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이학박사 학위논문

**Top-down inhibitory influence on memory  
by posterior alpha oscillation  
: An MEG study**

후측 알파 오실레이션에 의한 하향성 기억 억제

2013년 2월

서울대학교 대학원

협동과정 인지과학 전공

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이 논문을 이학박사 학위논문으로 제출함.

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**Top-down inhibitory influence on memory  
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: An MEG study**

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# ABSTRACT

## **Top-down inhibitory influence on memory by posterior alpha oscillation : An MEG study**

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In our daily lives, we are confronted with large amount of information. Since only a small fraction can be encoded in long-term memory, the brain must rely on powerful mechanisms to filter out the irrelevant information. To understand the neuronal mechanisms underlying the gating of information into long-term memory, I employed a memory paradigm where the encoding of pictorial stimuli was directed by a ‘Remember’ or a ‘No-Remember’ cue. I found that posterior alpha activity increased prior to the presentation of the irrelevant ‘No-Remember’ stimuli, whereas it decreased

prior to the 'Remember' stimuli. Subjects with a larger cue-modulation of posterior alpha activity had better memory for the relevant items. The sources of the alpha activity were localized in the posterior parietal cortex included in the dorsal attention network. The individual ability to control posterior alpha activity was predictive of memory performance. During the presentation of the memory items, there was more gamma activity for the 'Remember' compared to the 'No-Remember' stimuli in the same regions. Importantly, the anticipatory alpha power modulation during the cue interval predicted the gamma power during item presentation. These findings suggest that top-down controlled alpha activity in the posterior dorsal attention network serves to gate sensory information to long-term memory. This gating is achieved by inhibiting the processing of visual information reflected by neuronal synchronization in the gamma band. In conclusion, the functional architecture reflected by alpha band activity reflects modulations in attention which has consequences for long-term memory encoding.

Keywords:

alpha oscillation, gamma oscillation, magnetoencephalography (MEG), electroencephalography (EEG), oscillations, synchronization, episodic memory

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# **1. Introduction**

## **1.1. Memory suppression**

In order to retain the important information we encounter in our daily lives, it is essential to filter relevant from irrelevant information. This implies that efficient memory functioning involves not only successful remembering, but also successful forgetting (Johnson, 1994; Van Hooff et al., 2009). The mechanisms controlling memory encoding have been investigated by directed forgetting, Think/No-Think or To-be-remembered/Not-to-be-remembered (cued encoding) paradigms using various kinds of brain imaging techniques (Wagner et al., 1998; Anderson and Green, 2001; Wagner and Davachi, 2001; Anderson et al., 2004; Daselaar et al., 2004; Depue et al., 2007; Fawcett and Taylor, 2008; Wylie et al., 2008; Freunberger et al., 2009; Hanslmayr et al., 2009; Bauml and Hanslmayr, 2010; Hanslmayr et al., 2010; Norby et al., 2010).

Studies of memory suppression have dealt with various facets such as unnecessary/out-of-date, unwanted/negatively emotional or irrelevant memories. For example, difficulty of suppression of unwanted memories in post-traumatic stress disorder (PTSD) has been reported and Think/No-Think paradigm was used in the study of memory suppression for this

disorder (Anderson and Green, 2001; Anderson et al., 2004; Depue et al., 2007). They concluded that memory suppression does occur by the efforts of active forgetting process in time. Also, studies using direct forgetting paradigm proved the existence of active forgetting, as well as the fact that this forgetting helps enhancement of learning of items coming in the next (Bauml et al., 2008).

Furthermore, this suppression even can be facilitated by the anticipatory process in a way that this anticipation effectively boosts forgetting process via preparation of voluntary memory suppression (Hanslmayr et al., 2009; Hanslmayr et al., 2010; Snyder and Foxe, 2010). This means that the brain pre-activates central executive function by top-down control mechanism.

Besides the studies on active forgetting of encoded items using Think/No-Think and direct forgetting paradigms, the mechanism of suppression of to-be-encoded items was studied by To-be-remembered/Not-to-remembered paradigm. A working memory study using To-be-remembered and Not-to-be-remembered cues demonstrated the effective suppression of not-to-be-remembered items by ignorance (Freunberger et al., 2009).

Taken together, these studies have shown the existence of voluntary memory suppression which could be enhanced by mediation of anticipation.

This tells us the evidence of functional inhibition mechanism of our brain orchestrated by central executive control processes.

## **1.2. Brain oscillations**

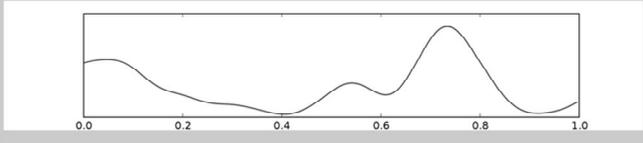
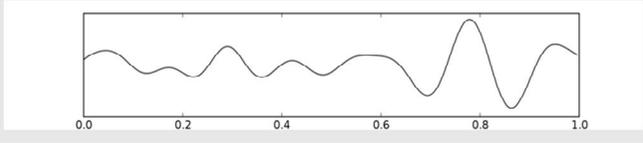
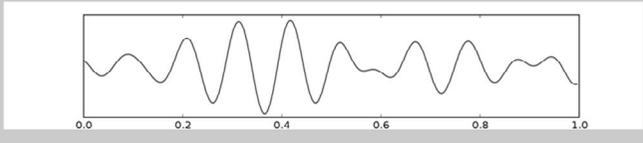
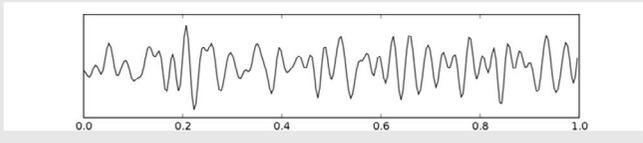
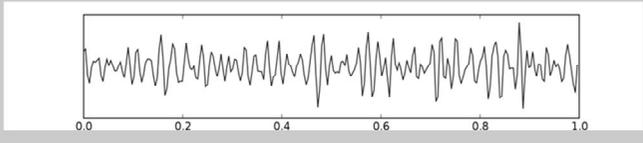
From these studies described above, it is clear that the human memory system engages and disengages various brain regions in order to facilitate and prevent memory encoding. In order to understand the physiological substrates of such mechanisms, oscillatory dynamics might be relevant since neuronal synchronization in different frequency bands is associated with different functions (Fries, 2005; Donner and Siegel, 2011; Siegel et al., 2012).

Physiological rhythms are ubiquitous in biological systems and central to life (Glass, 2001; Buzsaki and Draguhn, 2004; Thut et al., 2011; Thut et al., 2012). Especially in the brain, various oscillations have been described that differ in terms of frequency, origin and reactivity to sensory inputs and task demands by invasive as well as non-invasive electrophysiological recordings such as delta (1-3 Hz), theta (4-7 Hz), alpha (8-13 Hz), beta (14-30 Hz), and gamma (above 30 Hz) rhythms (Table 1).

Then, why studies on brain oscillations have importance in the field of neuroscience? Brain oscillations are fundamental for perception, cognition and behavior, as opposed to merely epiphenomenon (Thut et al.,

2012). Synchronization and de-synchronization within the same frequency or between different frequencies, and within or across brain areas leads to changes in various facets of human cognition, i.e., perception, attention, memory and behavior. Thus, researches on mechanisms and functions of human brain oscillations is essential for our understanding of functional architecture of human brain, and will bring further practical help on controlled intervention for brain dysfunction.

In the next section, each of brain oscillations and its functional roles, which have been known so far, will be briefly explained.

Frequency band	Example of oscillation	Anatomy	Function
Delta $\delta$ 1-3 Hz		Thalamus, visual cortex	Sleep, compromise of neuronal function, childhood, sensory selection, anticipation
Theta $\theta$ 4-7 Hz		Hippocampus, sensory cortex, prefrontal cortex	Memory, synaptic plasticity, top-down control, long-range synchronization
Alpha $\alpha$ 8-13 Hz		Thalamus, hippocampus, reticular formation, sensory cortex, motor cortex	Inhibition, attention, consciousness, top-down control, long-range synchronization
Beta $\beta$ 14-30 Hz		All cortical structures, subthalamic nucleus, basal ganglia, olfactory bulb	Sensory gating, attention, motor control, long-range synchronization
Gamma $\gamma$ above 30 Hz		All brain structures, retina, olfactory bulb	Perception, attention, memory, consciousness, synaptic plasticity

**Table 1. Brain oscillations.**

Description on anatomy and function was partly adapted from Uhlhaas and Singer (2010). Figures were adapted from Wikipedia.

### ***1.2.1. Delta oscillation***

Delta oscillation is one of the least understood oscillations so far in terms of cognition with a frequency range of 1-4 Hz. Traditionally delta rhythm was known for deep-sleep state and compromise of neural function (Steriade, 2006). However, recent studies suggested that this rhythm also plays a functional role in sensory/attentional selection (Lakatos et al., 2008; Schroeder and Lakatos, 2009) and anticipation (Stefanics et al., 2010).

Lakatos et al. (2008) examined that when attended stimuli are in a rhythmic stream, delta oscillations in the primary visual cortex entrain to the rhythm of the stream which then results in increased response gain for task-relevant events as well as decreased reaction times. Also, delta phase was observed to determine momentary power in higher frequency activity. They suggested that this could be the evidence for sensory selection by oscillatory phase-amplitude modulations.

Another study showed delta oscillation as a mechanism of expectation/anticipation. In an EEG study using auditory target detection task, delta oscillation was observed in association with higher levels of predictability. Further, reaction times were correlated with the phase of the delta oscillation (Stefanics et al., 2010).

Although there are currently numerous open questions on the delta oscillation, it is expected that cross-frequency oscillatory coupling might

improve the understanding of delta rhythm.

### ***1.2.2. Theta oscillation***

Theta oscillation is one of the most studied oscillations with a frequency range of 4-7 Hz using invasive electrophysiological recordings such as single unit recordings and LFP (local field potential) in animals and non-human primates as well as non-invasive ones such as EEG (Electroencephalography), MEG (Magnetoencephalography) or ECoG (Electrocorticography) in humans. The functional role of theta oscillation has been reported in association with mainly memory (Kahana et al., 2001; Raghavachari et al., 2001; Klausberger et al., 2003; Yamaguchi, 2003; Buzsaki, 2005; Huhn et al., 2005; Lengyel et al., 2005; Mormann et al., 2005; Scarpetta and Marinaro, 2005; Wolansky et al., 2006; Manns et al., 2007; Wagatsuma and Yamaguchi, 2007; Gong et al., 2009; Rutishauser et al., 2010; Fujisawa and Buzsaki, 2011; Kleen et al., 2011; Lega et al., 2012), spatial navigation (Cornwell et al., 2008; Cornwell et al., 2012), synaptic plasticity (Huerta and Lisman, 1993, 1995, 1996) and long-range synchronization (von Stein et al., 2000).

Especially, theta rhythm plays a key role in memory formation. In an MEG study, theta oscillation was observed to be stronger for later remembered than later forgotten items (subsequent memory effect) in

encoding session. Also, it was stronger for recognized compared with forgotten old items (recognition effect) during declarative memory operations in right parietotemporal areas (Osipova et al., 2006). A recent iEEG (intracranial EEG) study on epileptic patients has proved this finding (Lega et al., 2012).

Further it is also known to involve in long-range synchronization through hippocampal-neocortical communication in animal studies (Miller, 1991; von Stein et al., 2000). Recently, cross-frequency coupling studies have been supportive to this view in terms of coupling with gamma oscillation. It has been demonstrated that inter-regional synchronization in the gamma-band is modulated by theta rhythms and such cross-frequency dynamics underlie the integration of local processes into large-scale functional networks (Canolty et al., 2006; Canolty and Knight, 2010; Belluscio et al., 2012; Doesburg et al., 2012a; Doesburg et al., 2012b). Further researches are expected to elucidate neural synchrony and functional network in the brain using theta oscillation and cross-frequency couplings with this rhythm.

### ***1.2.3. Alpha oscillation***

Alpha oscillation is the dominant oscillation in the human brain with a frequency range of 8-13 Hz. The classical view of alpha oscillation

relied on the observation of German scientist, Hans Berger (1873-1941) who discovered the alpha rhythm using EEG (electroencephalography) and introduced the Greek letter alpha to refer it (1929). Given the fact that alpha oscillation was found to be dominant in the awake, conscious brain, it has been known to reflect cortical idling, i.e., ‘idling rhythm’ (Pfurtscheller et al., 1996).

However, this traditional view has been challenged by recent studies using various experimental paradigms. Based on a wide range of studies, it has been suggested that alpha band oscillations reflect active inhibition or disengagement of task-irrelevant brain regions (Foxe et al., 1998; Jokisch and Jensen, 2007; Klimesch et al., 2007; Hanslmayr et al., 2009; Jensen and Mazaheri, 2010; Meeuwissen et al., 2010; Foxe and Snyder, 2011; Hsieh et al., 2011; Park et al., 2011; Jensen et al., 2012; Roberts et al., 2012), even though there are other reports suggesting that it reflects active neuronal processing (Palva and Palva, 2007) (please also see Klimesch (2012)).

For example, in a delayed-match-to-sample task using MEG (magnetoencephalography), the subjects were asked to remember either the identity or the spatial orientation of presented faces (Jokisch and Jensen, 2007). This experimental design allows to examine brain activities engaging either the dorsal or ventral visual stream since it is well known that the

processing of identity engages ventral visual stream whereas the processing of orientation engages dorsal visual stream. The results revealed stronger alpha power around the parieto-occipital sulcus during retention of face identities (ventral stream) compared with the retention of face orientations (dorsal stream) and suggested that alpha increases reflect functional inhibition. A similar study using high-density EEG also demonstrated alpha suppression mechanism (Snyder and Foxe, 2010). Subjects were cued to attend either the color or direction of motion of an upcoming dot field array. This paradigm also can distinguish visual streams engaging each feature, i.e., color (ventral stream) or motion (dorsal stream). Alpha power from dorsal regions increased when color was cued, and alpha power from ventral regions increased when motion was cued.

This notion of functional inhibition by alpha oscillation is also supported by a recent monkey study demonstrating a decrease in firing rate with an increase in the alpha power of the local field potential (LFP) (Haegens et al., 2011).

In addition to working memory and attention tasks, the functional inhibitory role of alpha activity was also observed in the long-term memory formation (Meeuwissen et al., 2010). Parieto-occipital alpha power during rehearsal period was markedly stronger for successfully than unsuccessfully encoded long-term memory task using word sequences. The authors

suggested that this subsequent memory effect demonstrates that high posterior alpha activity creates an optimal brain state for successful long-term memory formation in a way that serves to reduce potential visual interferences and allocate resources for memory encoding.

In sum, alpha oscillation plays a key role in optimal cognitive performance by functional inhibitory mechanism. Furthermore, given that alpha oscillation is the most dominant and strongest activities in the human brain, and it reflects the most basic cognitive processes, I suggest that more studies should shed light on the functional role of alpha oscillation and its relationship with other frequency bands.

#### ***1.2.4. Beta oscillation***

Mainly two lines of accumulated evidences on beta oscillation have been formed in the literature. The first one is on its role in motor control, especially in relation to functional inhibition (Hari and Salmelin, 1997), and more recently, in cognitive process such as feature processing, representation of contents of working memory, and integrative function such as decision making (Pesonen et al., 2007; Donner and Siegel, 2011). However, the functional role of beta oscillation is the least understood one at present (see Engel and Fries (2010); Donner and Siegel (2011)).

Recently, in the review article on beta band oscillation (Engel and

Fries, 2010), it was proposed that beta oscillation might be reflecting *status quo*. Specifically, they hypothesized that the beta activity is expressed more strongly when the maintenance of the *status quo* is intended or predicted compared with when a change is expected. According to this view, one would predict that beta activity is also associated with working memory maintenance, which is about preserving a representation in time since endogenous top-down processes rather than exogenous bottom-up it is required during working memory maintenance (Park et al., 2011). Beta band activity has been also reported in the studies of bistable perception which engages endogenously triggered perceptual changes (Okazaki et al., 2008; Iversen et al., 2009).

Converging evidence from recent studies in the motor system, on the pathophysiology of movement disorders and on top-down mechanisms involved in cognitive and perceptual processing has been accumulated on the functional role of beta band activity. Also, it would be interesting to study further how such processes might modulated not only by beta oscillation but by interactions with other frequency bands.

