Brain Oscillatory Signatures of Working Memory
Control Processes

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Abstract

Mnemonic operations are vital in our everyday life and comprise a vast array of sub-processes that need to be co-ordinated constantly to ensure smooth functioning. The goal of this work was to investigate the superimposed control component responsible for the co-ordination of those individual sub-processes. Furthermore, by using neuroscientific methods like electroencephalography (EEG) and transcranial magnetic stimulation (TMS), the underlying oscillatory signatures were explored and their behavioural relevance tested.

It will be shown that increase in theta frequency (4-8 Hz) over medial frontal cortical areas is a local indicator of increasing task demand and task complexity. Moreover, findings will be presented that indicate that the phase of this local oscillation (frontal-midline theta, FMtheta) enables task-relevant processes in posterior cortical areas (represented by increased activity in the gamma frequency range, 30-80 Hz) to flexibly access prefrontal cognitive resources. This mechanism is implemented in a way that bursts of posterior gamma frequency are locked to specific phases of a FMtheta cycle. The higher the task complexity, i.e. the more prefrontal control processes are needed for its execution, the closer to the excitatory phase of FMtheta (trough) the posterior gamma bursts are nested. In contrast, when only very little cognitive control needs to be employed, the posterior fast frequency bursts are locked near the inhibitory FMtheta phase (peak) rather.

By using repetitive TMS it was furthermore possible to show the behavioural relevance of this mechanism and how the disruption thereof has a highly selective and immediate deteriorating effect on working memory performance. Moreover, it will be demonstrated that this mechanism does not only depend on task difficulty but can be influenced and controlled voluntarily by information prioritisation. Finally, based on these findings a model will be introduced that could potentially explain the mechanism of such flexible allocation of and access to prefrontal control processes.
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Declaration of originality

This thesis and the work to which it refers are the results of my own efforts. Any ideas, data, images or test resulting from the work of others (whether published or unpublished) are fully identified as such within the work and attributed to their originator in the text, bibliography or in footnotes. This thesis has not been submitted in whole or in part for any other academic degree or professional qualification. I agree that the University has the right to submit my work to the plagiarism detection service TurnitinUK for originality checks. Whether or not drafts have been so-assessed, the University reserves the right to require an electronic version of the final document (as submitted) for assessment as above.

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Chapter I  General Introduction and Aim of the Current Work

1. Memory and Cognitive Control Processes

Memory has long been a key area of research in cognitive psychology. More recently, biological psychology – or cognitive neuroscience – started to investigate how the human brain stores and retrieves information. This increased scientific research led to exponential growth of knowledge about the organization of human memory and about its subsystems in the last decades. One of those memory subsystems is working memory (WM). WM is comprised of a vast number of cognitive functions like maintenance of information that is no longer available in the environment and the manipulation thereof, inhibition of irrelevant information, incorporation of different types of information and integration of new information with the one already existing in other memory systems like episodic and semantic long-term memory (LTM). These particular working memory processes have been intensely researched and there are numerous models which compete for explaining the structure of WM as a unitary memory system (e.g. Cowan, 2009; D'Esposito, 2007; Postle, 2006). The most famous model was proposed in 1974 by Baddeley and Hitch. It assumes that WM consists of several individual material-specific storage sub-components – the visuo-spatial sketchpad for visual information and the phonological loop for verbal information. These storage components could be shown to be implemented in individual feature-selective posterior and frontal cortical structures (e.g. Jonides et al., 1998; Pasternak & Greenlee, 2005; Polanía et al., 2011). These structures consist of the dorsal stream for visuo-spatial information located at mainly right hemispheric posterior-parietal brain areas and the ventral stream for object information located at rather temporo-parietal brain areas (Baizer et al., 1991; Goodale & Milner, 1992). Verbal information, on the other hand, was shown to have its cortical representation over mainly left hemispheric posterior-parietal areas (e.g. Awh et al., 1996). In Baddeley’s model (1992) WM is strictly separated from LTM but is connected to episodic LTM via the episodic buffer, a further sub-component of WM that is specialised on the transfer of episodic traces from WM to LTM. Moreover, there are direct links between the visuospatial sketchpad and visual semantic LTM processing as well as the phonological loop and language processing (semantic LTM). In contrast, Cowan (2009), proposed a WM
model that is directly linked to LTM. In fact, he assumed that WM is not an individual memory system *per se* but a subset of LTM that is temporarily under attentional focus.

One thing that all the mentioned memory models have in common though, is the attentional control component – the central executive master component which is superimposed on the storage sub-components and serves a material unspecific monitoring and resource allocation and supervision function (e.g. Baddeley, 1992). The use of neuroimaging methods and electroencephalography (EEG) in memory research has led to a strong increase in our understanding of cognitive processes and their implementation in the human brain in general; and specifically, it enabled to show that the central executive control component is located at mainly frontal brain areas, more specifically in the anterior cingulate cortex (ACC; e.g. Liston et al., 2006) and is crucially embedded in the so-called fronto-parietal control network (e.g. Collette et al., 1999; Mizuhara & Yamaguchi, 2007; Sauseng, Klimesch, Schabus et al., 2005; Vogan et al., 2014). EEG working memory experiments with tasks that need increasing levels of cognitive control and allocation of cognitive resources repeatedly showed an increased activation in medial frontal brain areas and interactions between those frontal regions with task-relevant posterior (material specific) cortical sites. For instance, Gevins and colleagues (1997) found an increase in oscillatory power in the theta frequency range (4-8 Hz) over medial frontal brain sites that is sensitive to task difficulty but insensitive to material type (visuo-spatial and verbal) in a working memory task. Furthermore, it could be shown that this increase in focal medial frontal theta activity is prominent not only during the maintenance of information but also during the manipulation thereof as well as during sustained attention and unspecific processes of cognitive resource allocation (e.g. Cavanagh & Frank, 2014; Hanslmayr et al., 2008; Mitchell et al., 2008; Sauseng et al., 2007, 2010).

Considering the breadth of functions associated with memory processes and that those functions recruit a widespread network located at areas distributed over the whole cortex and furthermore, that mnemonic and cognitive control processes cannot possibly operate on a local scale only, it becomes obvious that there needs to be some sort of interaction and communication between local and distant brain areas cooperating during a given task. This local and long-range neural communication is
represented by neuronal synchronisation (for a review see Fries, 2009). Communication within a cortical network is reflected by synchronous firing of the neurons that are part of that network (locally as well as long-range). Unfortunately, this synchronisation of neuronal spiking cannot be studied non-invasively in humans. However, there are studies suggesting that rhythmical changes of the local field potential (which can be recorded with scalp EEG) are a correlate of rhythmically modulated firing patterns on cellular level (e.g. Haegens et al., 2011b). For that reason local and long-range oscillatory brain activity as recorded with the EEG is considered a key marker of neuronal communication in cortical networks (for a review see Fell & Axmacher, 2011).

2. Oscillations – informative parameters and how they could provide the basic mechanism for memory network operations

Individual neurons in the brain and neuronal networks (of no matter what size) do have the inherent property to show constant periodic changes in electrical activity. In other words, they oscillate (e.g. Buzsáki & Chrobak, 1995). Whether this intrinsic behaviour is a mere epiphenomenon of cognitive processes or is, in fact, a key mechanism through which cognitive processing is enabled, is not entirely clear yet (for an extensive discussion of this issue the reader is kindly referred to Buzsáki, 2006). Very recent evidence that it is rather the latter comes from Lozano-Soldevilla and colleagues (2014). The authors could show that the experimental manipulation of GABAergic inhibitory interneurons affect the generation of oscillatory activity at posterior areas in the human brain. Moreover, they found that those drug-induced modulations predicted performance in a demanding visuospatial WM task. Such oscillatory activity can be detected with the EEG when a large enough number of neurons (i.e. thousands) which are part of a neuronal population fire in a synchronised fashion in a superficial layer of the cortex. The electrical brain activity as recorded with the EEG is then the sum of various underlying neuronal populations that oscillate in different frequencies. This raw EEG can then be offline divided into its individual components, i.e. the various underlying oscillations. Finally, to describe those individual oscillations, three main functionally relevant parameters can be used – namely their frequency, amplitude/power and phase.
2.1. Frequency

The electrical activity as recorded with scalp level EEG comprises activity that oscillates in a wide range of frequencies and is represented as the sum thereof. This raw EEG signal can be subdivided into five main frequency bands that each has different associated functional specificities. Delta band activity (0-4 Hz), for instance, is mainly associated with deep, i.e. slow wave sleep (e.g. Amzica & Steriade, 1998) and signal detection and decision making (e.g. Bașar-Eroglu et al., 1992). Theta band activity (4-8 Hz) is strongly linked to cognitive control processes and working memory functions (e.g. Jensen & Tesche, 2002; Sauseng et al., 2007), visuo-spatial navigation (e.g. Buszáki, 2006), spatial memory and learning, clustering of related information (for a recent review see Colgin, 2013) as well as synaptic plasticity and long-term potentiation (LTP; e.g. Huerta & Lisman, 1993). The list of cognitive processes associated with activity in the theta frequency band is ever growing, as indicated by the following quote from Buzsáki (2005, p. 828): “By exclusion, the only firm message that can be safely concluded from this brief summary is that in an immobile animal no theta is present, provided that no changes occur in the environment (and the animal is not ‘thinking’)”. Oscillatory activity in the alpha frequency range (8-12 Hz), on the other hand, has first been observed by Hans Berger (1929) over posterior brain areas during rest and has mainly been associated with cortical idling. However, in more recent years alpha frequency oscillations have been found to represent active inhibition processes for task irrelevant information rather (for a recent review see Klimesch, 2012) and have been hypothesised to be relevant for semantic LTM access (e.g. Klimesch & Schack, 2003). Beta frequency oscillations in the range of 13 to 30 Hz were shown to be relevant for mainly motor functions (e.g. Jenkinson & Brown, 2011; Neuper & Pfurtscheller, 2001), attentional processes (e.g. Womelsdorf & Fries, 2007) and more recently episodic LTM encoding processes (e.g. Hanslmayr et al., 2009, 2012) and even semantic LTM encoding (Hanslmayr et al., 2011). Finally, fast frequency gamma oscillations (30-80 Hz) have been found to be associated with a wide range of cognitive processes. Gamma activity at posterior sensory areas of the brain, for instance, has been linked to early processing of visual information (e.g. Engel and Singer, 2001) and representation and maintenance of information in memory (e.g.
Axmacher et al., 2006; Friese et al., 2013; Gruber et al., 2004) and more generally to attention and memory processes (WM and LTM) both in sensory and non-sensory cortical areas (e.g. Jensen, Kaiser & Lachaux, 2007).

Given the large amount of cognitive operations, conscious, sub-conscious and unconscious processes that are happening in the brain at any given point in time, it is very unlikely though that any one oscillatory frequency represents any one cognitive function. Von Stein and Sarnthein (2000), for instance, propose that the frequency of an oscillation depends on the size of the neuronal network that is part of the specific operation. They conducted a study consisting of several tasks that are thought to differ in the size of the underlying neuronal network, i.e. the complexity of the involved neuronal assemblies, needed for successful completion. These tasks ranged from visual processing which was expressed by synchronisation in the gamma frequency to long-range fronto-parietal interactions in WM expressed by synchronisation in the theta and alpha frequencies. They suggest that while small networks tend to oscillate at fast frequencies like beta or gamma, larger networks and networks that span several cortical areas distributed over the whole cortex tend to synchronise at slower frequencies like delta, theta or alpha. Their findings and suggested mechanism gives a potential explanation for research discussed earlier, which links gamma activity with visual processing and feature binding while slower frequencies in the range of theta, for example, seem to be linked to cognitive control processes and WM functions.

2.2. Amplitude/Power

However, the question remains of how oscillations react to internal or external stimuli and generally, how they convey meaningful information and serve cognition and how this can be measured with EEG on macroscopic level. One way is by investigating a general increase or decrease in oscillatory power. In other words, changes in the amplitude, the strength, of an oscillation which is indicative for the synchronisation of the activity of the underlying neuronal population. One such example is the earlier mentioned increase in theta oscillatory power over medial frontal brain sites – frontal midline theta (FMtheta; e.g. Gevins et al., 1997) – which represents increased activation of prefrontal cognitive resources with increasing task difficulty and complexity (e.g. Sauseng et al., 2010). Sustained FMtheta increase has
been found as indication of attentional control processes necessary for the maintenance of information in WM and more generally, increased need for cognitive processing power (e.g. Griesmayr et al., 2014; Payne & Kounios, 2009).

While theta oscillations react with an increase in amplitude during active cognitive processing, alpha oscillations are usually found to exhibit a decrease of amplitude. Oscillatory activity in the alpha frequency range has been shown to be suppressed over task relevant cortical areas while there is an increase over task irrelevant areas. This led to the suggestion that prominent alpha activity represents active inhibition of cortical areas and task-irrelevant information that might interfere with the execution of the current task (e.g. Klimesch, Sauseng & Hanslmayr, 2007). Furthermore, a decrease of alpha oscillatory activity has been suggested to represent release of inhibition in order to retrieve relevant information from semantic LTM (e.g. Klimesch et al., 1996; Klimesch & Schack, 2003). Moreover, alpha oscillations were associated with stimulus detection at a very early processing level and changes in alpha amplitude were interpreted as reflecting variability in the excitability of the visual cortex. Romei and colleagues (2008), for instance, used TMS (transcranial magnetic stimulation) – a method with which a magnetic field is applied to specific cortical regions which in turn leads to the induction of an electric field in the cortex (see Wagner et al., 2007 for more details regarding the method and its applications) – to induce phosphenes (light flashes) near the perception threshold in blindfolded participants. They could show that whether a phosphene was perceived or not depended on the amount of prestimulus alpha oscillatory activity. When prestimulus alpha was high, the likelihood of perceiving a phosphene was significantly lower than when the prestimulus alpha activity was low (see also Hanslmayr et al., 2007 for similar results for the discrimination of visual letter stimuli that are presented only very briefly, i.e. 57 ms).

Similarly, beta band oscillations – which previously were associated with mainly motor functions – were found to decrease with increasing task difficulty as manipulated with working memory load in a study by Lundqvist, Herman and Lansner (2011). Furthermore, Hanslmayr and colleagues (2009) were able to link a decrease in beta (and alpha) power very specifically to semantic encoding processes while they found that theta and gamma power increase was linked to both, semantic and shallow encoding success. More generally, a decrease in beta oscillatory power
seems to be associated with general higher cognitive processing (e.g. Engel & Fries, 2010 for a review). Gamma oscillations, on the other hand, react with an increase in amplitude for increased processing demand. Gamma oscillatory increase has, for example, been associated with increased firing of specific cell assemblies in a rat’s hippocampus that react to very specific spatial locations (e.g. O’Keefe & Recce, 1993; for more details please see section 2.3. below). Furthermore, gamma oscillations have been associated with active maintenance and manipulation of information over task relevant posterior brain areas in human working memory (e.g. Honkanen et al., 2014; Van Vugt, Chakravarthi & Lachaux, 2014).

2.3. Phase

Any oscillation, no matter which frequency and how high the amplitude, is basically a sine wave comprising 360 degrees and ranging from $\pi$ to $-\pi$ with a trough, a rising phase, a peak and a falling phase. These periodic changes in electrical brain activity reflect rhythmic changes in the membrane potential of cells and were suggested to be linked to neural spiking (see for example Berger et al., 2014 for a recent review). As mentioned earlier, cell populations show the inherent property of oscillating and cells change their firing rate in response to external as well as internal stimulation. This increased firing rate can then lead to an increased firing rate of a postsynaptic cell. However, the increased synaptic discharge of a cell does not necessarily lead to the activation of the subsequent cell as discharges are usually irregular and vary randomly in response to a current stimulus (e.g. Stein et al., 2005). Whether the postsynaptic cell will respond or not does, in fact, additionally depend on the exact timing of the neuronal firing of the presynaptic neuron (e.g. Azouz & Gray, 2003; Buzsáki, 2001). Such a mechanism of information coding via the firing rate of neurons could be shown in respect to hippocampal place cells (see O’Keefe & Recce, 1993) in animal models (e.g. Jensen & Lisman, 2000) and was described as a potentially more general mechanism of information processing and coding (see Lisman, 2005). In order to use changes in neuronal firing rates effectively for cortical communication within and between networks there needs to be some form of pace maker or reference point to which the exact timing of the firing rates and changes thereof are calculated. For this purpose it was suggested that oscillatory activity serves the purpose of providing such a temporal reference
point. Cohen and Miles (2000) could, for instance, show that single neurons tend to spike constantly unless they are embedded in a population where they start to synchronise their firing pattern according to an oscillatory rhythm. Moreover, the frequency thereof seems to depend on the size of the neuronal population involved (see Buzsáki & Wang, 2012; or von Stein & Sarnthein, 2000 for a review). Following from that it seems that oscillations provide time windows for the integration of information (i.e. input from neurons and different neuronal assemblies; e.g. Buszáki & Draguhn, 2004) and that the frequency of the oscillation determines the exact size of the time window. For instance, gamma oscillations, given their high frequency, provide, very narrow time windows, and are therefore ideal for the very local integration of information on the scale of only a few milliseconds. This is ideal for the perception of coherent objects or feature binding mechanisms (see for example Singer, 1999). Furthermore, the high frequency of gamma oscillations enables individual neurons to synchronise very flexibly with various neuronal assemblies in close succession. Moreover, gamma oscillations have been found to be important for general synaptic plasticity (for a review see Axmacher et al., 2006). Slower oscillations, on the other hand, do not have the advantage of such fast, immediate and precise clocking but because of their longer cycle length they do allow for the integration of information from larger networks and especially from more distant networks with longer conduction delays. The origin of such pace-making oscillations and whether they are a product of single pace maker neurons (e.g. inhibitory interneurons, see for example Buszáki, 2001; Fries, Nikolić & Singer, 2007 for a review) or the inherent property of a network (e.g. Buzsáki, 2006) or in fact a combination thereof, is not yet known (for a detailed discussion on the manifold underlying physiological mechanisms, both chemical and electrical, the reader is kindly referred to Buzsáki, 2006).

In recent years it could be shown that the phase of an oscillation serves an important function ranging from basic signal processing to higher cognitive functions like allocation of cognitive resources. Mathewson and colleagues (2009) could, for instance, show that not only the amplitude of ongoing alpha oscillations over primary visual areas is important for stimulus detection but also that the phase into which a briefly presented visual stimulus falls into determines whether the stimulus is perceived or not. Furthermore, Busch and colleagues (2009) found this
relation to be true not only for the phase of alpha oscillations but also for the phase of ongoing theta activity; indicating that the phase of oscillatory activity represents an ideal and cost-effective candidate to serve as such an internal temporal reference point for information integration by the clustering of neuronal spiking patterns as a function of the phase of an oscillatory cycle (see for example Singer, 1999 for a review). Compelling evidence for the importance of this mechanism of phase coding and its immediate functional relevance comes from O’Keefe and Recce (1993) who identified place cells in the hippocampus of rats. Those place cells show increased firing rates when the rat passes through specific spatial location in a maze. Moreover, the firing rate of those cells follows a pattern in accordance with slow oscillations in the theta frequency range. This superimposed theta rhythm was interpreted as providing the framework for the sequentially represented specific spatial locations (represented by increased firing rates) while moving through the maze.

