 3 alpha oscillations were insensitive to the encoding condition, namely an intentional versus incidental learning instruction. However, the alpha suppression effect increased with age, closely reassembling the age differences in reaction times in the semantic encoding task.

In both entrainment studies (study 2 and study 4), we used alpha oscillations as a control stimulation frequency. In adults (study 2) entrained alpha oscillations did not explain

memory differences between conditions (SME difference between theta versus alpha entrainment) and in the infant study (study 4) entrained alpha oscillations were insensitive to the outcome of the presented sequences (expected versus unexpected outcomes). Thus, both studies are in favor with a rather passive role of the alpha rhythm in memory encoding.

To conclude, the alpha rhythm likely reflects the activation of semantic, associative networks during encoding. This corresponds to the activated LTM items, the medium gray shaded region in Figure 2A. Still, implicitly processes may certainly contribute to mnemonic processes, and the mere activation of associative networks may strengthen the connections within these cell assemblies. Yet, alpha suppression facilitates explicit processes, which act on activated semantic networks from LTM. Thereby the present findings are in line with the conceptual idea of the Cowan model (Cowan, 1988), and contemporary theoretical accounts on the alpha rhythm (Jensen & Mazaheri, 2010; Klimesch, 2012)

The development of neuronal oscillatory dynamics underlying encoding in childhood and infancy. This dissertation includes two of the first studies, which investigate the neuronal oscillatory dynamics underlying encoding processes in early childhood and infancy. This is surprising due to the immense learning and developmental changes in brain anatomy in the first year of life. One major insight of these developmental studies was that the theta rhythm marks encoding processes in childhood and infancy already. In study 3, theta oscillations increased for intentionally, compared to incidentally, encoded stimuli, when perceptual features were relevant for later encoding. This effect was present in adults, as well as in 7 and 10 year olds. Strikingly, in study 4, using visual brain stimulation in 9-month-olds, we also found that entrained theta oscillations are sensitive to the encoding of unexpected events, which are hallmarks for infants learning processes. Thus, the theta rhythm seems to guide learning processes in the first year already, an age at which critical brain structures, associated with theta driven encoding processes, namely PFC and MTL networks, are still immature and learning processes cannot yet be tested explicitly.

Regarding the alpha rhythm, it was interesting that, in study 3, we found a developmental effect in stimulus related alpha suppression. Alpha suppression was rather weak in 7 year olds and increased with age. The duration of the alpha suppression, being prolonged in younger children, closely resembled the gradually slower reaction times for the response to the semantic encoding task (i.e., indoor versus outdoor) in the younger age groups. This fits nicely with the Cowan model (Cowan, 1988), as well as a recently proposed framework on infants' memory development (Ofen & Shing, 2013), namely that infants learning initially relies on more explicit processes and that their learning experiences gradually change the structure of the maturing memory system. This is, when children learn new details, with repeated presentations these details become integrated into decontextualized, semantic representations. In turn, their increasingly abstract and optimized representations (based on chunking processes) allow children to process novel stimuli more efficiently. This is, to interpret and integrate novel information based on increasingly differentiated associative networks. Given that the theta rhythm is present and sensitive to learning from very early in ontogeny, theta-gamma coupling may facilitate the gradual formation of the differentiated semantic networks by integrating novel information bit by bit into existing representations, at a theta pace. However, given the methodological challenges to assess gamma oscillations (Hassler et al., 2011; Yuval-Greenberg et al., 2008), specifically at a young age (Köster, 2016), it is highly challenging to assess these processes in developmental research.

The picture about the development of encoding mechanisms in the early childhood year is yet very incomplete. However, making first steps into this direction in this dissertation, revealed that neuronal oscillations are an intriguing research tool to investigate the development of cognitive processes and, vice versa, how the results from developmental cognitive neuroscience may inform our theoretical understanding about memory formation

processes and, possibly, the marked structural changes in the neuronal architecture throughout ontogeny.

