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Cross-frequency phase synchronization: A brain mechanism of memory matching and attention

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Summary

Spatial attention amplifies the neural response, i.e. spike rates, brain metabolism, and oscillatory activity at gamma frequency (beyond 30 Hz). In this study we show that when a visual target is attended enhanced synchrony between gamma phase (30 to 50 Hz) and theta phase (4 to 7 Hz), representing bottom-up and top-down activity, respectively, can be observed. This is interpreted as memory matching between incoming visual information and stored (top-down) information. The results highlight the function of oscillatory brain activity in the integration of memory and attention processes. This seems to be true in particular for theta oscillations showing increased interregional phase-coupling. We conclude that memory information is stored within a distributed theta network and it is matched with an incoming sensory trace at posterior brain areas.
Introduction

Although the capacity of the visual system is impressingly large, it is nonetheless limited. Since we are continuously exposed to a tremendous amount of visual information, it is of crucial importance to select the relevant information. It has been shown that visual attention amplifies the evoked neural response (event-related potentials and/or BOLD signal) to selected items leading to increased efficiency of neuronal processing of attended information by the way of faster response times or higher detection rates (Hillyard and Anllo-Vento, 1998; Hillyard et al., 1998; Luck et al., 1997; Kastner and Ungerleider, 2000; Ungerleider et al., 1998; Desimone, 1998). This amplification of neuronal responses by attention was also reported for oscillatory brain activity. Increased power of fast rhythmic responses at gamma frequency (beyond 30 Hz) can be observed during processing of attended vs. unattended stimuli independent of sensory modality (Fries et al., 2001; Müller et al., 2000; Gruber et al., 1999; Bauer et al., 2006; Käser and Lutzenberger, 2005; Fell et al., 2003a; Steinmetz et al., 2000).

If we draw attention to an external stimulus it is important to hold a representation of the anticipated stimulus in mind. Thus, in most attention tasks working memory plays an important role. It was emphasized that attention and working memory share common cortical networks (Kastner and Ungerleider, 2000; Ungerleider et al., 1998; Desimone, 1998). Frontal and parietal brain areas seem to be involved in both processes. Slow brain rhythms, particularly theta oscillations (around 6 Hz), appear to be associated with memory processes (Jensen and Tesche, 2002; Kahana, 2006; Klimesch et al., 1996; Sarnthein et al., 1998; O’Keefe and Burgess, 1999; Raghavachari et al., 2001; Sederberg et al., 2003; Seager et al., 2002). It has been suggested that the function of large, distributed networks is associated with slow oscillations, such as theta and alpha (Von Stein and Sarnthein, 2000; Sauseng et al., 2002, 2005a; Schack et al., 2005). In contrast, high frequency oscillations, such as gamma, are
related to neural processes in more local networks (Von Stein and Sarnthein, 2000). This leads to the consideration that the integration between top-down processes guided by a complex working memory system and the bottom-up processing of perceptual information may be reflected by a dynamic interaction between theta and high frequency oscillations. There is supportive evidence for this view: (i) In working memory tasks the involvement of theta oscillations, particularly in a fronto-parietal network, is reported (Sarnthein et al., 1998; Sauseng et al., 2004, 2005a; Kopp et al., 2006). In addition, it was observed that gamma activity also is increased in short-term memory tasks (Kahana, 2006; Tallon-Baudry et al., 1998; Lutzenberger et al., 2002; Kaiser et al., 2003; Sederberg et al., 2003; Howard et al., 2003; Osipova et al., 2006). (ii) It is well established that the phase of theta oscillations is functionally related to gamma activity during memory tasks. This is theoretically elaborated and tested with neural networks (Lisman, 2005; Jensen and Lisman, 2005; Lisman and Idart, 1995; Jensen, 2004; Jensen, 2006) as well as in human EEG studies (Fell et al., 2003b; Schack et al., 2002; Burgess and Ali, 2002; Palva et al., 2005; Mormann et al., 2005; Demiralp et al., 2007; Canolty et al., 2006).