2.4. Working memory control processes and cognitive resource allocation in the human brain – a possible function for cross-frequency coupling

In humans, the co-occurrence of theta and gamma oscillations, more specifically, the modulation of gamma amplitude (indicating increased or decreased neuronal firing) by the phase of theta oscillations has been investigated in the context of working memory (see for example Friese et al., 2013; Lisman & Idiart, 1995). Jensen (2006), for instance, describes how it might be possible that exactly this mechanism of cross-frequency coupling between gamma amplitude and theta phase is the key for holding several items in memory simultaneously. Given that the individual items are represented by different neural assemblies and that each of those assemblies fires synchronously in the gamma frequency range and furthermore, given that those individually synchronised assemblies have their gamma bursts locked to different phases of a theta cycle, this would allow for a highly cost-effective and flexible mechanism of holding several sequential items in memory simultaneously. The amount of items that could be held in memory would then depend on the length of the theta cycle. Support for this comes from a study by Axmacher and colleagues (2010) who could show that the frequency of the gamma modulating theta oscillation depends on the amount of information that has to be
held in working memory; the higher the WM load the slower the theta frequency. The retention of information in working memory would thus be achieved by the recurrence of the theta cycle with the gamma bursts clustered within (e.g. Jensen, 2006). Further evidence for this comes from a study by Sauseng and colleagues (2009) who demonstrated that during the retention of information in short-term memory, gamma activity at task-relevant posterior brain areas is significantly locked to the trough of ongoing theta oscillations.

As discussed earlier, working memory comprises a vast array of cognitive processes ranging from information selection and retention to prefrontal control processes and resource allocation. The exact mechanism of this large-scale integration of cognitive processes is not clear yet but several WM studies in humans could find interactions between distant, task-relevant cortical areas as indicated by an alignment of the phases of theta oscillatory activity in those different areas (for a review see Sauseng et al., 2010). Moreover, using intracranial EEG recordings in humans, Canolty and colleagues (2006) could show that in a number of different cognitive tasks gamma amplitude is modulated by the phase of a theta oscillation in exactly the way as outlined above. This would indicate that local and long-range communication and co-ordination within and between networks in higher cognitive functions in the human brain is implemented by the clustering of bursts of fast frequencies in specific phases of a cycle of a slower frequency oscillation. Supporting this, in a recent review Roux and Uhlhaas (2014) suggest that successful WM operations rely on the interaction between (mainly) theta and gamma oscillations; where gamma serves the function of representing the individual pieces of information and theta has a superimposed temporal and spatial organising function. Alpha oscillations, on the other hand, represent the suppression/active inhibition of task-irrelevant information. Similarly, Lisman and Jensen (2013) propose that the interaction between theta and gamma oscillations represents the maintenance of multiple items in WM; where gamma activity bursts in different cell assemblies represent the different items and theta serves as sequencing oscillator providing the temporal frame.

Nicely in line with these propositions, Colgin (2013) outlines theta oscillations as a form of global synchroniser in the brain in her recent review. Additionally, further support for the idea of the necessity of fast oscillations being
locked to phases of a slow oscillation for cognitive processes comes from Jensen and colleagues (2014) who hypothetically outline a mechanism by which the coupling between the phase of alpha oscillations and changes in gamma amplitude over posterior – early visual processing – brain areas enable the visual system to prioritise information available in the environment from very early on. This can happen in a way that the item with the maximal visual contrast in a natural scene (where all individual items are coded by individual gamma clusters) is coded into a specific phase of the alpha oscillatory cycle. Depending on the alpha phase the gamma bursts occur at, the represented information gets more (or less) attention and is hence processed with (or without) priority.

While the exact mechanisms of such cross-frequency couplings and their exact functions for higher cognitive processes are not completely clear yet, there is little dispute about the crucial role of frontal midline theta oscillations as mechanism for the exertion of cognitive control (see for example Cavanagh & Frank, 2014) and of posterior gamma oscillations for local mnemonic operations (e.g. Howard et al., 2003; Jensen et al., 2014; Roux et al., 2012). Given that frontal midline theta oscillations are linked to the allocation of prefrontal working memory control processes (e.g. Gevins et al., 1997; Scheeringa et al., 2009) and gamma activity in posterior brain areas is associated with the maintenance and general representation of information in memory (e.g. Pesaran et al., 2002) and furthermore, given that the interaction and communication between and within specific cortical networks seems to rely on the coupling between the phase of slow oscillations and bursts of fast oscillatory activity, it stands to reason that working memory control processes are at least partly implemented in the brain by a coupling between frontal midline theta phase and gamma activity bursts at posterior brain areas.

3. Aim of the present work

The aim of the current work is to identify specific mechanisms representing the signatures of human mnemonic control processes. The central issue in question is the basic underlying EEG oscillatory mechanism which enables efficient and precise interactions and communication within and between cortical networks that are involved in higher cognitive functions vital for human memory.
First, we designed a verbal WM delayed-match-to-sample experiment where we tried to disentangle WM retention processes from processes representing the manipulation of information in WM and furthermore from the manipulation of information in WM with the involvement of semantic LTM (Chapter II). This was done in order to identify oscillatory signatures for increasing need for prefrontal control resources. We were not able to unambiguously identify specific correlates representing semantic LTM access within WM, but we found compelling evidence for an increase in frontal midline theta with increasing task complexity. Interestingly, we were also able to find evidence for the clustering of posterior gamma bursts into specific phases of the frontal midline theta cycle (Chapter III) indicating how the phase of FMtheta plays an active role in the exertion of prefrontal control processes in a mnemonic task.

Secondly, we went on to further investigate these findings on task complexity/difficulty dependent FMtheta increase and especially on the clustering of gamma activity in task relevant posterior brain areas in specific phase segments of frontal midline theta (Chapter IV, experiment 1). As our results on the comparison of basically three memory systems (short-term memory, WM and LTM; see Chapter III) do not allow to draw any clear conclusions - because there are too many factors that might have driven the underlying mechanisms - we decided to reduce the amount of possibly interfering/confounding factors and focus on WM only. For this purpose we designed a visuo-spatial WM delayed-match-to-sample task comparing WM retention with WM manipulation. We furthermore introduced the factor load (one vs four items) to be able to compare levels of difficulty. In this study we found increased frontal midline theta activity as a function of increased need for central executive resources. However, most interestingly, we again found gamma amplitude in task-relevant posterior brain areas being clustered into specific phases of a frontal midline theta cycle depending on task demands. The more demanding the task requirements and hence the need for the activation of prefrontal cognitive control resources, the closer to the trough of a frontal midline theta cycle the posterior gamma amplitude was clustered. This indicates that the phase of FMtheta influences the neuronal firing in task relevant posterior brain areas (as expressed by gamma frequency band activity). To investigate whether these cross-frequency coupling results are of causal nature and behaviourally relevant, we designed a combined
EEG-rTMS (repetitive transcranial magnetic stimulation) study where we disrupted this mechanism by applying a fast triple-pulse of TMS over the posterior brain areas that were previously coupled to FMtheta while participants performed the most difficult condition of the task in experiment 1 (Chapter IV, experiment 2). We found that only when the posterior rTMS pulse accidentally fell into the trough of the frontal midline theta cycle, the performance dropped close to chance level; whereas performance stayed unaffected when the pulse fell into any other phase of FMtheta. We interpreted this as further evidence for the immediate functional role of the described cross-frequency coupling mechanism between FMtheta phase and posterior gamma amplitude. Furthermore, we conclude that frontal midline theta allocates cognitive resources to processes at distant cortical areas in a way that the processes which need the most prefrontal resources are locked to the trough of FMtheta. These suggestions are in line with research by Haegens and colleagues (2011b) who showed that the trough seems to be the excitatory phase for slow oscillations. Additionally, in order to underpin the findings that the trough of FMtheta is the excitatory phase, we conducted a third experiment within the study (Chapter, IV, experiment 3) where we applied single TMS pulses over medial frontal electrode positions and then offline sorted the elicited event related potential (ERP) according to the FMtheta phase into which the pulse had fallen. Results confirmed that the trough is the excitatory phase of FMtheta while the peak seems to be inhibitory rather, as the brain responses elicited by TMS were significantly stronger for the trough than for the peak of the FMtheta phase.

Lastly, in a final study we wanted to investigate whether this mechanism representing working memory control processes and cognitive resource allocation by theta:gamma coupling is a purely automatic mechanism that reacts to task difficulty/complexity only; or whether it can be brought under voluntary control (Chapter V). For this purpose we implemented a spatial and figural delayed-match-to-sample dual-task where participants had to maintain two pieces of information simultaneously which were located at different cortical areas according to dual-stream theory. Importantly though, participants were instructed to prioritise always one piece of information, but not to ignore the other. The two material types showed the same level of difficulty (as demonstrated by the fact that there was no difference in task performance between spatial and figural material) and there was no
significant difference in FMtheta activity per se, indicating that any differences between the two conditions in brain activity and the coupling between FMtheta and posterior gamma activity cannot be attributed to differences in task difficulty. We investigated the nesting of gamma activity over areas sensitive to spatial information processing to the phase of FMtheta and could show that gamma bursts are locked to the excitatory trough of FMtheta when spatial information had to be prioritised. In contrast, gamma bursts over those spatially sensitive areas were locked near the inhibitory FMtheta phase (the peak) when figural information had to be prioritised.

These results, taken together, indicate that FMtheta serves as mechanism for working memory control processes and the allocation of cognitive resources to task-relevant cortical areas in higher cognitive processing. This cognitive control process is implemented in a way that the phase of FMtheta serves as gating mechanism for the access to prefrontal cognitive resources by posterior networks coding task-relevant information (see Chapter VI). Moreover, we were, for the first time, able to show that this mechanism is under immediate voluntary control and is not simply a function of task difficulty but can be influenced by active conscious prioritisation of otherwise neutral information.
Chapter II Interacting Memory Systems – Does EEG Alpha Activity Respond to Semantic Long-Term Memory Access in a Working Memory Task?

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Abstract

Memory consists of various individual processes which form a dynamic system co-ordinated by central (executive) functions. The episodic buffer as direct interface between episodic long-term memory (LTM) and working memory (WM) is fairly well studied but such direct interaction is less clear in semantic LTM. Here, we designed a verbal delayed-match-to-sample task specifically to differentiate between pure information maintenance and mental manipulation of memory traces with and without involvement of access to semantic LTM. Task-related amplitude differences of electroencephalographic (EEG) oscillatory brain activity showed a linear increase in frontal-midline theta and linear suppression of parietal beta amplitudes relative to memory operation complexity. Amplitude suppression at upper alpha frequency, which was previously found to indicate access to semantic LTM, was only sensitive to mental manipulation in general, irrespective of LTM involvement. This suggests that suppression of upper EEG alpha activity might rather reflect unspecific distributed cortical activation during complex mental processes than accessing semantic LTM.

Keywords: beta; brain oscillations; electroencephalography; synchronisation; theta
1. Introduction

Memory is a complex system which consists of various functions and cognitive processes. It can be divided into sub-systems defined by the length a mental representation is kept activated, i.e., short-term memory (STM) and long-term memory (LTM). Additionally, working memory (WM) is a short-term storage system (Baddeley, 2003) which also encompasses the utilisation of information no longer available in the environment and importantly, is updated with information from LTM (episodic and semantic) in order to successfully complete the task at hand (Baddeley, 2000). Baddeley (1992, 2000) introduced the concept of WM being divided into two modality specific storage components (visuo-spatial sketchpad and phonological loop) which are more or less independent from LTM. In contrast, memory models by Cowan (1995, 2001), Ruchkin and colleagues (2003) or Fuster (2003, 2009, 2012) assume that WM is not independent from LTM but just a subset thereof that is currently under attentional focus. A common feature of virtually all WM models, however, is the central executive (CE) which is a highly flexible attentional master component monitoring and co-ordinating all cognitive processing and is located at frontal brain areas (e.g. Baddeley, 1992; Ruchkin et al., 2003).

Another consensus between the above mentioned memory models is that memory is not located at one single area in the brain but spans a vast network mainly comprising prefrontal cortex and temporal and posterior parietal areas (D’Esposito, 2007; Postle, 2006). Furthermore, EEG oscillatory activity has repeatedly been suggested as energy-efficient physical mechanism for temporal co-ordination of cognitive processes, locally as well as interregionally (for a review see Buzsáki & Draguhn, 2004). Increase in oscillatory activity in the theta frequency range (4–8 Hz) over medial frontal brain sites (frontal midline theta, FMtheta) for instance is reported as likely candidate for representing the neural correlate of the central executive monitoring component which is essential to all memory models (Sauseng et al., 2010). Sustained increase in FMtheta is suggested to reflect the active maintenance of information in WM by attentional control processes (Klimesch et al., 2008). More specifically, FMtheta has been found to signal that more attentional resources and cognitive effort need to be allocated to a task (e.g. Griesmayr et al.,
In contrast, suppression of upper alpha (10–12/13 Hz) oscillatory activity over posterior brain areas has been reported to reflect processing of information from semantic LTM, more specifically the access to semantic LTM (Klimesch & Schack, 2003; Klimesch et al., 1996); with the strength of upper alpha suppression positively correlating with the performance in tasks targeting semantic LTM specifically (for a review see Klimesch, 1999). Moreover, it was found that the more semantically integrated the information to be retrieved is, the more upper alpha is suppressed over posterior brain areas (Klimesch, 2012). It was also shown that increase in upper alpha activity reflects active inhibition and protection of activated memory traces from interfering, task irrelevant LTM traces. The inhibition-timing hypothesis (Klimesch, Sauseng & Hanslmayr, 2007) highlights upper alpha increase and suppression as mechanism that actively inhibits interference from task-irrelevant information (upper alpha increase) and gradually releases this inhibition as access to LTM is needed to integrate information from LTM into WM in a given situation (Gould, Rushworth & Nobre, 2011; Haegens, Handel & Jensen, 2011; Jensen & Mazaheri, 2010; Palva & Palva, 2011; Pfurtscheller, 2002). Further supporting the claim of upper alpha reflecting a general gating mechanism for information from semantic LTM are findings by Sauseng and colleagues (2005) who conducted a visuo-spatial delayed-match-to-sample WM experiment and showed that under increased cognitive effort upper alpha increases over posterior brain areas. Similarly, Jensen et al. (2002) found an increase in upper alpha being correlated to load in a WM experiment. This indicates that if a situation does not require access to semantic LTM, upper alpha activity increases to prevent information from LTM being activated and from possibly interfering with the current task.

More recently oscillatory activity in the beta frequency range (13–30 Hz), which had been linked mainly to motor functions in the past, was associated with general higher cognitive processing (for a review see Engel & Fries, 2010) and memory processes (Hanslmayr, Staudigl & Fellner, 2012) and specifically semantic memory (Hanslmayr, Spitzer & Bäuml, 2009). Also, there is strong evidence that gamma oscillations (40–80 Hz) play an important role in information maintenance.
and utilisation both in humans and animal models (for a review see Buzsáki & Wang, 2012).

However, an important but unresolved issue is how WM and semantic LTM communicate with each other since a major part of successfully completing a task is the constant update of WM with information held in LTM. The episodic buffer which forms a direct interface between episodic LTM and WM and co-ordinates the interaction between these two memory systems is fairly well studied (Baddeley, 2000). Such direct interaction is less clear between WM and semantic LTM, however. Given the association of FMtheta with cognitive resource allocation (e.g., Sauseng et al., 2007) and monitoring of higher cognitive processes (Baddeley, 1992) FMtheta was suggested to be a prime candidate for representing the interfacing between different memory systems (for a review see Klimesch, 2012). More specifically, synchronisation in the theta frequency range over frontal areas indicates and monitors utilisation of information from LTM in WM at posterior brain sites (Baddeley, 1992; Gevins et al., 1997; Klimesch, 1999; Sauseng et al., 2002). Kizilirmak et al. (Kizilirmak, Rösler & Khader, 2012) for example showed that systematic manipulation of the complexity of the LTM retrieval processes (more specifically, LTM search) was associated with stronger slow wave negativity over the mid-frontal cortex suggesting an involvement of the anterior cingulate cortex (ACC). Since the ACC is repeatedly found as generator of FMtheta (Gevins et al., 1997; Ishii et al., 1999; Sauseng et al., 2007) this makes the assumption of FMtheta oscillations being the interface between WM and LTM all the more plausible. Similarly, Khader and Rösler (2011) conducted an experiment where they systematically manipulated the number of items from different material types (objects and locations) that needed to be retrieved from LTM. They found a linear effect in both, FMtheta increase and posterior upper alpha suppression, with memory load; but only the upper alpha suppression was also sensitive to material type. They interpret their results in a way that FMtheta depicts retrieval related control processes whereas upper alpha is functionally related to the activation of information stored in LTM.

In order to investigate the oscillatory correlates of the interfacing between WM and LTM we designed a verbal WM experiment similar to the one used by Griesmayr et al. (2010). There, the authors used a verbal delayed-match-to-sample
WM task where participants had to either retain a string of four consonant letters (maintenance) or re-arrange them according to alphabetical order (semantic manipulation with LTM access). During the delay interval they found increased FMtheta activity for the manipulation condition and attributed it to increased attentional demand. Unfortunately, Griesmayr and colleagues did not report results in the upper alpha range. In order to disentangle WM operations and semantic LTM utilisation, we added a third condition; a pure WM manipulation condition where participants had to re-arrange the consonants backwards as presented on the screen (backwards manipulation without LTM access). This should enable us to dissociate retention of information in WM from the manipulation thereof in WM. Furthermore, by comparing the two manipulation conditions we should be able to extract the neural signatures of WM accessing semantic LTM contents.

2. Experimental Section

2.1. Participants

Data were collected from 19 participants after they gave written informed consent; 11 were female (M\text{age} = 20.18, SD_{\text{age}} = 1.78) and eight were male (M\text{age} = 22.5, SD_{\text{age}} = 2.07). They had normal or corrected to normal vision and reported to have no prior neurological conditions. All but three were right handed (handedness was assessed with the Edinburgh Handedness Inventory; Oldfield, 1971). The study was approved by the University of Surrey Ethics Review Board.