3.5. Summary of the integrative framework

The central ideas of the integrative framework are summarized in Figure 5. When awake, the central nervous system continuously samples information from the environment (attentional selection), which is interpreted in the light of semantic knowledge (LTM in neocortical networks) and contextual information (associative networks in the MTL), to integrate them into existing representations (updating of MTL network). This real-time update of the brain networks accompanies the mental elaboration of perceptual information (working memory processes, problem solving) and serves the primary goal to guide behavior, in the light of the current context and goals.

This complex task requires a dynamic and selective recruitment of relevant brain networks (selective attention) and a precisely timed integration of novel information into existing networks (encoding). As outlined above, the promotion of perceptual information in sensory networks is reflected by the coherent firing of neurons at a gamma rhythm. Supposedly, the theta-gamma neuronal code implements a perceptual sampling loop that elaborates novel perceptual information based on existing representations and the present context (time and space), to integrate these information bit by bit, at a theta pace. Specifically, the PFC maintains and establishes novel associations between memory items (informational chunks) in the attentional focus. These items are reflected in gamma oscillations, nested in the theta phase and allow the integration of novel information at each theta cycle. Novel items might be semantic information in neocortical networks activated by perceptual information or PCF control processes, but may also be context information (recently established associations that constitute time and space) in MTL networks. The promotion of sensory information along the visual processing stream (e.g., from V1 to V4) is highly selective, dependent on the attentional focus, gated by the alpha rhythm.

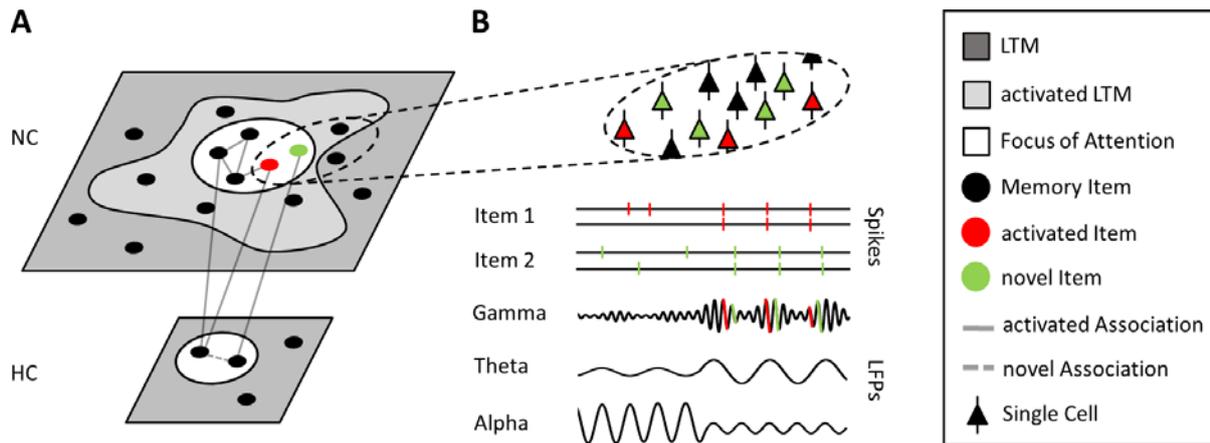


Figure 5. Brain rhythms implement mnemonic processes. (A) Novel items are integrated into an activated associative network by focused attention and mental elaboration of the novel item (white circles). The central executive (the PFC) controls attentional processes (not displayed here, see Figure 1A) acting on memory items (highly associated networks) within the neocortex (NC) and the medial temporal lobe (MTL), which stores and updates information of the present context. This is, like in the consolidation model (Squire & Alvarez, 1995), novel associations are initially formed within the MTL. (B) Activated memory items are distributed cell assemblies that synchronize their firing at a gamma rhythm (>30 Hz). Memory items are selected, maintained, and integrated at a theta (3-8 Hz) pace, squeezing real time events on a neuronal time scale. This acceleration of real time events serves long term potentiation processes in the MTL and the emulation of behavioral outcomes (e.g., a generative model, Friston, 2011). Alpha (8-14Hz) oscillations gate mnemonic processes in semantic networks by inhibiting task irrelevant networks.

