



Review

Control mechanisms in working memory: A possible function of EEG theta oscillations

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ABSTRACT

Neural correlates of control mechanisms in human working memory are discussed at two levels in this review: (i) at 'item level', where in multi-item working memory information needs to be organized into sequential memory representations, and (ii) at a 'process level', indicating the integration and control of a variety of cognitive functions involved in working memory, independent of item representations *per se*. It will be discussed that at both levels electroencephalographic theta activity is responsible for control of working memory functions. On item level, exact phase coding, e.g., approached by coupling between theta and gamma oscillations or phase resetting of theta frequency, is suggested to integrate information into working memory representations. At process level interregional theta synchronization is discussed to integrate brain structures necessary for working memory. When discussing the specificity of theta activity for control of working memory processes it will be suggested that theta oscillations might play an important general integrative role in organization of brain activity. And as working memory often involves a variety of cognitive processes which need to be coordinated there is particular need for an integrative brain mechanism like theta activity as suggested in this review.

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1. Introduction

Working memory (WM) describes a cognitive system which allows for the transient (up to a few seconds) storage and utilization of information (Baddeley, 1992, 2000, 2001; Postle, 2006). A prominent model of WM assumes two storage sub-systems, one for verbal and one for visual material. These sub-systems are considered to be mastered by a central executive (Baddeley, 1992). The latter also coordinates mental operations (that can be performed

on the stored information) and represents an interface to long-term memory and an episodic buffer (Baddeley, 2000). Thus, a typical example for a WM process would be the transient retention of a five digit consonant string where in addition to maintenance alphabetical sequencing of the stored information is required. Therefore, in contrast to the concept of short-term memory, here in addition to information storage there are other cognitive processes involved, such as (i) sustained attention to the task, (ii) the resolving of the consonant string into single items, (iii) access to long-term memory (access to the alphabet), (iv) re-organization and integration of the consonant sequence following rules from long-term memory, (v) retention of the 'new', transformed memory content and (vi) suppression of the original letter string. Accordingly, we can

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investigate control mechanisms in working memory on two different levels: first, organization of single items into comprehensive memory representations, and secondly, coordination of cognitive sub-systems involved in a specific WM process. The aim of this review is to investigate the specific role of oscillatory brain activity at theta frequency (rhythmic activity around 5 Hz) for control mechanisms in WM on the aforementioned two levels.

2. EEG theta activity during higher cognitive processes

The function of rhythmical brain activity around 5 Hz is relatively well investigated in the rat brain. There is a long tradition of research associating so called theta activity with hippocampal place cell firing patterns (see for reviews Buzsáki, 2006; O'Keefe and Nadel, 1978; Redish, 1999). However, in humans theta activity is less well investigated (during the waking state). Only during the last 10–15 years there has been a stronger focus on human electroencephalographic (EEG) theta activity and its relevance in spatial navigation (Kahana et al., 1999; de Araújo et al., 2002), memory processes (Klimesch et al., 1994, 1996, 1997, 1999, 2001a, 2006; Doppelmayr et al., 1998, 2008; Kahana et al., 2001; Raghavachari et al., 2001, 2006; Jensen and Tesche, 2002; Caplan et al., 2003; Sederberg et al., 2003; Sauseng et al., 2004; Onton et al., 2005; Kahana, 2006; Osipova et al., 2006; Rizzuto et al., 2006) and attention (Pennekamp et al., 1994; Gevins et al., 1997; Gevins and Smith, 2000; Deiber et al., 2007; Sauseng et al., 2007; Green and McDonald, 2008). Memory-related theta activity is most consistently reported in regard to episodic long-term and working memory.

Episodic long-term memory describes a system where information that is bound with a specific learning context and personal experience is stored and controlled (see e.g., Schacter et al., 2000; Baddeley et al., 2002). It has been reported that during encoding of information into episodic long-term memory as well as during retrieval of information from episodic memory, cortical theta activity is increased (Klimesch et al., 1994, 1996, 2001a,b, 2006; Weiss and Rappelsberger, 2000; Sederberg et al., 2003; Summerfield and Mangels, 2005). In a remember-knowing paradigm Klimesch et al. (2001b) showed that items which were remembered elicited a prolonged theta response compared to items which could not be remembered but were only familiar. Very similar results were obtained by Summerfield and Mangels (2005), namely a longer sustained theta response in the EEG for items which could be retrieved from episodic memory including a context which was given during encoding of the item compared with a short theta response to items with which the encoding context could not be retrieved. In a study by Klimesch et al. (2006) subjects had to rate the confidence with which they believed a certain item had previously been presented during a study phase. This confidence rating (which can be seen as a marker of episodic memory trace strength) was associated with dorsolateral-prefrontal and superior parietal theta activity.

Consistently, theta activity has also been reported to play a major role in working memory functions (e.g., Gevins et al., 1997; Sarnthein et al., 1998; Gevins and Smith, 2000; Sammer et al., 2007 and the literature reviewed below). In particular during encoding and retention of information increased amplitude of theta activity has been obtained. Raghavachari et al. (2001) demonstrated a strong increase of cortical theta activity in humans during the encoding of verbal information in a Sternberg-like working memory task. This increased theta activity sustained during a retention period until information had to be retrieved. The authors argued that theta reflected a gating mechanism controlling WM task-relevant and suppressing task-irrelevant information processing. Similar results were also found in the scalp EEG (Klimesch et al., 1999; Jensen and Tesche, 2002). Additionally, working

memory-load-dependent increase of (frontal) EEG theta activity has been suggested, i.e., with increasing amount of encoded information theta activity grows stronger (Jensen and Tesche, 2002). Not only local (mainly prefrontal) theta activity but also distributed theta networks are involved in working memory processes (see below). In general, it is of certain interest that despite the large heterogeneity of working memory processes (i.e., verbal versus visuospatial information and the large number of different operations that are run with information in working memory) involvement of EEG theta activity is still a relatively consistent finding. The question however is, (i) whether theta activity could be a correlate of control processes in WM, and if so, (ii) how specific is this relation?

3. Organizing single item representations into WM traces: theta phase coding in WM

When multiple items have to be held in WM it remains unclear how the brain manages to integrate or bind these item representations to a comprehensive memory entry. However, if we consider the example for a typical WM task from the introduction or think of a telephone number we transiently have to keep in mind, the exact position of single digits within a sequence of items is of major importance. There is a theoretical model highlighting the function of theta oscillations for multi-item WM storage. This model, originally put forward by Lisman and Idiart (1995) is based on the idea that individual items which should be held in WM are represented by single gamma periods. These gamma cycles are nested into a theta period. The phase relation between gamma and theta can then code the sequence of items. This is similar to phase coding during spatial navigation where a relation between firing of hippocampal place cells and hippocampal theta phase can be obtained (O'Keefe and Recce, 1993; Skaggs et al., 1996; Redish, 1999; Buzsáki, 2006; Pastalkova et al., 2008). Due to the oscillatory nature of the nesting of frequencies item representations will be sustained for seconds. Indeed, recent evidence suggests that theta phase to gamma amplitude coupling is obtained in human working memory processes (Canolty et al., 2006).