2.2. Stimulus Presentation

Participants were comfortably seated at a standardised distance of 150 cm in front of a 19 inch Dell flat screen monitor with a total resolution of 1280 × 1024 pixels in a well lit room. Presentation Version 0.71 (Neurobehavioural Systems, Inc., Berkeley, CA, USA) was used to control visual stimulation.
2.3. Experimental Task and Trial Setup

In the present experiment participants had to perform a verbal delayed-match-to-sample-task (see Figure 2.1). The verbal material consisted of visually presented consonant letter strings (target letter string) with four items each, shown simultaneously for a period of 1000 ms against a black background centrally on the computer screen (font = Arial; font size = 80). The letters were either coloured in grey, red or blue with the colour serving as indication of which condition had to be performed in the respective trial. When the letters were grey (retention condition) participants had to simply retain the letters in their exact order during the following retention interval of 2000 ms before comparing them to a probe letter string. When the letters were red (backwards manipulation condition), participants needed to re-order them backwards during the retention interval and retain the newly arranged letter sequence until the probe letters appeared on screen. When the letters were presented in blue (semantic manipulation condition) participants were instructed to re-arrange the letters according to alphabetical order. After the retention interval a probe letter string appeared on the monitor and participants had to decide and indicate by button press (left- or right-click on a computer mouse) whether it matched their mental representation of the target letter string (either retained or manipulated, depending on instruction) or not. The non-match trials always consisted of one new consonant letter in the probe letter string which was not part of the original set (probe letters were in alphabetical order in the SEM condition). The inter-trial interval varied between 2000 and 3000 ms (see Figure 2.1).

All participants carried out a practice run which consisted of 30 trials in total with 10 for each condition and an equal amount of match and non-match trials. The actual experiment consisted of 54 trials per condition, resulting in a total number of 162 trials with 50% of them being a match and 50% being a non-match between target and probe. All 162 trials were presented in a completely randomised order.
Figure 2.1 Example of the verbal delayed-match-to-sample task
Experimental design of the delayed-match-to-sample task with examples of match trials for the conditions “retention” (RET), “semantic manipulation” (SEM) and “backwards manipulation” (BACK). Participants had to either simply retain the letter string in memory (a), re-arrange the letter string according to alphabetical order (b) or re-order the letter string backwards (c) during the retention interval and compare it with a probe letter string. Target presentation was 1000 ms, retention interval 2000 ms and probe presentation 1000 ms.

2.4. EEG Acquisition

EEG data were continuously recorded from 30 Ag-AgCl electrodes inserted into an electrode cap (Easy-cap) according to the 10-10 international system; recording sites were FP1, FP2, F7, F3, AFz, Fz, F4, F8, FC5, FC1, FC2, FC6, T3, C3, Cz, C4, T4, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, PO3, PO4, O1 and O2. Scalp electrodes were referenced against a ring-electrode placed on the tip of the nose and the ground electrode was placed on the forehead. EEG signals were registered with a Brain Products BrainAmp MR+ 32-channel EEG amplifier within the bandwidth of 0.016 and 80 Hz and a sampling rate of 1000 Hz. The impedance of
each of the electrodes was kept below 6 kΩ. Vertical and horizontal eye movements and blinks were monitored with two electrodes placed above and next to the left eye (EOGs). Stimulus presentation and EEG acquisition were synchronised, and coded event triggers marked the onset of each stimulus, response screen and the participants’ responses in the EEG signal recorded with BrainVision Recorder software (Brain Products, Gilching, Germany).

2.5. EEG Analysis

For the analysis of the EEG signals Brain Vision Analyzer 2.0 (Brain Products, Gilching, Germany) was used. Data were filtered with a high- and a low-cutoff of 1 Hz and 80 Hz, respectively, and a Notch-filter was set to 50 Hz. Semi-automatic Ocular Correction with Independent Component Analysis (Ocular Correction ICA) was used to correct for eye blink artefacts. The ocular correction function as implemented in the Analyzer 2.0 is an ICA-based correction process and uses a simplified version of ICA allowing ocular artefacts in the EEG signal to be corrected specifically (for detailed information see Jung et al., 2000) Visual inspection of the data was then carried out in order to exclude segments which show artefacts created by muscle activity and extensive eye movements which could not be corrected with ICA.

The sampling rate of the raw EEG was changed from 1000 Hz to 1024 Hz based on spline interpolation in order to get a power of two for application of Fast Fourier Transformation later. The data recorded during the retention interval of each trial were then segmented into epochs of 1000 ms each, resulting in two time intervals per retention period (t1: from stimulus offset until 1000 ms later and t2: from 1000 ms after stimulus offset until probe onset at 2000 ms after stimulus offset). The rationale behind the subdivision of the retention interval into two separate time periods is that in the manipulation conditions the mental manipulation most likely takes place during the first half of the retention interval while retention processes like rehearsing the newly acquired letter sequence are taking place during the second half (see Griesmayr et al., 2010; Sauseng et al., 2005). The average number of segments per condition and time period was 45.91 artefact free trials (with a minimum of 42 trials per condition). The amount of match and non-match trials that
were included in the EEG analysis for each condition did not differ and hence should not influence obtained EEG results.

2.5.1. Scalp Level EEG Analysis

For the analysis of the EEG signal on scalp level (as recorded by the scalp electrodes) Laplacian Current Source Density Transformation (CSD) was calculated (order of splines: 4; maximal degree of Legendre polynomials: 10; Lambda: 1 e\(^{-5}\)) in order to attenuate effects of volume conduction. CSD reduces global unspecific activity while increasing local activity (for a detailed description see Perrin et al., 1989). In order to obtain frequency power estimates (power spectra) Fast Fourier Transformation (FFT) was carried out (Hamming window of 10%) and regions of interest (ROIs) were defined (see Jensen et al., 2002; Jokisch & Jensen, 2007; Palva, Palva & Kaila, 2005; Sauseng et al., 2005, 2008, 2009, or for a review Sauseng & Klimesch, 2008) for the frequencies of interest; resulting in one frontal ROI (frontal-midline/FM = electrode sites AFz and Fz) and one posterior ROI (parieto-occipital/PO = electrode sites P3, Pz, P4, PO3, PO4, O1 and O2) which was later additionally divided into one right lateral posterior ROI (rPO; P4, PO4 and O2) and one left lateral posterior ROI (lPO; P3, PO3 and O1) for complementary analysis of hemispheric distribution. Frequencies of interest for this study were theta (4–7 Hz), upper alpha (10–13 Hz), lower beta (beta1, 13–20 Hz), upper beta (beta2, 20–30 Hz), slow gamma (gamma1, 30–50 Hz) and fast gamma (gamma2, 50–70 Hz). The frequency specific EEG amplitude was then collapsed over electrodes to obtain the estimates for the defined ROIs and trials were averaged for every participant within each condition for time window one and time window two separately.

2.5.2. Source Level EEG Analysis

For the analysis on source level the derived scalp EEG signal was analysed using Standardized Low Resolution Electromagnetic Tomography (sLORETA; Pascual-Marqui, 2002) in order to estimate cortical sources of oscillatory activity in specific frequencies. The cortical grey matter and hippocampus are represented by 6430 voxels at 5 mm spatial resolution each, according to a three-shell spherical head model registered to the Talairach human brain atlas (for details see Pascual-Marqui, 2002). Taking volume conductance (CSD implemented into LORETA) and
possible dipole structure into account and assuming that neighbouring neurons tend
to fire in a synchronized fashion, sLORETA computes a current distribution
throughout the full volume of the brain directly and looks for the smoothest possible
3-dimensional current distribution (Pascual-Marqui, Michel & Lehmann, 1994). The
raw scalp EEG is estimated back to the most likely source. The procedure for present
analysis involved specification of a certain frequency band and comparison of two
different conditions or time intervals with each other across participants for each
single voxel. For each comparison (t-tests), 5000 randomisations were run in order to
correct for multiple comparisons and to determine a critical $t$-value (two-tailed; see
Nichols & Holmes, 2002). Cortical voxels exhibiting a $t$-value beyond the critical
(positive or negative) $t$-value obtained in the bootstrapping procedure were defined as
showing a significant difference in current source density between conditions.

2.6. Statistical Analysis

For statistical analysis of the scalp EEG data and behavioural data the
Statistic Package of Social Sciences (IBM SPSS Version 19, IBM, Armonk, NY,
USA) was used.

2.6.1. Behavioural Analysis

Behavioural performance was monitored in order to assess task difficulty as
higher task demand was shown to require allocation of more cognitive resources
reflected by oscillatory brain activity (e.g., Jensen et al., 2002). It is assumed that the
manipulation conditions are more difficult than the simple retention condition as
more cognitive effort is required for the execution of a mental manipulation than for
pure retention of information. Therefore, the mean percentage of correct responses
(hits and correct rejections) in each condition was calculated and statistically
compared using repeated-measures ANOVA (with the factor CONDITION) after
being tested for normal distribution. Paired sample $t$-tests were used for post-hoc
comparisons and FDR (false discovery rate, Benjamini & Hochberg, 1995)
correction was calculated to account for family-wise error rate.
2.6.2. EEG Data Analysis

For statistical analysis of scalp EEG signals all trials (match and non-match, correct and incorrect) were used. Incorrect trials were included in the analysis due to the fact that their number was rather small; and secondly, incorrect responses might also be caused by erroneous encoding or retrieval processes, whereas the current analysis exclusively focused on processes during the delay interval. For statistical analysis of amplitude estimates two-way repeated-measures ANOVAs with the factors CONDITION (retention, backwards manipulation, semantic manipulation), ROI (frontal, posterior) were calculated with the Fast Fourier transformed data for each frequency band individually for the first time window of the retention interval (see EEG Analysis 2.5.). Greenhouse-Geisser corrections were applied if necessary and significance level was set to \( p < .05 \). Paired sample \( t \)-tests were used for post-hoc comparisons of conditions for each time interval and ROI separately for all frequency bands; FDR correction was used to account for multiple testing.

3. Results and Discussion

3.1. Behavioural Data

Performance, as measured by percentage of correct responses, was very high for all three conditions (RET (92.98%, SD 5.71), BACK (84.79%, SD 10.13), SEM (82.65%, SD 10.36)). The one-way repeated measures ANOVA comparing correct responses between the three conditions revealed a main effect of CONDITION (\( F(1.54, 27.71) = 14.12, p < .001, \eta^2_p = .44 \)). Post-hoc paired sample \( t \)-tests show that both manipulation conditions differ significantly from the retention condition with performance being higher in the retention condition (RET vs. BACK \( t(18) = 4.14, p < .001 \) and RET vs. SEM \( t(18) = 6.67, p < .001 \)). Performance for the backwards manipulation and semantic manipulation conditions, on the other hand, does not differ significantly. These results indicate that the manipulation of the consonant letters was generally more difficult than the mere maintenance thereof. The nature of the manipulation on the other hand seemed to have no significant impact on task difficulty.
3.2. EEG Data

3.2.1. Frontal Midline Theta and Distributed Theta Activity (4–7 Hz)

An ANOVA comparing frontal midline theta activity (4–7 Hz) on EEG scalp level over the frontal region of interest (frontal ROI) between the retention (RET), backwards manipulation (BACK) and semantic manipulation (SEM) conditions yielded a significant main effect of CONDITION (F(2, 36) = 4.28, p = .024, \( \eta_p^2 = .19 \)) showing an increase of frontal midline theta activity with increasing cognitive demand (Figure 2.2). Post-hoc paired sample t-tests showed that frontal midline theta activity was significantly higher in the SEM than in the RET condition (t(18) = −2.67, p = .016) (Figure 2.2A,B). Furthermore, theta activity seems to be higher in the SEM than in the RET condition at posterior areas (posterior ROI; F(2, 36) = 4.05, p = .032, \( \eta_p^2 = .18 \); t(18) = −2.67, p = .028).

On source level (sLORETA), frontal midline theta showed significant differences in the anterior cingulate cortex (ACC) and medial frontal lobe (BA 9) between conditions. Current source density was higher in the SEM condition than in the RET condition (t > t_{crit} = 3.28, p < 0.05) (Figure 2.2C) and higher than in the BACK condition (t > t_{crit} = 3.32, p < 0.05) (Figure 2.2D). Additionally, the theta frequency band showed stronger activation in SEM than in BACK (t > t_{crit} = 3.32, p < 0.05) in the right parietal cortex (precuneus and cingulate gyrus). All p-values were corrected for multiple comparisons using the FDR correction approach (Benjamini & Hochberg, 1995).
Figure 2.2  Depiction of differences in frontal midline theta activity as a function of cognitive demand

Increase in frontal midline theta (FMtheta) activity with increasing cognitive demand. (A) Head map depicting significantly higher FMtheta activity over medial frontal electrode positions during semantic manipulation (SEM) of information in working memory (WM) than during the simple retention (RET) thereof; (B) Line chart depicting the significant amplitude difference between the retention (RET) and the semantic manipulation (SEM) conditions. Error bars show standard errors; (C) Standardised sLORETA cortex depicting areas with significantly higher FMtheta activity during the semantic manipulation (SEM) of information in working memory than the simple retention (RET) thereof; (D) Depiction of cortical areas on source level which show significantly stronger theta activity during the semantic manipulation (SEM) of information in working memory than during the backwards manipulation (BACK) thereof. Warm colours depict increase in activity and cold colours depict activity decrease.

This linear increase of FMtheta activity is well in line with existing literature highlighting the association of increase of activity in the theta frequency range over medial frontal brain sites with task difficulty (Gevins et al., 1997) and the complexity of mental operations (Griesmayr et al., 2014; Sauseng et al., 2010) as well as the need for increased cognitive control (Cavanagh & Frank, 2014). In our task this would indicate that simple retention of four consonant letters (RET) requires less cognitive resources or involvement of medial frontal executive processing than backwards manipulation thereof (BACK); which in turn is less effort than re-arranging the consonants according to alphabetical order (SEM). The fact that the behavioural results do not mirror this linear increase in FMtheta amplitude between conditions does not necessarily contradict this interpretation. The
behavioural measure might just not be sensitive enough to measure task difficulty/complexity as a function of our experimental manipulation in this particular paradigm/comparison. Especially as the behavioural performance is very high in all three conditions. It might be that the behavioural difference between the two manipulation conditions would be expressed by differences in reaction time; unfortunately, this cannot be assessed in the current experiment as participants were not instructed to provide speeded responses. EEG might just be a more sensitive measure to assess cognitive demand and increased cognitive effort in this particular setup than looking at percentage of correct responses (as the task is very simple overall).

In our experiment there is no specific difference in FMtheta activity between conditions that would indicate its special involvement in semantic LTM access or the interfacing between WM and semantic LTM specifically. Hence, we suggest that medial frontal theta activity is a measure of general cognitive processing effort and allocation of cognitive resources depending on the complexity of the task at hand rather.

3.2.2. Upper Alpha (10–13 Hz)

A repeated measures ANOVA comparing upper alpha (10–13 Hz) oscillatory activity over posterior brain areas between the three conditions (RET, BACK and SEM) showed a significant main effect of CONDITION ($F(1.224,22.03) = 8.33, p = .006$, $\eta^2 = .32$; see Figure 2.3) with the retention condition (RET) showing significantly stronger upper alpha synchronisation over posterior sites than both, the backwards (BACK) ($t(18) = 2.88, p = .01$) and the semantic manipulation (SEM) ($t(18) = 3.08, p = .006$) conditions. Importantly, no significant differences were found between the backwards manipulation (BACK) and the semantic manipulation (SEM) conditions ($t(18) = .479, p = .638$). Moreover, source level analysis did not show any significant differences between conditions after correcting for multiple comparisons using the FDR correction approach (Benjamini & Hochberg, 1995).
Figure 2.3  Depiction of posterior upper alpha activity for the three conditions
Line chart depicting the significant amplitude difference in posterior upper alpha activity between the two manipulation conditions and the retention condition. Upper alpha activity over posterior brain areas is stronger during the retention (RET) of information in working memory than during either the backwards manipulation (BACK) or the semantic manipulation (SEM) thereof. Error bars show standard errors.

Given the association between oscillatory activity in the upper alpha frequency range and semantic LTM access, we hypothesized that upper alpha activity over posterior brain areas would specifically respond to semantic LTM utilisation. Hence, we expected it to show a clear difference in strength of activity between the semantic manipulation condition (SEM) and the two conditions without semantic LTM access (RET and BACK). In our task no such difference was obtained but upper alpha seemed to respond to the manipulation of information in WM in general, as indicated by the significant difference between RET and BACK and RET and SEM but not between BACK and SEM. Our results suggest that suppression of oscillatory activity over posterior brain areas reflects unspecific distributed cortical activation during complex mental processes rather than access of semantic LTM specifically. This interpretation would be in line with findings by Rihs and colleagues (2009) who suggest that the purpose of alpha increase during a maintenance phase over occipito-parietal areas is attention related and the inhibition of interfering information processing in general and is not necessarily related to semantic LTM. In our experiment this would indicate that the manipulation of information (BACK and SEM), irrespectively of the nature of the manipulation (with
or without semantic information retrieved from LTM), needs less active inhibition of posterior cortical areas, *i.e.*, a larger posterior area/network being actively involved in the (more cognitively demanding) manipulation of information in opposition to simple retention thereof. Whereas, when the task is to simply retain four consonants (RET) a larger part of the posterior cortex can be inhibited to protect the actively maintained memory trace from interfering cortical activations.

3.2.3. Lower Beta (13–20 Hz)

A repeated measures ANOVA yielded a significant main effect for CONDITION (F(1.33,24.08) = 9.86, *p* = .002, η² = .35) at posterior areas of the brain in the lower beta frequency range (13–20 Hz). Post-hoc testing showed that lower beta power at posterior parts of the brain was significantly higher for the retention of the verbal material (RET) than the backwards manipulation (BACK) (*t*(18) = 2.84, *p* = .01) and the semantic (SEM) manipulation (*t*(18) = 3.62, *p* = .002) thereof. The backwards manipulation (BACK) condition and semantic manipulation (SEM) condition did not differ significantly over the posterior ROI (*t*(18) = 1.70, *p* = .106) but complementary analysis looking at hemispheric distribution (repeated measures ANOVA with the factor ROI split into left posterior and right posterior; (FCondition x Region(1.20,21.62) = 4.61, *p* = .037, η² = .21) showed a significant difference between the two manipulation conditions over the right hemisphere (BACK vs. SEM *t*(18) = 3.94, *p* = .001) (Figure 2.4). All comparisons were FDR corrected. No significant differences between conditions were obtained on source level after FDR correction (Benjamini & Hochberg, 1995) was applied.