The precisely timed interplay within neuronal networks promotes the flow of perceptual information from the environment, their processing in activated semantic networks (LTM) and a continuous update of internal representations in service of behavioral navigation. I posit that the phase-to-amplitude PAC between theta (3-8 Hz) and gamma (> 30 Hz) oscillations forms a mnemonic sampling and updating mechanism which controls the selection, manipulation, and integration of novel perceptual information within existing associative networks. Specifically, the theta-gamma code squeezes real time events onto a neuronal time scale and thereby solves two computational problems: First, speeding up real time events to facilitate long term potentiation processes in the MTL. Second, with regard to

its guiding function in behavior, speeding up real time events serves the emulation of generative models and advance ahead of real time to predict behavioral outcomes.

4. General Discussion

The integrative framework outlined here, like any theoretical framework, is far from complete. The empirical works, including those of my dissertation, each provide small pieces of a larger puzzle and, taken together, draw a rough picture, how memory formation processes may be implemented in the human brain. Thus, while some processes may be simplified and the empirical picture is certainly less consistent as presented here, I emphasized how neuronal oscillations may implement memory encoding processes on the neuroanatomic architecture, and thereby bridge the gap between psychological functions and neurophysiology. In the following I will outline some of the pieces of the puzzle which are still missing and thereby indicate directions for future research.

It is supposed here, that the alpha rhythm activates semantic networks, which are then recruited for explicit mnemonic processes by the theta rhythm. While this would require a neatly timed coordination of both rhythms in the prediction, selection and elaboration of novel sensory information, how these rhythms are coordinated and interplay with each other is largely unexplored. Yet another explanation for the co-occurrence of a reduced alpha and an increased theta power during encoding may be a shift in the operating rhythm, from alpha to theta, in utilized brain regions. This is, the activity may simply switch from an idyllic pace, the alpha rhythm, to a lower working pace, the theta rhythm, which indexes the utilization of neuronal networks in explicit processes. “Alpha suppression” may then simply be the byproduct of high alpha power in the idyllic state (i.e., default mode; Raichle, 2015) during the baseline condition. However, not all researchers may agree on the rather passive role of alpha oscillations for memory encoding.

Regarding the primacy role of the theta rhythm, there is also opposing evidence, indicating reduced theta activity during successful memory formation (Burke et al., 2013;

Greenberg, Burke, Haque, Kahana, & Zaghoul, 2015; Griffiths, Mazaheri, Debener, & Hanslmayr, 2016). Potential reasons for this divergence in results may be specificities of the task and the analysis strategy applied in the different studies. Another reason may be that not the theta power per se, but the theta phase (Clouter et al., 2017) or the theta-gamma PAC pattern is decisive for memory encoding (study 2). However, given the high consistency with which we found the prefrontal theta rhythm to increase with successful memory encoding (despite the inverse theta SME in the SSVEP study), the diverging findings may also result from a critical methodological difference: We adjusted frequency bands to the individual peak frequencies (Klimesch et al., 2001), which increases the signal to noise ratio drastically, but may also lead to very different results, compared to other studies, also because the definition and selection of the theta frequency (i.e., 3-8 Hz) vary largely across the literature.

Here, the theta rhythm is ascribed a prefrontal and medio-temporal control mechanism (Anderson, Rajagovindan, Ghacibeh, Meador, & Ding, 2010; Buzsáki, 1996), acting on perceptual information in a top-down manner. On the contrary, the finding that the visually entrained theta rhythm facilitates encoding by driving theta-gamma coupling processes, adds to recent evidence for a potential bottom-up function of the theta-gamma code in the visual cortical networks (Landau et al., 2015; Lowet, Roberts, Bosman, Fries, & de Weerd, 2016). Speculatively, as outlined above, the prefrontal and medio-temporal system, in concert with the oculomotor and the visual system may implement a mnemonic sampling loop. Novel perceptual information, reflected in gamma bursts, may be selected by frontally guided control processes and then sampled bit by bit, at a theta pace (Fries, 2015; VanRullen, 2016). For future research it would be intriguing to combine EEG (or MEG) measures during encoding with eye-tracking assessments to further scrutinize the interplay between the prefrontal theta phase, eye-movements and gamma bursts. This is, potentially, the front-parietal theta-gamma PAC observed here (study 2) and in a former study (Fries et al., 2013),

may be accompanied or even established by (micro-)saccadic eye-movements, linking attentional sampling to memory formation processes.