Based on Lisman and Idiart's idea of gamma oscillations nested into theta cycles Jensen and Lisman (1998) developed a computational model of short-term memory storage. One central idea in their model is that the number of items stored and therefore the number of gamma cycles nested into theta will affect the length of a theta period. This can come from a slowing of theta frequency with increasing number of items stored in memory or can be approached by phase resetting of theta always after the last nested gamma cycle. However, in any case it would be the theta frequency (or more precisely phase) that would bind multiple items together. Indeed, recently presented data by Axmacher et al. (2009c) are the first to show a slowing of theta frequency into which beta/gamma activity is nested as a function of WM-load in humans. They recorded hippocampal activity in epileptic patients who performed a Sternberg-like face memory task. The exciting results that were obtained demonstrate that by increasing the number of faces that had to be transiently maintained theta frequency to which high beta/slow gamma amplitude was coupled became slower. But there is also evidence that theta to gamma phase coupling can be approached by phase resetting of theta frequency (Givens, 1996; Tesche and Karhu, 2000; Williams and Givens, 2003; Mormann et al., 2005; Sauseng and Klimesch, 2008; Sauseng et al., 2008). Similar to Axmacher et al., a recent study reports sustained theta to gamma phase coupling during multi-item WM retention (Sauseng et al., 2009b). During an EEG experiment healthy human subjects performed in a visuospatial WM task in which the colors of squares presented in the previously

cued visual hemifield had to be retained for a short period of time (see Fig. 1a). By sorting instantaneous gamma amplitude according to simultaneous theta phase gamma amplitude bursts locked to the negative peak of theta oscillations were obtained during the retention period (Fig. 1b). This theta phase to gamma amplitude coupling, however, was not specific for brain areas processing targets but was found for all posterior recording sites (Fig. 1b). Additionally, this parameter did not exhibit any memory-load-dependent increase. When, in contrast, gamma phase was sorted according to theta phase, reflecting a measure of cross-frequency coupling with very high temporal precision, there was stronger theta:gamma coupling at posterior sites processing targets (contralateral to cued visual field). This lateralized theta:gamma phase coupling showed a WM-load-dependent increase up to a load of 4 (Fig. 1c), where memory capacity limit is usually reached (Cowan, 2001). The slope of memory-load-dependent increase of theta:gamma phase coupling was predictive for individual WM capacity (Fig. 1d), well in line with Jensen and Lisman (2001). In contrast to alpha amplitude for which Sauseng et al. (2009b) demonstrated that it was related to suppression of distracting information, highly specific theta to gamma phase coupling is suggested to reflect WM retention *per se*. The fact that lateralized theta:gamma phase coupling was decreased for memory arrays containing a number of items beyond memory capacity limits (see Fig. 1c, memory load 6) underpins this very precise nesting of gamma cycles into theta frequency in the human EEG to be in accordance with the concept of phase coding as we also know it from place cells in the hippocampus (O'Keefe and Recce, 1993; Skaggs et al., 1996; Redish, 1999; Jensen, 2005; Buzsáki, 2006; Pastalkova et al., 2008).

For the retention of sequentially presented multiple item information it is comprehensive that theta:gamma phase coding

could organize this information in order to maintain a temporal structure of the memory trace. This is, however, more difficult to follow when visuospatial information consisting of multiple simultaneously presented items has to be processed in WM. Zimmer (2008) suggested that in visuospatial WM objects always have to be bound with their spatial location. Therefore, with simultaneously presented visual information, such as in Sauseng et al. (2009b), it is plausible that theta to gamma phase coupling is responsible for organizing multiple items into a kind of 'spatial sequence' instead of a temporal one.

According to Jensen and Lisman's model (Jensen and Lisman, 1996, 1998; Jensen, 2006) the exact phase relation of single gamma cycles and theta is of great importance during the retrieval of information from short-term memory. Therefore, theta:gamma phase coupling should also be found during WM retrieval processes in the human EEG. There is recent evidence that memory matching in a visuospatial task is reflected by transient synchronization between theta and gamma phase in posterior brain areas (Sauseng et al., 2008). A Posner task in which a central cue indicated the visual hemifield where a peripheral target was presented with 80% validity was run. For the subjects the task was to decide whether the target was a large or a short vertical bar. Prior to the experiment participants were trained to dissociate long from short bars. This means that they learned to keep a template of the two kinds of targets in memory to be able to compare them with the presented stimuli in the experiment thereafter. A cascade of brain processes involving EEG theta activity was obtained prior and during the matching process (Fig. 2). (i) Shortly before target presentation as well as during the first few hundred milliseconds after target onset increased interregional synchronization in a large, distributed network was obtained at theta frequency compared to a reference interval. This pattern was interpreted