Suppression of oscillatory activity in the beta frequency range has recently been associated with higher cognitive processing outside of the motor domain (Engel & Fries, 2010) and has been linked to semantic LTM processing specifically (Hanslmayr et al., 2009). Hanslmayr and colleagues (2012) for example discuss the role of posterior beta frequency suppression in relation to retrieval of information from semantic LTM by reviewing studies which explicitly controlled for cognitive processes with and without semantic LTM access. They convincingly conclude that beta can not only be actively increased in order to prevent competing memories from interfering but also actively suppressed in order to promote sensory reactivation of a relevant memory. In the present study we could
not find an increase or decrease in the beta frequency specifically related to semantic LTM processing but rather a linear decrease in beta activity from the retention condition (RET) via the backwards manipulation condition (BACK) to the semantic manipulation condition (SEM). We suggest that decrease in the beta frequency band at posterior brain sites more generally reflects task complexity. In accordance with this, Engel and Fries (2010) argue that beta frequency oscillations seem to be related to the maintenance of a current cognitive or sensorimotor state. They reviewed literature reporting increase or decrease of oscillations in the beta frequency range and concluded that activity increase is strongly linked to the maintenance of the current status quo. Furthermore, they link abnormal enhancement in beta activity with abnormal persistence and deterioration of flexible behavioural and cognitive control. In our task this would mean that in the retention condition (RET) beta activity should be stronger than in the two manipulation conditions (BACK and SEM), which is exactly what we found. Moreover, following the hypothesis by Engel and Fries (2010), the significant difference between the backwards manipulation condition (BACK) and the semantic manipulation condition (SEM) would indicate that the maintenance of the status quo is more relevant in the backwards manipulation (BACK) while the re-arrangement according to alphabetical order (SEM) requires significantly more reshuffling, i.e., cognitive flexibility, as the consonant letters held in WM need to be shuffled according to a rule that gives the letters a very specific individual ranking based on a large template held in long-term memory (i.e. alphabet). In other words, while the backwards manipulation of the consonant letters simply requires the mirroring of a string of four consonants, the re-arranging according to alphabetical order requires the participant to re-order all the consonant letters individually.
Figure 2.4  Posterior lower beta activity for the three conditions
Line chart depicting the significant amplitude difference in right posterior lower beta activity between the three experimental conditions. Lower beta activity over posterior brain areas is stronger during the retention (RET) of information in working memory than during either the backwards manipulation (BACK) or the semantic manipulation (SEM) thereof. Furthermore, the backwards manipulation condition (BACK) shows significantly stronger lower beta activity than the semantic manipulation condition (SEM). Error bars show standard errors.

3.2.4. Other Frequency Bands

No significant differences were found on scalp or source level for the lower alpha (8–10 Hz), upper beta (20–30 Hz), lower gamma (30–50 Hz) or upper gamma (50–70 Hz) frequency bands after correction for multiple comparisons by applying FDR correction (Benjamini & Hochberg, 1995). This could be due to the gamma activity being strongly linked to general maintenance functions in memory contexts in general (Buzsáki & Wang, 2012), which did not differ significantly in our task. An alternative explanation could be that we were simply unable to pick up differences between conditions in the fast frequencies with EEG because of the spatial filtering which generally makes it harder to obtain subtle differences in the faster frequency ranges.
4. Conclusions

We conclude that oscillatory activity in the upper alpha frequency range might not, after all, have a clear-cut role as marker for accessing semantic long-term memory and its utilisation in working memory, specifically. Instead, it reflects rather unspecific cortical activation during complex mental processes in general. Activity in the lower beta frequency range on the other hand seems to be an indicator of general cognitive effort, complexity of the mental operation at hand and cognitive flexibility. Importantly, in contrast to the literature on alpha and beta frequencies as reviewed in this chapter, our findings did not highlight one specific oscillatory frequency band as indicator of the interfacing between working memory and semantic long-term memory. Rather our findings suggest that the boundary between the two memory systems might be blurry, which furthermore, does not suggest a clear-cut distinction between working memory and long-term memory.

Most interestingly though, the linear increase in synchronisation in the theta frequency range over medial frontal electrode positions and the ACC from WM retention through backwards manipulation to semantic manipulation fits nicely with research on frontal midline theta activity as indicator of task difficulty, cognitive effort and the need for increased allocation of cognitive resources. Taken together, literature on frontal midline theta in mnemonic tasks and the present study, suggest that synchronisation in slow oscillatory activity (4-8 Hz) over mid-frontal brain areas might be a prime candidate for representing the EEG oscillatory correlates for increased need for prefrontal cognitive control/resources. Whether this mechanism operates solely on a local prefrontal scale or also has implications for coordinating the allocation of cognitive resources to individual or co-operating distant neuronal assemblies (posterior local networks maintaining and manipulating information held in WM or LTM, for instance) in need of processing power, remains to be seen (see Chapters III, IV, V and VI).
Chapter III Interim – Investigation of the role of frontal-midline theta in a mnemonic task and how it is linked to memory control processes

In the previous experiment (Berger et al., 2015) investigating the interfacing between working memory (WM) and semantic long-term memory (LTM) we were not able to discern a specific oscillation that represents this interaction. The most likely candidate to represent such an interfacing was increase in posterior upper alpha oscillatory activity (e.g. Klimesch et al., 1996; Klimesch & Schack, 2003). In our experiment though, upper alpha seemed to reflect a more general mechanism of mental manipulation processes rather. This is indicated by the fact that it only differed between the manipulation of information in WM and the pure retention thereof, but proved to be insensitive to the nature of the mental manipulation (i.e. whether the four consonant letters needed to be re-arranged backwards – WM manipulation – or re-arranged according to their alphabetical order – semantic LTM manipulation; Berger et al., 2015). However, at the same time it was striking that there was a linear increase in oscillatory activity in the theta frequency range over medial frontal electrode positions (frontal midline theta, 4-8 Hz; FMT) from pure retention to backwards manipulation to semantic manipulation (see Berger et al., 2015). Following these findings and their potential neural background described below we went on to investigate this linear increase further and to try to identify the underlying mechanism which it represents.

FMT is associated with cognitive resource allocation and is implemented in a fronto-parietal control network (e.g. Chapter IV; Dosenbach et al., 2008) and highlighted as prime candidate for cortical long-range communication and coordination of different brain areas that work together during the execution of a task (mainly the phase of FMT seems to play a key role here; e.g. Sauseng et al., 2009). Local information processing on the other hand is associated with local increase of gamma oscillatory activity (30-80 Hz; e.g. Buszáki & Wang, 2012). In the light of theories about network oscillations (e.g. Buzsáki, 2006; von Stein & Sarnthein, 2000) it is reasonable to assume a similar mechanism in human mnemonic operations as has been shown in rats and mice. In animal models Siroti and colleagues (2008; see also Fries et al., 2005) for instance, could convincingly show
that the phase of theta oscillations in prefrontal cortex and hippocampus entrains neuronal firing in distant areas of the brain as expressed by bursts of gamma oscillatory activity.

Following from that, we went on to specifically investigate whether there is a comparable mechanism that is present in humans and detectable in our experiment which examines functional connection/interaction between prefrontal control areas and task-relevant posterior brain sites. We expected this mechanism to be implemented on neuronal level via a functional coupling between the phase of FMT and increased activity of gamma oscillations over task relevant posterior brain sites (for further information the reader is kindly referred to the following chapters; Chapter IV and Chapter V). However, as we did not find differences in posterior gamma oscillatory activity between the three conditions in the previous experiment (see Berger et al., 2015), it might seem puzzling at first why we selected gamma oscillations for further investigations. This can be explained by strong evidence that there does not necessarily have to be a difference between overall oscillatory power – as averaged over a specific time window (e.g. one second) – when looking at the interaction between local gamma activity and theta phase on a very detailed time scale (e.g. Griesmayr et al., 2010; Holz et al., 2010; Sauseng et al., 2008, 2009). Buzsáki (2006), for instance, describes very convincingly that overall changes in activity do not necessarily reflect how the underlying neuronal cluster is organized in respect to an external/distant clocking mechanism (i.e. in this case the phase of frontal midline theta).

To investigate this, we extracted the phase of frontal midline theta during the previously specified time window of linear frontal midline theta increase (see Berger et al., 2015) and sorted the activity of posterior gamma oscillatory activity according to FMT phase (for a detailed description of the analysis and statistical methods the reader is kindly referred to Chapters IV and V). What we found was, that even though there is no significant difference between the overall gamma power, there is a difference between conditions in terms of the FMT phase to which the left posterior gamma bursts (at a centre frequency of 40 Hz) are locked (see Figure 3.1). A repeated measures ANOVA with the factors CONDITION (Retention, Backwards, Semantic) and PHASE (10 FMT phase segments; see detailed description of the statistical methods in the following chapters IV and V) showed that during the early
retention interval (when the three conditions should differ the most with respect to the executed cognitive process; see Griesmayr et al., 2010) the gamma bursts (40 Hz) at left posterior brain sites are locked to different phases of a frontal midline theta cycle ($F(6.214, 111.853) = 2.52, p = .024; \text{corrected for familywise error}$). Closer inspection of the data shows that phase modulation of all three conditions exceeds a critical t-value ($p < .01$) obtained via bootstrapping procedure (please be kindly referred to the following chapters IV and V) and thus can be interpreted as significant modulation of posterior gamma amplitude by FMtheta phase. For the retention condition the 40 Hz gamma bursts at electrode site PO3 show a clearly defined clustering at the peak of the frontal midline theta cycle (phase of minimal excitability; see Haegens et al., 2011b; experiment 3 in Chapter IV); while they exhibit a clear nesting in the trough of the FMT cycle (phase of maximal excitability) during the semantic manipulation condition. Phase preference for the gamma bursts during the backwards manipulation condition, on the other hand, is less clearly defined, but has a maximum just before the peak (see Figure 3.1). Furthermore, the data also indicate that during the retention condition there is the least gamma synchronisation during the trough, while during the semantic manipulation condition the gamma bursts stay clear of the peak of the frontal midline theta cycle. During the backwards manipulation condition the posterior gamma bursts are the least prominent during the falling phase of frontal midline theta (see Figure 3.1).

These results of nesting of posterior gamma oscillatory activity increase into specific phases of a frontal midline theta cycle might actually represent a specific correlate of the interaction between WM and semantic LTM, more specifically, of accessing semantic LTM during a WM task. In contrast to the results regarding upper alpha decrease (see results in Chapter II; Berger et al., 2015) where we could only find differences between the retention condition and the two manipulation conditions, the coupling of posterior gamma amplitude to the excitatory phase of a frontal midline theta cycle would thus code for the semantic manipulation of information in WM specifically.

Unfortunately, the current task looking at the differences between essentially three memory systems, namely short-term memory (retention), working memory (backwards manipulation) and semantic long-term memory (semantic manipulation), has too many factors that might drive the underlying mechanisms to draw any clear
conclusions. For instance, it might be that the obtained results represent increasing task difficulty from the retention condition to the manipulation conditions as indicated by the behavioural results (see Berger et al., 2015). This might indicate that more cognitive resources are needed for the execution of the mental manipulations, and especially for the mental manipulation that involves information from semantic LTM, than for the pure retention of information (e.g. Chapter IV). Furthermore, manipulating a string of four consonant letters (and especially with knowledge from semantic LTM) is a more complex task than simply retaining them; which indicates that a larger cortical network needs to be recruited or recruited more strongly and hence locking local activity over task relevant cortical areas to the phase of maximal excitability (see Chapter IV; Haegens et al., 2011b; von Stein & Sarnthein, 2000) could benefit the task execution.

In order to be able to further investigate this coupling mechanism and what drives it, we decided to leave out the semantic long-term memory component, as it is hard to control the richness of participants’ activations and their ease of mnemonic access. We utilised a visuo-spatial working memory task with clear local hubs of information processing over cortical areas (see Goodale & Milner, 1992; Griesmayr et al., 2014; Sauseng et al., 2009a) readily measurable with scalp EEG and varying degrees of load and complexity (retention vs mirroring of location of squares in a matrix; for further details the reader is kindly referred to Chapter IV). With this paradigm, we then investigated the nesting of increased neuronal firing (expressed through increase in fast frequency oscillatory activity; see Buzáki & Wang, 2012) into specific phases of a frontal midline theta cycle – which is thought to be a prime candidate for being the mechanism which allocates prefrontal cognitive resources (see for example Liston et al., 2006) to task-relevant posterior cortical brain areas – more closely in a task with less possibly confounding factors.
Figure 3.1  FMT phase locked posterior gamma activity increase
Graphic depiction of the frontal midline theta cycle to which bursts of left posterior parietal (PO3) fast oscillatory activity during the early retention interval are clustered (warm colours) and during which FMT phase there is no increased local gamma activity (cold colours), respectively.
Chapter IV  The gear box in the brain: dynamic resource allocation through oscillatory coupling in the human cortex

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Abstract

Temporarily holding information in memory and mentally manipulating it is known as working memory. These operations have been shown to be implemented by a distributed cognitive control network in the brain comprised by the dorsolateral prefrontal, anterior cingulate and posterior parietal cortices. The neural mechanisms controlling interaction within this network are yet to be determined. Here we show that the brain uses a neuronal phase coding mechanism for gating prefrontal cognitive resources during a demanding working memory task, thereby dynamically allocating cognitive resources by controlling interaction between prefrontal cortex and remote neocortical areas. Using EEG recordings and combined EEG and non-invasive brain stimulation we obtained fast brain oscillations at posterior sites nested into prefrontal slow brain waves. Depending on cognitive demand this high frequency activity was nested into different phases of the slow wave enabling a dynamic coupling or de-coupling of the fronto-parietal control network adjusted to cognitive effort.
1. Introduction

Retaining information which is no longer available in the environment and mentally manipulating this information is known as working memory (WM) (Baddeley, 1992). These mnemonic operations require a high degree of cognitive control which has been suggested to be implemented by a distributed cognitive control network in the brain (Cole & Schneider, 2007; Dosenbach et al., 2008; Liston et al., 2006). Amongst other neural structures, the dorsolateral prefrontal, anterior cingulate, and posterior parietal cortices comprise this control network (Cole & Schneider, 2007; Dosenbach et al., 2008; Liston et al., 2006; MacDonald et al., 2000; Weissman et al., 2005). It is suggested that in particular cognitive monitoring functions rely on the interaction between anterior cingulate and posterior parietal cortices (Liston et al., 2006). The exact neuronal mechanisms by which posterior brain regions can dynamically access prefrontal resources in situations requiring high demand of cognitive control remain unknown, however. Here we present novel evidence that the human brain uses a neuronal phase coding mechanism for gating prefrontal cognitive resources during a demanding working memory task, thereby dynamically controlling communication between prefrontal cortex and remote posterior neocortical areas.

Allocation of cognitive resources is associated with rhythmical fluctuations of electrical brain potentials in a frequency range between 4 and 8 Hz in medial PFC and anterior cingulate cortex (Cavanagh & Frank, 2014; Gevins et al., 1997; Mitchell et al., 2008; Sauseng et al., 2007) - also known as frontal-midline (FM) theta activity. Theta oscillations entrain neuronal spiking as well as fast oscillatory activity in the human and the animal brain (Axmacher et al., 2010; Barry et al., 2012; Canolty et al., 2006; Fujisawa & Buzsáki, 2011; O’Keefe & Recce, 1993; Sauseng et al., 2009; Sirota et al., 2008), and can be found in the neocortex as well as in the hippocampus (Buzsáki, 2006). Fast brain oscillations and neuronal spiking are more likely to occur during the excitatory than the inhibitory phase of the theta period. This mechanism of phase coding has been reported not only on a local scale. Recent evidence in rats and mice suggests that neocortical and tegmental neurons are entrained by prefrontal as well as hippocampal theta oscillations (Fujisawa & Buzsáki, 2011; Sirota et al., 2008) – findings well in line with the idea that this kind
of temporal coding allows for the precise timing of widespread neuronal activity and thus, supports effective neuronal communication throughout the brain (Fries, 2005). Since WM processes particularly engage PFC and are associated with FM-theta activity we specifically investigated the role of these anterior theta oscillations in the coordination of neuronal activity in remote neocortical areas. We hypothesized that FM-theta activity and associated phase-coding principles represent a highly efficient gating mechanism (Raghavachari et al., 2001) within the fronto-parietal control network allowing or preventing access to prefrontal cognitive resources; i.e. constituting a prime mechanism for highly flexible, cost efficient and dynamic resource allocation.

2. Results

2.1. Experiment 1

Electroencephalographic (EEG) signals were recorded from healthy human participants while they performed a visuospatial WM task. In four different experimental conditions they either had to retain one or four spatial target positions in a grid display (retention load 1 and load 4), or mentally mirror one or four target positions around a vertical gap in the grid before retaining the newly formed mental image (manipulation load 1 and load 4) (Figure 4.1A).

2.1.2. Task Accuracy

Mean accuracy rate (correct responses in percent) was generally higher for retention (89.6 ± .9% SEM) compared to manipulation (82.8 ±1.1 %) and subjects generally performed better for load 1 (94.9 ±7%) compared to load 4 (77.6 ±1.3%), as indicated by significant main effects for CONDITION (F(1/24)=67.63; p<.001) and LOAD (F(1/24)=280.35, p<.001). Furthermore, a significant interaction was found for CONDITION x LOAD F(1/24)=38.51; p<.001. Post-hoc t-testing (FDR corrected for multiple comparisons; Benjamini & Hochberg, 1995) showed no difference in performance for load 1 between retention (95.7 ±5%) and manipulation (93.9 ±1%), whereas for load 4, performance declined by 11.8% for manipulation (71.7 ±1.5%) compared to retention (83.5 ±1.5%; Figure 4.1B).
2.1.3. FM-theta Event-Related Amplitude Increase

In line with the hypothesis that FM theta amplitude is modulated by cognitive load there were differences between the experimental conditions in FM-theta amplitude: the two more demanding conditions requiring the processing of four targets (retention load 4 and manipulation load 4) elicited significantly stronger FM-theta activity compared to the two easier conditions (retention load 1 and manipulation load 1) (main effect for factor LOAD $F_{(1/24)} = 12.4, p<.01$; Figure 4.1C), well in line with the idea that increased central executive demand provokes FM-theta activity. Note that even though no main effect for CONDITION or interaction effect for LOAD x CONDITION was found, we did find a significant FM theta increase for all four conditions (retention load 1 and 4, manipulation load 1 and 4) in comparison to baseline (as indicated by values well above 100% for all conditions, see figure 4.1 C).
Figure 4.1 Depiction of the task, behavioural results and FM theta amplitude increase of experiment 1

(A) Schematic depiction of single trials from experiment 1 with conditions „retention“ and „manipulation“ and variation in memory load (load 1 vs. load 4). In the retention condition spatial locations of one or four items had to be retained for 2000 ms and then compared to a probe. In the manipulation conditions spatial locations of items had to be mentally mirrored around the vertical gap in the grid, retained in memory and compared to the probe. (B) Mean accuracy rates (in percent) for the four conditions from experiment 1. Error bars represent standard error of mean. (C) Task-related FM theta amplitude increase during the delay period at electrode AFz. Values beyond 100% indicate increased amplitude compared to baseline. Error bars represent standard error. Brain maps show the topographical distribution of FM-theta activity difference between load 4 and load 1.
2.1.4. FM-theta Phase to Posterior Gamma Amplitude Coupling

Next we investigated how FM-theta phase entrains fast oscillatory activity as an indicator of increased neuronal firing (Buzsáki & Wang, 2012) in remote cortical areas using the following methodology: for each single trial and experimental condition, amplitude of EEG activity >30 Hz at any of the recorded EEG sites was sorted according to FM-theta phase and then averaged into equally large theta phase bins. This resulted in an estimate of high frequency amplitude as a function of FM-theta phase. In a first analysis step all electrode sites at which gamma amplitude was significantly modulated by FM-theta phase (non-uniform distribution of gamma amplitude across the FM-theta cycle indicated by either a significant main effect or significant interaction involving the factor FM-THETA PHASE in repeated measures ANOVAs; see online materials for details) were identified. At 20 out of 60 electrode sites gamma amplitude was modulated by FM-theta phase. These 20 sites formed three electrode clusters: one frontal cluster (electrode sites FP1, F7, FC5, FC1, FCz and FC2), one left temporo-parietal cluster (electrode sites C3, T7, CP1, CP3, CP5, CP7, TP7, P5 and P7) and one right temporo-parietal cluster (electrodes C6, CP6, TP8, P2, P4 and P6). FM-theta phase-sorted gamma amplitude was then averaged across electrode sites for each of the three clusters separately and then cross-correlated with a template in shape of a theta cosine-wave. Compared to surrogate data (for the bootstrapping procedure, see online materials for details) only high frequency EEG activity at the right temporo-parietal cluster was significantly entrained by FM-theta phase in each of the four experimental conditions (indicated by significantly higher peaks in the cross-correlograms, p<.01).