Memory representations change over time, in the process of consolidation. While discussed in detail elsewhere (Marshall & Born, 2007) there is good evidence that memories are reconsolidated by an internal replay and thereby transferred from context dependent MTL networks into semantic MTL networks (Deuker et al., 2013), with critical effects on memory representation (Moritz Köster, Finger, Kater, Schenk, & Gruber, 2017). Just to indicate one potential mechanism here, which is closely linked to the dual memory system account (Squire & Alvarez, 1995). One intriguing question related to this consolidation account is the change in memory representation over time. Which elements of a memory representation change in the process of consolidation, and which may remain constant over time? It would be intriguing to track the changes of representations of novel items over time. Presumably, they may initially be based on explicit processes, reflected in the theta pace, before they are gradually integrated into semantic networks, when their processing may mostly rely on alpha guided semantic processes.

Given that most studies assessing temporal neuronal dynamics are, due to the nature of the recording instruments, limited to a few, or at best a few hundred, sensors or recording sites and either focus on one, a macro-, meso-, or microroscopic scale. This limits the potential implications of each study and makes it also difficult to grasp the largescale dynamics underpinning memory formation. A promising approach would be the combination of methods, for example, supplementing intracranial MTL recordings from patients with scalp-recorded EEG data and possibly inform the analyses further by connectome data from fMRI scans.

It is a major challenge to assess the development of neuronal oscillations during memory formation. This is, from young children it is very hard to acquire sufficient noise free trials and get reliable measures of memory performance. Specifically, experimental designs,

which requiring explicit behavioral responses, are not yet applicable in the first years of life. As indicated by study 2 and study 3, SSVEPs may serve as an useful tool to test specific hypotheses about neuronal dynamics in the first years of life. In specific, SSVEP may be applied as a procedure for frequency tagging, separating the neuronal responses of simultaneously presented perceptual elements (Köster, Castel, Gruber, & Kärtner, 2017) or, as done here, to visually entrain brain oscillatory dynamics and experimentally test their involvement in specific perceptual or mnemonic processes (study 2 and study 4).

In the sense that “there is nothing more practical than a good theory” (Lewin, 1951, p. 169), the practical implications of the present work are manifold, adding critical empirical and theoretical aspects to our understanding of how brain oscillations may implement mnemonic processes in the human brain. As one major achievement of this dissertation, I would like to highlight the application of SSVEPs to visually entrain and experimentally manipulate neuronal oscillations, and thereby to experimentally test their functional relevance for cognitive processes. This is, with simple flickering visual stimuli I could entrain complex cognitive functions in the adult human brain (study 2) and pinpoint the relevant neuronal mechanisms for the encoding of unexpected events in the infant brain (study 4). Potential practical applications of sensory entrainment methods are innumerable. Most obviously, one could imagine learning material presented at a theta frequency to enhance learning processes. This may benefit from more subtle, less intrusive entrainment methods (e.g., varying the luminance of a visual stimulus), and by locking visually entrained stimuli more closely to ongoing neuronal activity. For example, one could link the pace and the phase of the stimulation to the ongoing theta processes via online, prefrontal EEG assessments. To indicate another intriguing way to practically apply SSVEPs, one may think of clinical diagnostic procedures. For example to diagnose early deficiencies in infants understanding physical laws and social behavior. Here SSVEPs may provide a much more robust tool to detect individual deficiencies at an early developmental age compared to eye tracking methods, which rarely

allow individual diagnoses. Thus, with my dissertation I hope to lay ground for the further investigation and possibly also the practical application of visual brain entrainment methods, to manipulate and enhance cognitive functions in the wake human brain.