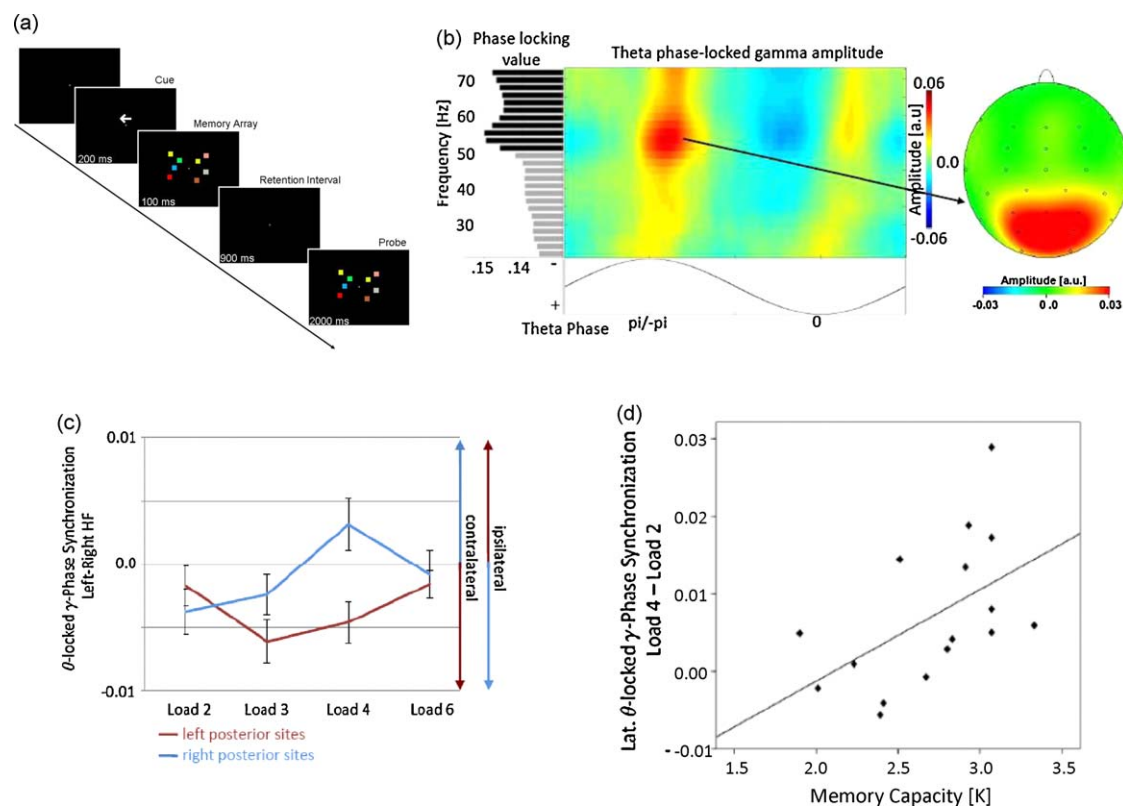


Fig. 1. Theta:gamma phase coupling coding multi-item WM representations. In a visuospatial working memory task colors of squares from a previously cued visual hemifield had to be retained (a). During the retention period gamma amplitude bursts were phase locked to negative peaks of theta frequency at posterior recording sites (b). Theta phase to gamma phase coupling was increased always at posterior electrode sites contralateral to the cued visual hemifield, thus, at sites where targets were stored. This lateralized cross-frequency phase coupling exhibited a WM-load-dependent increase (c) and predicted individual WM capacity (d). Adopted from Sauseng et al. (2009b).

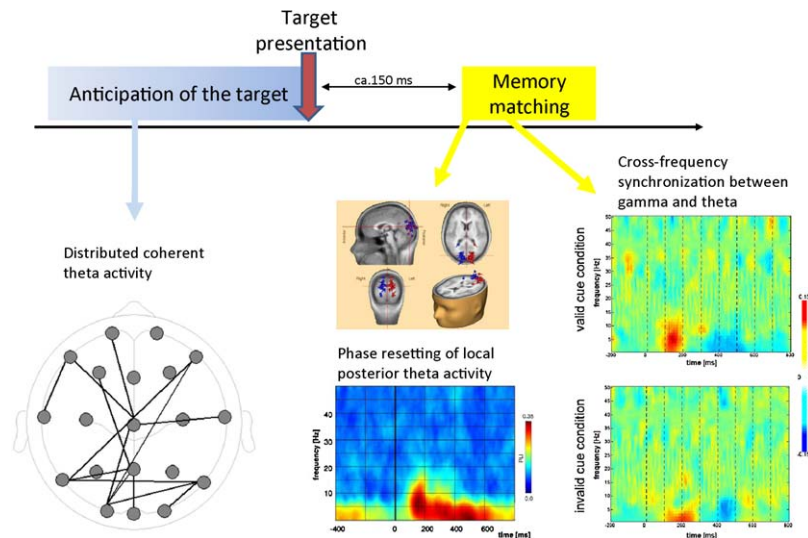


Fig. 2. A model on matching of information activated in working memory and visual bottom-up input based on evidence by Sauseng et al. (2008). In an interval prior to target presentation information from episodic memory is reactivated and held in working memory. This top-down memory trace is reflected by distributed coherent theta activity in a fronto-centro-posterior network. Around 100 ms after target presentation a reset of ongoing phase at local parieto-occipital sources can be seen. This phase reset enables the synchronization with local gamma activity reflecting the visual processing of sensory input. In a time window between 100 and 200 ms after target onset theta:gamma phase synchronization is exhibited at parieto-occipital sources reflecting the actual matching process, i.e., the binding between top-down memory information and bottom-up visual input. This mechanism is increased by attention.

as reflecting top-down working memory activity – with prefrontal areas providing a ‘mental template’ of the target for visual brain areas. (ii) Shortly after target onset local theta activity in posterior parietal/parieto-occipital brain areas exhibited a phase reset (increased phase stability over trials). No such effect was found in the high frequencies, such as gamma. With theta phase modulation low frequencies adapted to gamma activity, leading to (iii) increased cross-frequency phase synchronization between theta and gamma activity. Coupling between theta and gamma phase was stronger when the target was attended. This well resembles the idea that memory matching is increased when supported by attention (Herrmann et al., 2004). The finding that there is increased theta:gamma phase synchronization shortly after target presentation suggests that bottom-up sensory information provided by local posterior gamma oscillations is temporarily organized into an existing top-down memory representation. Phase coding is used to match retained with new sensory information, and theta oscillations seem to be responsible for the integration of top-down and bottom-up information. However, the task used by Sauseng et al. (2008) is no WM task in a strict sense. So the critical question arises whether in a classical WM task such as a delayed match-to-sample task similar results would be obtained. In a still unpublished work Holz et al. (submitted for publication) ran a visuospatial Sternberg-like task in which healthy subjects had to encode and retain spatial locations within a matrix presented on a computer screen. Then volunteers had to compare the retained positions to locations highlighted in a probe matrix. The retained and probed locations matched in 50% of trials. Holz et al. then investigated theta–gamma cross-frequency phase synchronization in response to probe item presentation and found that, in agreement to Sauseng et al. (2008), stronger theta–gamma phase synchronization was obtained for congruent than for incongruent trials. This effect occurred over right posterior parietal/occipital electrode sites, well in line with the view that holistic visual processing as one would expect in memory matching processes should be reflected by right hemispheric activation (Marsolek et al., 1996; Volberg and Hübner, 2007). These findings suggest that the mechanism of matching between top-down and bottom-up visual information as described

by Sauseng et al. (2008) is indeed relevant for integrative processes in WM.