However, interestingly, FM-theta phase associated with maximal right temporo-parietal gamma amplitude differed between conditions: with increasing task difficulty a precession of gamma amplitude to FM-theta phase coupling towards the trough of the theta cycle was observed (Figure 4.2A; significant interaction between MEMORY LOAD, CONDITION, and FM-THETA PHASE: $F_{(9/216)}=2.65$, $p=.033$, Huynh-Feldt corrected). In the easiest condition (retention load 1) the right temporo-parietal gamma burst was nested shortly prior to the peak of the FM-theta cycle, whereas in the hardest condition (manipulation load 4) this high frequency activity burst occurred slightly before the trough of the FM-theta period. Thus, the amount of
cognitive control required for the task determined the phase of FM-theta to which remote, right posterior gamma amplitude was locked. This suggests a dynamic and effort-related modulation of the interaction between prefrontal and temporo-parietal regions through fine-grained alterations in the phase-coupling between nested frequencies. More specifically, the findings from experiment 1 led to the proposition that FM-theta phase controls task-active posterior neuronal firing, and hence acts as a highly efficient gating mechanism for the allocation of cognitive resources. We therefore predicted that the impact of disrupting this temporo-parietal brain region with transcranial magnetic stimulation (TMS) should depend on the timing of the pulse in respect to the FM theta phase (see experiment 2).

2.2. Experiment 2

To demonstrate a causal relationship between the above described nesting of posterior gamma amplitude into specific FM theta phases and task performance, we conducted an experiment in which FM-theta phase-dependent neurostimulation was applied. EEG was recorded while participants performed the most difficult condition from experiment 1 (manipulation load 4; see above). In each single trial, randomly within the delay interval, a fast triple-pulse of TMS was delivered to the task-active right temporo-parietal site. Offline, the instantaneous phase of frontal midline theta was obtained for the time point when TMS was applied over the right posterior cortex, and single-trial task performance was sorted accordingly. This resulted in an estimate of task performance as a function of instantaneous FM-theta phase at which right temporo-parietal TMS had been applied. The idea behind this was that, as suggested by experiment 1 FM-theta phase controls task-active posterior neuronal firing as a gating mechanism, therefore TMS should be differentially effective at disrupting task performance dependent on instantaneous FM-theta phase: if TMS at posterior sites is delivered (incidentally) during the trough of the FM-theta cycle (the preferred phase for neural activity of task-active posterior neurons in this condition, as suggested by experiment 1) efficient neuronal processing should be disrupted. If, however, TMS pulses are applied while FM-theta expresses a peak, i.e. the non-preferred phase of the FM-theta wave, magnetic stimulation should be inefficient at disrupting task performance.
Figure 4.2 Depiction of the theta:gamma coupling results of experiment 1 and the effect of rTMS in experiment 2

(A) FM-theta phase-locked right temporo-parietal gamma amplitude (experiment 1) during the delay period. Z-transformed gamma amplitude from electrode sites within the blue-shaded area in the head map is represented as a function of FM-theta phase extracted from electrode site AFz. Warm colors indicate stronger gamma amplitude. Note that the more cognitive control an experimental condition required (retention load 1 < manipulation load 1 < retention load 4 < manipulation load 4) the more was posterior gamma activity nested into the trough of FM-theta phase. (B) Effect of right temporo-parietal triple-pulse rTMS on task accuracy for manipulation of four items (experiment 2). The strength of the disruptive effect of rTMS depends on instantaneous FM-theta phase at onset of stimulation. When posterior rTMS is applied close to the trough of FM-theta – the sensitive phase into which EEG gamma activity is nested in this condition during experiment 1 – accuracy rates drop close to chance level.
Nicely in line with the pattern we found in the initial EEG data (Figure 4.2A), task performance was significantly modulated by TMS depending on FM-theta phase during stimulation onset (Friedman-test: $\chi^2=21.22$, $p=.012$). Right temporo-parietal TMS applied during the peak of the FM-theta cycle virtually did not impact on task performance at all. However, if applied shortly before the trough of FM-theta – the phase to which increased gamma amplitude had been locked in experiment 1 – right posterior TMS led to a drop in performance close to chance level (Figure 4.2B). This directly suggests that task-relevant right temporo-parietal neural activity is pulsed and controlled by FM-theta waves.

2.3. Experiment 3

In order to underpin the assumption that the trough of FM theta represents the excitatory phase whereas the peak is rather inhibitory in the current study, we conducted this third experiment. It is common to find increased FM-theta and medial PFC activity during working memory processes (Gevins et al., 1997; Mitchell et al., 2008; Sauseng et al., 2007). This slow oscillatory activity has been shown to influence neuronal activity in a phase-dependent way with preferred spiking around the excitatory phase, and suppressed spiking during the inhibitory phase of each theta cycle (Buzsáki, 2002; Cavanagh & Frank, 2014; Womelsdorf et al., 2010). In a recent study by Haegens and colleagues (2011b) it was demonstrated that for slow oscillatory activity the trough seems to reflect the excitatory phase and the peak is associated with suppressed neuronal spiking. To investigate whether this is also the case for FM-theta activity as measured in the current study, we recorded EEG from a healthy human participant while single pulse TMS was applied over electrode site AFz, the site where strongest FM-theta activity had been obtained in experiment 1 and 2. Trials were then sorted according to FM-theta phase at TMS onset splitting the total number of trials into halves: trials with TMS applied within half a period of the FM-theta wave around the peak and trials with TMS delivered within half a period of the FM-theta cycle around the trough. Single-trial TMS evoked EEG potentials were then compared between the two trial categories. TMS pulses elicited a stronger evoked response when applied around the trough of FM-theta than around the peak from around 200 ms post stimulus onwards (Figure 4.3) (as suggested by a
marginally significant interaction between factors FM-THETA PHASE and TIME \((F_{(4/584)}=2.63, \ p=.053, \text{ Huynh-Feldt corrected})\) in a repeated measures ANOVA; see online methods for details). In agreement with previous work (Cavanagh & Frank, 2014; Haegens et al., 2011b; Womelsdorf et al., 2010) this suggests that in our dataset the trough of the FM-theta cycle represents the excitatory phase whereas the peak is rather associated with suppression of neuronal activity.

Figure 4.3  TMS-evoked responses from experiment 3
Single TMS pulses delivered over mid-frontal electrode sites result in different evoked EEG responses dependent on instantaneous phase of FM-theta at TMS onset: stimulating the PFC near the trough of the FM-theta wave evokes a stronger EEG response from 200 ms after TMS onset onwards compared to TMS at the theta peak. This suggests stronger PFC excitability around the trough of the FM-theta cycle.
3. Discussion

The current study strongly suggests that phase of FM-theta coordinates distributed neuronal activity during higher cognitive processes. It is demonstrated that right temporoparietal high frequency EEG activity is nested into FM-theta waves. Importantly, the alignment of this nesting with the theta peak or theta trough is dependent on the cognitive control required to effectively perform a working memory task. Thus, our studies show that under low load conditions gamma activity is aligned to the theta peak while under high load conditions gamma activity is aligned to the theta trough. Critically, our experiments demonstrate that the relationship between cognitive control required and this theta-gamma alignment is causal: rTMS delivered over the right temporoparietal cortex only disrupted WM task performance when applied while FM-theta was at its excitatory phase (i.e. near the trough) and thus at the phase to which temporoparietal gamma activity was coupled to, therefore, highlighting the direct causal relevance of this mechanism. This also suggests that fronto-parietal interaction relevant for WM control functions takes place only in short, periodic time windows.

Together, the current findings suggest that the relative alignment of posterior gamma to the FM theta peak or trough represents a highly efficient gating mechanism which controls access to cognitive resources through the dynamic coupling or decoupling of fronto-posterior networks with prefrontal areas. This theory is further supported by studies indicating that local neural activity is also modulated by slow oscillations. Specifically, Haegens et al. (2011b) reported the trough of slow oscillatory activity being associated with higher neuronal spiking than the more inhibitory peak of slow brain waves, a principle also suggested to hold true for frontal theta activity (Cavanagh & Frank, 2014; Womelsdorf et al., 2010). In the current study we found that TMS-evoked EEG responses over medial frontal electrode sites are stronger when the magnetic pulse had been delivered near the trough of FM-theta activity. Therefore, we theorize that PFC exerts greater neuronal activity during the theta trough than the theta peak. Moreover, oscillatory brain activity in the gamma range has been proposed as a marker of increased neural firing (Buzsáki & Wang, 2012). At the same time it is well accepted that right temporoparietal brain areas are associated with the processing and storage of visuospatial
information (Linden, 2007; Rahm et al., 2014). Consequently, when – like in the easiest experimental condition in the current study (retention load 1) – posterior gamma activity is coupled to the peak of FM-theta this suggests that increased neural activity in right temporo-parietal cortex and fronto-mediol brain regions is not occurring simultaneously. Given that increased neuronal activity in right temporo-parietal cortex (as indicated by gamma activity) and the excitatory FM-theta phase (the trough) are separated by up to 100 ms it is very unlikely that much neural communication between fronto-medial and temporo-parietal cortex takes place in this condition (Figure 4.4A). In this easiest condition it does not seem to be necessary allocating a lot of cognitive resources to task execution. Therefore, fronto-medial cortical regions associated with cognitive control and monitoring processes seem to actively de-couple from the temporo-parietal cortex by non-simultaneous neuronal firing. Increasing task difficulty and complexity, however, will require deploying more cognitive resources. This is achieved by a dynamic increase in fronto-parietal coupling: the more cognitive resources need to be allocated the closer towards the excitatory trough of FM-theta waves temporo-parietal gamma bursts will be nested. With time windows of increased neural activity (FM theta trough and posterior gamma bursts) between frontal monitoring areas and posterior visuospatial regions more and more overlapping in this way, it is suggested that there is increasingly simultaneous neuronal firing between right temporo-parietal and fronto-medial cortex (Figure 4.4B). Thus, the described mechanism seems very efficient in gating access to cognitive resources governed by fronto-medial brain areas.

Further support for the gating mechanism outlined above comes from a recent study by Polanía and colleagues (2012) who were able to increase working memory performance by applying transcranial alternating current stimulation (tACS) at theta frequency over frontal and parietal cortex simultaneously. Importantly, performance was only increased when stimulation was applied at zero phase lag between frontal and parietal cortex. When stimulation with an offset of 180 degrees was applied (excitatory FM theta trough occurring simultaneously with inhibitory parietal theta peak), this even had a deteriorating effect on working memory performance. This is in good agreement with our current results: similar to our finding of posterior gamma activity (representing increased neural activity) being aligned to the excitatory phase of frontal theta, synchronous theta stimulation, i.e.
with zero phase-lag (excitatory FM theta trough reoccurring with excitatory parietal theta trough), would allow simultaneous neural activity in frontal and parietal cortex. Phase-reversed neurostimulation at theta frequency, i.e. with 180 degrees phase shift, very similar to when posterior gamma activity is aligned to the inhibitory frontal theta phase might lead to non-simultaneous neural activity in a fronto-parietal network and consequently to communication breakdown between the involved brain regions.

Figure 4.4 Schematic depiction of alignment of frontal and posterior neuronal activity by theta-gamma phase-amplitude coupling

(A) A rather easy working memory process will not require deployment of large amounts of cognitive resources. Temporo-parietal cortex does not need to be coupled to fronto-medial cortex. Neuronal activity in frontal cortex is paced by FM-theta phase, with increased neuronal firing at the trough compared to the peak of the theta wave. Gamma activity is a signature of strong neuronal firing in temporo-parietal cortex. If posterior gamma activity is, thus, nested into the peak (the inhibitory phase) of FM-theta there will be non-simultaneous neural firing and therefore a state of decoupling within the fronto-parietal network. (B) A challenging working memory task such as the mental manipulation of four items will require maximal allocation of cognitive resources. Temporo-parietal cortex will need access to prefrontal cortex. This is achieved by alignment of frontal and posterior neural firing, enabled by nesting of posterior gamma activity into the excitatory trough of FM-theta phase. This will lead to effective coupling within the fronto-parietal network, with a dynamic adjustment of this neural synchronization pattern dependent on cognitive resource allocation to the particular task.
4. Conclusion

The current findings present converging evidence for FM-theta activity representing a neuronal mechanism by which fronto-parietal synchronization, and thus access to prefrontal cognitive resources by parietal neurons, is controlled — well in line with recent research in rodents (Lara & Wallis, 2014). Moreover, the current findings underpin the importance of brain oscillatory phase in the control of neuronal firing — not merely on a local but even on an interregional scale. Could, therefore, the described mechanism be a general principle of how the brain coordinates parallel processes and dynamically controls the allocation of resources towards cognitive tasks? We would argue that at least for processes involving the medial PFC this would be the case. And in fact, there is a broad spectrum of cognitive processes all associated with FM-theta activity generated in the medial PFC (Mitchell et al., 2008), in particular tasks involving parallel processing and the precise control of cognitive resources. Whether the suggested neuronal mechanism also exists for other brain frequencies and structures, however, needs to be addressed by further investigation.
5. Supporting Online Material: Methods

5.1. Experiment 1

5.1.1. Participants

EEG was recorded from 30 volunteers after giving written informed consent. Five subjects were excluded from analyses due to too many blinks and horizontal eye movements. The mean age of the remaining sample (n = 25) was 24.8 years (SD = 3.1). Sixteen out of 25 subjects were male, nine were female. All subjects had normal or corrected to normal vision and were not affected by neurological or psychiatric disorders. Handedness was assessed according to the Edinburgh-Handedness-Scale (Oldfield, 1971) which detected 22 right-handed and three left-handed subjects. Subjects were financially compensated for participation. The study was approved by the University of Surrey Ethics Committee.

5.1.2. Experimental Design

Participants performed a visuo-spatial delayed match to sample task (see Figure 4.1A) in a dimly lit room. Stimulus material was presented on a 24” LCD monitor with Presentation® 0.71. At the beginning of each trial a 6 x 6 matrix (covering a visual angle of 6.2° x 6.2°) was presented for 500 ms containing either one or four colored squares (load 1 vs. load 4). If the squares were shown in green subjects had to maintain their positions in memory for 2000 ms (retention condition). If they were shown in red, subjects had to mirror their positions around a vertical gap in the matrix and keep the new positions in memory (manipulation condition). Then, a probe matrix with one or four grey labelled squares, depending on the number of previously shown squares, was presented for 2000 ms. Subjects had to indicate by button press whether the maintained/mirrored positions matched the squares in the probe matrix or not. During the inter-trial interval which was jittered with a duration between 1500 and 2000 ms, a central fixation cross was presented. For each condition, manipulation load 1 (ManL1), manipulation load 4 (ManL4), retention load 1 (RetL1), retention load 4 (RetL4) 70 trials were run. Half of the trials were match and the other half non-match trials. In each non-match trial, the position of one square changed. Conditions were presented in randomized order and luminance
was equal between red and green squares. In order to avoid afterimages during the delay interval the matrix shown during the delay period was filled with a grey/black pattern. Subjects were instructed to answer as correctly as possible. A training block was carried out at the beginning of the experiment.

Behavioral data were statistically analyzed using a two-way repeated-measures ANOVA with factors CONDITION (retention vs. manipulation) and LOAD (load 1 vs load 4). Mean accuracy rate was the dependent variable. Post-hoc t-tests were corrected for multiple comparison using Benjamini and Hochberg’s false discovery rate (FDR) correction method (Benjamini & Hochber, 1995).

5.1.3. EEG Data Acquisition

EEG was recorded from 60 scalp electrodes (Ag/AgCl ring electrodes; Easycap®) mounted according to the international 10-10 system against a nose reference. Signals were amplified with a 64-channel amplifier system (BrainAmp, Brain Products®). In order to control for vertical and horizontal eye movements two electrodes were placed superior to and next to the right eye. Two additional electrodes were mounted on the left and right earlobe for re-referencing the data offline to a digitally linked earlobe reference. The ground electrode was set at the forehead. EEG-signals were registered between 0.016 and 80 Hz with a sampling rate of 1000 Hz. A Notch-Filter was set at 50 Hz and impedances were kept below 20 kΩ.

5.1.4. EEG Data Analyses

EEG data were analyzed by using BrainVision Analyzer 2.0 (Brain Products®) and Matlab 7.9.0.529 (The Math Works, Inc., Natick, Ma, USA). Statistical analyses were carried out with SPSS or Matlab. Data were offline re-referenced to digitally linked earlobes and high-pass filtered with a low cut-off at 1Hz, 48db/Oct (Butterworth Zero Phase IIR Filter, as implemented in BrainVision Analyzer 2.0). ICA ocular correction was applied in order to remove eye blinks and eye movements. Data were then inspected manually and corrected for remaining artefacts. Afterwards, Laplacian current source density (CSD) was calculated in order to attenuate micro-saccadic eye movements leading to spurious power effects and phase synchrony (Bäuml et al., 2008; Trujillo et al., 2005); and to attenuate
effects of volume conduction on interregional phase synchronization. For data analyses, data were segmented into epochs of 3100 ms for each experimental condition separately (comprising a 600 ms baseline period, a 500 ms encoding matrix and a delay period of 2000 ms). All artefact-free trials, involving correct as well as incorrect responses, were used. The mean number of artefact-free trials for retention load 1 and load 4 was 57.5 (SD=7.9) and 59.4 (SD=7.03), respectively. For manipulation the mean number of artefact-free trials was 58.5 (SD=7) for load 1 and 59.1 (SD=6.3) for load 4. The analyses as described below were applied to the 2000 ms delay period. For statistical analyses, the delay period was divided into 4 time windows (time 1: 500-1000 ms, time 2: 1000-1500 ms, time 3: 1500-2000 ms and time 4: 2000-2500 ms).

