The Influence of Ongoing Oscillatory Brain Activity on Evoked Responses and Behaviour

een wetenschappelijke proeve op het gebied
van de Sociale Wetenschappen

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General introduction: Spontaneous oscillatory neural activity sets the state of the brain.

Neurons are electrically excitable cells in the brain that process and transmit information. The summation of the synchronous activity of thousands of neurons can generate electric and magnetic fields that can be recorded from the surface of the scalp. The measurement of the electric activity produced by the brain is called electroencephalography (EEG) and was first done in the 1920’s by the German psychiatrist Hans Berger (Berger, 1929). The measurement of the magnetic fields produced by brain is called magnetoencephalography (MEG) and was first used by David Cohen (Cohen 1968). EEG/MEG are used in neuroimaging studies in order to provide real-time measure of respectively electric and magnetic fields produced by neuronal activity in the brain. EEG is believed to measure the potentials on the scalp arising from the return currents of intracellular dendritic currents while MEG primarily detects the magnetic fields produced by the intracellular dendritic postsynaptic currents (Hamalainen, et al. 1993). Even though EEG and MEG have different sensitivities with respect to current orientation, the two techniques essentially detect very related electrophysiological events. The ongoing EEG/MEG signal contains oscillatory activity which emerges due to the intrinsic membrane properties of the underlying neurons and the dynamics of synaptic processes.

Typically, most neuroimaging studies focus on how the neural activity of the brain changes after the occurrence of a sensory stimulus like a sound or an image. After an experimental event changes in MEG/EEG signals are typically characterized in two different manors: “evoked” activities which are exactly time-locked to the event, and
“induced” activities which are changes, often oscillatory, that are not phase-locked to the event (Pfurtscheller and Lopes da Silva 1999).

The underlying assumption in examining evoked responses is that the experimental event would result in synchronous neuronal firing that is phase-locked to the stimulus. This synchronous firing manifests itself as a wave form. Averaging event-locked trials would attenuate any activity that is not phase-locked to the stimulus and leave the evoked wave form. The average evoked activity in EEG/MEG is commonly referred to as the event related potential or field (ERP or ERF). Peaks and troughs in the evoked waveform are often classified as ‘components’ and mapped onto cognitive processes. Some typical ERP components are the N1 (reflecting stimulus perception), P300 (reflecting novelty detection) and N400 (reflecting language comprehension or semantic integration). The ERP nomenclature is sometimes a bit confusing. The letter of the ERP component corresponds to the sign of deflection of the peak or trough while the number refers to its latency.

Non-phase locked event induced changes in the MEG/EEG signal are typically studied by averaging the power spectrograms (power-frequency-time plots) of the ongoing activity calculated for individual trials. Such analysis captures any change in the power spectra of the ongoing activity that is time-locked but not necessary phase-locked to an experimental event. Event related changes in the oscillatory activity can be a result of a decrease or an increase in synchrony of the underlying neuronal populations. As such these changes are typically characterized as either: a power decrease within a frequency-band referred to as an event-related desynchronization (ERD), and a power increase referred to as event related synchronization (ERS) (Pfurtscheller and Neuper 1992). The ongoing activity of the brain prior to any stimulation exhibits large fluctuations on time scales of hundreds of milliseconds to seconds. Given that the measured electrophysiological signals is a consequence of coherently activated neurons, the ongoing activity measured by EEG/MEG can be viewed as a reflection of the brain’s neuronal state. There have been some recent animals studies suggesting that fluctuations in neuronal activity
might have a functional significance, and may account for the variability in neuronal responses to physically identical stimuli (Arieli, et al. 1996; Fries, et al. 2001; van der Togt, et al. 2005; Womelsdorf, et al. 2006). Yet to date the relationship between evoked responses and changes in the ongoing activity has remained elusive and controversial. Moreover, the underlying assumption behind evoked responses has recently been questioned in the literature (to be discussed further on this chapter). This is all the more surprising given they are derived measures (namely phase-locked and non-phase-locked activity) of the same signal.