As discussed above, in principle there are two mechanisms by which theta frequency can adapt in order to establish interaction to other frequencies: slowing of frequency or phase resetting. There are a number of reports about phase resetting of theta oscillations in humans during retrieval processes in WM. In a magnetoencephalographic study Tesche and Karhu (2000) obtained evoked theta oscillations from the human hippocampus during the retrieval phase in a verbal working memory task. The number of theta cycles in response to a probe item in a Sternberg task increased proportionally to the number of items in the memory set. This suggests that more pronounced retrieval attempts increase the duration of phase-locked theta activity. Evidence that a resetting of theta oscillations might provide a time window in which other frequency bands can easily couple with theta also comes from Gruber et al. (2005) and Mormann et al. (2005). They could show that a simultaneous phase resetting of theta, alpha and beta frequency can be observed during an early time window of the retrieval phase in visual WM tasks. This also suggests theta phase is not only important for phase coding in respect of an interaction with gamma oscillations, but in addition coupling between theta and other slow frequency bands seems to be of importance during WM retrieval. The question arises, however, what the exact function of theta is during WM retrieval, and how exactly phase coding can be achieved. A model by Hasselmo et al. (2002) offers a possible account. Instantaneous phase of theta is considered as a mechanism to segregate encoding and retrieval processes from each other. It is suggested that memory encoding is mainly possible during time windows in which EEG theta exhibits a theta trough. This enables strong entorhinal input into CA3 neurons of the hippocampus. If, however, EEG theta exhibits a peak there will be weak entorhinal input into the hippocampus but strong CA3 input into the entorhinal cortex. Therefore, retrieval processes will preferably occur at intervals exhibiting EEG theta peaks. Using intracranial EEG recordings in humans Rizzuto et al. (2006) obtained results in favor of this model. In a verbal Sternberg-task the authors could show that theta oscillations showed a phase difference of 180° between encoding and retrieval.

All the aforementioned studies provide good evidence that theta is important for phase coding of information in working memory. Theta organizes multiple items into comprehensive memory traces, mainly by integrating multiple cycles of higher frequency oscillations. And theta provides an ambiance, by e.g., controlling activity of neural populations, which enables efficient encoding and retrieval of information into/from WM.

4. Theta and integration of cognitive sub-processes in WM

As outlined in the introduction WM subsumes a large number of cognitive processes: information encoding, storage and retrieval, attentional control, mental manipulation, interfacing with long-term memory, sensory information processing, multi-modal integration, etc. These functions are represented by different neural correlates involving different brain areas which need to be coordinated in order to monitor and control complex WM tasks. In the following section theta oscillations are proposed as a mechanism for this kind of integration in WM.

According to [Baddeley \(1992\)](#) verbal and visuospatial WM involve two different, independent storage systems implemented in two different cortical networks. [Wu et al. \(2007\)](#) ran an EEG study in which healthy subjects either had to retain only verbal or visuospatial information, or participants had to bind material from both modalities. When the separate condition was compared with the binding condition stronger theta amplitude at bilateral dorsolateral prefrontal recording sites was obtained in the condition requiring binding of verbal and visuospatial material. In addition, stronger interregional phase coherence at theta frequency between frontal sites and between left frontal and right temporal sites was observed. These results are in line with the idea that theta is important for the integration of features to complex memory traces as suggested in the previous section. But even more important, they also are in accordance with the argument that particularly interregional theta synchronization is relevant for the co-activation of cortical networks involved in different sub-processes of complex WM functions. Synchronous theta activity between prefrontal and temporo-parietal recording sites during WM retention of verbal and visuospatial material was also described by [Sarnthein et al. \(1998\)](#). The authors obtained prefrontal to left temporo-parietal theta coupling particularly for retention of verbal information, whereas there was increased fronto-temporal connectivity in the right hemisphere during maintenance of visuospatial material. Similar findings were reported also during encoding and retrieval processes ([Sauseng et al., 2004](#)). The aforementioned evidence suggests that a prefrontal supervisory attention system (or central executive) accesses posterior, modality-specific storage sub-systems, and that this is approached by interregional theta phase coherence. Moreover, it is suggested that such WM related interregional theta coupling is initiated by the frontal cortex, and theta activity in posterior regions is trailing prefrontal sites ([Sauseng et al., 2004](#)).

A fronto-parietal theta network has also been suggested as important in a mental arithmetical task ([Mizuhara and Yamaguchi, 2007](#)). Backwards counting at larger steps needs the combination of mental manipulation of verbal material, continuous updating of a WM store and the transient storage of partial arithmetic results. Mizuhara and Yamaguchi obtained increased phase coherence at theta frequency between bilateral prefrontal sites, left prefrontal to right parietal and right prefrontal to left centro-parietal leads during backwards counting compared to rest. In good agreement with these findings and using an EEG-constraint fMRI analysis [Sammer et al. \(2007\)](#) obtained an EEG-theta network comprising frontal and cingulate cortex, superior parietal and superior temporal areas, hippocampus and insular cortex during a mental

arithmetic task. A fronto-parietal network was also described by [Sauseng et al. \(2005b\)](#) in a visual task requiring mental comparison of abstract visual shapes. The authors argued that interregional theta activity is associated with central executive functions mastering a variety of WM sub-components (see also [Sauseng and Klimesch, 2008](#)). There is further evidence that frontal and fronto-parietal theta connectivity reflects central executive functions ([Sauseng et al., 2006](#); [Hanslmayr et al., 2008](#)).

A good example for theta being involved in coordination of task-relevant brain areas, but also for theta as mechanism providing phase coding in WM, has recently been given by [Griesmayr et al. \(in press\)](#). A verbal delayed match-to-sample task with a simple retention condition ('retention') and a condition requiring alphabetizing of the encoded material ('manipulation') in the delay period was run. Local theta activity at frontal sites was increased during the manipulation condition compared to pure retention ([Fig. 3a](#)). Interestingly, however, frontal and left parietal gamma activity was phase-coupled to this frontal midline theta activity ([Fig. 3b](#)), topographically well in line with the idea of a frontal to left parietal network in verbal WM. Interregional theta:gamma phase coupling occurred only in the negative slope preceding a theta peak. Most stunning was that interregional theta to gamma phase coupling was higher in the manipulation condition than retention ([Fig. 3c](#)). These findings indicate that complex WM processes involving a variety of cognitive functions implemented at several brain areas which need to be integrated are not only reflected by interregional theta synchronization but can also be mastered by interregional coupling of theta and higher frequencies. In addition, the study suggests that when letter strings are alphabetized they need to get organized as a new sequence of letters, and as already outlined in a previous section, this seems to be established by phase-specific coupling of theta and gamma oscillations, which can occur at a local but also at an interregional scale as shown here.

5. Conclusion: what is the function of theta oscillations during binding in WM? And how specific is this relation?

To summarize the aforementioned potential functions of theta oscillations in WM, it is very likely that

- (i) Local theta activity is increased during WM processes as a gating mechanism, providing optimal neural ambiance for specific processing.
- (ii) Local instantaneous theta phase defines time windows optimal for encoding or retrieval of information in WM.
- (iii) Higher frequency oscillations can be nested into theta cycles. This seems to reflect organization of multiple items into sequential WM representations or integration between sensory bottom-up and top-down memory representations.
- (iv) Interregional synchronization of theta oscillations connects neural structures representing sub-functions of WM processes.