Based on this evidence, here we show that a shift of spatial attention modulates phase-synchronization between theta and gamma activity in the parieto-occipital cortex. When an internal representation of an expected stimulus meets a matching sensory input, theta activity (reflecting top-down processes) and gamma oscillations (representing bottom-up processes; Singer, 1993; Busch et al., 2004) become synchronized in phase. This might explain the functional interplay between working memory and attention.

**Methods**

**Participants**
29 healthy volunteers participated in the experiment after giving written informed consent.
EEG data of 7 subjects were excluded from analysis due to artifacts caused by eye-blinks and horizontal eye movements. The remaining sample of 22 participants consisted of 3 men and 19 women with a mean age of 23.6 years.

**Experimental Procedure**

Participants performed a cued visual attention task (Posner, 1980; Hillyard et al., 1994). They had to fixate the centre of a computer monitor (indicated by a fixation cross) throughout the whole experiment. At the beginning of each trial an arrow (1.2 x 0.6 °) either pointing to the right or to the left was foveally presented for 34 ms. Subjects were instructed to focus their attention to the cued hemi-field without moving their eyes to the target location. After an interval with a duration between 600 and 800 ms, a target was presented for 50 ms. Targets were white bars on black background and were shown 6.5° either right or left from the centre of the computer monitor. Subjects had to indicate by button press whether the bar was small (1 x 1.9°) or large (1 x 2.2°). Frequencies for small and large targets were 50% and were equally distributed to the different experimental conditions. A total of 1024 trials was run. In half of them attention was cued to the right and in the other half attention was cued to the left hemi-field. In 75% of the trials cue and target location were congruent (valid cue condition) and the remaining 25% were incongruent (invalid cue condition). To analyze approximately the same number of epochs for both conditions, only a third of the trials was randomly chosen from the valid cue condition.

Prior to the EEG experiment a training session consisting of 50 trials was run. The EEG experiment was started immediately after the training session.

**EEG Recordings and Analysis**
Using a Synamps 32-channel amplifier (Neuroscan Inc.), EEG was recorded from 30 Ag-AgCl electrodes at a sampling rate of 250 Hz. Impedance was kept below 15 kOhm. EOG correction was applied and data were visually inspected for artifacts. Data were segmented in intervals of 2000 ms (1000 ms preceding target onset to 1000 ms post-stimulus) for each condition separately. After artifact rejection at least 80 trials remained for further analysis in each subject and each experimental condition.

By averaging over trials event-related potentials (ERPs) were obtained. This was done independently of cue validity, i.e. all trials in which a target was presented in the left visual hemifield and all trials with right hemifield target presentation were averaged separately (the reason for that was that the following source localization should apply equally well for the valid and invalid conditions). Using BESA 5.1 (MEGIS Software Inc.) dipole source localization was run for the early ERP components. The time window between 100 and 250 ms after target onset was used for source localization. In each subject a bilateral symmetric dipole pair was set and fitted in position and orientation to minimize residual variance. Then, applying in each subject the resulting individual dipole model, source wave forms for the two dipoles were calculated for each single trial. This was done to reduce EEG data from 30 scalp electrodes to only two channels, i.e. one left and one right hemispheric dipolar source. All further analyses were then run using the estimated source wave forms.

Using Matlab 7.0.1 (Mathworks) Gabor expansion was applied to the single trials to obtain phase and amplitude information for 50 frequency bins between 1 and 50 Hz with a distance of 1 Hz between center frequencies.