#### ***1.2.5. Gamma oscillation***

Gamma oscillation is rhythmic synchronization with a frequency range above 30 Hz. Neuronal activity in the gamma band has been

associated with active processing, such as in attention, memory maintenance and encoding (Gruber et al., 2004; Osipova et al., 2006; Jensen et al., 2007; Jokisch and Jensen, 2007; Jerbi et al., 2009; Palva et al., 2010; Meeuwissen et al., 2011; Park et al., 2011; Kahlbrock et al., 2012; Lachaux et al., 2012; Roux et al., 2012b) yet their functions and mechanisms remain still a matter of debate (Buzsaki and Wang, 2012).

Attention-related gamma activity was recently shown in a varied degree of selective attention paradigm using audio-visual stimuli (Kahlbrock et al., 2012). Graded levels of visual attention modulated different intensities of gamma band synchronization, i.e., increased with the level of visual attention from low to high, in early visual areas (V1 and V2). This result showed that the level of gamma band synchronization is related to the level of selective attention.

In a long-term memory study using pictorial stimuli investigated by MEG (Osipova et al., 2006), gamma band activity (60-90 Hz) in occipital areas was stronger for the later remembered compared with the later forgotten items in the analysis of encoding trials. In the recognition, gamma activity was stronger for recognized items compared with correctly rejected new items and forgotten old items. It means that gamma synchronization reflects facilitation of memory encoding and retrieval. Gamma activity was also found to be stronger for later remembered compared to later forgotten

trials in a long-term memory paradigm using word sequences (Meeuwissen et al., 2011).

This memory-related gamma activity can even be crystallized by gamma activity with time in a long-term memory study, i.e., gamma activity involved in memory consolidation (Nieuwenhuis et al., 2012). In an associative memory paradigm using face-location associations, functional interactions between neocortical representation of high gamma (60-140 Hz) power increased over time. This result suggests that neocortical functional links are established via higher order semantic association areas represented by gamma activity.

In short, human gamma oscillation is associated with attention and memory. Given an important role in neuronal communication by gamma band activity, studies of gamma oscillation engaged in complex cognitive function will enrich our understanding of the brain.

### **1.3. Cross-frequency correlation**

Not only studies on a specific oscillatory activity, but there is a growing body of research on cross-frequency interactions. Lots of recent studies suggest that cross-frequency coupling might play a functional role in neuronal communication, computation and complex cognitive events (Canolty et al., 2006; Jensen and Colgin, 2007; Osipova et al., 2008; Tort et

al., 2008; Tort et al., 2009; Canolty and Knight, 2010; Park et al., 2011; Scheffzük et al., 2011; Canolty et al., 2012; Fiebelkorn et al., 2012; Frieze et al., 2012; Kawasaki and Yamaguchi, 2012; Roux et al., 2012a; Schutter and Knyazev, 2012; Spaak et al., 2012).

According to a review paper on cross-frequency coupling (Jensen and Colgin, 2007), there are several principles in which cross-frequency interactions occur; power to power, phase to phase, phase to frequency, phase to power (Figure 1). Among these several ways, phase to power coupling has taken considerable portion since it is sensible from a physiological perspective (Jensen and Colgin, 2007). For instance, slow oscillations such as theta rhythm has been reported to synchronize networks over long distances, whereas fast oscillations such as gamma rhythm are known to synchronize cell assemblies within short spatial scales. For long-range communication between brain areas, spatial integration from a local to a global scale is required. It however takes longer integration time, gamma oscillation might emerge at a particular phase of the theta cycle. In this way, high frequency amplitude is modulated by slow frequency phase (Canolty et al., 2006; Tort et al., 2009; Spaak et al., 2012).

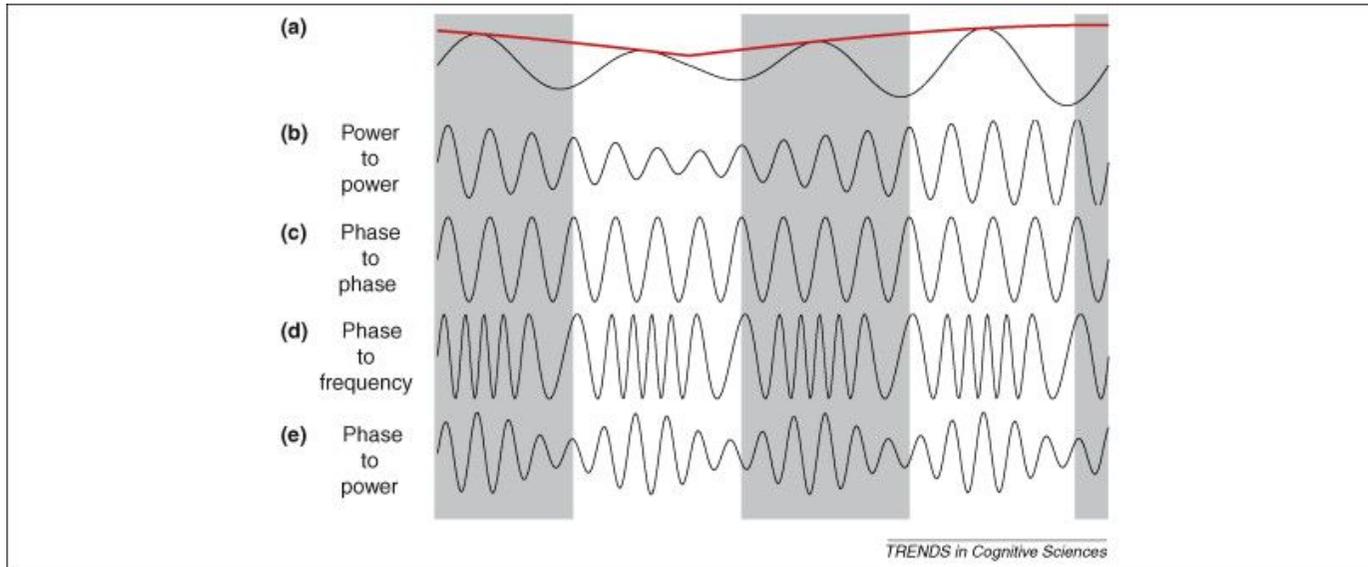
Coupling measure using power to power coupling has been proposed by Bruns et al. (2000), and has later been used to identify task-dependent modulations to assess functional connectivity (de Lange et al.,

2008; Mazaheri et al., 2009; de Pasquale et al., 2010). When using this measure, the correlation in power between neuronal sources is assessed over trials and task dependent changes are identified (Friston, 1994). This makes the measures quite related to the psychophysiological interaction index as applied to fMRI/BOLD (blood-oxygenated-level dependent) data (Friston et al., 1997). The measure of power-to-power correlations has the strong advantage that it allows to identify functional connectivity between oscillatory activities in different frequency bands (e.g., alpha and gamma bands). Further, it could decrease the concerns of cross-talk and volume conduction problem when it comes to nonlinear coupling such as interaction between different frequency bands across long-distance cortical areas where the timing accuracy required for phase coupling between different frequency, e.g. n:m coupling, is difficult to maintain.

For instance, in a working memory study for examining oscillatory interactions during retention period, alpha, beta, and gamma oscillations were observed across posterior-parietal-frontal brain regions in association with working memory maintenance. Using cross-frequency power to power correlation, the gamma activity in right superior temporal gyrus was found to serve as a hub (Park et al., 2011).

As described above, cross-frequency coupling reflects specific interplay between ensembles of neurons differently synchronized neuronal

firing which then affords profound implications for neuronal processing modulated by complex cognitive demands.



**Figure 1. Different principles of cross-frequency interactions.**  
Adapted from Jensen and Colgin (2007).

#### **1.4. Hypothesis of this study**

In the light of previous findings on memory suppression and brain oscillations, I hypothesized that oscillatory alpha activity can serve to suppress the encoding of irrelevant, i.e., unwanted, memories by top-down control in a setting where new information has to be either remembered or ignored. If the suppression fails, irrelevant memories might be created at the expense of memory performance for the to-be-remembered items. On the other hand, gamma activity will emerge in association with encoding process for the to-be-remembered items. Furthermore, alpha power and gamma power will be related to each other in a way that alpha power decrease during cue interval predicts gamma power during item presentation when to-be-remembered items are presented.

To this end, I have developed a novel long-term memory paradigm that affords the opportunity to examine brain activity associated with active encoding or ignoring. A cue directed subjects to either encode ('Remember') or ignore ('No-Remember') an upcoming picture presented 2 s later. I used magnetoencephalography (MEG) to record the ongoing brain activity in order to characterize oscillations and to identify the respective regions associated with intentional memory encoding.

I hypothesized that posterior alpha activity following the 'No-Remember' cue will suppress the encoding of irrelevant information. As a

consequence, individuals who are better at suppressing the irrelevant information by posterior alpha activity will benefit from an enhanced ability to remember the relevant information. Finally, I predicted that the cue-directed alpha band suppression would allow for a stronger gamma band response during memory encoding. In short, optimal performance requires the ability to ignore irrelevant information by alpha band suppression in order to remember relevant information.

## 2. Materials and Methods

### 2.1. Participants

Thirty-one healthy, young, right-handed volunteers (15 males, 16 females,  $25.0 \pm 3.2$  years old) participated in this study. However, eight participants who could not perform the task ( $n = 6$ , see below), or had signals with excessive superconducting quantum interference device (SQUID) noise due to a malfunctioning of the MEG system ( $n = 2$ ) were excluded from the analysis.

Three subjects reported that they did not follow the instruction because of task difficulty at the post-experimental inquiry. The post-experimental inquiry was performed based on both face-to-face with experimenter and paper-and-pencil methods including compliance questionnaire (Bulevich et al., 2006; Hanslmayr et al., 2010). One subject was examined to be fallen asleep during the encoding session when monitored by a monitoring system outside the shielding room and on-line electrooculogram (EOG) signals. Two subjects showed very high false alarm rates for the ‘New’ condition (memory foil) at recognition session (67.5 % and 78.1 %) which means they also did not follow the task

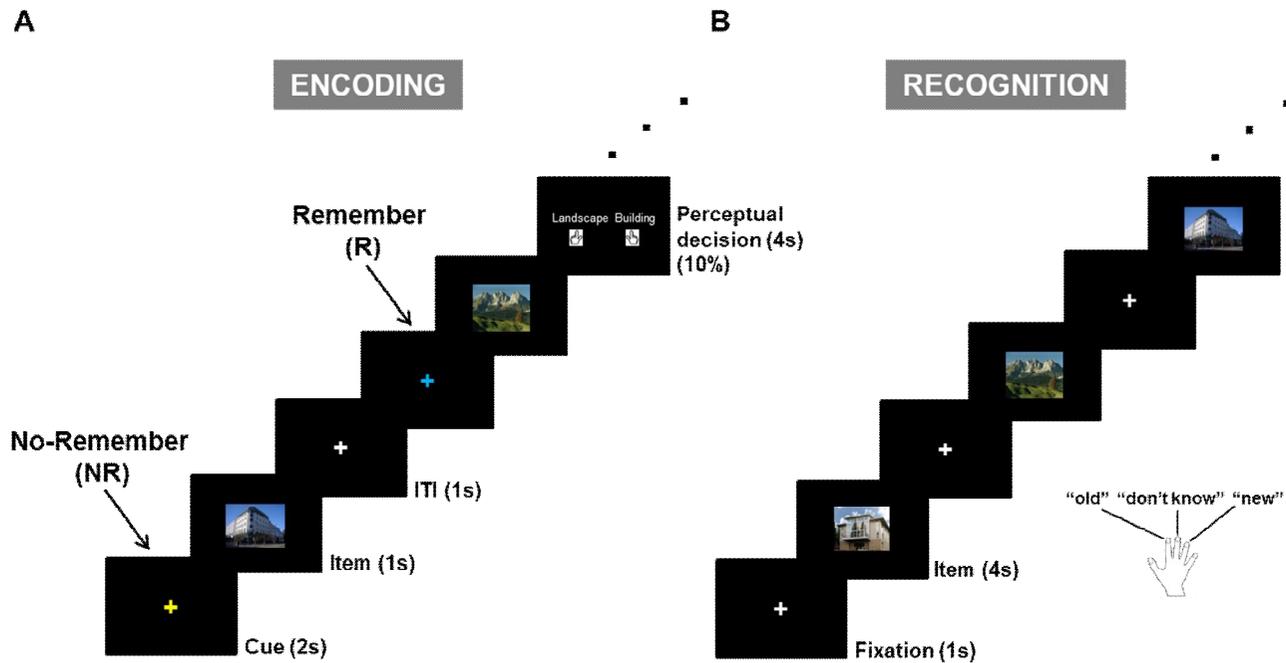
instruction.

This left datasets from 23 participants (11 males, 12 females) with a mean age of  $24.8 \pm 3.1$  years to be analyzed. None of the participants had a history of developmental, psychological, or neurological disorders. They all had normal or corrected-to-normal vision. The present study was approved by the Institutional Review Board (IRB) at Seoul National University Hospital (IRB No. C-1007-156-325). Written informed consent was obtained from all participants after complete description of the study.

## **2.2. Stimuli**

Six hundred forty real-life photographs of landscapes and buildings were used. Pictures were obtained from internet websites with resolutions exceeding  $480 \times 640$  pixels (the same stimuli used in Takashima et al. (2006), which excluded well-known landscapes and buildings). The pictures with a visual angle of  $8^\circ$  horizontally ( $334 \times 250$  pixels) were projected to a screen using STIM2<sup>TM</sup> software (Compumedics Neuroscan, Charlotte, NC). The stimuli were evenly divided into three sets to be used for the conditions: ‘Remember’ (R), ‘No-Remember’ (NR) and ‘New’. The ‘Remember’ (R) and ‘No-Remember’ (NR) conditions were used in both the encoding and

recognition sessions and the 'New' condition was used only in the recognition session. The stimuli for these three conditions were counterbalanced across subjects.



**Figure 2. A cued long-term memory paradigm.** (A) In the encoding session, subjects were presented memory items that were pictures of landscapes or buildings. Prior to each item, a ‘Remember’ or ‘No-Remember’ cue was presented, as indicated by the color of the fixation cross. In order to ensure that the subjects attended the stimuli, I randomly presented perceptual decision trials. Subjects were told that the ‘No-Remember’ items would not be tested in the recognition session. (B) In the recognition session, I presented, in random order, all the previous presented items (for both cue types) together with previously unseen new items. The subjects were instructed to indicate if they had seen the items in the encoding session by pressing one of three button corresponding to ‘old’, ‘don’t know’ or ‘new’.

### **2.3. Experimental paradigm and procedure**

The experiment was divided into a training followed by an experimental block. Each block consisted of encoding, interference, and recognition sessions (Figure 2).

In the encoding session of the main experiment, 440 pictures (220 pictures for respectively the ‘Remember’ and ‘No-Remember’ conditions) were presented. First a cue period was shown for 2 s, in which the color of the fixation cross indicated either to remember (e.g. blue, ‘Remember’) or not to remember (e.g. yellow, ‘No-Remember’) the upcoming picture. The color of the cue was counterbalanced across subjects. After the instruction cue, a picture was presented for 1 s, followed by an inter-trial interval (ITI) of 1 s (Figure 2A). In 10 % of the trials I asked the subjects to make a perceptual decision to ensure that the subjects perceived the presented stimuli in the ‘No-Remember’ condition. In these trials, subjects had to decide whether the picture was a landscape or a building as prompted by a question shown after the picture. To prevent motor preparation confounds, they were instructed to press the left or right button (left or right index finger) as instructed by the question screen. This question screen was turned off as soon as a response was given, but was displayed for a maximum of 4 s. The perceptual decision trials were not used in the MEG analysis.

A short interference task followed the encoding session in order to reduce recency effects for about five minutes. In this task, the subjects were presented with an arithmetic equation involving addition or subtraction following by a number on a next screen. They were instructed to indicate by button press whether the number was correct or incorrect according to the equation.

In the recognition session, the 440 stimuli, including perceptual decision trials from the encoding session (220 stimuli in each condition), were randomly intermixed with 200 new stimuli (Figure 2B). Each picture was presented for 4 s following the presentation of a fixation screen (1 s), during which subjects were instructed to indicate if the picture was presented before ('old') or not ('new'). Then, the subjects were presented with a picture of the index, middle, and ring fingers of the right hand, and each finger was associated with the appropriate response (i.e., '*old*', '*don't know*', and '*new*'). The fingers associated with the three responses were counterbalanced across subjects. To reduce guesses, they were instructed to press the '*don't know*' button when they were uncertain. Subjects were supposed to respond '*old*' even if they remembered that the item was associated with a 'No-Remember' cue. The response screen disappeared as soon as a response was made, but was displayed for not more than 4 s.