There remains, however, an important question: is theta specific for WM processes, or is control of WM also associated with activity at other frequency bands? Although there is large coherence in most of the literature there is also some evidence that central executive functions, interaction between memory systems or interaction between working memory and sensory processing could be reflected at other frequency bands. For instance, alpha oscillations have been associated with top-down functions ([Von Stein et al., 2000](#); [Sauseng et al., 2005a,c](#); [Klimesch et al., 2007](#); [Palva and Palva, 2007](#)). However, alpha seems mainly to be associated with top-down processing in visual attention ([Von Stein et al., 2000](#); [Sauseng et al., 2005c](#)) and perception or semantic categorization (e.g., [Freunberger et al., 2008](#)). On the other hand, in

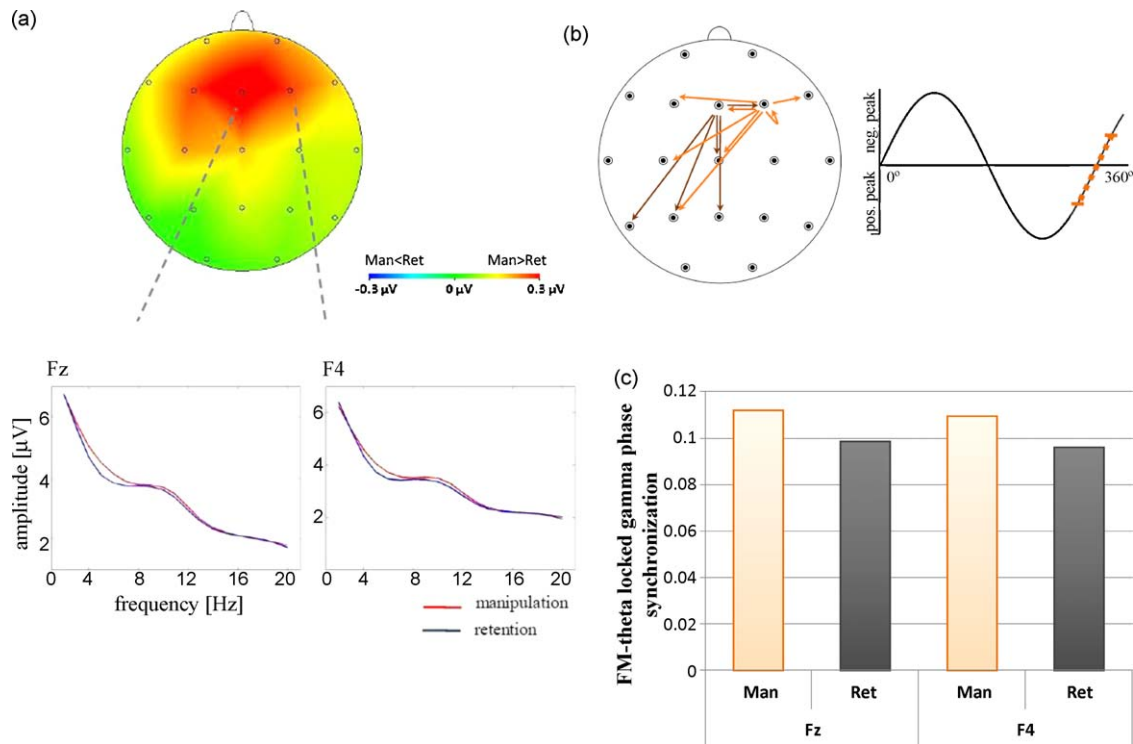


Fig. 3. Interregional theta:gamma phase coupling during alphabetizing of retained verbal material. During manipulation of verbal material in WM stronger frontal midline theta activity is obtained than during sole retention (a). Phase-locked to the negative slope preceding theta peaks enhanced phase coupling between frontal theta and frontal as well as left parietal gamma activity is obtained (b) in the manipulation condition compared to pure retention (c). This suggests that interregional theta:gamma coupling binds central executive with verbal storage functions and binds single verbal items into new, rearranged letter strings (adopted from Griesmayr et al., in press).

a classical visuospatial working memory experiment Sauseng et al. (2005a) obtained fronto-occipital coupling at upper alpha frequency. And recently, specific WM encoding was associated with evoked alpha activity (Freunberger et al., 2009). There are further examples of increased alpha amplitude mainly during retention of visual or verbal material in WM (Jensen et al., 2002; Busch and Herrmann, 2003; Jokisch and Jensen, 2007). However, in contrast to theta activity and as suggested by Klimesch et al. (2007) EEG alpha amplitude seems to reflect inhibitory activity (see also Romei et al., 2008a,b; Sauseng et al., 2009a; Thut, 2009), and therefore it seems plausible that increased local alpha amplitude is associated with preventing information uptake during WM retention rather than control and organization of the WM specific processes.

Even more critical is the question whether theta is specifically involved in control processes of WM or also control within other cognitive systems. As initially outlined, in general theta activity is also associated with attentional processing, spatial navigation and (episodic) long-term memory processes. In particular, for episodic memory theta has also been suggested to play a key role in binding. In this issue Nyhus and Curran (in press) argue that cross-frequency interaction between theta and gamma fulfills a very similar function in episodic memory as suggested for WM in this current article. Although there is some overlap between episodic and working memory it appears plausible that theta is of relevance for control processes in general and not necessarily specific for any certain cognitive system. More specifically, in this review article the role of theta–gamma cross-frequency interaction is highlighted for organization of WM contents. There are, however, reports that interaction between these two frequencies can be found in a very broad range of cognitive tasks (Canolty et al., 2006). Even more critical, it has been suggested by Lakatos et al. (2005) that a phase-amplitude relation of theta and gamma activity can also be found during rest without any WM involvement. And they further could show that this interaction between theta and gamma is only

a part of a hierarchical organization of oscillatory brain activity with delta phase influencing theta and gamma amplitude (see also Bruns and Eckhorn, 2004), theta phase having impact on gamma amplitude and multi-unit activity, and gamma phase and multi-unit activity being associated. This suggests that cross-frequency coupling might be a general mechanism of how cortical processing is organized. Due to this fact a particular relevance for WM processes might be given considering the fact that WM involves a broad range of sub-functions needed to be coordinated.

Summarizing, it can be concluded that theta activity is relatively specific for control in working memory (with the exception that some findings pointing to these functions are also represented by alpha or delta oscillations – frequency bands adjacent to theta), but it is not necessarily the case that control of WM is specific for theta activity. Instead theta seems to reflect a more general brain integrative mechanism which by this definition is also of great importance in working memory. An important question remaining is why it is theta frequency which seems to be so important for executive functions in WM. Von Stein and Sarnthein (2000) argue that the frequency relevant for a specific cognitive process is determined by the size of its cortical networks on which the cognitive function relies on. The more distributed the network the slower its underlying brain oscillation. In most complex WM processes a fronto-parietal cortical network seems to be involved. Therefore, one hypothesis would be that the resonance frequency of such a network is within the theta range. Another hypothesis would be that an interaction between prefrontal and hippocampal structures (Siapas et al., 2005) is the reason why the dominant brain oscillations from the hippocampal formation – namely theta frequency – could be also used as the most relevant frequency within fronto-parietal WM related networks. This is underpinned by recent research suggesting involvement of the medial temporal lobe and the hippocampal formation in WM processes (e.g., Axmacher et al.,

2008, 2009a,b,d). However, the exact physiological basis of control functions in working memory is not completely clear yet and will therefore need further research.