Gabor expansion is applied to transform a signal $x(t)$ from the time domain into a complex time-frequency signal $y(f_n, t)$ which is obtained from the inverse Fourier transform $F^{-1}$ of $Y(f_n, f)$ with
\[
Y(f_n, f) = \begin{cases} 
2 \cdot F_x(f_n) \cdot G(f_n, f) &; f > 0 \\
0 &; f \leq 0
\end{cases} \quad n \in \mathbb{N}_0
\]  

(1)

with \( F_x(f) \) being the Fourier-transformed signal \( x(t) \) and
\[
y(f_n, t) = F^{-1}\{Y(f_n, f)\},
\]

(2)

where \( G(f_n, f) \) is a window filter in the frequency domain defined as:
\[
G(f_n, f) = e^{-a^2(f-f_n)^2},
\]

(3)

with \( a^2 \) as the parameter that controls the time-frequency resolution. The Gabor filter with the Gaussian window (3) represents a linear time-frequency-representation with optimal time-frequency resolution. From (2) the instantaneous phase of the signal may be obtained as a function of frequency and time:
\[
\Phi(f_n, t) = \arg[\text{Re}\{y(f_n, t)\} - \text{Im}\{y(f_n, t)\}],
\]

(4)

where \( \arg\{\cdot\} \) denotes the generalized \( \arctan \), \( \text{Re}\{\cdot\} \), \( \text{Im}\{\cdot\} \) the real and imaginary component of the complex representation and \( n \) the \( n \)'th frequency (see also Schack & Weiss, 2005).

Due to a sampling rate of 250 Hz during EEG acquisition no phase estimates of frequencies higher than 50 Hz were analyzed. The synchronization between two oscillations with different frequencies may be described as follows. Let
\[
\Phi_1^k(f_n, t) = \arg[y_1^k(f_n, t)] \\
\Phi_2^k(f_m, t) = \arg[y_2^k(f_m, t)]
\]

be the instantaneous phases of two oscillators with frequencies \( f_n \) and \( f_m \) of one or two signal components of the \( k \)-th trial with an \( m:n \) frequency relationship. The generalized phase difference is calculated according to
\[
\frac{m+n}{2n} f_n = \frac{n+m}{2m} f_m
\]

\[
\Delta\Phi_1^k(f_n, f_m, t) \equiv \left( \frac{n+m}{2m} \Phi_1^k(f_n, t) - \frac{m+n}{2n} \Phi_2^k(f_m, t) \right) \mod 2\pi
\]

(8)

The \( m:n \) phase synchronization index is defined by
\[ \hat{\Gamma}_\Phi(f_n, f_m; t) = \left| e^{j \Delta \Phi_k(f_n, f_m; t)} \right|, \quad j = \sqrt{-1} \tag{9} \]

The \( m:n \) phase synchronization index may be calculated for the arbitrary frequency pair \( (f_n; f_m) \), \( m \neq n \) of one or two signal components.

Phase differences across frequencies were calculated for each single trial, each time frame and each possible frequency pair between 1 and 50 Hz (1225 frequency pairs). In equation (9), \( F \) is the instantaneous phase, \( n \) and \( m \) indicate the two frequencies (e.g. 30 Hz and 10 Hz), and \( k \) indicates trials. The consistency of phase difference between the two frequencies over trials (see equation 2), ranging from 0 to 1, with 1 denoting highest phase synchrony, was then used as a measure for \( m:n \) cross-frequency phase synchrony. Cross-frequency phase synchronization between frequency bins from 1 to 50 Hz (1 Hz frequency steps) and each other was calculated similar to Schack et al. (Schack et al., 2005; Schack & Weiss, 2005) or Palva et al. (Palva et al., 2005).

In Fig. 2 an example for the resulting data in one subject is depicted. The cross-frequency phase-synchronization estimates were then averaged over time (five time windows: 0 to 100 ms, 100 to 200 ms, 200 to 300 ms, 300 to 400 ms, 400 to 500 ms, in respect to target onset) and over frequency ranges (delta: 1-4 Hz; theta: 4-8 Hz; alpha: 8-12 Hz; beta1: 12-20 Hz; beta2: 20-30 Hz; gamma1: 30-50 Hz). The purpose of this was to reduce data for statistical analysis and to smooth the data. Using the above mentioned frequency ranges statistic analyses were run for the resulting 15 frequency combinations.