5.1.4.1. Analyses of event-related amplitude (ERA) increase/decrease

For ERA calculation, single trials were first submitted to complex Morlet wavelet filtering (as implemented in BrainVision Analyzer 2.0). Data were filtered separately for low (1-30 Hz) and high (30–70 Hz) frequencies in 1 Hz steps (Continuous wavelet demodulation using an 8 cycle Complex Morlet for low frequencies and a 10 cycle Complex Morlet for high frequencies). Amplitude estimates of filtered trials were then averaged for each condition and ERA was calculated. ERA is defined as the percentage of increase or decrease with respect to a predefined baseline period ([activity period – baseline period]/baseline period *100). We extracted a baseline period from – 500 to -200 ms for low frequencies and from -300 to -200 ms for high frequencies prior to the encoding matrix. Amplitude estimates from the delay interval were then averaged into four time windows (as described above). For statistical analysis a three way ANOVA with factors CONDITION (retention, manipulation), LOAD (load 1, load 4) and TIME (time 1, time 2, time 3, time 4) was run for theta (4-7 Hz) ERA at electrode AFz. We selected AFz for statistical analysis, as we found strongest synchronization at this site compared to neighboring electrodes.

For gamma ERA at 30-50 Hz (gamma 1) and 50-70 Hz (gamma 2), a four way ANOVA with factors CONDITION (retention, manipulation), LOAD (load 1, load 4), TIME (time 1, time 2, time 3, time 4) and ROIs (nine regions of interest) was applied. Electrodes were pooled together into nine different ROIs in order to
enhance signal-to-noise ratio. ROIs were defined as follows: anterior left: Fp1, AF7, AF3, F7, F5, F3; anterior midline: AFz, F1, Fz, F2, anterior right: Fp2, AF4, AF8, F4, F6, F8; central left: FT7, FC5, FC3, T7, C5, C3, TP7, CP5, CP3; central midline: FC1, FCz, FC2, C1, Cz, C2, CP1, CPz, CP2; central right: FC4, FC6, FT8, C4, C6, T8, CP4, CP6, TP8; posterior left: P7, P5, P3, PO7, PO3, O1; posterior midline: P1, Pz, P2, POz, Oz and posterior right: P4, P6, P8, PO4, PO8, O2. Greenhouse-Geisser correction was applied and paired-sample t-tests (FDR corrected for multiple comparison; Benjamini & Hochberg, 1995) were used for post-hoc comparisons.

5.1.4.2. Frontal midline Theta locked Gamma Amplitude Modulation

For each experimental condition, single trial phase values for theta (5 Hz) at AFz and single trial amplitude values for gamma at 30, 40, 50, 60 and 70 Hz (10 Hz frequency bins) at 60 electrode sites were estimated (wavelet filter parameters see above). Then, z-transformed amplitude values of 30, 40, 50, 60 and 70 Hz were sorted with respect to instantaneous AFz theta phase angles (see Sauseng et al., 2009 for a similar approach) and averaged into 10 theta phase bins (each bin covering 36° of a theta cycle). As an explorative analysis, five way repeated measure ANOVAs with factors FREQUENCY (30 Hz, 40 Hz, 50 Hz, 60 Hz, 70 Hz), TIME (time 1, time 2, time 3, time 4), CONDITION (retention, manipulation), LOAD (Load 1, Load 4), and FM-THETA PHASE (segment 1-10) were calculated for each of the 60 electrodes with FM theta phase sorted gamma amplitude as the dependent variable. This was done in order to determine whether there is a significant main effect or any interaction involving the factor THETA PHASE SEGMENT as an indicator for modulation of gamma amplitude by FM-theta phase. Explorative analysis revealed three electrode clusters showing gamma amplitude modulation by FM-theta phase: a frontal cluster (FP1, F7, FC5, FC1, FCz, FC2), a left centro-temporo-parietal cluster (C3, CP1, CP3, CP5 T7, TP7, P7, P5) and a right centro-temporo-parietal cluster (C6, CP6, TP8, P2, P3, P6). In a next step, analyses were focused on these three clusters and five way repeated measures ANOVAs with factors FREQUENCY, TIME, CONDITION, LOAD, and FM-THETA PHASE with frontal midline theta phase sorted gamma amplitude averaged within each of the three electrode clusters as the dependent variable were applied.
5.1.4.3. Theta Phase and Gamma Amplitude Cross Correlations

In order to further evaluate whether gamma amplitude is significantly modulated by FM-theta phase, cross-correlations between the cosine function of a theta cycle and theta phase-sorted gamma amplitude were carried out for each condition within an electrode cluster (see above) separately. Two full theta periods (and equivalent sorted gamma amplitudes) were used for cross correlations. If posterior gamma amplitude was not modulated by frontal midline theta phase one would expect a flat cross-correlogram with coefficients close to zero. Substantial gamma amplitude modulation by frontal midline theta phase, however, should result in a cross-correlogram with a clear peak different from zero. A bootstrapping procedure (500 runs) was run in order to determine a critical coefficient at which the cross-correlogram peak in the real data was considered significantly different from randomised data (p<.001). Moreover, this approach allowed determining the value of frontal midline theta phase to which posterior gamma bursts were locked.

5.2. Experiment 2

5.2.1. Participants

Ten healthy volunteers (six females; mean age 25.7, (SD=3.7)) were tested after giving written informed consent. All but one of the participants were right handed, and none of the volunteers suffered from any psychiatric or neurological disorders. Participants had normal or corrected to normal vision. The study was approved by the University of Surrey Ethics Committee.

5.2.2. Experimental Design

A similar experimental design as in experiment 1 was used. The exception was that only trials with four items that had to be mentally manipulated were used (manipulation load 4). The experiment consisted of a total of 280 trials. In each of the trials the memory set was shown for 500 ms, followed by a 2000 ms delay period and 2000 ms of presentation of the probe stimulus and a variable inter-trial-interval between 1500 and 2000 ms (see experiment 1 for details). In this experiment, however, in 210 trials a TMS triple-pulse was delivered within the delay period. The
onset of the triple-pulse was jittered between 500 and 1500 ms after memory set offset. Subjects were instructed to answer as correctly as possible. A training block was carried out at the beginning of the experiment.

5.2.3. EEG Data Acquisition

EEG data were recorded from 30 scalp sites arranged according to the extended 10-10-system using a BrainAmp MRplus amplifier (BrainProducts®) and a TMS compatible electrode cap with Ag-AgCl electrodes (Easycap®). Signal was acquired at a rate of 1000 Hz in a frequency range between 0.016 and 80 Hz (with a notch filter at 50 Hz). During recording a reference on the tip of the nose was used and the ground electrode was placed at electrode position FPz. Horizontal and vertical EOG was recorded.

5.2.4. TMS protocol

A MagStim Rapid2 TMS stimulator (MagStim®) with a 7 cm figure-eight coil (MagStim®) was used. In TMS trials a 50 Hz triple-pulse at 80% of individual resting motor threshold was delivered to the right parietal cortex. The stimulation site was EEG electrode site CP6, a position directly in the middle of the right posterior electrode cluster identified in experiment 1. Mean stimulation intensity was 43.7 (SD=5.4) % maximal stimulator output. The triple-pulse was delivered during the delay period with an onset jittered across trials (see above). EEG was recorded throughout the experiment.

5.2.5. EEG Data Analysis

Preprocessing and artefact rejection was done as described for experiment 1. Data were segmented into epochs starting 1000 ms prior to and ending at onset of the TMS triple-pulse. For electrode site AFz segments were then filtered between 4 and 7 Hz, and instantaneous phase was derived. EEG phase at TMS onset was estimated based on the value gathered 91 ms prior to the triple-pulse (half period of the centre frequency at 5.5 Hz) to avoid results being influenced by filter ringing artefacts at the segment edges. Trials were then sorted into ten frontal midline theta phase bins.
of 36° and the rate of correct responses was calculated for each of the theta phase bins.

Due to the relatively small sample size a non-parametric Friedman test comparing accuracy rates across the ten frontal midline theta phase bins was run.

5.3. Experiment 3

5.3.1. Participants

One healthy, right handed, male volunteer (aged 35) was tested after giving written informed consent. The participant had corrected to normal vision. The study was approved by the University of Surrey Ethics Committee.

5.3.2. Experimental Design

To provoke FM-theta activity the participant was asked to silently count down from 10000 in steps of 17. While the subject performed the task with open eyes TMS single-pulses were delivered and EEG was recorded. In a second condition EEG was recorded while the participant was silently counting down from 10000 in steps of 13 without TMS being applied.

5.3.3. EEG Data Acquisition

EEG data were recorded from 30 scalp sites arranged according to the extended 10-10-system using a BrainAmp MRplus amplifier (BrainProducts®) and a TMS compatible electrode cap with Ag-AgCl electrodes (Easycap®). Signal was acquired at a rate of 1000 Hz in a frequency range between 0.016 and 80 Hz (with a notch filter at 50 Hz). During recording a reference on the tip of the nose was used and the ground electrode was placed at electrode position FPz. Horizontal and vertical EOG was recorded.

5.3.4. TMS protocol

A MagStim Rapid2 TMS stimulator (MagStim®) with a 7 cm figure-eight coil (MagStim®) was used. Every four to six seconds a single TMS pulse at 120% of
the individual motor threshold was delivered. The stimulation site was EEG electrode site AFz. EEG was recorded throughout the experiment.

5.3.5. EEG Data Analysis

EEG data from electrode site AFz were filtered (see above) and segmented from -1000 ms to +500 ms in respect to the TMS pulse (or a null-event trigger in the no-TMS condition). Then single trial data were baseline corrected according to the 1000 ms pre-pulse interval. For each single trial instantaneous theta phase (4 – 6 Hz) at electrode site AFz was estimated 200 ms prior to TMS onset (as an estimate of theta phase at TMS application one cycle later). Next ICA was applied to single trial EEG data to reduce the artefact caused by TMS pulses. There were, however, residual TMS artefacts between 100 ms before TMS (due to data filtering) and 100 ms post-TMS. Segments containing any additional artefacts (such as EOG or EMG artefacts) were removed from the analysis. Next, trials were sorted into two categories: trials with the estimated theta phase at the peak +/- π/2 and trials with the estimated theta phase at the trough +/- π/2. This phase sorting was also done for no-TMS trials; they were then averaged, and the according no-TMS average was subtracted from TMS single trials to take out any post-stimulus artefact merely based on phase-sorting (Kruglikov & Schiff, 2003). Then for each single trial, amplitude was averaged for a baseline interval (-500 to -250 ms), 100 to 199 ms post-TMS, 200 to 299 ms post-TMS, 300 to 399 ms post-TMS, and 400 to 499 ms post-TMS. Finally, a repeated measures ANOVA with within-group factor TIME (five time windows as defined above) and group factor FM-THETA PHASE (peak vs. trough) was run. Huynh-Feldt correction was applied.
Chapter V  The role of frontal EEG theta activity in voluntary resource allocation in working memory

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Abstract

Working memory (WM) consists of various cognitive processes and maintains and manipulates information no longer available in the environment. Individual processes are co-ordinated by a central monitoring component ensuring their efficient interaction. On cortical level, frontal-midline theta (FMT, a slow EEG frequency found in prefrontal brain areas) was repeatedly found to be a prime candidate for serving as such monitoring component. FMT has been shown to orchestrate local activity as well as distant brain areas in visual WM by synchronising fast oscillations (gamma, 30-80 Hz) in posterior brain areas into specific phases of the FMT cycles. This mechanism has been shown to be sensitive to task demands (the more demanding the task the closer to the excitatory phase of the FMT cycle) and causally linked to behavioural performance. The aim of the current study was to investigate whether this fronto-parietal theta-gamma synchronisation reflects voluntary executive control in WM. We designed a dual-task delayed-match-to-sample EEG experiment where participants retained visuospatial and figural information simultaneously. Most importantly, they were instructed to either prioritise the visuospatial or the figural information in alternating blocks. We found that in brain areas sensitive to visuospatial information (dorsal stream of the visual system) gamma activity was locked to the excitatory phase of FMT when participants prioritised visuospatial information. In contrast, when participants prioritised figural information gamma in the dorsal stream was locked to the inhibitory FMT phase. This suggests that FMT-phase acts as a central relay orchestrating distributed neuronal activity according to the subjective importance of task specific information to be retained in WM.
1. Introduction

The concept of working memory (WM) has been an area of intense interest in cognitive psychology and especially since the 70s when Baddeley and Hitch (1974) proposed their influential model of the working memory system consisting of material specific storage-sub-components (visuo-spatial sketchpad and phonological loop) and a supervising master component (central executive). They defined working memory as short-term storage and utilisation of information that is no longer available in the environment (Baddeley, 1986; 1992). There are numerous other similar working memory models, for instance Cowan’s (1995) which did not isolate WM from long-term memory strictly but assumed that the one is just a subset of the other, currently under attentional focus. What the models had in common though, was that both proposed that the system consists of numerous cognitive processes and functions and that the storage components are material-specific; whereas the supervising/mediating attentional super-component is material unspecific and hierarchically superior.

The neuronal implementation of WM reflects its diverse sub-processes as it comprises various cortical and subcortical brain areas which form a large neuronal network (Braunlich et al., 2014; Fuster, 1997; Gazzaley, Rissman & D'Esposito, 2004). Furthermore, several hub regions could be identified which can switch flexibly between networks depending on task requirements (e.g. Cole et al., 2013 for a meta-analysis of functional imaging studies) and task goals (e.g. Chadick & Gazzaley, 2011; Zanto and Gazzaley, 2013). Working memory processes which require a high degree of cognitive monitoring have repeatedly been associated with a network comprising mainly posterior-parietal material-specific areas and material-unspecific prefrontal areas (Fuster, 1997; Gazzaley et al., 2004; Linden, 2007; Vogan et al., 2014). In such tasks the cognitive control and monitoring hub which is responsible for allocation of resources has long been suspected to be mainly located at prefrontal areas, specifically at the anterior cingulate cortex (ACC; see for example Miller and Cohen, 2001 for a review; Liston et al., 2006). Such increase of top-down activity, reflecting increased cognitive demand and attention processes, was furthermore shown to react not only to external stimulation but also to internal stimulus processing, for instance during the delay period in a working memory.
delayed-match-to-sample paradigm (DMtS; for a review see Gazzaley & Nobre, 2011). This focal increase of activity at medial frontal brain areas has also been observed in numerous EEG studies. Gevins and colleagues (1997) for example showed that increase of oscillatory activity in the theta frequency range (4-8 Hz) over Fz and AFz electrode positions is strongly associated with increased task difficulty, i.e. increased executive demand. Furthermore, source localization methods enabled to pinpoint the likely origin of this focal theta activity increase (frontal midline theta, FMT) in the ACC (e.g. Ishii et al., 1999; Onton et al., 2005). Moreover, increased FMT activity was found to be strongly associated with increased task difficulty and working memory load as well as sustained attention and rather unspecific allocation of cognitive resources during for instance DMtS WM studies (e.g. Chapter IV; Hanslmayr et al., 2008; Sauseng et al., 2007, 2010; for a review see Cavanagh & Frank, 2014 or Mitchell et al., 2008). During the delay interval of such tasks (the working memory maintenance) sustained interactions between perceptual areas that code for the to-be-retained information, parietal cortices and prefrontal control areas are being kept activated (e.g. Collette & Van der Linden, 2002; Gazzaley et al., 2004). Given that local increase of neuronal firing in WM operations is expressed by the increase of posterior fast frequency oscillatory activity (gamma band oscillations; e.g. Buzsáki & Wang, 2012; Howard et al., 2003) and that frontal control functions are linked to FMT activity (e.g. Berger et al., 2015; Griesmayr et al., 2010, 2014; Sauseng et al., 2010), it is highly plausible that this fronto-parietal network is implemented by interactions between posterior gamma and frontal theta oscillations (e.g. for a review see Von Stein & Sarnthein, 2000; Canolty & Knight, 2010). Indeed numerous EEG studies demonstrated functional coupling between theta and gamma oscillations in perceptual processes (e.g. Demirlap et al., 2007) as well as in memory processes (e.g. Canolty et al., 2006; Fell & Axmacher, 2011; Sauseng et al., 2008; Schack et al., 2002). For instance, in a recent study (see Chapter IV) we were able to show that during active maintenance or manipulation of information in WM bursts of gamma oscillations in task relevant posterior areas are nested into specific phases of frontal midline theta oscillations. This phase:amplitude coupling is expressed in a way that the more cognitive resources are needed to carry out the task (i.e. the higher the task demand) the closer to the trough (the phase of maximal excitability; see Chapter IV experiment 3; Haegens et al., 2011b) of a
frontal midline theta cycle the posterior gamma bursts are nested. Conversely, if the task is very easy, posterior gamma bursts are nested more towards the peak of frontal midline theta (the phase of minimal excitability; Chapter IV; Haegens et al., 2011b). We interpreted these findings in a way that the phase of frontal midline theta oscillations represent a highly efficient and cost effective gating mechanism for the allocation of cognitive resources determined by task demands (see also Chapter VI). It allows the dynamic coupling and decoupling of areas within a functional network, and allows task relevant posterior cortical areas to flexibly access cognitive resources implemented in the prefrontal cortex (see Chapter IV). Moreover, we were able to demonstrate that this functional coupling between frontal midline theta phase and posterior gamma bursts is behaviourally relevant. By combining EEG with rTMS (repetitive transcranial magnetic stimulation; see Pascual-Leone et al., 2002; Wagner et al., 2007, for a description of the method) we were able to significantly disrupt behavioural performance selectively according to frontal midline theta phase (Chapter IV). We applied a triple TMS pulse (50 Hz) over task-relevant right posterior parietal areas during the retention interval of a difficult visuo-spatial DMtS task (for which we had found posterior gamma nested into the trough of the FMT cycle, see Chapter IV) and offline sorted the trials according to the frontal midline theta phase the posterior TMS pulses had accidentally fallen into. We found significant performance decline only for those trials where the TMS pulse was delivered during the FMT trough while performance was unimpaired for all other phases comprising the falling and rising phase and the positive peak (Chapter IV).

A somewhat similar mechanism was proposed by Jensen and colleagues (2014), but in the perceptual domain and on local scale. They suggest that the local coupling between gamma power and alpha phase reflects a mechanism for the organization of information in the visual cortex by means of phase-coding. Furthermore, they introduce the concept of prioritization of information (in this case contrasts in natural scenes) in early visual regions in the cortex via top-down allocation of attention expressed by alpha phase to gamma amplitude coupling (Jensen et al., 2014).