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References

- Axmacher, N., Elger, C.E., Fell, J., 2009a. Working memory-related hippocampal deactivation interferes with long-term memory formation. *Journal of Neuroscience* 29, 1052–1060.
- Axmacher, N., Haupt, S., Cohen, M.X., Elger, C.E., Fell, J., 2009b. Interference of working memory-load with long-term memory formation. *European Journal of Neuroscience* 29, 1501–1513.
- Axmacher, N., Henseler, M., Jensen, O., Weinreich, I., 2009c. Interaktion von theta- und gamma-band aktivität bei der aufrechterhaltung mehrerer items im arbeitsgedächtnis [Interaction of theta and gamma band activity during retention of multiple items in working memory]. In: Eder, A.B., Rothermund, K., Schweinberger, S.R., Steffens, M.C., Wiese, H. (Eds.), *Proceedings of the 51st TeP. Friedrich-Schiller University, Jena, Jena*, p. 45.
- Axmacher, N., Henseler, M., Schmitz, D., Cohen, M., Elger, C., Fell, J., 2009d. Working memory processes in the medial temporal lobe. *Epilepsia* 50, 53.
- Axmacher, N., Schmitz, D.P., Wagner, T., Elger, C.E., Fell, J., 2008. Interactions between medial temporal lobe, prefrontal cortex, and inferior temporal regions during visual working memory: a combined intracranial EEG and functional magnetic resonance imaging study. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 28, 7304–7312.
- Baddeley, A., 1992. Working memory. *Science* 255, 556–559.
- Baddeley, A., 2000. The episodic buffer: a new component of working memory? *Trends in Cognitive Sciences* 4, 417–423.
- Baddeley, A., 2001. Is working memory still working? *American Psychologist* 56, 851–864.
- Baddeley, A., Conway, M., Aggleton, J. (Eds.), 2002. *Episodic Memory: New Directions in Research*. Oxford University Press, Oxford.
- Bruns, A., Eckhorn, R., 2004. Task-related coupling from high- to low-frequency signals among visual cortical areas in human sub-dural recordings. *International Journal of Psychophysiology* 51, 97–116.
- Busch, N.A., Herrmann, C.S., 2003. Object-load and feature-load modulate EEG in a short-term memory task. *NeuroReport* 14, 1721–1724.
- Buzsáki, G., 2006. *Rhythms of the Brain*. Oxford University Press, Oxford.
- Canolty, R.T., Edwards, E., Dalal, S.S., Soltani, M., Nagarajan, S.S., Kirsch, H.E., Berger, M.S., Barbare, N.M., Knight, R.T., 2006. High gamma power is phase-locked to theta oscillations in human neocortex. *Science* 313, 1626–1628.
- Caplan, J.B., Madsen, J.R., Schulze-Bonhage, A., Aschenbrenner-Scheibe, R., Newman, E.L., Kahana, M.J., 2003. Human alpha oscillations related to sensorimotor integration and spatial learning. *Journal of Neuroscience* 23, 4726–4736.
- Cowan, N., 2001. The magical number 4 in short-term memory: a reconsideration of mental storage capacity. *Behavioral and Brain Sciences* 24, 87–114.
- de Araújo, D.B., Baffa, O., Wakai, R.T., 2002. Theta oscillations and human navigation: a magnetoencephalography study. *Journal of Cognitive Neuroscience* 14, 70–78.
- Deiber, M.P., Missonnier, P., Bertrand, O., Gold, G., Fazio-Costa, L., Ibanez, V., Giannakopoulos, P., 2007. Distinction between perceptual and attentional processing in working memory tasks: a study of phase-locked and induced oscillatory brain dynamics. *Journal of Cognitive Neuroscience* 19, 158–172.
- Doppelmayr, M., Finkenzeller, T., Sauseng, P., 2008. Frontal midline theta in the pre-shot phase of rifle shooting: differences between experts and novices. *Neuropsychologia* 46, 1463–1467.
- Doppelmayr, M., Klimesch, W., Schwaiger, J., Auinger, P., Winkler, T., 1998. Theta synchronization in the human EEG and episodic retrieval. *Neuroscience Letters* 257, 41–44.
- Freunberger, R., Fellinger, R., Sauseng, P., Gruber, W., Klimesch, W., 2009. Dissociation between phase-locked and nonphase-locked alpha oscillations in a working memory task. *Human Brain Mapping* 30, 3417–3425.
- Freunberger, R., Klimesch, W., Griesmayr, B., Sauseng, P., Gruber, W., 2008. Alpha phase coupling reflects object recognition. *NeuroImage* 42, 928–935.
- Gevens, A., Smith, M.E., 2000. Neurophysiological measures of working memory and individual differences in cognitive ability and cognitive style. *Cerebral Cortex* 10, 829–839.
- Gevens, A., Smith, M.E., McEvoy, L., Yu, D., 1997. High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice. *Cerebral Cortex* 7, 374–385.
- Gevens, B., 1996. Stimulus-evoked resetting of the dentate theta rhythm: relation to working memory. *NeuroReport* 8, 159–163.
- Green, J.J., McDonald, J.J., 2008. Electrical neuroimaging reveals timing of attentional control activity in human brain. *PLoS Biology* 6, 730–738.
- Griesmayr, B., Gruber, W., Klimesch, W., Sauseng, P., in press. Human frontal midline theta and its synchronization to gamma during a verbal delayed match-to-sample task. *Neurobiology of Learning and Memory*.
- Gruber, W.R., Klimesch, W., Sauseng, P., Doppelmayr, M., 2005. Alpha phase synchronization predicts P1 and N1 latency and amplitude size. *Cerebral Cortex* 15, 371–377.