Three-way ANOVAs with factors ATTENTION (directed towards left vs. right), HEMISPHERE (left vs. right hemispheric source) and TIME (5 time windows) were run for each (averaged) frequency pair (the 15 frequency combinations) separately for the valid cue and invalid cue condition. Greenhouse-Geisser correction was applied where necessary (Greenhouse & Geisser, 1959).
It can be argued that a simultaneous resetting of oscillatory phase at two different frequencies in response to an external event (stimulus) could lead to artificial cross-frequency phase synchronization, although the two frequencies do not interact with each other at all but only respond to a third variable, namely stimulus presentation. To test this interpretation, phase-locking index (PLI; Schack & Klimesch, 2002) was calculated, measuring inter-trial phase stability in relation to target presentation. If a simultaneous increase in phase-locking towards stimulus onset can be found at frequencies showing effects of cross-frequency phase synchronization this alternative interpretation will hold true. Three-way ANOVAs with factors ATTENTION (directed towards left vs. right), HEMISPHERE (left vs. right hemispheric source) and TIME (5 time windows) were calculated for each frequency band (delta: 1-4 Hz; theta: 4-8 Hz; alpha: 8-12 Hz; beta1: 12-20 Hz; beta2: 20-30 Hz; gamma1: 30-50 Hz) and valid as well as invalid conditions separately with PLI as dependent measure.

To cross-validate the results obtained by BESA source localization all analyses of phase synchronization were also performed with the raw EEG recorded from the scalp at electrode positions P3 (left parietal) and P4 (right parietal). These two electrode sites were selected for the analysis because they showed strongest condition-related effects in the ERPs (see Fig. 1).

To obtain information about the involvement of a distributed theta network, phase coherence (Lachaux et al., 1999) between electrode pairs was calculated on the scalp level. This measure yields information about the similarity of oscillatory processes between distinct electrode sites. High phase coherence between two sites indicates functional coupling of the underlying brain regions. To rule out spurious coherence due to common source projection Laplacian current source density was calculated for twenty 10-20-electrode sites (see Fig. 5). These were calculated as the second spatial derivative by spherical spline interpolation and are implicitly
reference-free. Because this method intrinsically uses information from all electrodes, it provides a highly accurate estimation of the source current. Phase coherence was calculated for 190 electrode pairs (resulting from 20 transformed channels) for (i) a reference interval between -600 and -400 ms preceding beginning of each trial, (ii) an interval from -200 to 100 ms immediately prior to target presentation when subjects already expected a target to occur, and (iii) a time window in which increased gamma:theta coupling was obtained, namely 100 to 200 ms after target onset. For both, theta and gamma frequency bands (defined as above), phase coherence in the reference interval was compared with the other two time windows by t-tests for each electrode pair. To compare experimental conditions and frequencies Cochran’s Q-Tests were calculated using the number of electrode pairs exhibiting significant phase coherence increase in the relevant time windows compared to the reference interval.

Usually, most measures of phase synchronization do not show normal distribution. Therefore, cross-frequency phase synchronization index, phase-locking index and phase coherence were all Fisher-Z transformed prior to parametrical statistic analysis.

Results

Behavioral results

In a visuo-spatial attention task in each trial subjects had to shift their attention either to the left or the right visual hemi-field according to a central cue presented on a monitor. Subsequently, one of two possible targets was presented. In most of the trials the target was presented in the attended hemi-field (valid cue condition) but in 25 % of the trials the unattended visual field was stimulated (invalid cue condition). 71.2% (SE = 1.84) of responses in the valid cue condition were correct and 70.2% (SE = 1.89) in the invalid condition. This difference was not significant (t_{21} = 1.07, p > .05). In contrast to that, response
times were significantly ($t_{21} = 4.01, p < .01$) shorter in the valid cue condition (600.4 ms, SE = 12.5) than in the invalid cue condition (615.7 ms, SE = 11.9).