The aim of the studies presented in this thesis were to understand how seemingly random fluctuations in the brain’s ongoing activity, are related to the brain’s averaged stimulus evoked response and the subject’s behavioral response. Specifically the goal here was not to see what changes occurred in brain activity after a stimulus, but rather examine what influence the brain’s state prior to the arrival of stimulus had on neuronal response and behavior.

The remainder of this chapter provides a background on some of the basic assumption in MEG/EEG research along with a brief review of the two theories about the relation between ongoing and evoked activity namely additivity and phase resetting. This chapter concludes with an overview of the rest of the thesis.

**Ongoing and evoked activity: additivity versus phase resetting?**

There are currently two different theories which attempt to account for the relationship between stimulus evoked components and the ongoing activity: additivity and phase resetting. The additive theory implies that evoked and ongoing activity are separate and distinct neuronal phenomena. According to this view the stimulus ‘evokes’ an additive, phase-locked response in each trial. Averaging trials removes the ongoing activity that is not phase-locked to the onset of the stimulus and leaves behind the evoked components. The phase resetting theory implies the evoked and ongoing activity pertains to the same neuronal phenomena. According to the phase-resetting view, upon the onset of a stimulus the phases of the ongoing
background oscillations become aligned (phase-reset or partially phase-reset) to the stimulus. By averaging the stimulus-locked trials, the phase-locked oscillatory activity emerges as the evoked component in the average. Since alpha oscillations (8-12 Hz) are the predominant ongoing activity in the EEG/MEG it is believed that the phase-resetting of these oscillations is particularly relevant for producing the evoked activity (Gruber, et al. 2005; Klimesch, et al. 2004; Makeig, et al. 2002).

Part of the issue in disambiguating the additive and phase-resetting theory is that because adding an evoked waveform with set phase, to randomly phased oscillations causes the phase of the oscillations in the summed signal to move toward the phases of the evoked waveform. The addition of a signal to an unchanging background can therefore look much the same as a phase locking of the background activity. Thus, phase synchronization alone during evoked activity cannot be used as evidence for phase-resetting.

Some support for phase-resetting comes from studies reporting no net-power change in the ongoing activity at the time of the evoked response (accompanied by an increase in phase-synchronization across trials). However, this cannot disambiguate between the two theories, since the occurrence of a decrease in the amplitude of the ongoing activity (particularly in the alpha band) at the same time as the evoked potential could mask out any transient evoked increases (Hanslmayr, et al. 2007).

Evidence in favor of the additive model is that intracortical animal recordings have shown that the visual-evoked ERP can occur when there is little ongoing EEG activity (Shah, et al. 2004). This is contradictory to the phase-resetting model since one key requirement of the phase modulation theory is the existence of ongoing pre-stimulus activity whose phases can be modulated. However, there has been evidence showing clear phase-resetting of ongoing activity (7–16 Hz) without any consistent increase in amplitude in human intracortical recordings during cognitive processing (Rizzuto, et al. 2003). Thus it is apparent that the current methods in the literature have not been able to provide equivocal proof for either the additive or
phase-resetting theory of evoked activity. Moreover, it is important to point out that
the additive versus phase-rest debate has focused almost exclusively early evoked
components. What has thus far been virtually ignored is how the late occurring
evoked components that are often sustained for hundred milliseconds or longer are
generated at the scalp. It is often the slower components of the ERFs/ERPs that have
been found to correlate with higher cognitive processes such as working memory
(Vogel, et al. 2005), long-term memory encoding and recognition (Rugg and Curran
2004), language comprehension (Hagoort and Brown 2000; Kutas and Hillyard
1980), response preparation (Walter, et al. 1964) and novelty detection (Soltani and
Knight 2000). While some ideas have been proposed there are no well established
physiological mechanisms accounting for the slow potentials. In chapter 4 we
propose a novel mechanism, not based on phase-resetting, which can account for the
production of the slow components of the ERPs/ERFs.