- Hanslmayr, S., Pastötter, B., Bäuml, K.H., Gruber, S., Wimber, M., Klimesch, W., 2008. The electrophysiological dynamics of interference during the Stroop task. *Journal of Cognitive Neuroscience* 20, 215–225.
- Hasselmo, M.E., Bodelón, C., Wyble, B.P., 2002. A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning. *Neural Computation* 14, 793–817.
- Herrmann, C.S., Munk, M.H., Engel, A.K., 2004. Cognitive functions of gamma-band activity: memory match and utilization. *Trends in Cognitive Sciences* 8, 347–355.
- Holz, E.M., Glennon, M., Prendergast, K., Sauseng, P., submitted for publication. Theta:gamma phase synchronization during memory matching in visual working memory. *NeuroImage*.
- Jensen, O., 2005. Reading the hippocampal code by theta phase-locking. *Trends in Cognitive Sciences* 9, 551–553.
- Jensen, O., 2006. Maintenance of multiple working memory items by temporal segmentation. *Neuroscience* 139, 237–249.
- Jensen, O., Gelfand, J., Kounios, J., Lisman, J.E., 2002. Oscillations in the alpha band (9–12 Hz) increase with memory load during retention in a short-term memory task. *Cerebral Cortex* 12, 877–882.
- Jensen, O., Lisman, J.E., 1996. Novel lists of 7 ± 2 known items can be reliably stored in an oscillatory short-term memory network: interaction with long-term memory. *Learning Memory* 3, 257–263.
- Jensen, O., Lisman, J.E., 1998. An oscillatory short-term memory buffer model can account for data on the Sternberg task. *Journal of Neuroscience* 18, 10688–10699.
- Jensen, O., Lisman, J.E., 2001. Dual oscillations as the physiological basis for capacity limits. *Behavioral and Brain Sciences* 24, 126.
- Jensen, O., Tesche, C.D., 2002. Frontal theta activity in humans increases with memory load in a working memory task. *European Journal of Neuroscience* 15, 1395–1399.
- Jokisch, D., Jensen, O., 2007. Modulation of gamma and alpha activity during a working memory task engaging the dorsal or ventral stream. *Journal of Neuroscience* 27, 3244–3251.
- Kahana, M.J., 2006. The cognitive correlates of human brain oscillations. *Journal of Neuroscience* 26, 1669–1672.
- Kahana, M.J., Sekuler, R., Caplan, J.B., Kirschen, M., Madsen, J.R., 1999. Human theta oscillations exhibit task dependence during virtual maze navigation. *Nature* 399, 781–784.
- Kahana, M.J., Seelig, D., Madsen, J.R., 2001. Theta returns. *Current Opinion in Neurobiology* 11, 739–744.
- Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T., 1996. Theta band power in the human scalp EEG and the encoding of new information. *NeuroReport* 7, 1235–1240.
- Klimesch, W., Doppelmayr, M., Schwaiger, J., Auinger, P., Winkler, T., 1999. 'Paradoxical' alpha synchronization in a memory task. *Cognitive Brain Research* 7, 493–501.
- Klimesch, W., Doppelmayr, M., Schimke, H., Ripper, B., 1997. Theta synchronization and alpha desynchronization in a memory task. *Psychophysiology* 34, 169–176.
- Klimesch, W., Doppelmayr, M., Stadler, W., Pöllhuber, D., Sauseng, P., Röhm, D., 2001a. Episodic retrieval is reflected by a process specific increase in human electroencephalographic theta activity. *Neuroscience Letters* 302, 49–52.
- Klimesch, W., Doppelmayr, M., Yonelinas, A., Kroll, N.E.A., Lazzara, M., Röhm, D., Gruber, W., 2001b. Theta synchronization during episodic retrieval: neural correlates of conscious awareness. *Cognitive Brain Research* 12, 33–38.
- Klimesch, W., Hanslmayr, S., Sauseng, P., Gruber, W., Brozinsky, C.J., Kroll, N.E.A., Yonelinas, A.P., Doppelmayr, M., 2006. Oscillatory EEG correlates of episodic trace decay. *Cerebral Cortex* 16, 280–290.
- Klimesch, W., Sauseng, P., Hanslmayr, S., 2007. EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Research Reviews* 53, 63–88.
- Klimesch, W., Schimke, H., Schwaiger, J., 1994. Episodic and semantic memory: an analysis in the EEG theta and alpha band. *Electroencephalography and Clinical Neurophysiology* 91, 428–441.
- Lakatos, P., Shah, A.S., Knuth, K.H., Ulbert, I., Karmos, G., Schroeder, C.E., 2005. An oscillatory hierarchy controlling neuronal excitability and stimulus processing in the auditory cortex. *Journal of Neurophysiology* 94, 1904–1911.
- Lisman, J.E., Idiart, M.A.P., 1995. Storage of 7 ± 2 short-term memories in oscillatory subcycles. *Science* 267, 1512–1515.
- Marsolek, C.J., Schacter, D.L., Nicholas, C.D., 1996. Form-specific visual priming for new associations in the right cerebral hemisphere. *Memory and Cognition* 24, 539–556.
- Mizuhara, H., Yamaguchi, Y., 2007. Human cortical circuits for central executive function emerge by theta phase synchronization. *NeuroImage* 36, 232–244.
- Mormann, F., Fell, J., Axmacher, N., Weber, B., Lehnertz, K., Elger, C.E., Fernandez, G., 2005. Phase/amplitude reset and theta-gamma interaction in the human medial temporal lobe during a continuous word recognition memory task. *Hippocampus* 15, 890–900.
- Nyhus, E., Curran, T., in press. Functional role of gamma and theta oscillations in episodic memory. *Neuroscience and Biobehavioral Reviews*.
- O'Keefe, J., Nadel, L., 1978. *The Hippocampus as a Cognitive Map*. Oxford University Press, Oxford.