Before the main experiment, the subjects were trained in a block in which 160 pictures, of which 10 % were perceptual decision stimuli, were presented during an encoding session. Only the pictures for ‘Remember’ trials were tested for recognition, along with 50 new stimuli as foils. This procedure was the same as in the main experimental phase; however, the ‘No-Remember’ items were not tested in the recognition session of the training phase, i.e., only ‘Remember’ and new foil items were tested. This was intended to trick subjects into believing that they would not be tested on the ‘No-Remember’ stimuli. Further, the large number of stimuli used in the main experiment (440 during the encoding) reduced the chances that subjects encoded the ‘Remember’ and ‘No-Remember’ cues along with a given picture. In short, as confirmed by the behavioral results, the task design promoted a strategy in which only the ‘Remember’ stimuli were encoded.

The total duration of the experiment was approximately 100 minutes, including the training phase and halfway break (~20 min) between training and main experiment. After the experiment, all participants were debriefed in a post-experimental interview, and asked to fill in an evaluation form to determine what strategies they used.

## 2.4. Behavioral analysis

The response trials from the recognition session were characterized as follows. The ‘old’ and ‘new’ responses from the ‘Remember’ condition were labeled as *R-Hits* and *R-Misses*, respectively, those from the ‘No-Remember’ condition as *NR-Hits* and *NR-Misses*, and those from the ‘New’ condition (the memory foils) as *False Alarms* and *Correct Rejections*. The encoding trials were categorized according to subsequent recognition as *Later R-Hits* and *Later R-Misses* for the ‘Remember’ condition, and *Later NR-Hits* and *Later NR-Misses* for the ‘No-Remember’ condition. *Later NR-Hits* comes from ‘old’ responses as a result of unsuccessful inhibition of memorization whereas *Later NR-Misses* comes from ‘new’ responses as a result of successful inhibition of memorization (please refer Table 2).

The encoding trials were also categorized regardless of task conditions, but according to subsequent recognition only, i.e., *Later Remembered* and *Later Forgotten* trials. *Later Remembered* is combined trials of *Later R-Hits* and *Later NR-Hits*, i.e., later remembered trials regardless of task condition, and *Later Forgotten* is combined trials of *Later R-Misses* and *Later NR-Misses*, i.e., later forgotten trials regardless of task condition. This was for examining oscillatory brain activity involving remembering and forgetting of item.

In addition, cueing effect means the comparison between ‘No-Remember’ cue condition versus ‘Remember’ cue condition or vice versa and subsequent memory effect means the comparison between trials sorted according to subsequent recognition within the same cue condition: *Later NR-Misses* versus *Later NR-Hits* or *Later R-Hits* versus *Later R-Misses*.

**A**

		Response	
		old	new
Item	old	Hits	Misses
	new	FA	CR

**B**

	Remember		No-Remember		New	
Item	old		old		new	
Response	old	new	old	new	old	new
Label	<b>R-Hits</b>	<b>R-Misses</b>	<b>NR-Hits</b>	<b>NR-Misses</b>	<b>FA</b>	<b>CR</b>

**Table 2. Labels for conditions.** (A) Labels in typical memory paradigm. (B) The ‘old’ and ‘new’ responses from the ‘Remember’ condition were labeled as *R-Hits* and *R-Misses*, respectively, those from the ‘No-Remember’ condition as *NR-Hits* and *NR-Misses*, and those from the ‘New’ condition (the memory foils) as *False Alarms (FA)* and *Correct Rejections (CR)*. The encoding trials were categorized according to subsequent recognition as *Later R-Hits* and *Later R-Misses* for the ‘Remember’ condition, and *Later NR-Hits* and *Later NR-Misses* for the ‘No-Remember’ condition. *Later NR-Hits* are unintentional responses as ‘old’ as a result of unsuccessful inhibition of memorizing item whereas *Later NR-Misses* are ‘new’ responses as a result of successful inhibition of memorizing item. Abbreviations. FA, false alarm; CR, correct rejection.

## 2.5. MEG measurement

Electromagnetic brain activity was recorded using a whole-head MEG Neuromag (VectorView™, Elekta Neuromag Oy, Helsinki, Finland) acquisition system installed at the MEG center of Seoul National University Hospital. It consists of 306 sensors arranged in triplets of two planar gradiometers and one magnetometer. Data were collected continuously at 1200 Hz (following a 300 Hz low-pass filter).

The vertical and horizontal electrooculogram (EOG) was also measured with EOG electrodes placed near the outer canthus and beneath the left eye for subsequent exclusion of eye movements and blinks artifacts. The electrocardiogram (ECG) was also recorded to remove cardiac artifacts from the data.

Before entering the electromagnetically shielded and sound attenuated room, head position indicator (HPI) coils were sparsely attached on the head of each subject, and anatomical landmarks such as nasion and bilateral preauricular points were spatially identified by 3D digitizer (FASTRAK™, Polhemus, Colchester, VT). Then the subject's head position was registered by localizing HPI coils in the MEG device. This allowed the sources reconstructed from the MEG to be superimposed on structural MR images of each individual with high precision. Before data analysis, a

Maxwell filter (Signal Space Separation), which separates brain-related and external interference signals, was applied to reduce the confounding influence of biological and environmental noises (Taulu et al., 2005; Taulu and Simola, 2006).

## **2.6. Structural MR image acquisition**

Structural MR images (T1-weighted gradient-echo pulse sequence) were acquired at 3.0 T using a Siemens Trio Tim scanner (Siemens, Erlangen, Germany) with the following parameters:  $1.0 \times 0.98 \times 0.98 \text{ mm}^3$  voxels; 208 sagittal slices.

## **2.7. Data analysis**

The data analysis was performed in Matlab toolbox 2012a (MathWorks, Natick, MA) using the Fieldtrip open source Matlab toolbox developed at the Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging, Nijmegen, The Netherlands (Oostenveld et al., 2011) (<http://fieldtrip.fcdonders.nl>), and custom scripts. Trials contaminated with SQUID jump and muscle artifacts were rejected. Before the analysis, the data were downsampled at 600 Hz after applying a

low-pass filter at 200 Hz for the computational reason. Electrooculographic (EOG) and electrocardiographic (ECG) artifacts were removed using independent component analysis (ICA). The recorded ECG helped identifying MCG components. After the artifact rejection the number of trials for *Later R-Hits*, *Later R-Misses*, *Later NR-Hits*, and *Later NR-Misses* were on average 90, 67, 51, and 103 trials, respectively.

## **2.8. Spectral analysis**

Oscillatory signals measured by ongoing electrophysiological methods such as EEG or MEG show power changes relative to experimental events. Time-frequency representations of these power changes were computed based on Fourier analysis and wavelets. Calculating time-frequency representations of power is performed using a sliding time window which is either the time window which has a fixed length independent of frequency, or the time window decreases in length with increased frequency. The power is calculated for each time window. Prior to calculating the power, one or more tapers are multiplied and the purpose of multiplying the tapers is to control the frequency smoothing and reduce spectral leakage (Percival and Walden, 1993; Mitra and Pesaran, 1999).

For lower frequencies, time-frequency representations of power (1-

32 Hz) were computed based on a sliding time window (steps of 50 ms) from the data segments covering the whole trial length: cue (2 s), item (1 s), and inter-trial interval (1 s). The length of the sliding time window was adapted to the frequency, and contained four cycles (i.e.,  $\Delta T = 4/f$ , e.g. 400 ms for 10 Hz). It means that time-frequency representations of power were calculated with respect to a time window that varies with frequency because the time window typically gets shorter with an increase in frequency. This approach has an advantage in terms of decreased temporal smoothing with higher frequencies, but at the expense of frequency smoothing. Prior to the Fourier transformation, the data from the sliding time windows were multiplied by a Hanning taper, resulting in adaptive spectral smoothing of  $\Delta f \sim 1/\Delta T$ .

For high frequency ranges (20-200 Hz), I applied multitapering method. Typically multitapers are used to achieve better control over the frequency smoothing in a way that more tapers for a given time window results in greater smoothing. Since high frequency oscillatory activities above 30 Hz, i.e. gamma oscillation is quite broad band activities, multitapering method is particularly beneficial to the analysis of this oscillation. Prior to calculating the power, the data are tapered by several orthogonal tapers. The power is calculated for each tapered data segment and then combined (Percival and Walden, 1993). In my data analysis, a

fixed time window of 200 ms was used together with a multitaper approach involving three orthogonal Slepian tapers, which resulted in a spectral smoothing of  $\sim 10$  Hz. The grand-averaged power values were then calculated for the different conditions and then compared.

## **2.9. Source analysis**

In order to identify the sources of the oscillatory activities I applied a beamforming approach based on an adaptive spatial filter (Dynamic Imaging of Coherent Sources, DICS) (Gross et al., 2001).

The beamforming algorithm, which was originally developed for radar applications (van Veen and Buckley, 1988), has been shown to be a useful tool for MEG brain imaging (Gross et al., 2001; Hillebrand et al., 2005). Hillebrand et al. (2005) reviewed several studies comparing beamforming to other source reconstruction algorithms for MEG, and concluded that beamforming was successful in identifying induced changes in cortical oscillatory power. Beamforming results are quite consistent with those of fMRI/BOLD recordings for the same experimental design (Singh et al., 2002). It applies selective weighting on target locations forming a volumetric grid. This weighting computation relies on the data covariance matrix, exploited as a spatial filter applied to the recorded MEG data to

produce the beamformer output (Barnes et al., 2004; Hillebrand et al., 2005).

First, cross-spectral density matrices were calculated from the Fourier transformed data for each condition. I used a Hanning taper for the 10 Hz alpha band, resulting in 3 Hz smoothing for a 500 ms window and three Slepian tapers for the gamma frequency (80 Hz) resulting in a 10 Hz spectral smoothing. Realistically shaped single-shell descriptions of the brains were constructed from each individual's MRI. The brain volume of each individual subject was divided into a grid with a 0.8 cm resolution and normalized to the template MNI brain (International Consortium for Brain Mapping, Montreal Neurological Institute, Canada) using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). The lead field was calculated for each grid point. Then, a spatial filter was constructed for each grid point using the cross-spectral density matrices for the frequency of interest and the lead fields. The spatial distribution of power of oscillatory activities was estimated in each condition albeit the cross-spectral densities were calculated for the data combined.

## **2.10. Statistical analysis**

The statistical significance of the spectral power changes was assessed using a cluster-based nonparametric randomization test (Maris and

Oostenveld, 2007) which effectively controls the Type I-error rate with respect to multiple comparisons over sensors, frequency, and time. This is achieved by clustering neighboring sensors, time, and frequency points. For the first-level statistics, sensors, frequency and time-points below a threshold ( $t$ -test;  $p < 0.05$ ) were identified from the  $t$ -statistics and subsequently spatially contiguous points in terms of sensor, frequency and time-points below this threshold were defined as a cluster. Then, the sum of the  $t$ -values for a given cluster was used for the cluster-level statistics. By randomization of the data between conditions across the subjects, the cluster-level  $t$ -statistics were created from 5000 randomization routines. For the second-level statistics, the  $p$ -value was estimated according to the proportion of the randomization distribution exceeding the observed maximum cluster-level statistics.

## 3. Results

### 3.1. Behavioral performance

The behavioral data from the recognition session are reported in Figure 3A. The recognition rate for items preceded by the ‘Remember’ cue, i.e., *R-Hits* ( $56.7 \pm 3.2\%$ ) was significantly greater than for items preceded by the ‘No-Remember’ cue, i.e., *NR-Hits* ( $33.3 \pm 2.2\%$ ) (paired *t*-test;  $t_{(22)} = 12.3$ ,  $p < 0.001$ ). Both the *R-Hits* and *NR-Hits* were significantly greater than the *False Alarm* rate ( $24.2 \pm 2.0\%$ ) ( $t_{(22)} = 14.5$ ,  $p < 0.001$  and  $t_{(22)} = 9.0$ ,  $p < 0.001$  respectively). These results demonstrate that the subjects remembered more items following the ‘Remember’ cue compared to the ‘No-Remember’ cue. Further the low *False Alarm* rate indicates that guessing was relatively low during retrieval.

Behavioral performance was also assessed by *d*-prime (*d'*) and beta ( $\beta$ ) analysis (Table 3). These are well known measures for testing recognition memory based on signal detection theory (Swets, 1962; Coombs et al., 1970; Salton and McGill, 1983; Stanislaw and Todorov, 1999; Neath and Surprenant, 2003). Brief introduction of these two measures will be followed. For more details, please see the references above.

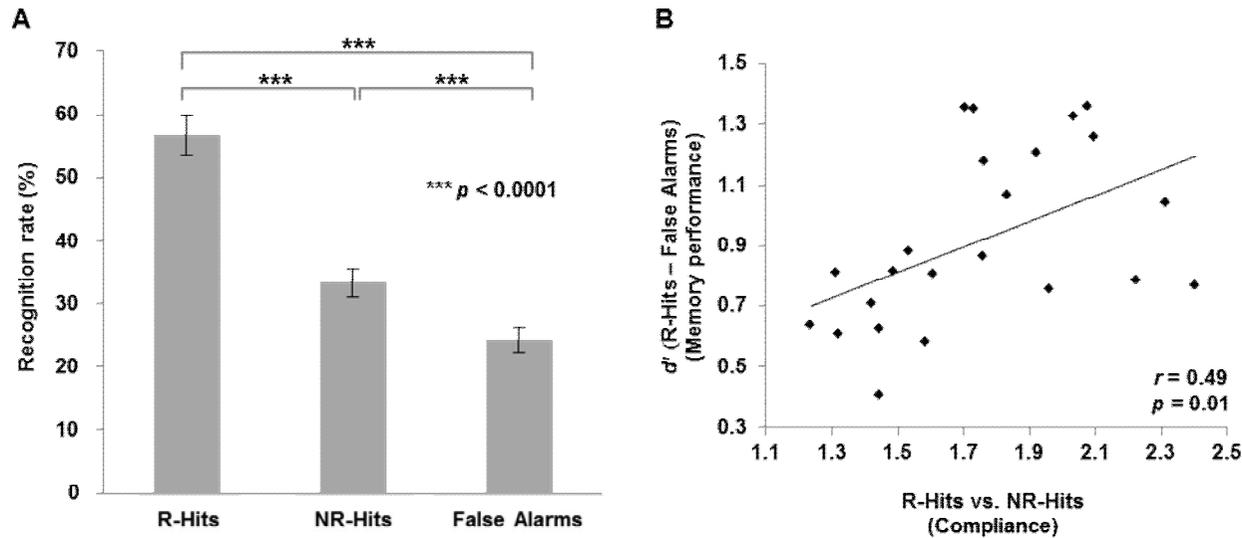
$D$ -prime ( $d'$ ) is a discriminability index (also known as sensitivity index) and it is calculated by the following way:  $d' = \text{norminv}(\text{hit}) - \text{norminv}(\text{false alarm})$ . Here 'norminv' means normal inverse cumulative distribution function. In other words, the value for  $d$ -prime is standard  $z$ -value of the hit rate minus the false alarm rate. This reflects the distance between the two distributions: signal and signal + noise. Thus, it means the larger  $d$ -prime, the better the subject's ability to discriminate between old and new items.

Beta ( $\beta$ ) is an index of response bias (also known as decision bias) and it is calculated by the following way:  $\beta = \text{EXP}((\text{norminv}(\text{hit})^2 - \text{norminv}(\text{false alarm})^2) / 2)$ . The value for beta is the ratio of the normal density functions at the criterion of the  $z$ -values used in the computation of  $d$ -prime. This reflects a subject's bias to say 'yes' (old) or 'no' (new) with the unbiased subject having a value around 1. As the bias to say 'yes' (old) increases, it results in a higher hit and false alarm rates, thus beta value approaches 0. On the contrary, as the bias to say 'no' (new) increases, it results in a lower hit and false alarm rates, thus beta value increases over 1. Beta value has an open-ended scale. Further, beta value above 0 indicates a conservative bias, i.e. less willing to guess old, whereas value below 0 indicates a liberal bias, i.e., more willing to guess old.

As shown in Table 3, no subjects showed beta values below 0.6 (minimum value is 0.622 when considering *R-Hits* versus *False Alarms*). It means that all subjects showed less willing to guess old. For the *d*-prime, the values were all around value 1 (minimum value is 0.403 when considering *R-Hits* versus *False Alarms*). This outcome confirms that all subjects tried to follow task instruction and had ability to discriminate between old and new items. When I analyzed *d*-prime for the excluded subjects for the behavioral reasons (as described in the section above; 2.1. Participants), the value was 0.069 on average ( $n = 6$ ). This means that they were not able to discriminate between old and new items as they reported after the experiment.