Ongoing activity and behavioral response: Can brain state influence
processing?

Brain states which might predict behavioral errors can be investigated by various
techniques. One option is to use fMRI (Weissman, et al. 2006) however, due to the
temporal smearing of the hemodynamic response function it is difficult to separate
pre- from post-stimulus activity. Characterizing brain states by analyzing ongoing
activity is however possible since there is little temporal smearing. Several recent
studies point to visual and somatosensory perception being modulated by pre-
stimulus ongoing oscillatory activity. In particular activity in the alpha band has
been shown to predict failures in perception (Ergenoglu, et al. 2004;Thut, et al.
2003; van Dijk, et al. 2008). Posterior alpha used to be considered an idling rhythm;
however, over the last few years the view has emerged that periods of low ongoing
alpha activity reflects a state of enhanced cortical excitability while periods of high
alpha activity reflects state of deactivation or functional inhibition (Jensen, et al.
Nevertheless, the significance of ongoing pre-stimulus oscillations for conscious perception and behavior remains largely unexplored.

**Outline of this thesis**

The following chapters are aimed at providing further insight how the pre-stimulus state of the brain as assessed by its ongoing oscillatory activity influences the brain’s response to events. Furthermore we will provide insight into how changes in brain states as assessed by changes in ongoing oscillations have consequences for evoked responses and behavior.

Chapter 2 examines both ongoing and evoked changes in the activity of the EEG during an auditory and visual target detection study. The specific aim of this study was to see if it was possible to provide a unified account of the additive and phase-resetting model.

Chapter 3 describes a measure called the phase preservation index (PPI). With this measure it was possible for the first time to disambiguate phase resetting or additivity as the mechanism underlying visual evoked responses.

Chapter 4 proposes and provides evidence for a new novel mechanism for the late occurring sustained evoked activity, which are not accounted for by neither the additive or phase-resetting models. One consequence of this mechanism is that the pre-stimulus oscillatory fluctuations have a profound influence on the post-stimulus evoked changes in brain activity.

Chapter 5 used ongoing oscillatory activity to reveal a pre-stimulus brain state associated with the subject’s failure to inhibit a motor response.

Chapter 6 summarizes the results obtained, its relevance, and provides suggestions for further research.
References


CHAPTER 2

EEG spectral dynamics during discrimination of auditory and visual targets

Ali Mazaheri and Terence W. Picton

Adapted from: Cognitive Brain Research
Volume 24, Issue 1, June 2005

Summary

This study measured the changes in the spectrum of the EEG (electroencephalogram) and in the event-related potentials (ERPs) as subjects detected an improbable target in a train of standard stimuli. The intent was to determine how these measurements are related, and to what extent the ERPs might represent phase-locked changes in EEG rhythms. The experimental manipulations were the stimulus modality (auditory or visual), the discriminability of the target, and the presence or absence of distraction. The ERPs showed sensory-evoked potentials that were specific to the modality and a target-evoked P300 wave that was later in the visual modality than in the auditory, and later and smaller when the discrimination was more difficult. The averaged EEG spectrograms showed that targets increased the frontal theta activity, decreased posterior and central alpha and beta activity, and decreased the central gamma activity. The scalp topography of the changes in the alpha and beta activity indicated a posterior desynchronization specific for the visual task and occurring with both targets and standards and a more widespread desynchronization for targets in either modality. Increased phase synchronization occurred during the event-related potentials, but modeling demonstrated that this can be seen when an evoked potential waveform is simply added to the background EEG. However, subtracting the spectrogram of the average ERP from the average spectrogram of the single trials indicated that phase-resetting of the background EEG rhythms can occur during the ERP. The idea that the ERPs and the EEG rhythms “share generators” can explain these findings.
Introduction

The neuronal processes underlying human of target discrimination are commonly studied using the oddball paradigm, wherein subjects are asked to distinguish infrequent (target) stimuli from frequent (standard) stimuli.