- O'Keefe, J., Recce, M.L., 1993. Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 3, 317–330.
- Onton, J., Delorme, A., Makeig, S., 2005. Frontal midline EEG dynamics during working memory. *NeuroImage* 27, 341–356.
- Osipova, D., Takashima, A., Oostenveld, R., Fernandez, G., Maris, E., Jensen, O., 2006. Theta and gamma oscillations predict encoding and retrieval of declarative memory. *Journal of Neuroscience* 26, 7523–7531.
- Palva, S., Palva, J.M., 2007. New vistas for alpha-frequency band oscillations. *Trends in Neurosciences* 30, 150–158.
- Pastalkova, E., Itskov, V., Amarasingham, A., Buzsaki, G., 2008. Internally generated cell assembly sequences in the rat hippocampus. *Science* 321, 1322–1327.
- Pennkamp, P., Bosel, R., Mecklinger, A., Ott, H., 1994. Differences in EEG-theta for responded and omitted targets in a sustained attention task. *Journal of Psychophysiology* 8, 131–141.
- Postle, B.R., 2006. Working memory as an emergent property of the mind and brain. *Neuroscience* 139, 23–38.
- Raghavachari, S., Kahana, M.J., Rizzuto, D.S., Caplan, J.B., Kirschen, M.P., Bourgeois, B., Madsen, J.R., Lisman, J.E., 2001. Gating of human theta oscillations by a working memory task. *Journal of Neuroscience* 21, 3175–3183.
- Raghavachari, S., Lisman, J.E., Tully, M., Madsen, J.R., Bromfield, E.B., Kahana, M.J., 2006. Theta oscillations in human cortex during a working-memory task: evidence for local generators. *Journal of Neurophysiology* 95, 1630–1638.
- Redish, A.D., 1999. *Beyond the Cognitive Map*. MIT Press, Cambridge.
- Rizzuto, D.S., Madsen, J.R., Bromfield, E.B., Schulze-Bonhage, A., Kahana, M.J., 2006. Human neocortical oscillations exhibit theta phase differences between encoding and retrieval. *NeuroImage* 31, 1352–1358.
- Romei, V., Brodbeck, V., Michel, C., Amedi, A., Pascual-Leone, A., Thut, G., 2008a. Spontaneous fluctuations in posterior alpha-band EEG activity reflect variability in excitability of human visual areas. *Cerebral Cortex* 18, 2010–2018.
- Romei, V., Rihs, T., Brodbeck, V., Thut, G., 2008b. Resting electroencephalogram alpha-power over posterior sites indexes baseline visual cortex excitability. *NeuroReport* 19, 203–208.
- Sammer, G., Blecker, C., Gebhardt, H., Bischoff, M., Stark, R., Morgen, K., Vaitl, D., 2007. Relationship between regional hemodynamic activity and simultaneously recorded EEG-theta associated with mental arithmetic-induced workload. *Human Brain Mapping* 28, 793–803.
- Sarnthein, J., Petsche, H., Rappelsberger, P., Shaw, G.L., von Stein, A., 1998. Synchronization between prefrontal and posterior association cortex during human working memory. *Proceedings of the National Academy of Sciences of the United States of America* 95, 7092–7096.
- Sauseng, P., Hoppe, J., Klimesch, W., Gerloff, C., Hummel, F.C., 2007. Dissociation of sustained attention from central executive functions: local activity and inter-regional connectivity in the theta range. *European Journal of Neuroscience* 25, 587–593.
- Sauseng, P., Klimesch, W., 2008. What does phase information of oscillatory brain activity tell us about cognitive processes? *Neuroscience and Biobehavioral Reviews* 32, 1001–1013.
- Sauseng, P., Klimesch, W., Doppelmayr, M., Hanslmayr, S., Schabus, M., Gruber, W.R., 2004. Theta coupling in the human electroencephalogram during a working memory task. *Neuroscience Letters* 354, 123–126.
- Sauseng, P., Klimesch, W., Doppelmayr, M., Pecherstorfer, T., Freunberger, R., Hanslmayr, S., 2005a. EEG alpha synchronization and functional coupling during top-down processing in a working memory task. *Human Brain Mapping* 26, 148–155.
- Sauseng, P., Klimesch, W., Schabus, M., Doppelmayr, M., 2005b. Fronto-parietal EEG coherence in theta and upper alpha reflect central executive functions of working memory. *International Journal of Psychophysiology* 57, 97–103.
- Sauseng, P., Klimesch, W., Stadler, W., Schabus, M., Doppelmayr, M., Hanslmayr, S., Gruber, W.R., Birbaumer, N., 2005c. A shift of visual spatial attention is selectively associated with human EEG alpha activity. *European Journal of Neuroscience* 22, 2917–2926.
- Sauseng, P., Klimesch, W., Freunberger, R., Pecherstorfer, T., Hanslmayr, S., Doppelmayr, M., 2006. Relevance of EEG alpha and theta oscillations during task switching. *Experimental Brain Research* 170, 295–301.
- Sauseng, P., Klimesch, W., Gerloff, C., Hummel, F.C., 2009a. Spontaneous locally restricted EEG alpha activity determines cortical excitability in the motor cortex. *Neuropsychologia* 47, 284–288.
- Sauseng, P., Klimesch, W., Heise, K., Gruber, W., Holz, E.M., Karim, A.A., Glennon, M., Gerloff, C., Birbaumer, N., Hummel, F.C., 2009b. Brain oscillatory substrates of human visual short-term memory capacity. *Current Biology* 19, 1846–1852.
- Sauseng, P., Klimesch, W., Gruber, W.R., Birbaumer, N., 2008. Cross-frequency phase synchronization: a brain mechanism of memory matching and attention. *NeuroImage* 40, 308–317.
- Schacter, D.L., Wagner, A.D., Buckner, R.L., 2000. Memory systems of 1999. In: Tulving, E., Craik, F.I.M. (Eds.), *Oxford Handbook of Memory*. Oxford University Press, Oxford, pp. 627–644.
- Sederberg, P.B., Kahana, M.J., Howard, M.W., Donner, E.J., Madsen, J.R., 2003. Theta and gamma oscillations during encoding predict subsequent recall. *Journal of Neuroscience* 23, 10809–10814.
- Siapas, A.G., Lubenov, E.V., Wilson, M.A., 2005. Prefrontal phase locking to hippocampal theta oscillations. *Neuron* 46, 141–151.
- Skaggs, W.E., McNaughton, B.L., Wilson, M.A., Barnes, C.A., 1996. Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus* 6, 149–172.
- Summerfield, C., Mangels, J.A., 2005. Coherent theta-band EEG activity predicts item-context binding during encoding. *NeuroImage* 24, 692–703.
- Tesche, C.D., Karhu, J., 2000. Theta oscillations index human hippocampal activation during a working memory task. *Proceedings of the National Academy of Sciences of the United States of America* 97, 919–924.
- Thut, G., 2009. Insight into the alpha oscillation from combined EEG-TMS studies. *Psychophysiology* 46, S8.
- Volberg, G., Hübner, R., 2007. Do the hemispheres differ on their preparation for global/local processing? *Experimental Brain Research* 176, 525–531.
- Von Stein, A., Chiang, C., König, P., 2000. Top-down processing mediated by interareal synchronization. *Proceedings of the National Academy of Sciences of the United States of America* 97, 14748–14753.
- Von Stein, A., Sarnthein, J., 2000. Different frequencies for different scales of cortical integration: from local gamma to long-range alpha/theta synchronization. *International Journal of Psychophysiology* 38, 301–313.
- Weiss, S., Rappelsberger, P., 2000. Long-range EEG synchronization during word encoding correlates with successful memory performance. *Cognitive Brain Research* 9, 299–312.
- Williams, J.M., Givens, B., 2003. Stimulation-induced reset of hippocampal theta in the freely performing rat. *Hippocampus* 13, 109–116.
- Wu, X., Chen, X., Li, Z., Han, S., Zhang, D., 2007. Binding of verbal and spatial information in human working memory involves large-scale neural synchronization at theta frequency. *NeuroImage* 35, 1654–1662.
- Zimmer, H.D., 2008. Visual and spatial working memory: from boxes to networks. *Neuroscience and Biobehavioral Reviews* 32, 1373–1395.