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5. Empirical Studies: Full Articles

Excluded in the online version.

6. Declaration of Own Contribution (Eigenständigkeitserklärung)

Erklärung über die Eigenständigkeit der erbrachten wissenschaftlichen Leistung

Ich erkläre hiermit, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe der Quelle gekennzeichnet.

Bei der Auswahl und Auswertung folgenden Materials haben mir die nachstehend aufgeführten Personen in der jeweils beschriebenen Weise ~~entgeltlich~~/ unentgeltlich geholfen:

Studie 1

Köster, M.*, Finger, H.*, Graetz, S., Kater, M., & Gruber, T. (under review). Fronto-parietal theta-gamma coupling binds visual perceptual features in an associative memory task. *under review in Scientific Reports* (*shared first authors)

MK konzipierte, designte und implementierte die Studie. MK und MKa führten die Studie durch. Celia Post half bei der Datenerhebung. MK, HF und SG analysierten die Daten. HF führte die Wavelet-Analysen durch, MK und SG führten die Phasen-Amplituden-Kopplungsanalysen durch. TG stellte Stimulusmaterialien und Analysewerkzeuge zur Verfügung. MK und HF bereiteten die Graphen vor. MK schrieb den ersten Entwurf des Manuskripts. Alle Autoren haben das Manuskript überarbeitet.

Studie 2

Köster, M., Martens, U., & Gruber, T. (under review). Memory entrainment by visually evoked theta-gamma coupling. *under review in NeuroImage*

MK und UM hatten die Studienidee. MK, UM und TG designten die Studie. MK implementierte die Studie und führte die Studie durch. TG stellte Stimulusmaterialien und Analysewerkzeuge zur Verfügung. MK analysierte die Daten, beraten von TG. MK erstellte die Graphen und schrieb das Manuskript. MK und TG haben das Manuskript überarbeitet. Malte Wöstmann und Nikolai Axmacher haben eine frühere Version dieses Manuskripts kommentiert.

Studie 3

Köster, M., Haese, A., & Czernochowski, D. (2017). Neuronal oscillations reveal the processes underlying intentional compared to incidental learning in children and young adults. *PloS one*, 12(8), e0182540.

DC konzipierte und designte die Studie. AH führte die Studie durch. Julia Saße und Steffen Herff assistierten bei der EEG-Datenerhebung, Sofia Kermas und Julia Saße halfen bei der Reizvorbereitung. MK, AH und DC analysierten die Daten. MK führte die Wavelet-Analysen

durch und erstellte die Graphen. MK und DC schrieben den Originalentwurf und alle Autoren überarbeiteten das Manuskript. AH und DC verwalteten das Projekt und DC beaufsichtigte die Forschung.

Studie 4

Köster, M.*, Langeloh, M.*, & Höhl, S. (submitted). Infants encode unexpected events at the 4Hz theta rhythm. *submitted to Nature Communications* (*shared first authors)

MK und SH haben die Studie konzipiert. MK, ML und SH designten die Studie. MK und ML erstellten das Stimulusmaterial, zum Teil auf der Grundlage von Stimulusmaterial von Vincent M. Reid. Vincent M. Reid stellte auch EEG-Daten aus einer früheren Studie für die Voranalyse der Theta- und Alpha-Aktivität von Säuglingen zur Verfügung. ML führte die Studie durch. MK analysierte die Daten und bereitete die Graphen vor. MK, ML und SH haben das Manuskript geschrieben und überarbeitet.

Weitere Personen waren an der inhaltlichen materiellen Erstellung der vorliegenden Arbeit nicht beteiligt. Insbesondere habe ich hierfür nicht die entgeltliche Hilfe von Vermittlungs- bzw. Beratungsdiensten (Promotionsberater oder andere Personen) in Anspruch genommen. Niemand hat von mir unmittelbar oder mittelbar geldwerte Leistungen für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen.

Die Arbeit wurde bisher weder im In- noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

.....
(Ort, Datum)

.....
(Unterschrift)