The main ERP correlate of target discrimination is the P300, a large positive potential occurring at around 300-500 ms over the parietal electrode sites in response to the target stimuli. The P300 for a target that is easy to distinguish from the standard has a peak latency between 300-350 ms in the auditory modality and about 50 ms later in the visual modality (Picton et al., 1984). The scalp distribution of the P300 differs between the modalities, indicating that at least part of the processing derives from modality specific generators (Johnson, 1989ab). However, the P300 is at least partially independent of the physical characteristics of the stimulus since an omission of a stimulus can also result in its occurrence (Sutton et al, 1967). In all likelihood, several cerebral processes contribute to what is recorded from the scalp as the P300 wave.

When the brain perceives a stimulus, two types of changes in the EEG may occur: “evoked” activities which are exactly time-locked to the stimulus, and “induced” activities which are changes in the EEG that are not phase-locked to the stimulus (Galambos, 1992). Evoked activity is caused by direct neuronal activation whereas induced activities are caused by changes in functional connectivity within the cortex (Pfurtscheller and Lopes da Silva, 1999).

Evoked activity can be extracted from the ongoing EEG by averaging the EEG voltage-time waveforms following multiple repetitions of a stimulus. Induced activities are studied by averaging the EEG power spectrograms (power-frequency-time plots) following the same stimuli.

Changes in the EEG spectrogram are of two types: a power decrease within a frequency-band referred to as an event-related desynchronization (ERD), and a
power increase referred to as event related synchronization (ERS) (Pfurtscheller, 1977; Pfurtscheller, 1992).

An occipital ERD in the alpha frequencies (8-13 Hz) typically occurs during visual stimulation (Aranibar and Pfurtscheller 1978; Pfurtscheller et al., 1977; 1994; Pfurtscheller and Klimesch, 1990). A more central alpha rhythm referred to as the mu rhythm becomes desynchronized during motor movement or somatosensory stimulation (Chatrian et al., 1959). These rhythms are considered to be ‘idling rhythms’ of the visual and sensorimotor cortex respectively. A “tau” rhythm may occur in the temporal lobe but this is only visible in intracortical EEG or magnetoencephalography (MEG) (Lehtola et al., 1997; Hari et al. 1997; Niedermeyer, 1997).


Voluntary movement elicits two specific reactivity patterns: an ERD of the alpha and beta (~20Hz) rhythms preceding and during the movement followed by a transient rebound ERS (Pfurtscheller and Berghold, 1989; Salmelin et al., 1995).

Several studies have looked specifically at EEG spectral dynamics during target detection. Probably the most consistent finding is a theta ERS occurring in response to the target with a peak amplitude about 300 ms after stimulus onset (Basar-Eroglu et al., 1992). This EEG theta response is influenced by the same task variables that affect the P300 component such as stimulus probability and task difficulty (Basar-Eroglu et al., 1992; Spencer & Polich, 1999; Cacace et al., 2003). In addition, targets induce an ERD of the alpha activity (Spencer and Polich, 1999), sometimes preceded by a brief ERS (Yordanova et al, 2003). Cacace et al., 2003) reported an ERD of the beta frequencies for attended targets. The amount of this beta ERD was greatest over the left hemisphere, contralateral to the response finger,
suggesting that it was mainly related to the motor response. The relationship between the gamma band response and the target stimuli is less clear with different studies reporting an increase (Haig et al., 1999, Watanabe et al., 2002, Gurtaby et al., 2001) or a decrease in gamma power (Marshall et al., 1996; Fell et al., 1997; Bertrand et al., 1998).