**ERPs and dipole source analysis**

Detailed results on ERPs in these data can be found in Sauseng et al. (2005c). As can be seen in Fig 1a early ERP components, the N1 in particular, are enhanced contralaterally to target presentation. The topographical distribution of the ERPs shows exact hemispheric preferences for processing of left or right presented targets (Fig. 1b), and already suggests bilateral posterior-parietal dipolar sources. For each individual subject a bilateral symmetric dipole pair was fitted into the brain using BESA 5.1. In each subject this dipole pair was localized in the parietal or occipital part of the brain. Fig. 1c depicts an overlay of all (N=22) individual dipole solutions. On average these individual 2-dipole models explained 91.74% variance of the ERP (sd = 3.69%). Although this is a good estimate of brain activity, we do not assume that only posterior brain areas are involved in the current task. It is important to note that the purpose of this analysis was not to localize brain areas involved in this experimental task but to reduce multi-channel EEG data to meaningful source estimates for further analysis of cross-frequency phase synchronization and to attenuate effects of volume conduction which can be problematic on the scalp level.

- insert Fig. 1 about here -

**Cross-frequency phase synchronization**

The main focus of this study is on cross-frequency phase synchronization (Schack & Weiss, 2005; Schack et al., 2005; Palva et al., 2005). The ongoing EEG activity, transformed into bilateral posterior dipolar sources (see Fig. 1), was used to calculate a cross-frequency phase synchronization index between frequency bins from 1 to 50 Hz. This measure, which
ranges between 0 and 1, is an indicator for the synchronization of two oscillations of different frequencies. As an example, when the phase of two oscillations (at different frequency) exhibits a completely consistent phase relationship, this index will be 1, when these two oscillations show complete inconsistency of phase relation, it will be 0. With this method it is possible to investigate the interrelation / coupling between cortical networks oscillating at different frequencies and reflecting different cognitive processes. However, it should be noted that this measure does not require the two oscillations to be coupled for a longer time interval. This cross-frequency phase synchronization estimate only relies on the phase difference between two oscillations over trials. This means that high phase synchrony will be achieved when in every single trial oscillation n is in a fixed relation to oscillation m, independent of absolute phase difference between the two frequencies and independent of phase-locking to stimulus of either oscillation. Therefore, cross-frequency synchronization can be achieved for a few hundred milliseconds and does not necessarily have to be ongoing for a longer time interval. An exemplary depiction of cross-frequency phase synchronization for a single subject can be found in Fig. 2.

- insert Fig. 2 about here -

Fig. 3 depicts results for cross-frequency phase synchronization between theta (4-8 Hz) and gamma (30-50 Hz) oscillations. In the valid cue condition a three-way interaction between factors ATTENTION, HEMISPHERE and TIME was significant ($F_{4/84} = 2.95; p < .05$), indicating stronger theta:gamma phase synchronization in the time window between 100 and 200 ms after target presentation always for the hemisphere contralateral to the attended and stimulated visual hemifield compared to the ipsilateral hemispheric source. This means that target presentation in the right visual hemifield elicited stronger theta:gamma phase synchronization in the left posterior cortex than in the right posterior source. When the target
was shown within the left hemifield phase synchronization between theta and gamma activity was higher in the right hemispheric source. No such effect was found in the invalid cue condition, i.e. the conditions in which subjects attended the visual hemifield opposite the one where the target was presented. The three-way interaction did not reach significance in the invalid cue condition ($F_{4/84} = 1.81; \text{n.s.}$).

Significant three-way interactions were also found for the frequency pairs delta:theta; delta:alpha, theta:alpha, theta:beta1 and alpha:beta1. For these frequency pairs, however, the hemisphere ipsilateral to target presentation showed increased cross-frequency phase synchronization. And these effects were found in the valid as well as invalid cue conditions. The only frequency combination that showed a specific effect of attention was theta to gamma, as reported above.