Next, I asked whether subjects who managed to ignore the ‘No-Remember’ items were those with better memory performance. I refer to the ability to follow the memory cue as *Compliance* and I quantified it as the ratio of *R-Hits* divided by *NR-Hits*. Memory performance was assessed by the standard *d*-prime measure calculated by *R-Hits* and *False Alarm* ratios. These two measures were significantly correlated ( $r = 0.49, p = 0.01$ ; Figure 3B), i.e. individuals who follow the cue instructions showed better memory performance. Thus the ability to ignore the ‘No-Remember’ cue stimuli improves memory for the ‘Remember’ cue stimuli. This also confirms that subjects need to ignore the irrelevant items in order to optimally remember relevant items.

For perceptual decision trials, *R-Hits* ( $56.5 \pm 2.9$  %) for the ‘Remember’ cued items were significantly higher than for *NR-Hits* ( $30.0 \pm 2.9$  %) for the ‘No-Remember’ cued items (paired *t*-test:  $t_{(22)} = 9.2$ ,  $p < 0.001$ ). The mean accuracy for judging the perceptual decision trials was high, i.e.,  $98.0 \pm 0.5$  % for the ‘Remember’ cue and  $87.0 \pm 1.6$  % for the ‘No-Remember’ cue. Although this effect was significantly different ( $t_{(22)} = 6.3$ ,  $p < 0.001$ ), subjects were able to perform the perceptual decisions with high accuracy demonstrating that the subjects were attentive during the course of the experiment.



**Figure 3. Behavioral results from the recognition session. (A)** The hit-rate was significantly higher for *R-Hits* (items preceded by a ‘Remember’ cue) compared *NR-Hits* (items preceded by a ‘No-Remember’ cue). The *False Alarm* rate for completely new items was also relatively low. In short, subjects respectively remembered and ignored the items according to the cue. **(B)** Subjects who block out the irrelevant items had better memory performance. On the *x*-axis, I measured the *Compliance* according to the cue as calculated by the ratio of *R-Hits* versus *NR-Hits*. The higher the ratio, the better the subjects were at remembering the ‘Remember’ cue items at the expense of the ‘No-Remember’ cue items. The *y*-axis shows the memory performance assessed by the *d*-prime score taking *R-Hits* and *False Alarm* rates into account. The positive correlation ( $r = 0.49$ ,  $p = 0.01$ ) means that individuals who followed the cue instructions showed better memory performance. This means that subjects who ignore the irrelevant items are also those who are better at remembering the relevant items.

sub#	$d'$ (discriminability index)		$\beta$ (response bias)	
	R-Hits vs. FA	R-Hits vs. NR-Hits	R-Hits vs. FA	R-Hits vs. NR-Hits
4	0.603	0.258	1.439	1.117
5	1.353	1.034	0.622	0.590
6	0.859	0.540	1.573	1.220
7	1.175	0.831	0.972	0.849
9	0.705	0.419	1.161	1.029
10	0.577	0.460	1.232	1.150
12	0.621	0.407	1.189	1.072
14	0.779	0.767	1.329	1.317
15	0.802	0.442	1.605	1.199
16	1.202	0.739	1.546	1.101
17	0.811	0.293	2.356	1.263
18	0.876	0.411	1.694	1.164
19	1.256	0.893	1.321	1.036
20	0.403	0.342	1.195	1.151
22	0.631	0.356	0.884	0.888
23	0.805	0.453	0.885	0.862
24	1.357	0.876	1.480	1.044
25	1.040	0.764	1.822	1.398
26	0.765	0.781	1.425	1.444
27	0.750	0.756	1.106	1.110
28	1.322	0.844	1.486	1.053
29	1.065	0.864	0.933	0.867
30	1.349	1.029	0.655	0.615

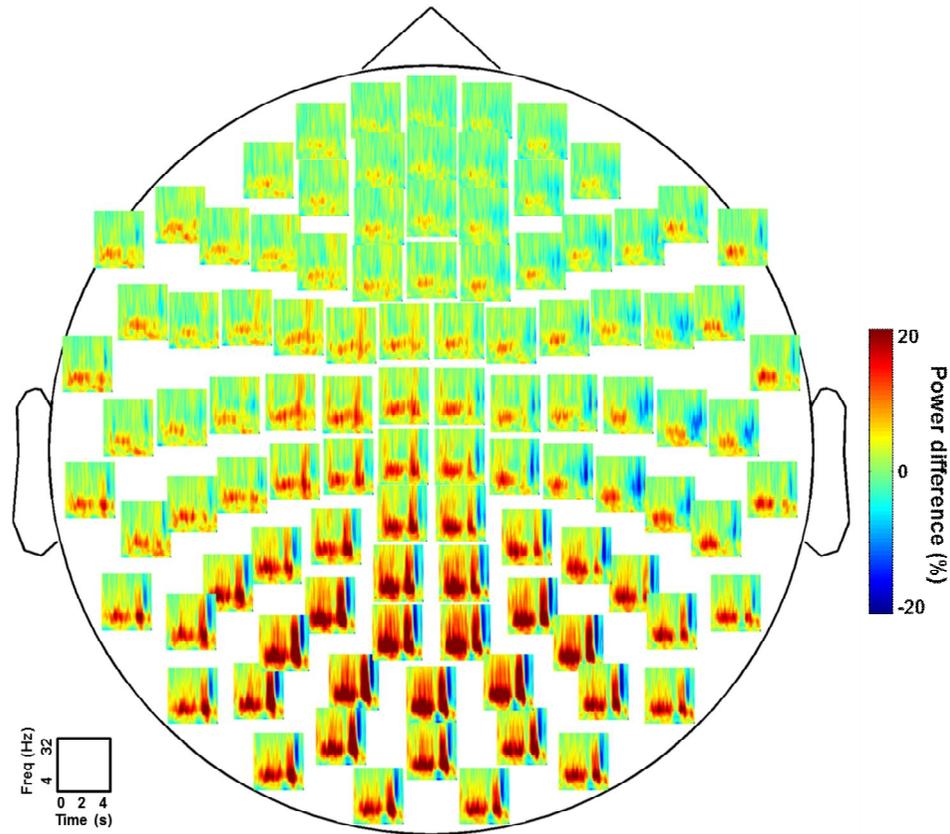
**Table 3. Behavioral performance assessed by  $d'$  and  $\beta$ .** Discriminability index (also known as sensitivity index, left column) was calculated by  $d$ -prime ( $d'$ ):  $\text{norminv}(\text{hit}) - \text{norminv}(\text{false alarm})$ . Response bias (also known as decision bias, right column) was calculated by beta ( $\beta$ ) analysis:  $\text{EXP}((\text{norminv}(\text{hit})^2 - \text{norminv}(\text{false alarm})^2) / 2)$ . Here, ‘norminv’ means normal inverse cumulative distribution function. Abbreviation. FA, false alarm.

### **3.2. Alpha band activity for ‘No-Remember’ versus ‘Remember’ task conditions**

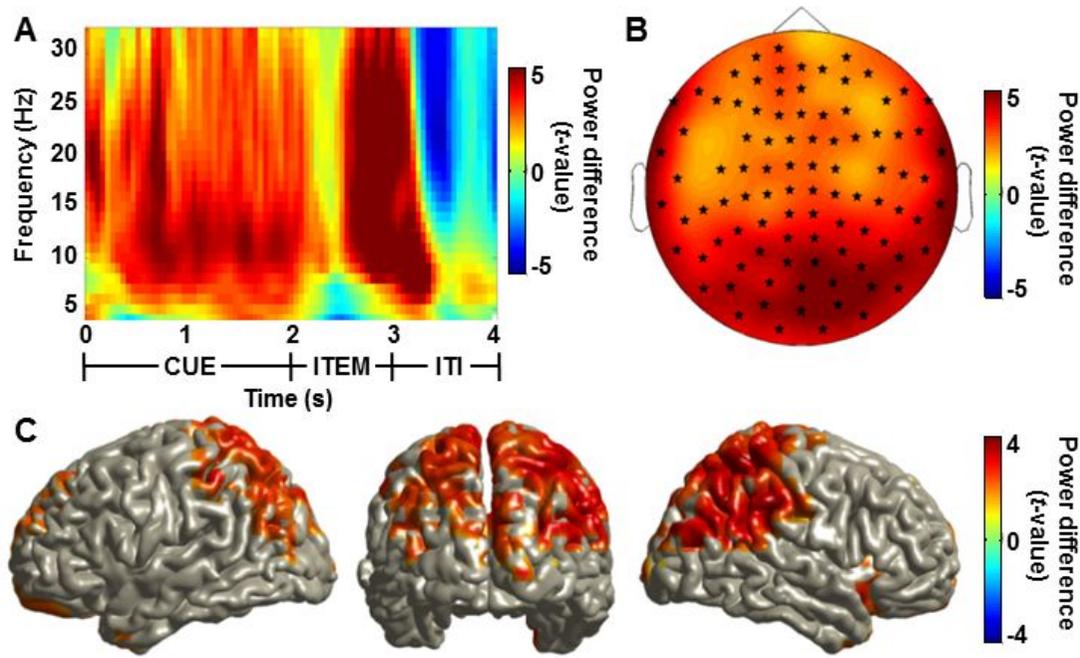
I first set out to identify electrophysiological modulations according to the ‘No-Remember’ versus the ‘Remember’ cue. I found a highly robust alpha power increase over posterior regions when comparing the trials for the ‘No-Remember’ to the ‘Remember’ cues (Figure 4). Figure 5A shows a time-frequency representation of power for 20 posterior sensors over the parieto-occipital areas (Neuromag sensor labels: 173, 183, 184, 191, 192, 193, 194, 201, 202, 203, 204, 211, 212, 223, 224, 231, 232, 233, 234, 251). This effect was present during the cue interval and increased further during the item presentation ( $f = 8-12$  Hz;  $t = 1-2$  s and  $t = 2-3$  s; permutation,  $p < 0.05$ ).

The modulation in the alpha band was also observed in a number of studies on memory encoding (Freunberger et al., 2009; Hanslmayr et al., 2009; Khader et al., 2010; Meeuwissen et al., 2010; Park et al., 2011). I thus focused the subsequent analysis on the 10 Hz band (8-12 Hz when considering spectral smoothing) considering the 1 s time interval just prior to the memory item onset. The topographical distribution of the alpha power difference for the ‘No-Remember’ and ‘Remember’ cues during the cue interval is shown in Figure 5B. This difference was found to be highly significant (cluster-level permutation controlling for multiple comparisons

over sensors,  $p < 0.001$ ). Note that the widespread cluster reflects the robustness of the effect in terms of signal to noise ratio, rather than the spatial extent of the underlying neuronal source. Next, I identified the neuronal sources reflecting the difference in the alpha band during the cue interval (1-2 s) using a beamformer analysis (Figure 5C). I found that the alpha power increase was dominated by extended sources mainly in posterior parietal regions (cluster-level permutation,  $p < 0.05$ ) included in the dorsal attention network.



**Figure 4. Time-frequency representation for the ‘No-Remember’ cue compared to the ‘Remember’ cue for all sensors (4-32 Hz).** Strong alpha power increases in posterior regions were also observed during both cue and item presentations (-20 ~ 20 % relative power increase with respect to the mean).



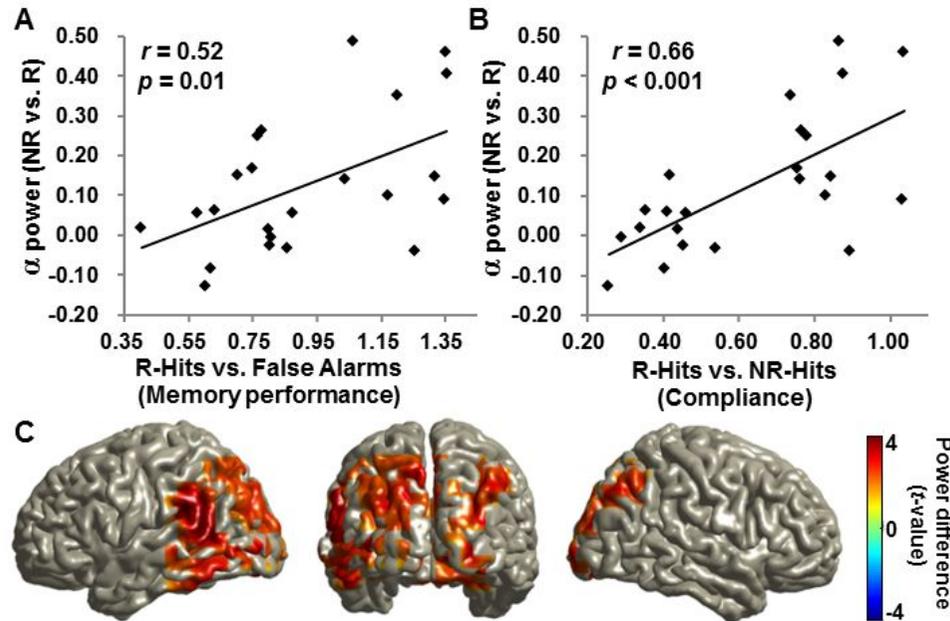
**Figure 5. The posterior alpha power (10 Hz) for the ‘No-Remember’ cue compared to the ‘Remember’ cue. (A)** A time-frequency representation of power calculated for 20 posterior sensors (Neuromag sensor labels: 173, 183, 184, 191, 192, 193, 194, 201, 202, 203, 204, 211, 212, 223, 224, 231, 232, 233, 234, 251) revealed a strong increase in the alpha band when comparing the ‘No-Remember’ to the ‘Remember’ cue. This effect was pronounced in the cue interval (0-2 s), but also during item presentation and beyond (permutation,  $p < 0.05$ ). **(B)** Topographical distribution of alpha power increases during the cue interval (10 Hz; 1-2 s) was found in a huge cluster including most sensors (cluster-level permutation,  $p = 0.0002$ ). **(C)** Source reconstruction using a beamforming technique of the ‘No-Remember’ versus ‘Remember’ effect (10 Hz; 1-2 s). The alpha power increase was localized in posterior parietal regions (cluster-level permutation,  $p < 0.05$ ).

### 3.3. Correlation between alpha band difference and behavioral performance

Next I set out to investigate the behavioral relevance of the cue-related alpha power modulation. I correlated the alpha power difference for the cueing effect with the memory performance (assessed by the standard *d*-prime measure calculated by *R-Hits* versus *False Alarm* rates) as well as *Compliance* (assessed by the standard *d*-prime measure calculated by *R-Hits* versus *NR-Hits* rates). As a first step, I used the beamformer approach as a spatial filter to extract the alpha band activity from posterior parietal cortex. The spatial filter was centered at the location producing the maximal cue directed difference in the alpha band (as in Figure 5C; left posterior parietal cortex; MNI coordinates  $x, y, z = [-8, -58, 32]$ ). The cue-directed difference in the alpha band was correlated with memory performance over subjects (memory performance:  $r = 0.52, p = 0.01$ , Figure 6A). When I correlated the same cue-directed alpha power difference with *Compliance* over subjects, I also found a highly significant effect (*Compliance*:  $r = 0.66, p < 0.001$ ; Figure 6B).

Next, I performed the analysis using the beamformer approach applied to the full discretized brain volume. I did this by calculating the regression coefficients for the difference in alpha activity ('No-Remember'

versus ‘Remember’ cue) and the measure for *Compliance* at every grid point in the brain volume. These values were subjected to a cluster randomization analysis (testing for non-zero regression coefficients while controlling for multiple comparisons over grid points) that revealed a significant cluster in posterior parietal cortex extending to visual and temporal areas (cluster-level permutation,  $p < 0.05$ ; Figure 6C). These findings demonstrate that subjects with a stronger cue-directed alpha band modulation are also the subjects with better memory performance. The better memory for the ‘Remember’ cue items is at the expense of the ‘No-Remember’ cue items.