The present study compared the spectral dynamics of the EEG during the detection of the auditory and visual targets. We also manipulated the difficulty of the task by having the target/standard stimuli be physically similar for the difficult condition and different for the easy condition. A final manipulation was to add a distracting stimulus in the form of speech babble in the opposite ear during the auditory task, and a feature movie in the right visual field during the visual task. The rationale behind this manipulation derived from auditory ERP studies in which speech babble played in one ear attenuates the ERPs to stimuli in the opposite ear. (Fisher et al., 2000; Hymel et al., 1998; Cranford & Martin, 1991).
Methods

Participants

Ten normal young adults (5 females) with a mean age of 25 (range 20–29) years and a mean of 18 (range 20–29) years of education participated in the experiment. All participants were right-handed and all had normal or corrected-to-normal (better than 6/8) vision, normal hearing (<20 dB HL) at 1000 and 2000 Hz, and no history of neurological disease.

Experimental procedure

The stimuli were presented in 12 blocks of 250 trials. Six of the blocks presented the auditory task, while the other six presented the visual task. Each of the three conditions (easy/difficult/distraction) occurred for two blocks. The stimulus onset asynchrony was 1000 ms, and targets occurred randomly with a probability of 0.2. Participants were asked to respond to the target by pressing a button with the index finger of the right hand.

The auditory standard stimulus was a 1000-Hz tone, the easy target a 1500-Hz tone, and the difficult target a 1100-Hz tone. The stimuli lasted 100 ms with rise and fall times of 5 ms each and were presented to the left ear using insert earphones at 70 dB SPL. During the distraction condition, the difficult target stimulus was presented in the left ear and an Auditec recording (CD101R2 Basic Auditory Tests) of multi-talker speech babble was presented in the right ear using insert earphones at 60 dB HL. In the auditory conditions, the subjects looked at a fixation point at the center of a video screen.

The visual stimuli were ‘O’ for the standard, ‘X’ for the easy target, and ‘0’ for the difficult target. During the visual distraction condition, the difficult target stimulus was presented with a close-captioned movie (of the subject's choice) simultaneously
being played on a computer screen placed to the right of subjects. Each stimulus lasted for 100 ms and between visual stimuli a blue ‘+’ was presented at the center of the screen for fixation. The fixation point and the visual stimuli were 3 cm in height and were presented centrally on a black computer screen placed approximately 60 cm from the participants' eyes (visual angle 2.9°).

**Behavioral measurements**

The presence or absence of a button-press within 0–800 ms after stimulus onset was assessed for each trial within a block. Each trial was then categorized as a “hit” (response to target), “correct rejection” (no response to standard), “false alarm” (response to standard), or “miss” (failure to respond to target). False alarms and misses occurred too infrequently to be evaluated. The mean overall RTs for hits were calculated for each block.

**Recordings**

Each participant was fitted with a cap (Electro-Cap International) containing 64 tin electrodes. The cap sites were Fp1, Fp2, F4, F3, C3, C4, P4, P3, O2, O1, F8, F7, T4, T3, P8, P7, Pz, Fz, Cb1, Cb2, TP7, TP8, Oz, Iz, PO4, PO3, CP5, CP6, CP1, CP2, FT9, FT10, FC2, FC1, AF3, AF4, FC6, FC5, CPz, P1, POz, P2, P6, C6, P5, C1, C2, C5, F2, F6, F1, AF8, F5, AF7, Fpz, and FCz (American Electrophysiological Society, 1991). Electrodes were also placed on the left and right mastoids (TP9, TP10), on the left and right zygomatic arch (F9, F10), at the outer canthus of the each eye (LO1, LO2), and on the infraorbital ridges directly below each eye (IO1, IO2). In addition, electrodes at AFz and Cz were used as ground and reference sites, respectively. Inter-electrode impedances measured at 10 Hz were below 5 kΩ. EEG and EOG signals were amplified with Neuroscan SynAmps at a gain of 2500 with an on-line analog filter bandpass of .05 to 100 Hz (−3 dB points; 12 dB/octave). Data were recorded on disc at an A–D conversion rate of 250 Hz and converted to an average-reference montage with 65 channels prior to further analysis.
EOG compensation was applied using ocular source components (Berg & Scherg, 1991; Picton, et al., 2000). A separate ocular calibration recording was obtained during which participants blinked and made saccades in the up, down, right, and left directions. Five saccades in each of the four directions and ten blinks were averaged. An ocular data set was put together by concatenating average recordings of each of the saccades and the blinks. A principal component analysis of these data provided a set of components that represented the variance related to the eye movements. Between two to four components, each explaining more than 1% of the variance and each specifically related to the EOG waveforms were used as source components to subtract EOG contamination from the recorded EEG. For average ERPs, ocular correction could be performed on the average waveforms. However, for the spectral data, ocular correction was necessarily performed on each trial prior to conversion to the frequency domain. We found no difference in the average ERPs when the correction was performed on single trials or on the average.