*Phase resetting at theta and gamma frequency*

It can be argued that cross-frequency phase synchronization might only reflect an epiphenomenon elicited by simultaneous phase clustering (or phase resetting) after stimulus onset. Then two oscillations could show synchronization with being completely independent of each other, but with their phases being confounded by modulation after onset of an external event such as a visual stimulus. To test this alternative interpretation, a phase locking index (PLI; Schack and Klimesch, 2002) which is a measure for stimulus locked phase clustering over trials was calculated. Neither theta nor gamma frequency showed significant effects of PLI regarding direction of attention or cue validity. However, compared to a baseline interval prior to the beginning of each trial at theta frequency there was a significant increase of phase locking from 100 ms post-stimulus on in all experimental conditions (indicated by a significant main effect for factor TIME in the three-way ANOVAs; valid cue condition: $F_{5/105}$
= 33.73, p<.01; invalid cue condition: F_{5/105} = 33.64, p<.01; and also indicated by post-hoc t-tests between baseline PLI and post-stimulus PLI; all t-values from 100 ms post-stimulus on >5.00, p<.01 Bonferroni-corrected). This was not the case for gamma frequency at which no significant main effect for factor TIME was found in the ANOVAs (valid cue condition: F_{5/105} = 1.00, n.s.; invalid cue condition: F_{5/105} = 0.01, n.s) and significant deviance from PLI at baseline was found at no single time window post-stimulus by post-hoc t-tests. It can be seen in Fig. 4 that there is strong PLI at theta frequency from 100 ms post-stimulus on, but obviously no phase clustering at the gamma frequency range.

- insert Fig. 4 about here -

Scalp level

To cross-validate the findings based on BESA source localization phase synchronization analysis was also carried out with data of parietal electrode sites on the scalp level (see methods section). Similar to the results from BESA, an attention-related effect on gamma:theta phase synchronization was found significant in the valid cue condition (F_{4,84} = 9.36, p < .01) and failed to show significance in the invalid cue condition (F_{4,84} = 2.73, n.s.).

Fronto-parietal theta phase coupling

With respect to theta, our results suggest an involvement in top-down processing. There is convincing evidence that top-down activation in memory is reflected by activity of a prefrontal-parietal network (Kastner and Ungerleider, 2000; Ungerleider et al., 1998; Desimone, 1998) oscillating primarily at slower frequencies (at or below 10 Hz; Sauseng et al., 2004, 2005a, 2005b). Also, in an attention task it could be shown that prefrontal brain areas controlled the activation level of the visual cortex in a top-down manner (Sauseng et al., 2005c). Thus, we calculated phase-coherence at theta frequency (4 to 8 Hz) and at gamma (30
to 50 Hz) between electrode sites for the time intervals when a stimulus was expected (200 ms to 100 ms preceding target presentation) and the time window where gamma:theta phase synchronization exhibited the attention-related increase (100 to 200 ms post-stimulus). We then compared this to a reference interval before the beginning of each trial. We found that during expectancy of a stimulus as well as in the time window shortly after stimulus onset coupling in a distributed theta network including prefrontal, central and in particular posterior electrode sites. This effect was independent of attention (200 ms to 100 ms pre-stimulus: Q = 1.20, n.s; 100 to 200 ms post-stimulus: Q = 1.16, n.s.), and thus rather reflects a processing mode. Therefore the average of the four experimental conditions was calculated for the pre-stimulus and the post-stimulus time window and compared to the reference interval. As can be seen in Fig. 5 at theta frequency there was a distributed network showing increased phase coherence in the pre-stimulus interval and in the post-stimulus time window. Fronto-central and fronto-parietal coupling was very similar in both time intervals. However, during the post-stimulus window there were far more significant electrode pairs showing increased theta phase coherence than in the pre-stimulus interval (Q = 12.60, p<.01). Mainly these were due to increased parieto-occipital coupling. At gamma frequency there were only a few sporadic significant electrode pairs. In the pre-stimulus interval as well as for the post-stimulus time window there were significantly more electrode pairs showing increased phase coherence at theta than at gamma frequency (200 ms to 100 ms pre-stimulus: Q = 5.56, p<.05; 100 to 200 ms post-stimulus: Q = 29.43, p<.01.)