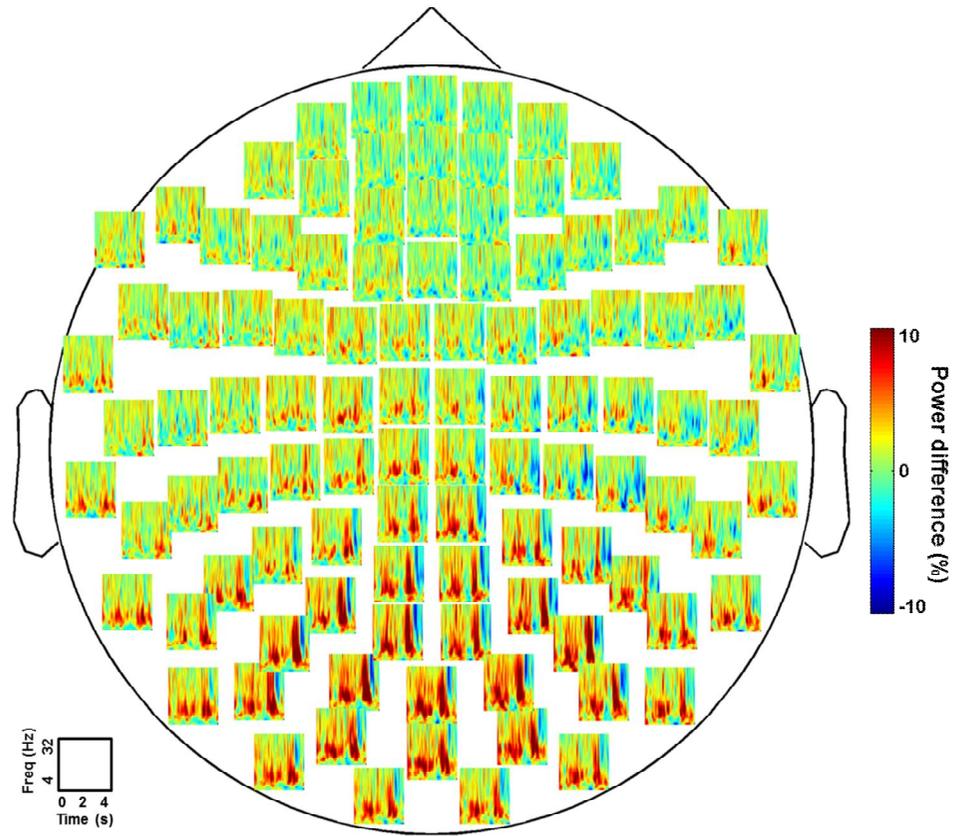
**Figure 6. The relationship between cue-related alpha band modulation and behavioral performance.** (A) The correlation between alpha power modulation (‘No-Remember’ versus ‘Remember’ cue; 10 Hz; 1-2 s) from signals in the posterior parietal cortex (local maxima of the source reconstruction of ‘No-Remember’ versus ‘Remember’ cue in Figure 5C; MNI coordinates  $x, y, z = [-8, -58, 32]$ ) and memory performance (assessed by the standard  $d$ -prime measure calculated by *R-Hits* versus *False Alarm* rates) over subjects was highly significant ( $r = 0.52, p = 0.01$ ). (B) The same correlation as in (A) with respect to *Compliance* (assessed by the standard  $d$ -prime measure calculated by *R-Hits* versus *NR-Hits* rates) over subjects was also highly significant ( $r = 0.66, p < 0.001$ ). (C) The regression values between the difference in the alpha band at source level (‘No-Remember’ versus ‘Remember’ cue; 10 Hz; 1-2 s) and *Compliance* (cluster-level permutation,  $p < 0.05$ ). I found that subjects with a stronger difference in cue-directed alpha activity in posterior parietal regions were also the subjects who were able to perform the task better. Thus, the blocking of irrelevant items by the alpha activity has positive consequences for memory performance.

### 3.4. Subsequent memory effect in the alpha band for *Later Forgotten* versus *Later Remembered* trials

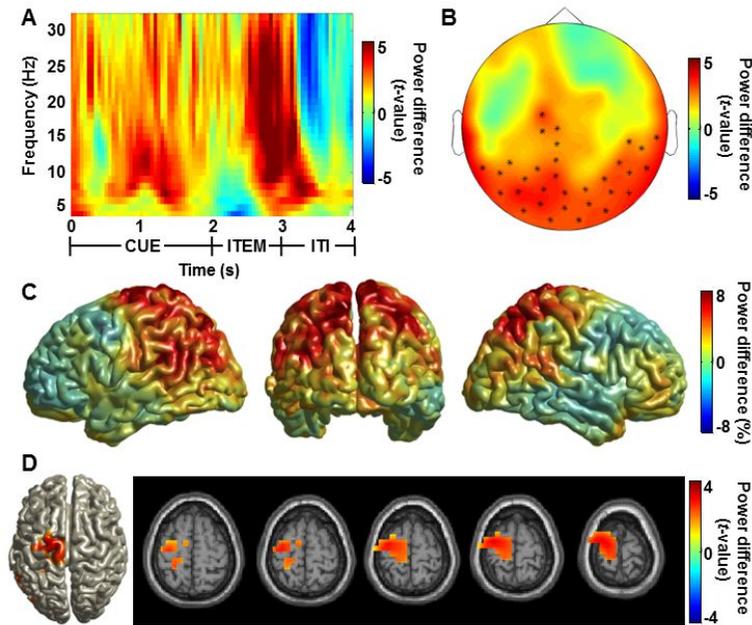
Next, I investigated the brain activity associated with subsequent memory effect regardless of the task conditions. Thus I sorted the encoding trials according to whether they were *Later Forgotten* and *Later Remembered*. In the first part of the analysis to be reported below, I combined the ‘No-Remember’ and ‘Remember’ cues. This was intended to examine how oscillatory activities are modulated in successful remembering and forgotten encoding trials before investigating oscillatory modulation according to task conditions and subsequent memory effect within a task condition.

I found a strong alpha power increase over posterior areas when comparing *Later Forgotten* to *Later Remembered* trials (Figure 7). A time-frequency representation of power for 20 posterior sensors over the parieto-occipital regions showed strong alpha power increase during both the cue and item presentation (permutation,  $p < 0.05$ ; Figure 8A). The posterior alpha power (8-12 Hz) during the cue interval (1-2 s) was highly significant when comparing the *Later Forgotten* to the *Later Remembered* trials as shown in Figure 8B (cluster-level permutation controlling for multiple comparisons over sensors,  $p = 0.008$ ). When localizing the alpha power

difference during the cue interval using a beamformer analysis, I identified an extended source in posterior parietal regions (-8 ~ 8 % relative power increase with respect to the mean; Figure 8C). When this difference was statistically tested, it revealed frontal midline structures including the left supplementary motor area (SMA (Brodmann Area 6); MNI coordinates x, y, z = [-32 -8 72]; cluster-level permutation,  $p < 0.05$ ; Figure 8D). The exact location from the randomization analysis should be interpreted with caution since it probably only reveals a peak in an extended network. I concluded that successful memory encoding is associated with a relative increase in alpha power in an extended areas overlapping with the dorsal attention network.



**Figure 7.** Time-frequency representation for the *Later Forgotten* compared to the *Later Remembered* trials for all sensors (4-32 Hz). Strong alpha power increases in posterior regions were observed during cue interval as well as item presentation (-10 ~ 10 % relative power increase with respect to the mean).



**Figure 8. The posterior alpha power (10 Hz) for the *Later Forgotten* compared to the *Later Remembered* trials.** (A) A time-frequency representation of power calculated for 20 posterior sensors showed a strong increase in the alpha band when comparing the *Later Forgotten* to the *Later Remembered* trials in the encoding session. The strong alpha power increase was observed in the cue interval as well as during item presentation (permutation,  $p < 0.05$ ). (B) Topographical distribution of alpha power increase during the cue interval (10 Hz; 1-2 s) was found in posterior and central sensors (cluster-level permutation,  $p = 0.008$ ) for the *Later Forgotten* versus the *Later Remembered* trials. (C) Source reconstruction using a beamformer approach to localize the alpha power for *Later Forgotten* versus *Later Remembered* trials during the cue interval (10 Hz; 1-2 s). The alpha power for the *Later Forgotten* trials was relatively increased compared to the *Later Remembered* trials (-8 ~ 8 % relative power increase with respect to the mean). (D) Statistical testing of the source reconstruction in (C) revealed the involvement of frontal midline structures including the left supplementary motor area (SMA (Brodmann Area 6); MNI coordinates  $x, y, z = [-32 - 8 72]$ ; cluster-level permutation,  $p < 0.05$ ).

### **3.5. Subsequent memory effect in the alpha band for the ‘No-Remember’ cue**

Given the interests in functional inhibition by alpha band activity in long-term memory task, I considered brain activity in the cue interval for the ‘No-Remember’ cue. Specifically I compared later correctly forgotten trials, i.e., *Later NR-Misses* to later unintentionally remembered trials, i.e., *Later NR-Hits*. When I compared these conditions, alpha power increase was examined over central sensors during cue interval in a time-frequency representation (Figure 9). It was confirmed when 12 central sensors were averaged and compared between conditions (Neuromag sensor labels: 042, 043, 063, 071, 072, 073, 074, 104, 111, 114, 182, 221;  $f = 8-12$  Hz;  $t = 1-2$  s; permutation,  $p < 0.05$ ; Figure 10A). The topographical distribution of alpha power centered at 10 Hz (8-12 Hz when considering spectral smoothing) during cue interval (1-2 s) was found in central region (permutation,  $p < 0.05$ , uncorrected; Figure 10B). When I localized this effect using a beamformer, I found a weak but significant alpha power increase in frontal midline structures including the left supplementary motor area (SMA (Brodmann Area 6) bordering to the frontal eye field; MNI coordinates  $x, y, z = [-26, -4, 80]$ ; permutation,  $p < 0.05$ , uncorrected; Figure 10C). Even though this effect was not significant when controlling for multiple comparisons, it did include sensors from the cluster identified when

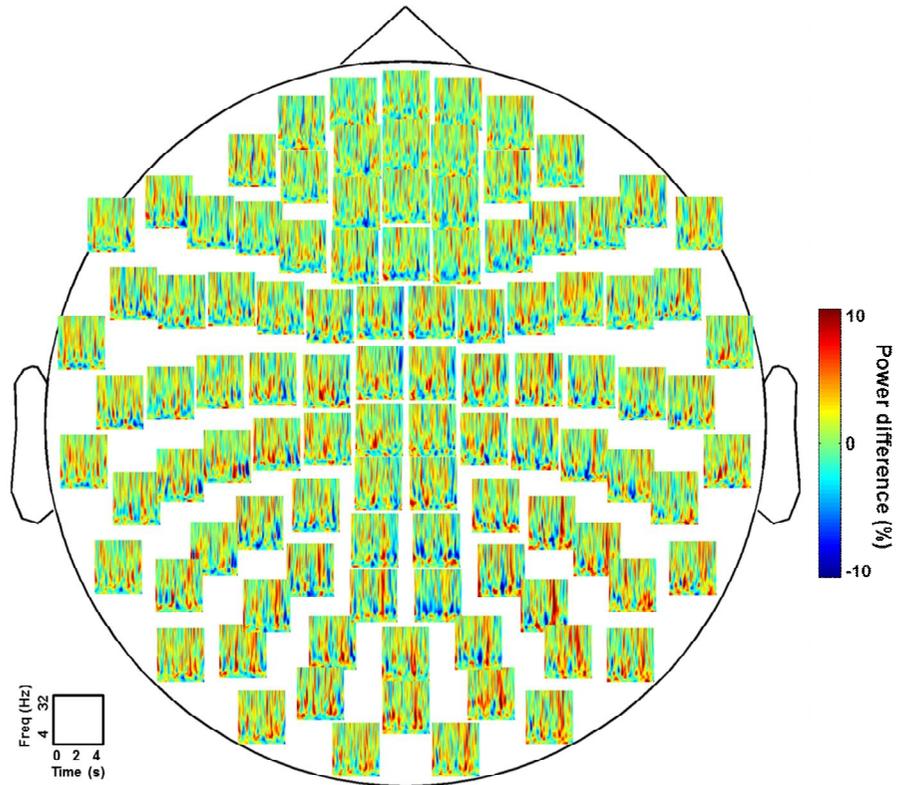
comparing all the *Later Forgotten* versus *Later Remembered* trials in Figure 8B. Statistical power is lost when only considering the ‘No-Remember’ cue trials. I therefore consider the effect reliable and conclude that the modulation in the alpha band reflects the predicted inhibition of irrelevant memory encoding.

I next asked if subjects having a larger difference in alpha band power between *Later NR-Misses* and *Later NR-Hits* are also the subjects who are better at ignoring the ‘No-Remember’ items. To do so, I performed a regression analysis considering the alpha band differences from the beamformer applied to each grid point in the full brain volume (*Later NR-Misses* versus *Later NR-Hits*;  $f = 10$  Hz;  $t = 1-2$  s) and the *Compliance* measure (the same analysis as in Figure 6C). As demonstrated in Figure 11A, this revealed correlations in posterior parietal regions. The effect was consistent with the cueing effect observed in Figure 6C albeit not significant when controlling for multiple comparisons. To further illustrate the results, I computed the correlation between power values from a location in brain volume and *Compliance* over subjects. I here selected a grid point of the local maxima of posterior parietal cortex (precuneus; MNI coordinates  $x, y, z = [0, -72, 64]$ ) from the regression analysis in Figure 11A. This computation revealed a significant positive correlation between power and *Compliance* ( $r = 0.52, p = 0.01$ ; Figure 11B). Although this location is

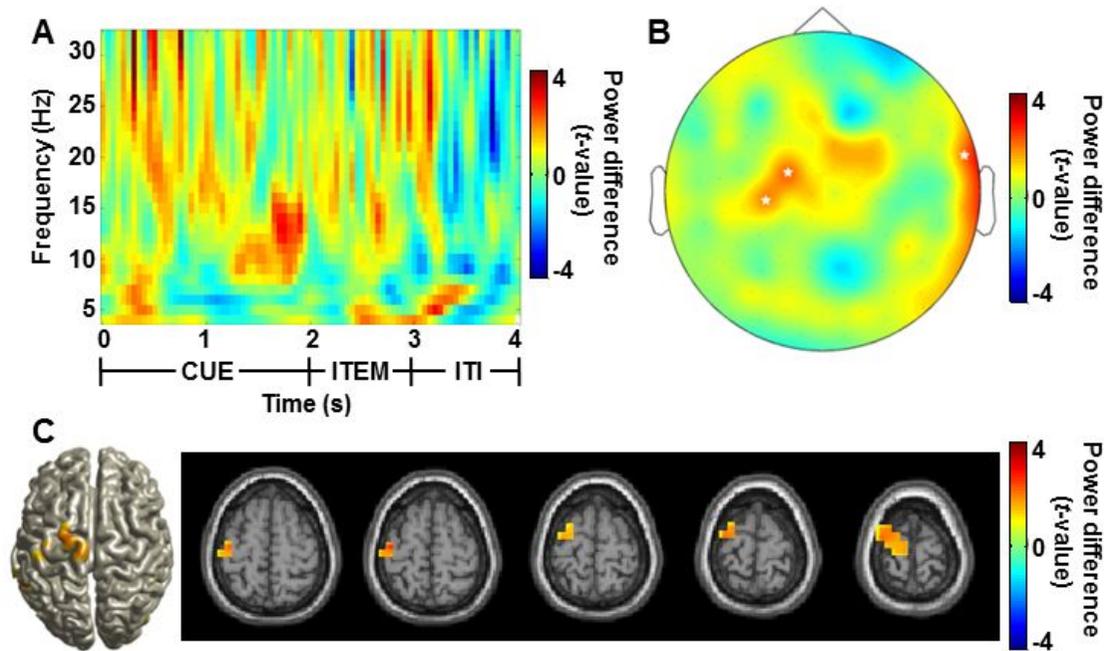
included in the sources in Figures 5C and 6C, the correlation should be considered as a trend given it was not robust when considering multiple comparisons.

I also compared the subsequent memory effect in the alpha band for the 'Remember' condition i.e. *Later R-Hits* versus *Later R-Misses*. Even though trends were present consistent with the previous results, no significant effects were identified when taking multiple comparisons into account.

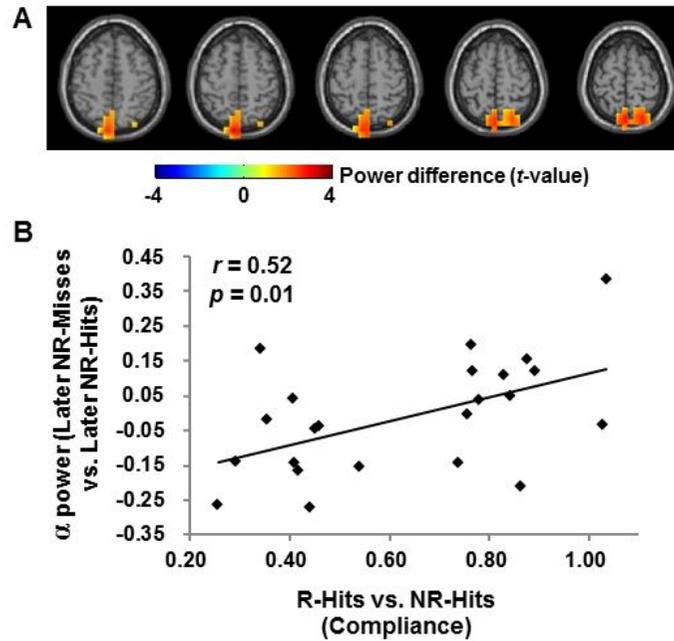
In conclusion, an analysis of the subsequent memory effect for the 'No-Remember' trials revealed that alpha activity in the cue interval serves to prevent encoding of the irrelevant memory items. This alpha band modulation is predictive of performance over subjects. Further an increase in alpha activity in frontal midline structures did reflect the ability to successfully ignore the encoding of items not to be remembered.