**ERP analysis**

The ERP data were averaged with the sweep beginning 200 ms before the stimuli and lasting until 800 ms after stimulus onset. The maximum amplitudes and peak latencies of the visual and auditory N1 and the P300 ERP components were measured. Latencies were measured relative to the stimulus onset and amplitudes measured relative to the mean value in the 200 ms preceding stimulus onset. Statistical analyses evaluated for each wave were limited to measurements at the electrode site where the peak amplitude was maximal. The Oz electrode was chosen to be the site of measurement for the visual N1, while the vertex (Cz) was chosen for the measurement of the auditory N1. The visual N1 was measured as the maximal negative peak occurring between 100 and 200 ms. The auditory N1 was measured as the maximal negative peak occurring between 50 and 150 ms. The amplitude and latency of the P300 were measured at the maximum value within the latency range 250–700 ms at the Pz electrode.
Spectrogram analysis

The spectrogram of single-trial EEG sweeps was obtained using a Wavelet Transform (WT) according to the procedures of Tallon-Baudry et al 1997. The time-varying energy in the single trial was calculated by convolving the recorded activity with four cycles of a complex Morlet wavelet that was then varied in width (and frequency) to obtain the energy at different frequencies in the spectrogram. The WT uses short windows at high frequencies and long windows at low frequencies. This is in contrast to the short-term Fourier transformation, which uses the same window for each frequency. The time resolution of a WT is better at high frequencies whereas its frequency resolution is better at lower frequencies. The WT is well suited for the dynamics of EEG signal, in which low frequencies change more slowly than higher frequencies.

Because a 1-s epoch was used, only the wavelet coefficients corresponding to frequencies 3 Hz and above were evaluated. Since the Morlet wavelet is a modulated Gaussian curve, time points at the beginning and end of the wavelet window would show an attenuation of the frequencies. Consequently, we subjected the entire 1-s epoch to the WT, but examined only the time interval from 100 ms before the stimulus onset to 700 ms after.

Analyses of the resultant spectrogram were conducted separately for each of four frequency bands: theta (4–7 Hz), alpha (9–12 Hz), beta (15–26 Hz), and gamma (35–46 Hz). These bands were loosely based on the main frequency bands used to classify the spontaneous EEG (International Federation of Societies for Clinical Neurophysiology, 1974) allowing for some separation between the bands and some limitation of their widths.
Figure 1. Formation of spectrogram waveforms. The spectrogram is shown in the left half of the figure. Each of the wavelet estimations of the time changes in energy at a particular frequency, averaged across single trials, has been converted to a scale based on the percentage of the average activity in the 100 ms before the stimulus. The activity within a range of frequencies can then be combined and plotted out as the simple time-varying waveforms shown on the right. The event-related spectral change combines the activity over the entire frequency band. Although the middle of the theta band shows a peak of activity (red) at about 400 ms, the desynchronization concentrated in the alpha and beta frequencies spreads to involve the theta band near 400 ms and the peak of the spectral change occurs near 300 ms.