In order to investigate whether this prioritization of information via top-down modulation – as proposed for the perceptual domain by Jensen and colleagues (2014) – is also present in higher cognitive processing and moreover, whether it is under
voluntary control, we integrated it with our findings on the theta:gamma coding mechanism (Chapter IV) in working memory processes. For this purpose we made use of the dual-stream theory (Baizer et al., 1991; Goodale & Milner, 1992) and neuroimaging studies (e.g. Haxby et al., 1991, 1994) which show that spatial information is processed in posterior parietal areas (i.e. follows the dorsal stream in the brain; the Where-path) while object information is represented mainly in temporal brain regions (i.e. the ventral stream; What-path). We designed a dual DMtS task where participants had to maintain spatial and object (figural) information simultaneously (see Figure 5.1) but were instructed to actively prioritize one over the other while EEG was recorded. This enabled us to investigate how the described coupling mechanism between FMT phase and gamma power behaves over posterior parietal cortical regions relevant for visuo-spatial information processing while we manipulate the active allocation of cognitive resources; i.e. whether participants mainly allocate attention and processing resources to the areas responsible for processing spatial information or to areas which process figural information located in the temporal lobe. If indeed the top-down dynamic allocation of cognitive resources as expressed by the nesting of fast frequency bursts over task relevant posterior areas in specific phases of a frontal midline theta cycle is under voluntary control then we should find: firstly, gamma bursts coupled to the FMT trough (the phase of maximal excitation) over posterior parietal areas during the prioritization of spatial information indicating allocation of maximal cognitive resources to the retention of spatial information. Secondly, gamma bursts coupled to the peak of FMT (the phase of minimal excitability/maximal inhibition) over posterior parietal areas during the prioritization of figural object information indicating that maximal resources are being directed away from areas processing spatial information to areas processing figural information.
2. Material and Methods

2.1. Participants

Data were collected from 30 volunteers (23 female; \(M_{\text{age}} = 24, \text{SD}_{\text{age}} = 5.2\)) after giving their written informed consent. All participants had normal or corrected to normal vision and reported having no prior neurological conditions. Five out of the 30 participants were left-handed and 25 were right-handed (assessed with the Edinburgh-Handedness-Inventory, Oldfield, 1971). The study was approved by the University of Surrey Ethics Review Board.

2.2. Experimental Design

For the duration of the EEG experiment volunteers were seated at a standardized distance of 150 cm in front of a Dell flat screen monitor (total resolution of 1280 x 1024 pixels) in a well lit room. Participants needed to perform a delayed-match-to-sample working memory task which consisted of two visual pieces of information (visuo-spatial [squares] and figural [symbols]) which were simultaneously presented centrally on the screen (see Figure 5.1). They were instructed to memorize the presented information as correctly as possible during the 3 seconds of stimulus presentation. Next they needed to retain the mental image of the stimuli for 2 seconds where they saw a mask on the screen to prevent retinal afterimages. Finally, they needed to compare the mental image to probe items. In every trial participants had to give a match/non-match answer (left- or right-click on a computer mouse) to every one of the two probe items – visuo-spatial (location of green squares) and figural (symbols) probes – which were presented sequentially in randomized order.

Most importantly, participants had to complete four blocks in total and in two blocks they were instructed to actively prioritize the location of the green squares (SPAT block) over the symbols (i.e. they were told they should retain spatial as well as figural information but should make absolutely sure they would get the spatial information correct). Conversely, in the other two blocks, participants had to focus mainly on the symbols (FIG block) while still trying not to forget the location of the green squares. Each block consisted of 32 trials (8 where both probes matched the stimulus-screen, 8 where neither of the probes matched the stimulus-screen, 8 where
the visuo-spatial probe matched the stimulus-screen but the figural did not, 8 where the figural probe matched the stimulus-screen but the visuo-spatial did not) which were presented in randomized order. The SPAT blocks and the FIG blocks alternated and the presentation order was counterbalanced across participants.

Participants carried out a practice run consisting of 16 trials with an equal amount of match/non-match and double-match/double-non-match trials. For those 16 practice trials participants were instructed to simply retain both pieces of information (visuo-spatial AND figural) as correctly as possible. The concept of prioritization was only introduced after the practice run at the beginning of the experimental trials. Visual stimulation was controlled with Presentation Version 0.71 (Neurobehavioural Systems) throughout.

Figure 5.1  Depiction of the delayed-match-to-sample dual-task
Timeline of a trial of the experimental paradigm. Participants had 3 seconds to encode both pieces of information (square location and symbols) while prioritizing one over the other depending on the instruction. The information then needed to be retained for 2 seconds before it had to be compared to a probe for the symbols and a probe for the square locations (in randomized order) where participants had to make a match/non-match decision for each of them.
2.3. EEG Data Acquisition

The EEG data were continuously recorded from 30 Ag-AgCl electrodes inserted into an Easy-cap electrode cap according to the 10-20 international system. The recording sites were FP1, FP2, F7, F3, AFz, Fz, F4, F8, FC5, FC1, FC2, FC6, T3, C3, Cz, C4, T4, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, PO3, PO4, O1 and O2; these scalp electrodes were referenced against a ring-electrode on the tip of the nose and the ground electrode was placed on the forehead. For registering the EEG signals a BrainAmp MR+ 32-channel EEG amplifier (Brain Products) was used and the bandwidth was selected as between 0.016 and 80 Hz with a sampling rate of 1000 Hz. A Notch-filter was set to 50 Hz. Impedances were kept below 8 kΩ. Two electrodes placed above and next to the right eye were used to monitor vertical and horizontal eye movements and blinks. The stimulus presentation and EEG acquisition were synchronized and event triggers marked the onset of the stimulus and probe screens as well as participants’ responses in the EEG signal (recorded with Brain Products BrainVision Recorder).

2.4. Behavioural Data Analysis

For the assessment of participants’ performance the percentages of correct responses in the two conditions were used and statistical analysis was carried out in SPSS. A repeated-measures two-factorial ANOVA with the factors CONDITION (prioritizing SPAT and prioritizing FIG) and PROBE-TYPE (response to SPAT and response to FIG) was run. Post-hoc paired-sample t-tests were used for pairwise comparisons. False discovery rate (FDR) correction (Benjamini and Hochberg, 1995) was applied to control for multiple comparisons.

2.5. EEG Data Analysis

Brain Vision Analyzer 2.0 (Brain Products) was used for analyzing the EEG signal. The EEG data were offline filtered with a low- and a high-cutoff of 1 Hz and 80 Hz, respectively, 48db/Oct filter (Butterworth Zero Phase IIR Filter). To correct for artefacts due to eye blinks and excessive eye movements a semiautomatic Ocular Correction with Independent Component Analysis (Ocular Correction ICA; for detailed information on this method see Jung et al., 2000) was used. Data were then
visually inspected in order to exclude segments with artefacts created by muscle movements or remaining eye movement artefacts which could not be detected by the ICA. The EEG data recorded during the retention interval of the trials were then segmented into two time windows of 1000 ms each (t1: from stimulus offset until 1000 ms into the retention interval; t2: from 1001 ms after stimulus offset until probe onset). The reasoning behind this segmentation of the retention interval is that during the second half of the retention interval the retention processes (like rehearsing the newly acquired material) might be purer than during the first half, where participants might still carry out mental processes and individual strategies that help them to encode the material (Deiber et al., 2007; Postle et al., 2000; see also Griesmayr et al., 2010 for a study comparing working memory retention and manipulation processes during several time windows of the retention interval in a verbal delayed match to sample task). The anterior cingulate cortex (ACC) was then offline selected as region of interest (frontal ROI; see Figure 5.2A) to estimate frontal midline theta activity. Low resolution electromagnetic tomography analysis (LORETA; Pascual-Marqui, 1994) as implemented in Brain Vision Analyzer 2.0 was used for extracting current source density estimates from bilateral ACC for the first time window and the second time window of every single trial for both conditions separately. This source level analysis allows the estimation of cortical sources of oscillatory activity by taking volume conductance and possible dipole structure into consideration when estimating the raw scalp EEG back to its most likely source with the underlying assumption that neighbouring neurons have the tendency to fire in synchronized fashion (for further details to this algorithm please see Pascual-Marqui et al., 1994). Similarly, LORETA was used to select two posterior ROIs, the left BA7 and the right BA7, respectively (Brodmann Area 7; the precuneus and superior parietal lobe; see Figure 5.2B), for estimating fast oscillatory activity (gamma band activity, 30-80 Hz).
Figure 5.2 Sources for FMT and posterior Gamma
Depiction of estimation of the sources of frontal midline theta and posterior gamma. Frontal midline theta (A) was estimated from the bilateral anterior cingulate cortex (ACC). Posterior fast oscillations (B) were estimated from left and right Broadmann Area 7 (posterior parietal cortex, precuneus). Here, only the left BA7 is depicted as significant effects were only obtained from there.

To estimate the dominant center frequency of frontal midline theta (as estimated from the ACC) in our task we carried out Fast Fourier Transformation (FFT; Hamming window of 10%) in order to obtain frequency power estimates for the two time windows for every condition. We then calculated t-tests between the theta amplitude during the task (for each time window and every condition separately) and the prestimulus interval (from -1500 until -500 stimulus onset). The highest t-values (i.e. strongest increase of frontal midline theta in response to task execution) were consistently obtained around a theta frequency of 4 Hz ($t_{\text{SPAT.time 1}} = 6.30$, $SD = +/- 0.21$; $t_{\text{SPAT.time 2}} = 2.72$, $SD = +/- 0.212$; $t_{\text{FIG.time 1}} = 6.82$, $SD = +/- 0.22$; $t_{\text{FIG.time 2}} = 3.10$, $SD = 0.25$); all of which were higher than a critical value of $t_{29} = 2.05$, $p < .05$). Hence we performed all subsequent analyses with a frontal midline theta center-frequency of 4 Hz. The lower center frequency in the current task compared to the one we found in previous delayed-match-to-sample WM experiments (see for example Chapter IV) is not surprising considering a few critical points. Firstly, the current experiment is a dual-task where participants had to carry out two working memory tasks at the same time (i.e. memorizing two individual pieces of information at the same time). This means that the task is much more difficult and complex than presentation of each of the two items on their own since more information has to be kept in memory (e.g. Axmacher et al., 2010). Secondly,
the obtained oscillatory frequency depends on the scale of the network involved in the current process. This means that depending on the size of the involved cortical network the frequency that can be obtained with scalp EEG becomes slower (Buzsáki, 2006; for a review see von Stein and Sarnthein, 2000). Taken together this means that the less complex the task the smaller the cortical network that needs to be activated and likewise, the more complex the cognitive processes needed for task completion the larger the underlying cortical neuronal network resulting in a slower dominant oscillatory frequency (e.g. Crespo-Garcia et al., 2013; Pinal et al., in press).

2.6. Frontal Midline Theta Amplitude

To establish whether general task-specific frontal midline theta activity estimated from the ACC differs significantly not only from the prestimulus interval but importantly, whether it is different between conditions, we calculated a repeated measures ANOVA with the factors CONDITION (SPAT, FIG) and TIME (time window one and two). Paired-sample t-tests were used as post-hoc comparisons. All data were FDR corrected for multiple comparisons.

2.7. Posterior Gamma Amplitude modulation by Frontal Midline Theta Phase

To investigate whether frontal midline theta orchestrates the increase of neuronal firing at remote areas of the cortex (indicated by amplitude increase in fast oscillatory activity at posterior cortical sites; see Buzsáki, 2006; Buzsáki & Wang, 2012), we first obtained the single trial phase values of frontal midline theta (estimated from bilateral ACC) and the amplitude values of gamma activity (left and right BA7). For frontal midline theta phase estimation the EEG signal was wavelet filtered with a center-frequency of 4 Hz (5 cycle Continuous Complex Morlet Wavelet Transformation as implemented in Analyzer 2.0). To obtain the amplitude values of posterior parietal gamma activity, data were wavelet filtered with a continuous 7 cycle Complex Morlet Wavelet Transformation (frequency steps = 5) for five frequency bands with center-frequencies of 30, 40, 50, 60 and 70 Hz. The amplitude values of the oscillations in the five different gamma frequency bands at the left and right posterior ROIs for each condition separately were then sorted according to instantaneous frontal midline theta phase and averaged into ten equal
theta phase angle bins, each comprising 36° of a full theta cycle (for more details on the methodological approach see supplementary material in Chapter IV; or Sauseng et al., 2009).

To establish whether posterior gamma amplitude is significantly modulated by frontal midline theta phase three-factorial repeated-measures ANOVAs were conducted with the factors CONDITION (SPAT, FIG), PHASE (the 10 frontal midline theta phase bins), and FREQUENCY (the 5 fast frequency bands). Theta phase-sorted and -averaged gamma amplitudes served as dependent variable for time window one and two separately.

2.8. Cross Correlations between Frontal Midline Theta Phase and posterior Gamma Amplitude

When the ANOVAs described above indicated significant modulation of posterior gamma amplitude by frontal midline theta phase, the modulation was further investigated by calculating the cross correlations between a standardized cosine function of two full theta cycles and the phase-sorted posterior gamma amplitudes for each condition separately. The coefficients of the obtained cross-correlogram indicate whether the modulation is considerable by showing a peak that clearly differs from zero. Alternatively, when the coefficients form a flat line close to zero, no modulation of gamma amplitude by frontal midline theta phase is present. Furthermore, in order to be considered significantly different from data modulated by chance, the obtained coefficients needed to be higher than a critical coefficient obtained via bootstrapping procedure (1000 randomisations). For the bootstrapping procedure the phase values of the theta cycles were randomly shifted and cross-correlations were calculated for every one of the 1000 randomisations. The bootstrapped cross-correlograms were then averaged and real coefficients were compared to the bootstrapped coefficients across participants using t-tests (p < .01 after FDR correction). Moreover, the latency at which the cross-correlogram produced the strongest coefficient indicates the frontal midline theta phase the posterior gamma amplitude bursts are nested to.
3. Results

3.1. Behavioural Data

Overall performance in the two prioritization conditions (responses for spatial and figural information taken together in each block) did not differ significantly \((t(29) = -0.937, p = .357)\), but was above chance level in both conditions (overall performance in the SPAT-block: 60.63%, SD 4.48; FIG-block: 61.69%, SD 5.4) as indicated by one-sample t-tests \((t_{SPAT}(29) = 12.993, p < .01; t_{FIG}(29) = 11.876, p < .01\) after FDR correction, see Benjamini and Hochberg, 1995) comparing the irrespective performances to the chance level value (set to 50).

A two-factorial ANOVA with the factors CONDITION (prioritizing SPAT and prioritizing FIG) and PROBE-TYPE (response to SPAT and response to FIG) revealed no main effect of CONDITION but a significant interaction effect of CONDITION x PROBE-TYPE \((F(1,29) = 45.80, p < .001, \eta_p^2 = .612\) (see Figure 5.3). Further post-hoc t-tests revealed that when participants were instructed to prioritize SPAT, their performance for the visuo-spatial material was significantly better than for the figural material \((t(29) = 5.65, p < .01\) after FDR correction); likewise, when participants were instructed to prioritize FIG their performance for figural material was significantly better than for visuo-spatial material \((t(29) = 4.406, p < .01\) after FDR correction). Similarly, the performance for the visuo-spatial material was significantly better when they had to prioritize SPAT than when they had to prioritize FIG \((t(29) = 3.003, p < .01\) after FDR correction); and the performance for the figural material was significantly better when participants had to prioritize FIG over SPAT \((t(29) = 5.295, p < .01\) after FDR correction). These results indicate that performance differed significantly between visuospatial and figural test materials only as a function of task instruction.

Importantly though, the performance for visuo-spatial material in the SPAT condition did not differ significantly from the performance for figural material in the FIG condition \((t(29) = .150, p = .882)\). Similarly, there was no significant difference between performance for visuo-spatial material in the FIG condition and figural material in the SPAT condition \((t(29) = 1.436, p = .162)\).
Behavioural results of the dual-task show that overall performance regarding the two materials (spatial and figural) did not differ significantly from each other. Crucially however the instruction, i.e. what material the participants needed to prioritize, had a significant impact on the behavioural performance, as the correct response rate was significantly higher when the information was prioritized.

3.2. EEG Data

3.2.1. Frontal Midline Theta Amplitude

A two-factorial repeated-measures ANOVA with the factors CONDITION (SPAT, FIG) and TIME (time window 1 and 2) revealed no main effect (F(1,29) = .127, p = .724, $\eta_p^2 = .004$) or interaction effect for the factor CONDITION but only a main effect of TIME (F(1,29) = 26.001, p < .001, $\eta_p^2 = .473$) indicating stronger frontal midline theta amplitude in the time window one than in the time window two within the SPAT condition ($t(29) = 3.545$, p < .01 after FDR correction) and also within the FIG condition ($t(29) = 4.534$, p < .01 after FDR correction).
3.2.2. Posterior Gamma Amplitude modulation by Frontal Midline Theta Phase

A three-factorial repeated measures ANOVA with the factors CONDITION (prioritize SPAT, prioritize FIG), FREQUENCY (30, 40, 50, 60 and 70 Hz) and PHASE (the posterior fast frequency amplitude values sorted into the 10 frontal midline theta phase segments) showed a significant three-way interaction \((F(19.151, 555.367) = 1.873, p = .014, \eta_p^2 = .061)\) over the left posterior ROI during the second time window. This indicates differential modulation of the amplitudes of different posterior fast frequencies by frontal midline theta phase depending on the condition, i.e. priority of information that needs to be retained. Additional ANOVAs with the factors CONDITION (SPAT and FIG) and PHASE (the 10 frontal midline theta phase bins) for each of the fast posterior frequencies separately revealed that only the amplitude of the posterior fast frequency around 30 Hz showed significant modulation by frontal midline theta phase – as indicated by the significant interaction effect of CONDITION x PHASE \((F(4.634, 134.396) = 2.716, p = .026, \eta_p^2 = .086)\).

Finally, the calculation of a cross-correlogram between posterior fast frequency (30 Hz) amplitude and a template of frontal midline theta for the two conditions separately (see Data Analysis section) confirmed the results obtained by the ANOVA. It furthermore highlighted that neuronal firing, as indicated by bursts of increase in fast oscillatory activity, over left dorsal posterior parietal cortical areas was locked to the trough of a frontal midline theta cycle during the SPAT condition. In contrast it was locked to the peak of a frontal midline theta cycle during the FIG condition (see Figure 5.4). This indicates selective nesting of bursts of neuronal activity in specific frontal midline theta phase bins depending on subjective priority of the information that needs to be retained.
3.2.3. Post-hoc investigation of total Gamma Amplitude differences

Post-hoc investigation of general amplitude difference of posterior gamma amplitude (25-35 Hz with the center frequency at 30 Hz; see above) as found to be significantly modulated by frontal midline theta phase revealed no significant overall power difference between conditions (a repeated measures ANOVA with the factors CONDITION (SPAT and FIG), LOCATION (left posterior ROI and right posterior ROI; left and right BA7, respectively) and TIME (time window 1 and time window 2) revealed no main effect for CONDITION nor any interaction involving this factor. Main effects for TIME (F(1,29) = 13.698, p = .001, $\eta_p^2 = .321$) and LOCATION (F(1, 29) = 33.947, p = .000, $\eta_p^2 = .539$) but no interaction between those two were found; indicating generally higher posterior gamma power during the second time window and over the left posterior ROI.
4. Discussion

The aim of the present study was to investigate whether flexible cognitive resource allocation in a fronto-parietal control network and the basic underlying mechanisms thereof as measurable with EEG, are under immediate voluntary control. In an earlier study we were able to show that FMT activity represents a hub for flexible resource allocation by providing a gating mechanisms through which posterior brain areas involved in the execution of the current operation can access prefrontal cognitive resources (see Chapter IV). This mechanism is implemented in a way that posterior fast oscillatory activity bursts - representing local information processing – are locked to specific phases of frontal midline theta oscillations. We were able to show that the FMT phase to which the posterior bursts are nested depends on the complexity/difficulty of the task at hand. The more complex the task, the closer to the excitatory theta phase (i.e. the trough) the bursts are locked and conversely, the easier the task, the closer to the phase of minimal excitability (i.e. the inhibitory peak of FMT).