**Figure 9.** Time-frequency representation for subsequent memory effect in the ‘No-Remember’ condition, i.e., later correctly forgotten trials (*Later NR-Misses*) versus later unintentionally remembered trials (*Later NR-Hits*) for all sensors (4-32 Hz) (-10 ~ 10 % relative power increase with respect to the mean).



**Figure 10. Alpha band activity for subsequent memory effect in the ‘No-Remember’ condition, i.e., later correctly forgotten trials (*Later NR-Misses*) versus later unintentionally remembered trials (*Later NR-Hits*).** (A) A time-frequency representation of power calculated for 12 central sensors (Neuromag sensor labels: 042, 043, 063, 071, 072, 073, 074, 104, 111, 114, 182, 221) when compared the *Later NR-Misses* to the *Later NR-Hits* revealed an alpha power increase during the cue interval as well as item presentation (permutation,  $p < 0.05$ ). (B) Topographical distribution of the alpha power increase (10 Hz; 1-2 s) for the *Later NR-Misses* versus the *Later NR-Hits* was found over central sensors (permutation,  $p < 0.05$ , uncorrected). (C) For the same comparison, a beamformer analysis revealed frontal midline structures including the left supplementary motor area (SMA (Brodmann Area 6) bordering to the frontal eye field; MNI coordinates  $x, y, z = [-26, -4, 80]$ ; permutation,  $p < 0.05$ , uncorrected).

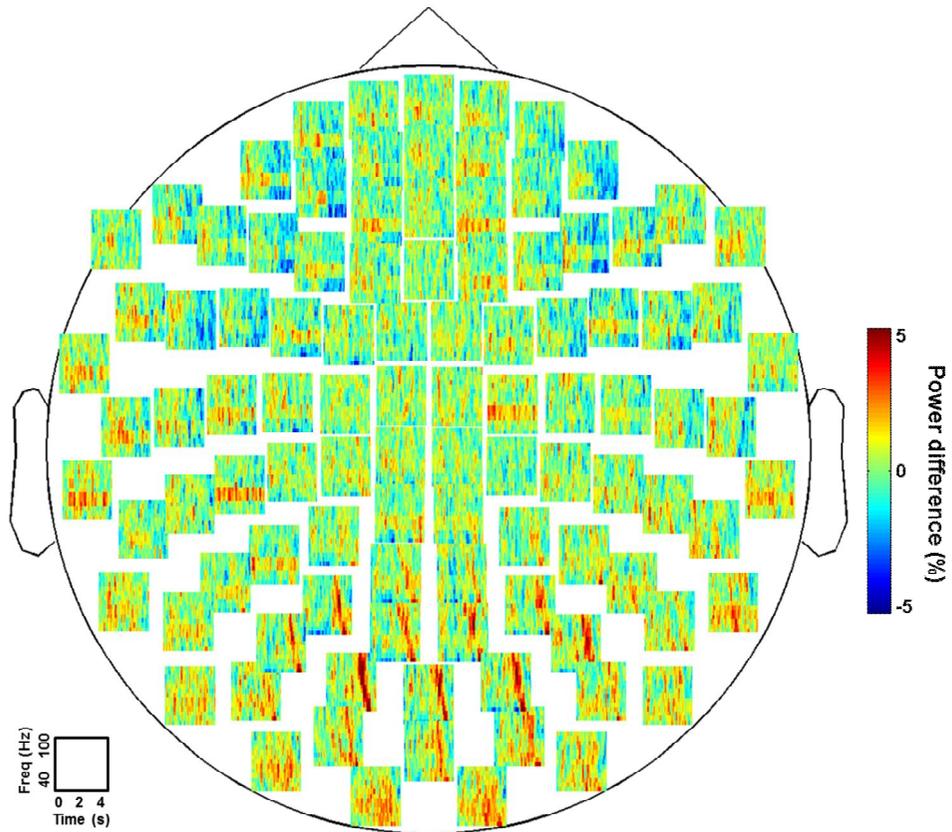


**Figure 11. The relationship between cue-related alpha band modulation for subsequent memory effect in the ‘No-Remember’ condition, i.e., *Later NR-Misses* versus *Later NR-Hits* and *Compliance* during cue interval (1-2 s). (A) The regression results between source level difference in the alpha band for the subsequent memory effect in the ‘No-Remember’ condition (*Later NR-Misses* versus *Later NR-Hits*) and *Compliance*. This showed a similar trend as the regression values for the cueing effect (‘No-Remember’ cue versus ‘Remember’ cue; Figure 6C) albeit weaker (permutation,  $p < 0.05$ , uncorrected). (B) The correlation between the alpha band effect for subsequent memory effect in the ‘No-Remember’ condition (*Later NR-Misses* versus *Later NR-Hits*) and *Compliance* over subjects. Here, I selected a grid point of the local maxima of posterior parietal cortex (precuneus; MNI coordinates  $x, y, z = [0, -72, 64]$ ) from regression analysis in (A). This revealed a significant positive correlation ( $r = 0.52, p = 0.01$ ).**

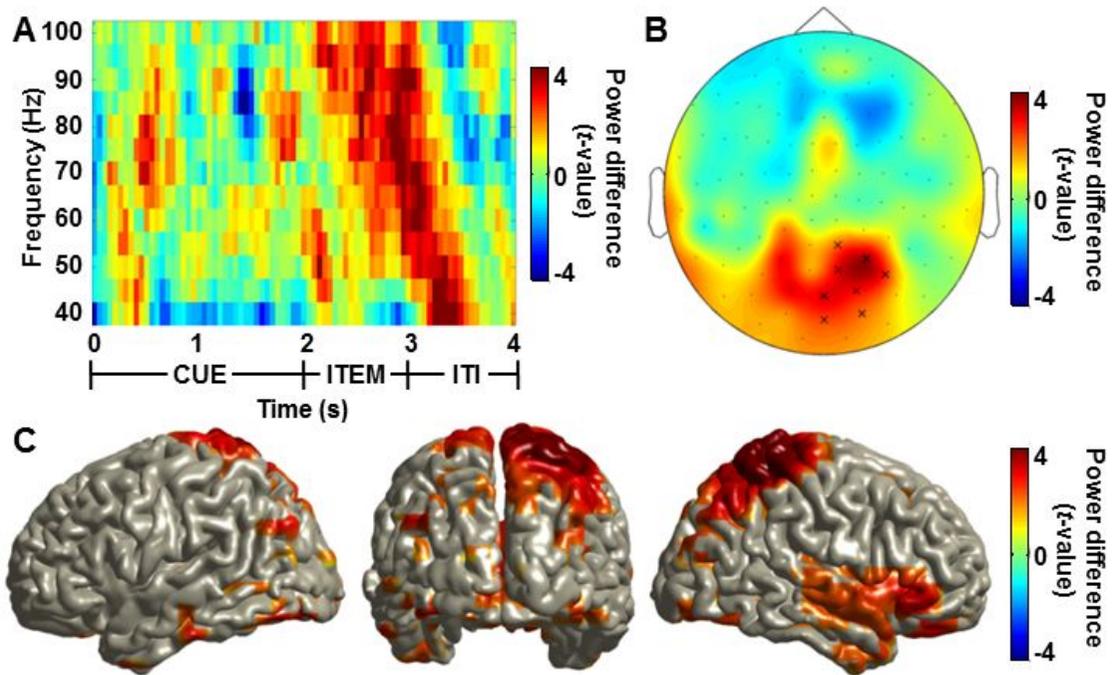
### **3.6. Gamma band activity for ‘No-Remember’ versus ‘Remember’ task conditions**

Given the well-known role of gamma band activity in active information processing in cognitive tasks (Fries et al., 2007; Jensen et al., 2007; Jutras and Buffalo, 2010; Fell and Axmacher, 2011; Park et al., 2011; Roberts et al., 2012), I extended the analysis to the higher frequency bands. First I investigated gamma band activity for the ‘Remember’ versus the ‘No-Remember’ cue. In the cue interval, I did not find any significant effects; however, during the item presentation period, I found a highly robust gamma power increase in posterior regions when comparing the ‘Remember’ to the ‘No-Remember’ encoding trials (see Figure 12 and Figure 13A; averaged over 8 posterior sensors in Figure 13B;  $f = 40\text{-}100$  Hz;  $t = 2\text{-}3$  s; permutation,  $p < 0.05$ ). The effect was somewhat broadband (40-100 Hz) and lasted for about 1 s with an onset of about 200 ms after item presentation. The topographical distribution of the gamma power difference for the ‘Remember’ compared to the ‘No-Remember’ cue at sensor level revealed a highly significant effect over posterior regions (cluster-level permutation,  $p = 0.01$ ; Figure 13B). Source reconstruction of the gamma power increase was localized in posterior parietal cortex, extending into temporal areas bilaterally (maximum MNI coordinates  $x, y, z = [24, -48, 72]$ ; cluster-level permutation,  $p < 0.05$ ; Figure 13C). This source

overlaps strongly with the source reflecting the reverse effect in the alpha band during the cue interval (Figure 5C). These results demonstrated that the encoding of the to-be-remembered items is associated with an increase in gamma band activity.



**Figure 12. Time-frequency representation for the ‘Remember’ to the ‘No-Remember’ cue for all sensors (40-100 Hz).** Strong gamma power increases in posterior regions were observed during item presentation (-5 ~ 5 % relative power increase with respect to the mean).

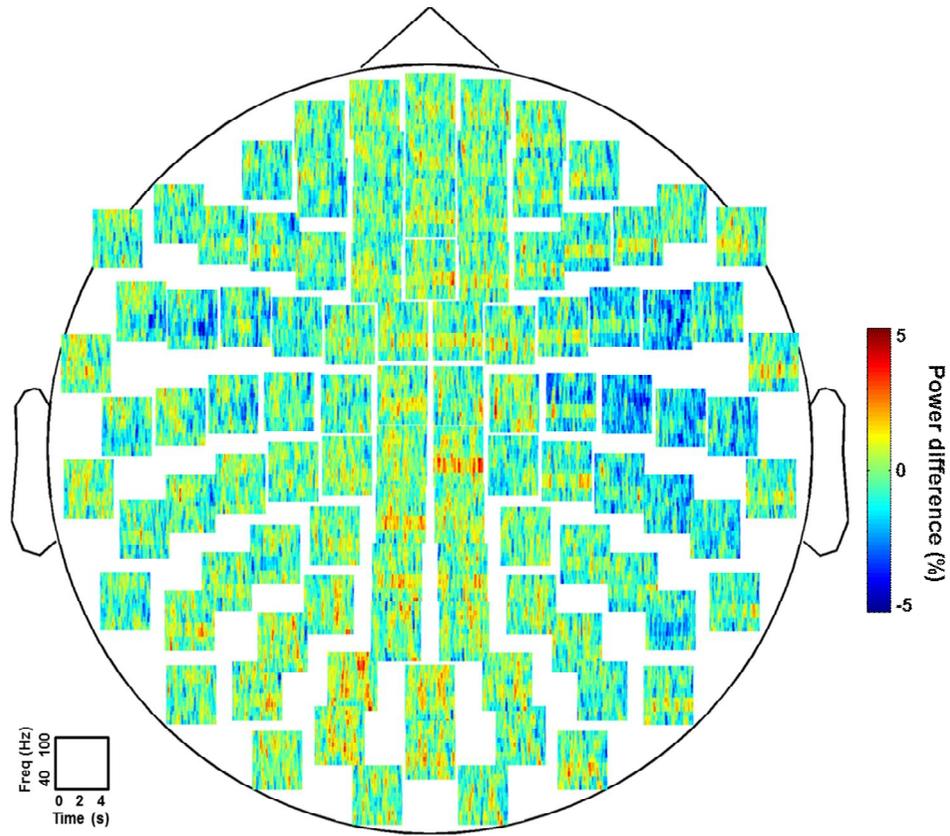


**Figure 13. Modulations of high-frequency power for the ‘Remember’ to the ‘No-Remember’ cue.** (A) A time-frequency representation of power when comparing the ‘Remember’ to the ‘No-Remember’ cue calculated for 8 posterior sensors marked in (B). I observed a robust difference in the gamma band during item presentation (permutation,  $p < 0.05$ ). (B) The topography of the gamma band difference at 80 Hz when comparing the ‘Remember’ to the ‘No-Remember’ condition during item presentation (2-3 s). I found a significant difference over posterior regions (cluster-level permutation,  $p = 0.01$ ). (C) Source reconstruction using a beamformer approach to localize the gamma power increase during item presentation (80 Hz; 2-3 s) revealed sources in posterior parietal cortex, extending into temporal cortex bilaterally (maximum MNI coordinates  $x, y, z = [24 -48 72]$ ; cluster-level permutation,  $p < 0.05$ ).

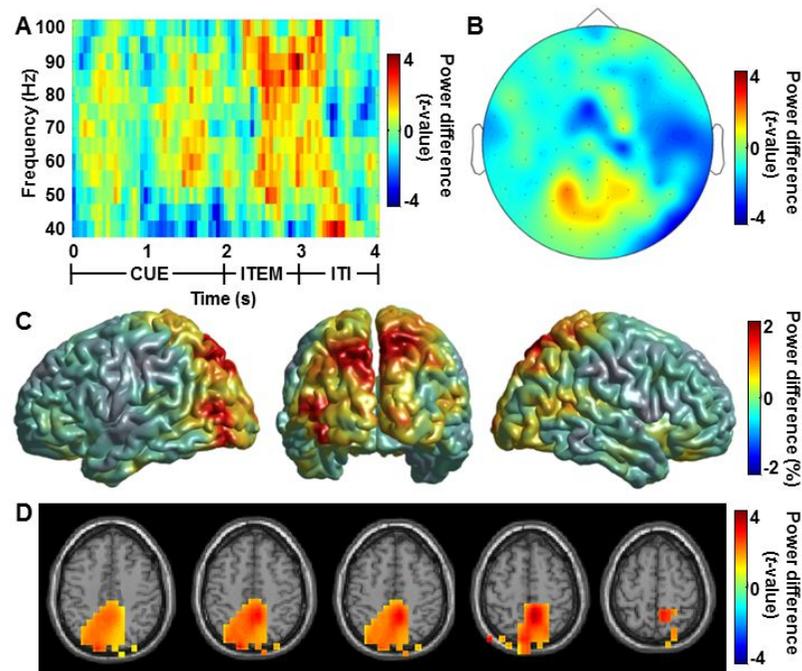
### 3.7. Gamma band activity for *Later Remembered* versus *Later Forgotten* trials

Next I examined the subsequent memory effect regardless of the ‘Remember’/‘No-Remember’ cue by comparing the *Later Remembered* to the *Later Forgotten* trials. I found a robust gamma power increase during item presentation which reflected the subsequent memory effect (Figure 14). It was also confirmed when posterior sensors were averaged and compared (5 posterior sensors with power increase in Figure 15B;  $f = 40\text{-}100$  Hz;  $t = 2\text{-}3$  s; permutation,  $p < 0.05$ ; Figure 15A). When I focused on the 80 Hz band power (70-90 Hz when considering spectral smoothing) during item presentation (2-3 s), the activity was most pronounced in posterior sensors. While consistent with the cueing effect in Figure 13B, it was however not significant when controlling for multiple comparisons over sensors (permutation,  $p < 0.05$ , uncorrected; Figure 15B). Next, the source reconstruction of this activity has shown that gamma power for *Later Remembered* was increased than the *Later Forgotten* trials over posterior parietal regions (-2 ~ 2 % relative power increase with respect to the mean; Figure 15C). When this difference was statistically tested, it revealed posterior parietal cortex including precuneus (MNI coordinates  $x, y, z = [8 - 48 56]$ ;  $p < 0.05$ , uncorrected; Figure 15D). Albeit not significant when controlling for multiple comparisons over grid points, the regions of the

subsequent memory effect in the gamma band overlapped strongly with the subsequent memory effect in the alpha band (Figure 8C).



**Figure 14.** Time-frequency representation for the *Later Remembered* compared to the *Later Forgotten* trials for all sensors (40-100 Hz). Strong gamma power increases in posterior regions were observed during item presentation (-5 ~ 5 % relative power increase with respect to the mean).