ERD and ERS were assessed in terms of percentage change scores from baseline ($\Delta P$) using the following formula:

$$\Delta P = 100\frac{(P_t - P_r)}{P_r}$$

where $P_r$ was the mean power during the reference period (100 ms before the onset of the stimulus), and $P_t$ was the power at each specific time point. The derivation of the time courses of the changes in power within the frequency bands of the spectrogram is illustrated in Fig. 1. Problems that might arise when using percentage change to represent ERD and ERS are considered in the discussion.
We did not subtract the spectrogram of the average ERP from the averaged spectrogram from the individual EEG trials. Theoretically, this should remove phase-locked evoked activity and leave only the induced changes in the background activity. Some previous studies have chosen to perform this subtraction (Cacace and McFarlanand, 2003) others have not (Makeig, 1993). When we initially performed this subtraction, we found a large theta ERD in the target responses, occurring in the same time windows of the P1 and N1 ERP components (right side of Fig. 2). Similar results were seen for the burst of gamma activity occurring at the onset of the visual stimulus, which showed up as a brief ERD when the spectrum of the average ERP was subtracted (left side of Fig. 2). We decided that these findings indicated that the averaged ERP was partly composed of synchronized background activity. This is considered in more detail in the discussion. For the purpose of these experiments, we therefore decided not to perform this subtraction.

**Measurements of spectral power**

In order to illustrate the time courses of the frequency bands across the scalp, the percent change scores of each of the frequency bands were converted at 100-ms intervals to topographical maps. These maps were computed using an inverse-distance spline interpolation (Sandwell, 1987) and plotted on a two-dimensional plane using an equi-azimuthal polar projection that descended to 20° below the midtemporal (T7–T8) equator. (Spectral changes do not follow the same topographic rules as scalp voltages, in terms of summing to zero over a spherical surface. Mapping procedures that assume such rules are therefore not appropriate.) Since previous literature has found that different frequencies exhibit different scalp topographies, the ΔP measurements for the alpha, theta, and beta bands were made over frontal, central, parietal, and occipital sites (F3/4, C3/4, P3/4, O1/2).
Figure 2. Evoked and induced activity. The energy in the spectrogram following a stimulus, calculated by averaging the spectrogram following each stimulus (thin line), may be considered a combination of evoked and induced activity. If so, the evoked activity, measured by taking the spectrogram of the average event-related potential (dashed line), could be subtracted away from the total energy to leave the spectrogram of the induced activity (thick line). This difference waveform is then plotted in percentages of the baseline power at the bottom of the graph (“Induced Activity”). The two examples shown here show a desynchronization of the induced activity at the same time as the activity in the event-related potential. This suggests that some of the activity in each of the observed frequency bands becomes synchronized to the stimulus to form the evoked activity.

In terms of the gamma band, the electrodes Cz, P3, and P4 were chosen since these channels are the furthest away from the scalp muscles. Mean ΔP measurements were made over seven 100-ms epochs starting from stimulus onset and ending 700 ms after the stimulus (i.e., 0 to 100 ms, 100 to 200 ms, … 600 to 700 ms).

Phase measurements

For each frequency, the wavelet transformation of the EEG produces a complex time series, from which the phase of the signal as well as the energy can be calculated. In order to consider the idea of phase locking in the generation of the visual-evoked potentials, we examined the phase distribution of the 7–20 Hz frequencies at the Oz electrode for the visual easy targets in all subjects. These measurements were
obtained at 100 ms before stimulus onset and at the peak latency of the N1 wave (near 180 ms). The null hypothesis of uniformity for the distribution of the phases was tested using the Rayleigh statistic (Fisher, 1993). Phase locking across trials at a given frequency was recognized if the phase distribution at a particular frequency departed significantly ($P < 0.05$) from uniformity.

In order to determine whether significant phase synchronization could occur when simple evoked potential waveform was added to a background EEG rhythm, we added a single sine wave of 10 Hz to a background EEG rhythm of 10 Hz of random phase and varying amplitude. These modeled waveforms were then analyzed for phase locking and power changes in the same way as the human ERPs. Phase locking was tested using the Rayleigh statistic and differences in power relative to baseline were evaluated with a $t$ test.