- insert Fig. 5 about here -

Discussion

Cross-frequency phase synchronization

The task of the current experiment requires the differentiation between two targets, which could be attended or not. To perform this task, one has to hold a template of the targets’ visual
properties in mind (the bar’s length) so that it can be matched with the incoming stimulus. There is a large body of evidence that in the human EEG retention of visual information and executive functions of working memory processes are reflected by oscillatory activity at about 5 or 6 Hz (Jensen and Tesche, 2002; Klimesch et al., 1996; Raghavachari et al., 2001; Sederberg et al., 2003; Sauseng et al., 2002, 2004, 2005a). During bottom-up visual processing, on the other hand, coherent gamma activity is observed in the visual cortex (Busch et al., 2004). Thus, one would expect that a matching between incoming visual input and internal memory representations is most likely reflected by synchronization between theta and gamma. There is increasing evidence that during (short-term) memory retention and retrieval, and other tasks which require continuous updating of information, synchronization between gamma and theta or alpha frequency is obtained (Schack et al., 2002; Burgess and Ali, 2002; Palva et al., 2005; Mormann et al., 2005). The present results show that cross-frequency phase synchronization between theta and gamma frequency is increased by attention. This means that a shift of visuo-spatial attention does not only amplify bottom-up visual processing of a stimulus, but also enhances a memory match between internally generated information and input from the external world. It can be argued that the task does not require working memory activation in a strict sense as the subjects underwent a training session in which they trained to dissociate the target stimuli before the EEG experiment was started. Therefore, in this task working memory could be more like seen as reactivation of long-term memory as proposed by Ruchkin et al. (2003). Another possibility would be that the described pattern does rather reflect activation of the episodic buffer - an interface between working and long-term memory (Baddeley, 2000).

The reported effects are specific for theta:gamma phase synchronization. However, there are several other frequency combinations that show significant three-way interactions in the ANOVA. In contrast to theta:gamma synchronization these frequency combinations (ranging from delta to low beta) do not show any effect of cue validity, i.e. there is no difference
between attended and unattended targets. As the frequency range from delta up to low beta activity shows stimulus-locked phase resetting after target onset independent of experimental condition (see Fig. 4) the effects of cross-frequency phase synchronization between these frequencies might be an artifact of common phase resetting. As discussed below this is implausible for theta:gamma phase synchronization.

**Phase resetting at theta and gamma frequency**

The results on phase resetting (in contrast to theta oscillations gamma frequency did not show any stimulus-locked resetting of phase) indicate that it is implausible that the effects of cross-frequency phase synchronization are due to simultaneous phase resetting of theta and gamma oscillations. They further suggest that theta:gamma phase synchronization is established by a phase modulation at theta frequency rather than by gamma oscillations in the present data. This is well in line with simulation data (Jensen and Lisman, 2005) and EEG findings in humans (Mormann et al., 2005; Tesche and Karhu, 2000) and animals (Givens, 1996; Williams & Givens, 2003) suggesting that the reset of theta phase is important for inducing the gamma:theta synchronization and/or for cognitive processing.

**Fronto-parietal theta phase coupling**

It was shown that distributed interregional phase coupling at theta frequency is associated with top-down working memory activity (e.g. Sauseng et al., 2004, 2005a). In the current experimental paradigm one should find top-down activity already in a time interval preceding target presentation as the visual hemifield at which subjects expected a target was previously cued. As can be seen in Fig. 5 there was indeed distributed theta coupling preceding target presentation as well as in a post-stimulus interval. In particular the network in the pre-stimulus interval seems to reflect top-down activity, as there is no visual input at this time window. In the post-stimulus time interval there are more significant electrode pairs.
However, these electrode pairs are particularly found at parieto-occipital cortex and might be elicited by the visual stimulation. The effects of theta coupling are independent of cue validity. This suggests that interregional theta activity reflects a kind of working memory top-down processing mode. Phase coherence at gamma activity, on the other hand, does not show substantial increase compared to the baseline interval.