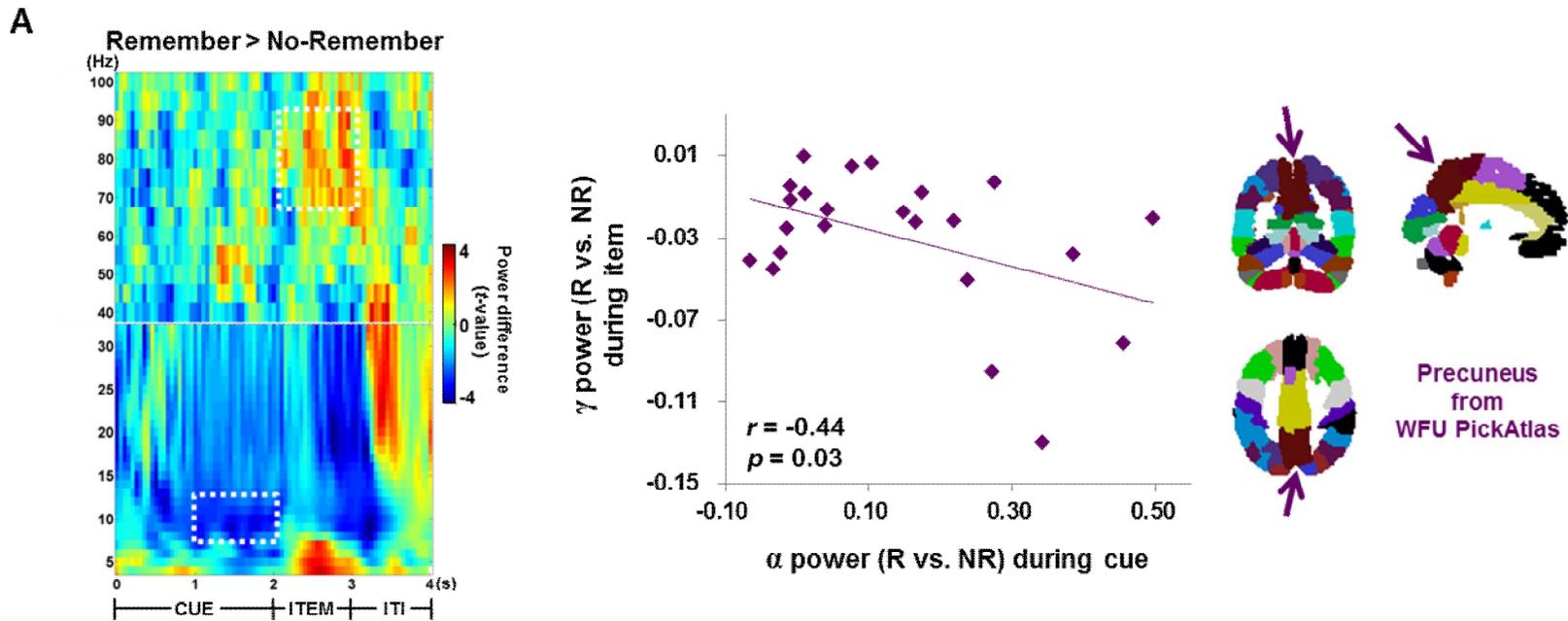


**Figure 15. Modulations of high-frequency power for the *Later Remembered* compared to the *Later Forgotten* trials.** (A) A time-frequency representation of power when comparing *Later Remembered* to the *Later Forgotten* trials calculated for 5 posterior sensors with power increase in (B) (permutation,  $p < 0.05$ ). (B) Topographical distribution of gamma power during item presentation (80 Hz; 2-3 s) increased over posterior sensors. (C) Source reconstruction using the beamformer approach for the *Later Remembered* versus the *Later Forgotten* trials (80 Hz; 2-3 s). The gamma power for the *Later Remembered* trials was relatively increased compared to the *Later Forgotten* trials over posterior parieto-occipital regions (-2 ~ 2 % relative power increase with respect to the mean). (D) Statistical testing of the source reconstruction in (C) revealed the involvement of posterior parietal cortex including precuneus (MNI coordinates x, y, z = [8 -48 56];  $p < 0.05$ , uncorrected).

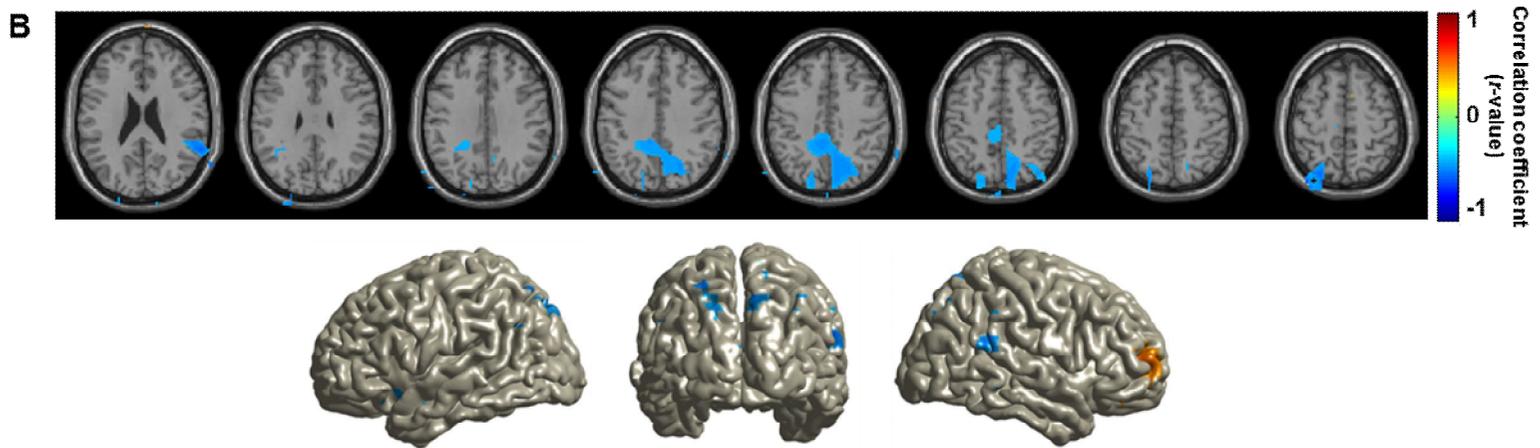
### **3.8. Correlation between alpha power during cue interval and gamma power during item presentation**

As I hypothesized, alpha power increased during cue interval and gamma power increased during item presentation. Motivated by this fact, I was interested in the relationship between these two oscillatory modulations. In order to find this relationship, I performed a correlational analysis between alpha power during cue interval (1-2 s; Figure 5C) and gamma power during item presentation (2-3 s; Figure 13C) for the ‘Remember’ versus ‘No-Remember’ cue condition. The source analyses in the previous analyses for both the alpha and gamma band effects produced sources in the precuneus. Thus I investigated the relationship between the power in these two bands using signals from the precuneus (WFU PickAtlas; available from <http://fmri.wfubmc.edu/software/PickAtlas>). This region includes large portion of posterior parietal cortex and it overlaps with central areas of the dorsal attention network. The alpha power during the cue interval (1-2 s) and gamma power during the item presentation (2-3 s) were extracted from the grid points in left and right precuneus using the beamformer approach and the ‘Remember’ versus ‘No-Remember’ difference was calculated. Then, these alpha and gamma power values were correlated over subjects. This procedure revealed a significant negative correlation ( $r = -0.44$ ,  $p = 0.03$ ; Figure 16A).

To identify the brain regions with the strongest correlations, I performed the correlational analysis using the power values from subjects obtained from every grid point in the brain volume using the beamformer approach. I found negative correlations in posterior parietal cortex including bilateral precuneus (local maxima: precuneus; MNI coordinates  $x, y, z = [14, -68, 72]$ ;  $r = -0.54$ ,  $p < 0.05$ , uncorrected; Figure 16B). The location is consistent with the regions where the alpha and gamma sources were identified in the previous analysis. I concluded that subjects in which the alpha band power decreases during a ‘Remember’ cue are also subjects in which the gamma band power increases during encoding.



**Figure 16.** Correlations between alpha power during cue interval (1-2 s; lower dashed box at the left figure) and gamma power during item presentation (2-3 s; upper dashed box at the left figure) for the cueing effect. (A) Correlation between alpha power during cue interval (1-2 s) and gamma power during item presentation (2-3 s) when comparing ‘Remember’ cue to ‘No-Remember’ cue condition. Figures on the left side show time-frequency representations from maximum coordinates of alpha (left precuneus, MNI coordinates  $x, y, z = [-8, -58, 32]$ ) and gamma band (right posterior parietal cortex, MNI coordinates  $x, y, z = [24 -48 72]$ ) activities. The power values were derived using a beamformer approach, averaging signals from within the precuneus (ROI analysis; left and right precuneus from the WFU PickAtlas; see the right figure). I observed a significant negative correlation for these values ( $r = -0.44$ ,  $p = 0.03$ ).



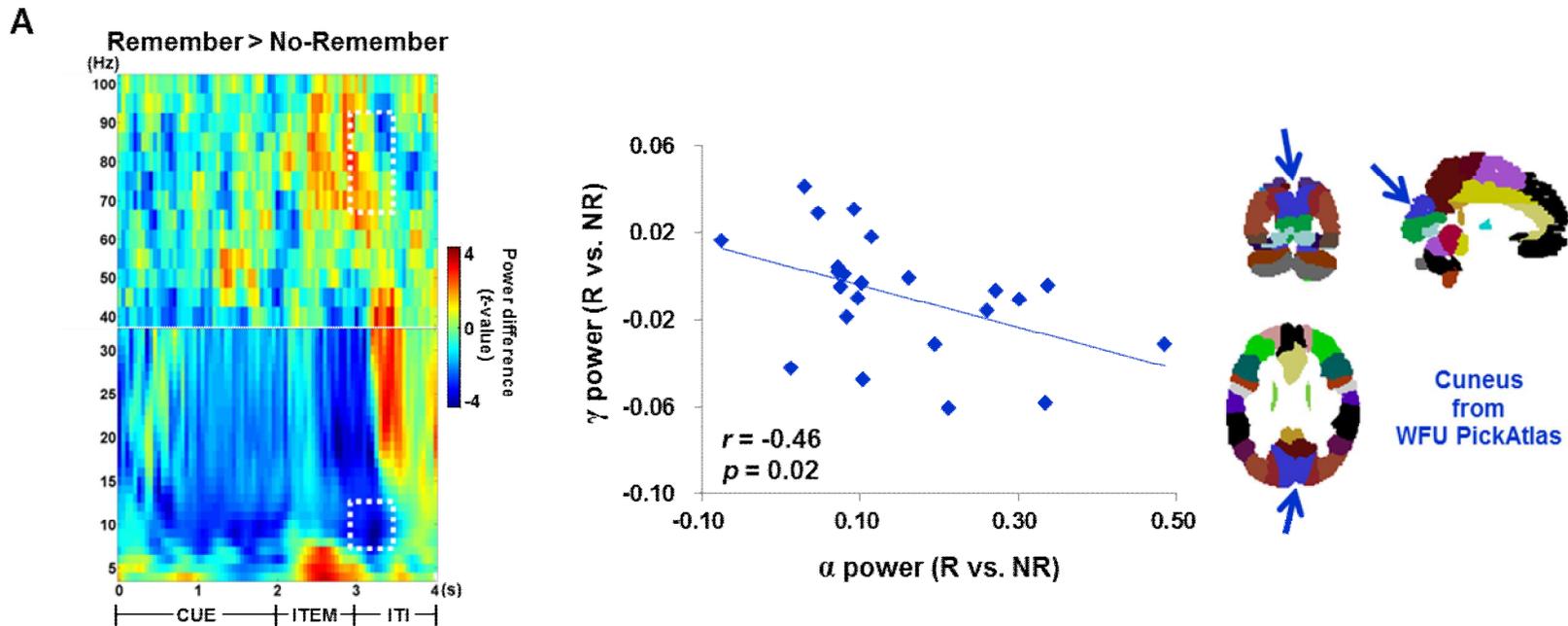
**Figure 16. (B)** The correlation analysis in the source domain between alpha power during cue interval (1-2 s) and gamma power during item presentation (2-3 s) when comparing ‘Remember’ cue to ‘No-Remember’ cue condition. The correlation analysis was performed at every grid point in brain volume and confirmed the negative correlation in posterior parietal cortex including bilateral precuneus (local maxima: precuneus; MNI coordinates x, y, z = [14, -68, 72];  $r = -0.54$ ,  $p < 0.05$ , uncorrected).

### **3.9. Correlation between alpha power and gamma power during item presentation**

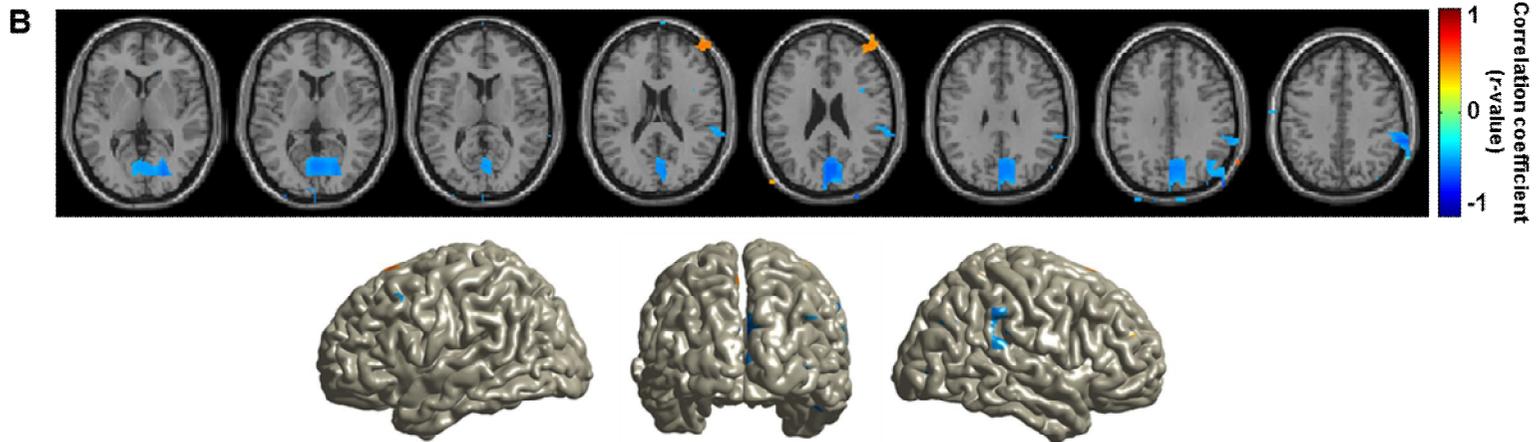
Next, I examined correlation between alpha and gamma power during the item presentation which reflects encoding-related modulation. The correlational analysis was performed between alpha power and gamma power during item presentation (3-3.5 s) for the ‘Remember’ versus ‘No-Remember’ cue condition. During the item presentation, I hypothesized occipital regions would be involved since visual stimulus was presented. Thus, cuneus as a region-of-interest (ROI) from the WFU PickAtlas was used. The alpha power and gamma power during item presentation (3-3.5 s) were extracted from each grid point in left and right cuneus and averaged using each individual’s source reconstruction like virtual electrode approach. Then, these alpha and gamma power values were correlated over subjects and revealed significant negative correlation ( $r = -0.46$ ,  $p = 0.02$ ; Figure 17A).

Likewise, in order to identify the brain regions with the strongest correlations, I performed the correlational analysis using the power values from subjects obtained from every grid point using a beamformer approach. It also revealed negative correlations in posterior occipito-parietal cortex including bilateral cuneus (local maxima: cuneus; MNI coordinates  $x, y, z =$

[0, -74, 24];  $r = -0.57$ ,  $p < 0.05$ , uncorrected; Figure 17B). Although this effect was not significant when considering multiple comparisons either, I suggest that alpha power decrease and gamma power increase for memorizing item after a 'Remember' cue are interconnected modulations.



**Figure 17. Correlations between alpha power and gamma power during item presentation (3-3.5 s; dashed boxes at the left figure) for the cueing effect. (A)** Correlation between alpha power and gamma power during item presentation (3-3.5 s) when comparing ‘Remember’ cue to ‘No-Remember’ cue condition. Figures on the left side show time-frequency representations from maximum coordinates of alpha (left precuneus, MNI coordinates  $x, y, z = [-8, -58, 32]$ ) and gamma band (right posterior parietal cortex, MNI coordinates  $x, y, z = [24 -48 72]$ ) activities. The power values were derived using a beamformer approach, averaging signals from within the cuneus (ROI analysis; left and right cuneus from the WFU PickAtlas; see the right figure). I observed a significant negative correlation for these values ( $r = -0.46, p = 0.02$ ).