With that background we designed a delayed-match-to-sample dual-task where participants had to retain spatial and figural information simultaneously but importantly, were instructed to prioritize either the spatial or the figural information (see Figure 5.1). According to the dual-stream theory (Goodale & Milner, 1992), local information processing (as expressed by local fast oscillatory power increase; see Buzsáki & Wang, 2012) should be represented at different cortical areas depending on whether it is spatial or figural information (e.g. Haxby, 1991, 1994). While spatial information is primarily processed/maintained in dorsal parietal cortical areas which are easily accessible with the EEG, figural information is mainly processed in ventral temporo-parietal regions of the brain which are not reliably measurable with scalp EEG recordings. Hence, we investigated dorsal parietal cortical areas only and interpret them in the light of their preference for spatial information processing.

By systematically manipulating what participants prioritized and by then comparing the two prioritization conditions in respect to the FMT phase in which fast posterior oscillatory bursts were nested, we were able to monitor access of posterior cortex to cognitive resources implemented in the prefrontal cortex. Our
main results are that task relevant areas in the left posterior parietal cortex that code mainly for spatial information show increased local firing during the excitatory trough of the FMT cycle only when participants had to prioritize the spatial information; indicating active maximal engagement of the dorsal stream. Moreover, when they had to direct their main focus on figural information those spatial-sensitive areas clustered local activity bursts near the inhibitory peak of the FMT cycle; suggesting active disengagement of the dorsal stream to keep maximal resources allocated to the ventral stream (see Figure 5.4; see also Figure 6.1A and 6.1B in Chapter VI). This finding is well in line with previous results that outline a fronto-parietal control network for working memory operations that allows local information processing at posterior brain areas to dynamically access cognitive resources depending on the complexity of the current operation (see Chapter IV). Furthermore, we were now able to show that this basic coupling mechanism between distant brain areas working together for a given task is under voluntary control and can be actively influenced by the subjective importance of the material.

These results were obtained during the active maintenance of information when the information was no longer available in the environment and hence supports findings by Cowan or Postle and colleagues (see Gazzaley and Nobre, 2011 for a review). They argue that selective attention is the mechanism by which the information stays or becomes activated and therefore maintained during the delay period in a WM task. Furthermore, in an imaging study Gazzaley and colleagues (2004) showed that WM maintenance is implemented in the brain by the sustained interaction between coding-relevant perceptual areas and prefrontal control areas. This was shown to play an active role as top-down signals (for instance through retro-cueing) were found to be able to continue to prioritize information maintenance even after the encoding stage (e.g. Chun, 2011; Murty et al., 2011).

Similarly, in early visual processing (i.e. before the encoding stage), a coding mechanism was outlined by Jensen and colleagues (2014) who propose that – similarly to findings on theta oscillations in the hippocampus (e.g. Sirota et al., 2008) – in humans alpha oscillations might serve the purpose of temporal coding of incoming information represented by local increase of fast oscillatory activity driven by attentional processes. They propose that this is a way in which the early visual system might be able to prioritize incoming information driven by the amount of
contrast in the respective receptive fields. By attention being directed directly to the areas in the visual fields that contain the biggest contrasts, it is then those receptive fields that are processed first and consequently receive most attention. In our study exactly such a mechanism of temporal coding was found between the phase of frontal midline theta oscillations and posterior fast oscillatory activity increase; but not driven by bottom-up attention capturing features in the visual field but by conscious top-down prioritization of items during the maintenance of previously presented neutral information.

Importantly it needs to be highlighted that the current coupling results are not due to task complexity/difficulty as our previous findings (see Chapter IV), since there is no difference between the two prioritization conditions with respect to difficulty (see behavioural performance). Furthermore, there is no difference in frontal midline theta activity between the two conditions (i.e. prioritizing figural versus visuospatial information). This clearly shows that the described differential gating mechanism is independent of the magnitude of theta oscillations; as long as prefrontal cognitive resources are engaged - as shown by a general increase in frontal midline theta power during task execution equally for both conditions compared to a prestimulus interval. Similarly, with respect to increased local activity of posterior fast oscillations, we did not find a significant difference between the two conditions but only a generally higher local activity during the time of significant coupling over areas of significant coupling (left posterior parietal cortex during the late maintenance phase). These findings are at odds with research by Sala and colleagues (2003) who suggest that the retention of spatial information shows generally greater activity than the retention of figural information (e.g. Sala et al., 2003).

An important fact that needs clarification and might give an alternative explanation for our findings is that the distinction between dorsal and ventral pathways seems to be not as clear-cut as previously assumed (e.g. Konen & Kastner, 2008; Zachariou et al., 2013). In a very recent neuroimaging study Zachariou and colleagues (2013) could, for example, show that spatial information is not exclusively processed in the dorsal stream but also in areas of the ventral stream. Similarly, while the dorsal stream is clearly specialized in spatial information processing it does also code for object information to a limited extent. We suggest that the differential coupling represents the spatial information and how much
priority is placed on it (i.e. how much the dorsal stream is engaged in the task). But as there seems to be some object coding in posterior parietal areas (i.e. the dorsal stream) too it would need to be investigated further. In order to shed more light on the outlined mechanism of dynamic resource allocation and the conscious manipulation thereof, it would be important to contrast for instance verbal and spatial material or even different modalities, i.e. visually presented information and auditory stimuli.

Another important fact that - given the nature of the material used in the current study - seems puzzling at first and might need clarification is that we found a significant result over the left posterior parietal cortex only. This finding, however, is well in line with research by Morgan and colleagues (2011) and fMRI research by Jackson and colleagues (2011). Importantly, Morgan et al. (2011) conducted an MEG (magnetoencephalography) study where participants saw two coloured semicircles and they had to either merge the colours (ventral stream) and after a retention interval indicate whether a probe semicircle matched that mentally constructed colour or not; or they had to mentally merge the angles in which the semicircles were presented (orientation, dorsal stream) and compare it to a probe semicircle. The third condition, however, was a dual-task and participants had to combine the two features and create and maintain a mental image by merging both characteristics of the semicircles: colour and orientation. Interestingly, what they found is that while the single tasks both showed bilateral activation, the only region that showed stronger activation in the dual-task as compared to the single tasks was the left posterior parietal cortex (precuneus). Moreover, it did so only during the late delay period and only in the frequency range of 25-40 Hz; thus reflecting the results we obtained in the present study. Similarly, Fan and colleagues (2012) obtained very similar results in a serial chaining dual-task where participants had to either individually react to serially presented information or react to a combination of them. Again, an increase in activity in left posterior parietal cortical areas only was a marker for the chaining (reaction to the combination of two items) of information.

Taken together, the results of the present study suggest that posterior parietal cortical areas that actively maintain relevant information expressed by increase of local fast oscillatory activity have flexible access to prefrontal cognitive resources expressed by increased frontal midline theta oscillations. This dynamic resource
allocation is implemented in the brain by a locking of posterior activity bursts to specific phases of the FMT cycle. The closer to the trough (the excitatory phase) the bursts are clustered the more resources are allocated to the operation. Conversely, the closer to the peak (the inhibitory phase) the bursts are nested, the less prefrontal cognitive resources are provided. Moreover, and most strikingly, this basic mechanism of gating of frontal cognitive resources is under voluntary control and can be manipulated by conscious prioritization of otherwise neutral information.
Chapter VI  General Conclusion

The main goal of this thesis was to investigate and identify EEG oscillatory signatures of cognitive control processes in human memory. Evidence that the amount of cognitive control needed for task execution determines to which frontal midline theta phase gamma bursts at task-relevant posterior cortical areas are locked, was presented. Furthermore, by employing a combination of EEG and rTMS (and TMS) it could be demonstrated that this mechanism of phase-coding is behaviourally relevant and causally involved in human mnemonic operations. Moreover, evidence was presented that this mechanism is not solely dependent on task difficulty and complexity but can be influenced with conscious prioritisation of information – by actively directing cognitive resources/attention.

Based on these findings we propose a model that could possibly explain the mechanism with which such flexible allocation of and access to prefrontal control processes might be implemented (see Figure 6.1). It is well known that neurons in the medial prefrontal cortex (PFC) are strongly linked to numerous cortical areas dispersed over the whole brain (for a recent review see e.g. Solbakk & Løvstad, 2014) and are strongly involved in a number of cognitive processes for example in working memory operations (see Chapter IV). This indicates that the PFC is part of a vast array of cortical networks that are involved in numerous cognitive processes. Hence, subpopulations of PFC neurons are linked to different local and distant neuronal populations and thus are part of different functional networks [for simplicity reasons those distant neuronal populations will be referred to as posterior populations for the remainder of this chapter].

One such example of a network between posterior and prefrontal brain areas is the interaction between prefrontal areas and posterior dorsal stream (see Chapter V). This network links neuronal subpopulation of the PFC with neuronal populations in posterior parietal cortex processing visuospatial information. In contrast, processing figural information likewise involves PFC subpopulations but links them with areas in the temporo-parietal cortex. A further example would be the processing of verbal information which activates a functional connection between left hemispheric posterior parietal areas and the PFC (see Chapter III).
As shown in Chapter IV, it seems that activity within such networks depends on the complexity and difficulty of the task at hand. Hence we suggest that, when the task does only require a very negligible amount of prefrontal control processes/cognitive resources, other unspecific networks that are task-irrelevant can be activated and receive prefrontal processing resources (this might for example be thinking about what to buy for dinner or bodily discomfort etc.).

Our model (see Figure 6.1) assumes that the subpopulations of PFC neurons embedded in such cognitive control networks are strongly influenced by oscillatory activity in the theta frequency range (frontal midline theta) and that spiking of those neurons does preferentially occur during the excitatory trough of a theta cycle (see Chapters III, IV and V). Importantly, the subpopulations of PFC neurons share excitatory connections with various different posterior populations (as outlined above). When a specific posterior population is actively processing information (i.e. synchronously active), it activates the PFC subpopulation that it shares connections with – hence, the respective fronto-posterior task-relevant network is activated (Figure 6.1A). The exact frequency of the frontal midline theta (4–8 Hz) oscillations should depend on the size of the network that needs to be co-ordinated (von Stein & Sarnthein, 2000).

If the task at hand is difficult (see Figure 6.1B), posterior task-relevant populations need increased access to PFC control processes (and cognitive resources) and the PFC subpopulation is strongly activated bottom-up by the network and increases its firing in the excitatory frontal midline theta cycle (the trough). Alternatively, it might be that the PFC subpopulation signals increased need for cognitive resources for processing in the relevant posterior population and that the synchronisation to the excitatory frontal midline theta cycle of the task-relevant posterior population is modulated in a rather top-down fashion. Importantly, and irrespective of whether the mechanism is bottom-up or top-down driven, we propose that posterior populations share inhibitory connections (functional lateral inhibition). This means that, when a task-relevant posterior population is strongly activated and activates the respective PFC subpopulation (or top-down alternative: when the respective PFC subpopulation strongly activates the respective task-relevant posterior population), the posterior population simultaneously inhibits other posterior populations. These task-irrelevant posterior populations will then decrease their
firing rate and de-couple from their respective associated PFC subpopulations (or top-down: be de-coupled by the PFC subpopulations due to decreased firing). These task-irrelevant PFC subpopulations will then have a lower firing rate but will still be enslaved by the rhythmical modulation of excitability due to theta oscillations. However, since their posterior counterparts will be inhibited while task-relevant posterior neurons are excited (i.e. during the FMtheta trough) and will only be allowed to fire when this inhibitory drive from competing posterior neurons is attenuated (i.e. during the FMtheta peak), there will be no simultaneous firing between task-relevant PFC and posterior neurons in this case. This manifests itself in a way that task-irrelevant networks will only show bursts of neuronal activity during the more inhibitory theta peak.

In contrast, when the current task is easy and does not need much cognitive control, task-relevant posterior populations will be activated less strongly, will not significantly increase the firing rate of their associated PFC subpopulation (or top-down: the PFC subpopulation will be activated less strongly and will not increase the firing rate of the associated posterior population) and task-irrelevant posterior populations will not be inhibited. The task-irrelevant posterior populations will then increase their firing rates and increase the coupling with their respective PFC subpopulations (or top-down: the coupling will increase which also leads to increased firing rate of the task-irrelevant posterior populations). This will then result in the firing rates of the task-irrelevant posterior populations being locked to the excitatory FMtheta trough and hence allow increased access to prefrontal control processes and resources to the task-irrelevant posterior populations. Simultaneously, the strongly activated task-irrelevant posterior populations will exert lateral inhibition over the task-relevant posterior population which will lead to decreased firing of the task-relevant PFC subpopulation while task-irrelevant neurons are firing. Consequently, the task-relevant posterior populations will only be able to fire during the inhibitory FMtheta peak (see above; Figure 6.1C).

In the case of the working memory dual-task (see Chapter V) this would mean that both, the dorsal and the ventral stream populations are connected to individual PFC subpopulations and form a fronto-posterior network for the dorsal and the ventral stream, respectively (Figure 6.1A) while both also need to be coordinated at the same time and form a transient larger network. When priority is
actively placed on processing spatial information (Figure 6.1B), the dorsal posterior areas are activated preferentially and hence the neurons in dorsal parietal cortex show increased firing during the excitatory frontal theta trough. This allows maximal cognitive resources being allocated to maintaining information processed in the dorsal stream, i.e. visuospatial information. This access to prefrontal resources is gained by simultaneous firing of frontal and parietal neurons. If their firing is separated by 100 ms (as would be the case for theta) the parietal neurons would fire in the peak of the frontal theta cycle and consequently the activation of posterior and frontal areas would be decoupled. Simultaneously, the dorsal posterior population exerts inhibition over the ventral posterior population and hence secures its access to PFC cognitive control and cognitive resources even further while making it nearly impossible for the ventral neurons to fire during the FMtheta phase at which the PFC neurons are active (the trough). When, on the other hand, the figural information is prioritised (Figure 6.1C), the ventral stream sub-network is activated stronger, lateral inhibition from dorsal areas is released and the ventral posterior population starts increased firing in the excitatory theta trough of their associated PFC subpopulation to allocate maximal resources to the maintenance of figural information. At the same time the dorsal parietal population will only be able to fire in the inhibitory theta peak where the lateral inhibition from ventral neurons has temporarily stopped, i.e. when the PFC neurons linked to dorsal parietal areas are already quiet again because the FMtheta cycle is at the peak.

Whether the proposed mechanism operates in a feed-forward/bottom-up way or is implemented as a top-down process, we do not yet know. It might be that posterior neurons will be more or less strongly activated and therefore will increase or will not increase PFC firing. This would clearly describe a bottom-up mechanism. Alternatively, a top-down interpretation might be that task-relevant PFC neurons increase their firing rate and consequently task-relevant posterior neurons are activated more strongly and keep firing in the FMtheta trough, while task-irrelevant posterior neurons will become inhibited and will move their firing to the peak of FMtheta. This top-down approach would be nicely in line with findings by Lakatos and colleagues (2005) who outline an oscillatory hierarchy with theta phase modulating gamma. The results that the mechanism can be controlled voluntarily (see Chapter V) indicate that the mechanism is at least partly top-down guided. We
cannot say with certainty whether the top-down approach or the bottom-up approach is more correct but we assume that it is most likely a combination of both.

In summary, our model, supported by the data presented in this work, represents a mechanism which allows highly efficient gating of access to prefrontal control processes and resources via the phase of frontal midline theta. We propose that FМtheta phase-dependent firing is an ideal and cost-effective way of dynamic coupling (and de-coupling) of cognitive networks in order to assign prefrontal cognitive resources and allow posterior processes to actively access cognitive control processes. This means that brain oscillatory signatures of working memory control processes are represented by bursts of posterior gamma oscillatory activity (representing increased local synchronous firing) being locked to specific phases of frontal midline theta oscillations (which represent a gating mechanism to prefrontal cognitive resources) (Figure 6.1D).
Figure 6.1  Schematic depiction of the mechanism for the implementation of prefrontal control processes during mnemonic operations in the human brain

(A) Task-relevant and task-irrelevant neuronal populations in posterior brain areas (here dorsal stream populations and ventral stream populations, respectively) share excitatory connections with subpopulations of neurons in the medial prefrontal cortex (PFC). Furthermore, the posterior populations share inhibitory connections (lateral inhibitions). (B) When task-relevant posterior populations (e.g. dorsal stream populations during a visuospatial task) require a high amount of cognitive control (e.g. when the task demand is high; or when visuospatial information is prioritised),
the posterior neurons will increase their firing rate locked to the excitatory FMthetapha trough. This increased firing rate will then increase firing of the associated PFC subpopulation. Moreover, it will exert lateral inhibition over other posterior populations (e.g. ventral stream populations) who will then only be able to fire after the lateral inhibition is released – in the inhibitory phase of FMthetapha. (C) Similarly, when task demands are low (here – when the figural information has to be prioritised) posterior populations in the dorsal stream network will receive less cognitive control and will only fire in the inhibitory FMthetapha phase when the lateral inhibition from the ventral stream populations (which now receive stronger access to prefrontal resources and fire during the excitatory FMthetapha phase) is released. (D) When task-relevant posterior populations need a high amount of cognitive control, those populations are strongly coupled to their associated PFC subpopulation in order to ensure unrestricted access to prefrontal control resources. In contrast, when the posterior population does not need a high amount of cognitive control, the network becomes de-coupled. (Figure adapted from an earlier version of the manuscript as used in the doctoral thesis of Griesmayr, B.)
Chapter VII Publications

The individual chapters of this thesis are either based on or identical to the following papers:


Complete list of publications in peer-reviewed journals:


Griesmayr, B., Berger, B., Stelzig-Schoeler, R., Aichhorn, W., Bergmann, J., & Sauseng, P. (2014). EEG theta phase coupling during executive control of
visual working memory investigated in individuals with schizophrenia and in healthy controls. *Cognitive, Affective, and Behavioral Neuroscience*, doi:10.3758/s13415-014-0272-0.

Chapter VIII References


Sauseng, P., Klimesch, W., Gruber, W., Doppelmayr, M., Stadler, W., & Schabus, M. (2002). The interplay between theta and alpha oscillations in the electroencephalogram reflects the transfer of information between memory systems. *Neuroscience Letters*, 324, 121–124.