**Conclusion**

To conclude, our source specific analysis of gamma phase-locking shows that shifting attention to a location in the relevant visual field leads to enhanced theta:gamma phase synchronization in posterior brain areas which is stronger contralateral than ipsilateral to the attended location. Thereby in contrast to gamma, theta frequency undergoes a phase resetting enabling gamma and theta frequency to synchronize when a target is attended. This seems to be a neuronal correlate of a memory match between internal expectancy and external visual input. When cortical circuits oscillating at theta frequency which retain top-down memory contents and gamma networks – processing incoming visual input - become synchronized in phase, it will be possible to exchange information between the different networks. And visuo-spatial attention is found to amplify this process. The results further highlight the function of oscillatory brain activity in the integration of different neuronal and cognitive processes. This seems to be especially the case for slow oscillations. The integrative role of theta has been shown repeatedly, particularly in memory tasks (Von Stein and Sarnthein, 2000; Sauseng et al., 2002; Schack et al., 2005). We show that during the performed task a distributed theta network is active. This further suggests the integrative function of slow brain rhythms such as theta. Our findings show in addition that phase synchronization of theta and gamma reflects a memory match between working memory and a new sensory trace.
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**Figure 1:** Event-related potentials (ERPs) elicited by targets presented in the left or the right visual hemifield are depicted in (a) for electrodes P3 and P4. As can be seen in the figure, the N1 component is always stronger on the site contralateral to target presentation. ERP scalp topography is shown in (b). The brain maps already suggest dipolar posterior sources for the ERP scalp distribution. BESA dipole localization was carried out and for each subject one symmetric parietal or occipital dipole pair was fitted into the brain. (c) shows an overlay of all individual dipolar sources.

**Figure 2:** The principal structure of results of cross-frequency phase synchronization is shown. For each subject, experimental condition and dipolar source phase synchronization between all 1-Hz frequency bins between 1 and 50 Hz to each other was calculated over trials. This was done for every time frame (4 ms) from 1000 ms prior to target presentation to 1000 ms post-stimulus. For statistical analysis frequency-pairs were averaged into defined clusters and time frames were averaged into intervals of 100 ms.

**Figure 3:** Results from theta:gamma phase synchronization. For the valid cue condition theta:gamma synchronization always peaked between 100 and 200 ms in the hemisphere contralateral to target presentation, whereas ipsilateral there was hardly any modulation of cross-frequency phase synchronization over time. In the invalid cue condition, however, theta:gamma phase synchronization peaked in the time window between 200 and 300 ms post-stimulus, and there was no significant difference between ipsi- and contralateral.

**Figure 4:** Phase-locking index (PLI) for frequencies between 1 and 50 Hz. There is no effect of cue validity or direction of attention for the PLI. However, as can be seen in the figure, theta exhibits a modulation of phase from about 100 ms post-stimulus on (independent of
experimental condition). Gamma frequency on the other hand does not show any phase resetting.

**Figure 5**: Interregional phase coherence for theta and gamma. Compared to a baseline interval there is increased theta phase coherence in a distributed network in a pre-stimulus interval (200 to 100 ms preceding target presentation) as well as post-stimulus (100 to 200 ms after target onset). Gamma does not show such distributed network activity.
Figure 1

(a) Electrode P3
Electrode P4
-2.0 µV 2.0 µV 0 µV
Time [ms]

-100 100 200 300 400 500 600 700

Blue: target left
Red: target right

(b) Target left
Target right
Difference (left-right)

140 ms

(c) A set of brain scans showing activity at 140 ms, with color-coded regions indicating differences between left and right.
Figure 2
Figure 3

target presented left

left hemifield attended

right hemifield attended

valid

invalid

target presented right

left hemifield attended

right hemifield attended

left hemisphere

right hemisphere
Figure 4

left hemisphere

right hemisphere

[Heatmaps showing spatial and temporal distribution of neural activity for left and right hemispheres with target presentation on the left and right sides.]
Figure 5

Theta

Post-stimulus Interval

Gamma

Post-stimulus Interval