**Figure 17. (B)** The correlation analysis in the source domain between alpha power and gamma power during item presentation (3-3.5 s) when comparing ‘Remember’ cue to ‘No-Remember’ cue condition. The correlation analysis was performed at every grid point in brain volume and confirmed the negative correlation in posterior occipito-parietal cortex including bilateral cuneus (local maxima: cuneus; MNI coordinates  $x, y, z = [0, -74, 24]$ ;  $r = -0.57$ ,  $p < 0.05$ , uncorrected).

## 4. Discussion

The aim of the current study was to test whether alpha oscillations provide a mechanism for gating long-term memory encoding. A cue indicated whether pictorial items presented 2 s later should be encoded or not. The first finding was that alpha power in the cue interval already prior to presentation of the memory items was predictive of memory formation. Second, I found that alpha activity in posterior parietal regions increased dramatically for the ‘No-Remember’ compared to the ‘Remember’ cue, just prior to the item presentation. Subjects with the strongest cue-directed alpha power increase were also subjects who performed better on the memory task. Further, during item presentation, I found that there was stronger induced gamma activity for the ‘Remember’ compared to the ‘No-Remember’ condition. Importantly, the decrease of alpha power before the presentation of the item correlated with the increase in gamma activity during memory encoding when ‘Remember’ was compared to the ‘No-Remember’ condition.

The subsequent memory effect regardless of task conditions, i.e., *Later Forgotten* versus *Later Remembered* trials was weaker than cueing effect, i.e., ‘No-Remember’ versus ‘Remember’ cue conditions both for alpha and gamma activities even though the number of trials was similar. I

suggest that this reflects experimental manipulation which was given as ‘No-Remember’ and ‘Remember’ cues was so strong that made subjects tried to follow the task instruction.

#### **4.1. Alpha activity in posterior parietal regions gates memory encoding**

Our sensory systems are constantly exposed to large amount of information of which only little is of relevance for our behavior. To be able to remember the relevant information, it is essential to have powerful mechanisms that filter out irrelevant information prior to encoding. The findings of this study suggest that posterior alpha activity is under top-down control and serves to actively gate information to long-term memory. This interpretation is consistent with previous findings from attention and working memory studies supporting the idea that posterior alpha activity gates the information flow in an anticipatory manner (Klimesch et al., 2007; Freunberger et al., 2009; Hanslmayr et al., 2009; Jensen and Mazaheri, 2010; Foxe and Snyder, 2011; Handel et al., 2011; Hsieh et al., 2011; Park et al., 2011; Jensen et al., 2012; Roberts et al., 2012).

From a physiological perspective, this gating is achieved through inhibition. For instance, it has been shown that both neuronal firing and the BOLD signal are reduced with a local increase in the alpha activity

(Goldman et al., 2002; Laufs et al., 2003; Moosmann et al., 2003; Hanslmayr et al., 2007; Mantini et al., 2007; de Munck et al., 2009; Scheeringa et al., 2009; Haegens et al., 2011; Scheeringa et al., 2011; Scheeringa et al., 2012). Also, both visual detection and phosphene detection are reduced as posterior alpha activity increases (Romei et al., 2008; van Dijk et al., 2008; Mathewson et al., 2009).

I extend these principles by demonstrating that alpha power increase during memory cueing reflects the intentional inhibition of visual processing. This inhibition prevents the encoding in long-term memory. Further I showed that the decrease in alpha power during the cue interval was complemented by an increase in gamma power during item presentation. I therefore propose that alpha power modulation sets the state of the network controlling the subsequent encoding reflected by gamma band synchronization (Gruber et al., 2004; Osipova et al., 2006; Jutras and Buffalo, 2010). I found the alpha band modulation to be most robust in the dorsal attention network including posterior parietal regions. This is in good agreement with neuroimaging studies demonstrating the involvement of parietal regions in tasks requiring top-down attentional control (Hopfinger et al., 2000; Corbetta and Shulman, 2002; Giesbrecht et al., 2003; Fox et al., 2006; Slagter et al., 2007; Asplund et al., 2010; Wen et al., 2012; Chica et al., 2013). It should also be noted that the location of the alpha band modulation

is somewhat widespread and does somewhat vary when comparing the different conditions (compare Figures 6, 8 and 10); however, the sources do consistently overlap with the dorsal attention network (Fox et al., 2006).

Corbetta and Shulman (2002) showed that partially segregated brain networks are involved in goal-directed versus stimulus-driven attentional system. The authors suggested that dorsal frontoparietal network including intraparietal cortex and superior frontal cortex is involved in preparing and applying goal-directed selection by top-down manner whereas ventral frontoparietal network including temporoparietal cortex and inferior frontal cortex is involved in detection of stimuli, particularly when they are salient or unexpected by bottom-up processing.

Also, there was a report that alpha oscillation correlates with the successful inhibition of unattended stimuli using attentional task (Handel et al., 2011). This study proved that the attentional inhibition of alpha oscillation. Further, in the study of Capotosto et al. (2009), they linked control of attention by dorsal frontoparietal network and anticipatory alpha activity. Using repetitive transcranial magnetic stimulation (rTMS), the stimulation was delivered in intraparietal sulcus (IPS) and frontal eye field (FEF). This finally impaired identification of target visual stimuli and associated with the disruption of anticipatory (prestimulus) alpha decrease in parieto-occipital cortex. They suggested that this result supports the

causal role of the dorsal frontoparietal network in the control of visuospatial attention. Also functional inhibitory role of alpha oscillation was supported.

During the cue interval in this paradigm, subjects had to prepare inhibition or facilitation of encoding for upcoming memory items according to the cue. This anticipation is processed by attentional mechanism through voluntary, goal-directed (top-down) manner. For this goal, alpha oscillations control the attention at the prestimulus stage, which then it blocks irrelevant information coming into long-term memory system. The control of the memory encoding reflected by alpha band modulation should therefore be attributed to the dorsal attention network rather than a single region *per se*.

In short, these results provide important new insights into how the encoding of visual information can be prevented. I suggest the alpha band modulation reflects a filter mechanism allowing us to remember only the relevant information when operating in a complex world.

#### **4.2. Better memory performers had an improved ability to modulate the posterior alpha power**

Individuals who remembered more of the relevant information at the expense of the irrelevant information showed better memory performance. Thus individuals who are better at flexible suppressing the irrelevant items will benefit in terms of remembering the relevant items. To

understand this mechanism from a physiological perspective, I found that individuals with a stronger difference in the cue-directed alpha activity in posterior parietal regions were also those with better memory performance. These results crystalize the functional inhibitory role of alpha band activity in terms of blocking the processing of irrelevant information. This fact could be even more substantiated by the results of alpha band modulation for the subsequent memory effect regardless of task conditions, i.e., *Later Forgotten* versus *Later Remembered* since this means that alpha oscillation gates memory encoding.

#### **4.3. Gamma increase in parietal regions for the ‘Remember’ cue during item presentation**

I observed a gamma band increase when comparing the ‘Remember’ versus ‘No-Remember’ condition during memory encoding. Several regions including parietal-occipital-temporal areas accounted for this gamma band activity. Gamma band activity is typically associated with active neuronal processing in attention and memory tasks (Fries et al., 2007; Jensen et al., 2007; Jutras and Buffalo, 2010; Fell and Axmacher, 2011; Park et al., 2011; Roberts et al., 2012). For instance, it has been shown that spiking phase-locked to gamma oscillations facilitates synaptic plasticity

(Wespataat et al., 2004). Further neuronal synchronization in the gamma band is bound to results in a stronger feed-forward drive that could promote encoding in downstream structures (Salinas and Sejnowski, 2001). I did find a trend towards a subsequent memory effect in the gamma band during item presentation. Albeit the effect was statistically significant in regions where I observed the strongest alpha band modulation, it was not robust after controlling for multiple comparisons. The reliability of the effect is likely to increase with more trial numbers. Nevertheless, the gamma band subsequent memory effect is consistent with several previous reports (Gruber et al., 2001; Gruber et al., 2004; Osipova et al., 2006; Meeuwissen et al., 2011).

#### **4.4. Cue-induced alpha power modulation predict encoding-related gamma activity**

As I argue above, the alpha power decreases in the cue interval to open the gate to the memory system, whereas the gamma power increases during item presentation to facilitate memory encoding. This analysis revealed that the encoding-related alpha decrease observed when comparing the ‘Remember’ to the ‘No-Remember’ condition predicted the gamma band increase over subjects. This effect was observed in posterior parietal regions included in the dorsal attention network. I suggest that the inhibitory control

by the alpha activity sets the state of the network determining the subsequent memory processing reflected in the gamma band.

#### **4.5. Alpha activity in frontal midline structures might prevent encoding of irrelevant information**

When I compared the brain activity for later correctly forgotten to later unintentionally remembered trials regardless of task conditions (*Later Forgotten* > *Later Remembered* trials), I found significant alpha power increase in frontal structures including the supplementary motor area (SMA) which also partly overlap with the dorsal attention network. The same regions were found in the subsequent memory effect for the ‘No-Remember’ cue condition (*Later NR-Misses* > *Later NR-Hits*). This suggests that successful suppression of upcoming irrelevant information is reflected by alpha activity in this region.

This finding is consistent with previous studies suggesting that the SMA plays an inhibitory role (Shadmehr and Holcomb, 1999; Ikeda et al., 2000; Mostofsky et al., 2003; Sumner et al., 2007; Chen et al., 2009; Boy et al., 2010; Chen et al., 2010; Aron, 2011; Konishi et al., 2011). It is well known that the SMA being part of the dorsal attention network is not only involved in motor-related functions, but is also involved in attention and

memory (Hopfinger et al., 2000; Chein and Fiez, 2001; Simon et al., 2002; Ortuno et al., 2005; Cole and Schneider, 2007). The cue-related activity in this paradigm could be translated into preparatory activity for internally generated action for remembering or not-remembering upcoming memory item like action according to the ‘go’ (‘Remember’ cue) or ‘no-go’ (‘No-Remember’ cue) signals of traffic lights (Mostofsky et al., 2003; Jaffard et al., 2007; Aron, 2011). Future work is required to better understand how the alpha activity produced in frontal regions and posterior parietal cortex are associated.

#### **4.6. Oscillatory brain activity predicting memory encoding**

Prestimulus oscillatory activity has been found to predict memory encoding in other studies as well (Guderian et al., 2009; Addante et al., 2011; Fell et al., 2011; Gruber et al., 2012). For instance, Gruber et al. (2012) recently reported that encoding-related theta activity reflected memory encoding in an EEG study using a monetary reward expectancy paradigm. Guderian et al. (2009) also found theta band activity to predict episodic encoding in an MEG study. In addition to theta power enhancement, Fell et al. (2011) observed alpha power enhancement for successful memory encoding before stimulus presentation in an intracranial EEG study. They suggested that theta and alpha band activity reflects inhibitory top-down

control in preparation for stimulus-triggered memory processing. Consistently I suggest that alpha band activity in the dorsal attention network is predictive of memory encoding.

## **5. Conclusion**

In conclusion, posterior alpha activity gates memory encoding. Memory is improved if one manages to block out irrelevant information by an increase in alpha activity. Finally, alpha and gamma activities interact such that a decrease in the alpha band activity allows for stimulus-induced memory encoding reflected in the gamma band. As such, posterior alpha activity might play an important role in real-life situations where we are confronted with massive amounts of information. Under such circumstances, it is essential to have powerful mechanisms that suppress the irrelevant input so that the relevant information can be remembered. Future work employing measures of cross-frequency coupling between brain regions may shed further light on the network properties and interactions between oscillations in different frequency bands.

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## 후측 알파 오실레이션에 의한 하향성 기억 억제

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협동과정 인지과학 전공

우리는 매 순간 수많은 정보를 접하며 살아간다. 그러나 우리 뇌의 장기기억 시스템에 저장할 수 있는 정보의 양은 지극히 제한적이다. 따라서 우리 뇌는 효율적인 기억 시스템을 유지하기 위해 우리가 접하는 많은 양의 정보들 중 자신에게 꼭 필요한 정보만을 걸러내는 여과 기능을 사용하고 있다. 최근의 뇌 오실레이션 연구에 의하면 8-13 헤르츠(Hertz; Hz)의 주파수 활동에 해당하는 알파파는 정보가 주어졌을 때 주어진 정보 처리와 관련하여 방해 정보의 억제나 과제 비관련 뇌 영역에서의 억제 활동에 관여한다는 사실이 보고되어 왔다. 한편, 30 헤르츠 이상의 주파수 활

동에 해당하는 감마파는 지각, 주의, 기억 등의 직접적인 정보 처리와 관련하여 증가됨이 관찰되어 왔다. 본 연구는 이러한 기존 연구들에 기반하여 앞서 언급한 효율적인 장기기억 시스템에 필수적인 필요없는 정보의 억제 활동에 알파파가 관여할 것이라고 가정하였다. 알파파가 기억 시스템으로의 정보 저장에 관문(關門; gate)으로서의 역할을 할 것이라는 것이다. 더불어 이는 필요한 정보의 저장에 직접적으로 관여하는 감마파의 활동과도 관련되어 있을 것이라고 가정하였다.

이러한 장기기억으로의 정보 저장에 관여하는 여파 기능의 신경학적 기제를 이해하기 위하여 ‘기억’(Remember), ‘비기억’(No-Remember)의 단서 제시를 이용한 장기기억 패러다임으로 실험을 실시하였다. 기억 혹은 비기억 단서를 먼저 제시한 이후 사진 자극(풍경 혹은 건물)을 제시하여 피험자들로 하여금 사진 자극을 기억 혹은 기억하지 못하게 하였다. 뇌 오실레이션을 측정하고 보다 정확한 뇌 영역 국소화 분석을 위하여 뇌자도(腦磁圖; Magnetoencephalography)를 사용하여 뇌 신호를 측정하였고, 시간-주파수(time-frequency) 분석 방법을 통하여 뇌파 활동 분석과 빔포밍(beamforming) 알고리즘을 사용하여 뇌파 활동의 뇌

영역 국소화 분석을 수행하였다. 또한 알파파와 감마파 활동의 기능적 연결성을 이해하기 위하여 상관분석을 뇌의 각 복셀 수준에서 실시하였다.

분석 결과, 비기억 단서를 제시하였을 때 사진 자극이 제시되기 전인 단서 제시 동안 후두-두정 영역에서 알파파 활동이 증가하는 것을 관찰할 수 있었다. 이러한 비기억 단서 제시시 알파파 증가 양상은, 행동 결과에서 비기억 단서 자극을 잘 기억하지 못하고 기억 단서 자극을 더 잘 기억한 수행을 보인 피험자들에게서 더욱 강하게 나타났다. 사진 자극 제시 동안에는 감마파 활동이 기억 단서 제시 동안 후두-두정 영역에서 강하게 관찰되었다. 또한 상관 분석을 통하여 단서 제시 동안의 알파파 증가 활동이 사진 자극 제시 동안의 감마파 증가 활동과 의미 있는 관련성이 있음을 보여주었다.

이러한 결과는 필요없는 정보가 제시되었을 때 알파파 활동이 이미 자극이 제시되기 이전부터 하향식(下向式; top-down) 정보 전달 방식으로 통제 역할을 수행한다는 사실을 보여주고 있다. 즉, 시각적 정보 처리를 억제함으로써 결국 장기기억으로의 정보 저장을 억제하는 역할을 수행하는 것이다. 이는 이러한 알파파

활동이 행동적 양상으로 관찰되는 기억 수행 결과와 의미 있는 상관성을 보여주고 있다는 사실에 뒷받침될 수 있다. 또한 자극 제시 전 억제 기능으로서의 역할을 하는 알파파 활동과 자극 제시시 기억 저장 기능으로서의 역할을 하는 감마파 활동의 의미있는 상관성은 알파파가 자극이 제시되기도 전에 필요없는 정보의 억제 기능을 수행함으로써 감마파의 기억 저장 기능을 효율적으로 향상시킴을 보여준 결과라고 설명할 수 있다.

이 연구는 기억 억제 과정에 관여하는 뇌 오실레이션의 역할과 오실레이션 간의 상관성에 대한 이 분야의 지식을 축적하는데 중요한 역할을 하였고, 임상적으로는 기억상실증, 알츠하이머 치매, 외상후 스트레스 장애, 노화로 인한 기억 관련 장애 등의 치료에 대하여 중요한 함의를 제공할 수 있다고 판단된다.

주요어: 일화기억, 기억 억제, 기억 단서, 비기억 단서, 뇌자도(腦磁圖; MEG; Magnetoencephalography), 뇌 오실레이션, 알파 오실레이션, 감마 오실레이션, 주파수간 상관성

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