**Statistical analyses**

Repeated-measures ANOVAs were used to analyze the behavioral responses, the ERPs and the event-related spectral changes. $F$ ratios were tested using degrees of freedom adjusted using the Greenhouse–Geisser procedure. Post hoc pairwise comparisons between means were made using Tukey's honestly significant difference. Significant interactions were analyzed using simple effects analyses. Results were considered significant at $P < 0.01$. RT effects were assessed using a 2 Modality (visual/auditory) $\times$ 3 Condition (easy/difficult/distraction) ANOVA. The effects for peak amplitude and latency measures of the P300 were assessed using a 2 Modality (visual/auditory) $\times$ 3 Condition (easy/difficult/distraction) ANOVA. Peak amplitude and latency effects of the auditory and visual N1 were assessed using a 2 Stimulus (target/standard) $\times$ 3 Condition (easy/difficult/distraction) ANOVA. Since the auditory and visual N1 measurements were not homologous across the modalities, modality effects were not assessed. The measurements of spectral changes were analyzed using factors of Electrode...
(right/left) × Modality (auditory/visual) × Stimuli (target/standard) × Condition (easy/difficult/difficult with distractions) × time (0–100 ms … 600–700 ms). These analyses were performed separately for the different electrode locations, e.g., for the occipital locations data from O1 and O2 were evaluated.

Spatiotemporal principal components analysis (PCA)

In order to disentangle the scalp topography and time course of the alpha oscillations with respect to stimulus modality and target processing, a spatial PCA was performed on the alpha data set. The original data space is vast: power measurements at 200 time points (from −100 to +700 ms) from 65 electrodes, recorded from ten subjects in two modalities with two stimulus types (target and standard). A necessary step in distinguishing different alpha ERD components would be to reduce the data space into smaller spatial and temporal dimensions. The reduced dimensions should be orthogonal, so that the statistical hypothesis could be applied to each dimension without confounds or interactions between the dimensions (Spencer et al, 2001).

A spatial PCA was performed on the data using the channels as variables and the time points of the alpha band (measured as percentage change from baseline) as observations. The spatial PCA provided a set of linear combinations of electrode weightings that preserves the information in the original 65 electrodes. Each combination is called a “spatial factor” and is considered to represent a particular pattern of activity in the data (Dien et al,2003) and (Spencer et al, 2001). The spatial factor can be visualized as a topographic map through “factor loadings”. Since the goal of the PCA was to distinguish different alpha components with respect to target processing and since the PCA is susceptible to latency changes, we simplified our analysis by using only the visual easy conditions (target and standard) for the spatial PCA. The number of factors considered as significant was determined by the Scree test (Cattel,1966). The spatial factors were subsequently subjected to a temporal...
Results

Behavioural results

Table 1 presents the averaged RTs to targets. The mean RT was significantly faster in the auditory (403 ms) than visual modality (462 ms) \( F(1,9) = 17.9, P < 0.002 \). There was no significant difference in the accuracy between the two modalities. The RTs were significantly longer in the difficult conditions than the easy conditions \( F(2,18) = 55.6, P < 0.001 \). However, there was no significant difference between the difficult and distraction conditions.

Table 1.

Reaction times (ms)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Visual</th>
<th>Auditory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy</td>
<td>414 (12)</td>
<td>360 (20)</td>
</tr>
<tr>
<td>Difficult</td>
<td>484 (16)</td>
<td>423 (16)</td>
</tr>
<tr>
<td>Distraction</td>
<td>489 (14)</td>
<td>427 (16)</td>
</tr>
</tbody>
</table>

Mean values with SEs in brackets.
ERPs

Fig. 3 shows some of the ERP waveforms. The peak amplitude of visual N1 response was bigger for target stimuli than the standard [−3.1 μV vs. −2.0 μV, F(1,9) = 18.5, P < 0.002]. Moreover, peak amplitude of the visual N1 response was bigger for the easy targets than the difficult and distraction targets [−4.9 μV vs. −2.3 μV and −2.1μV, F(2,19) = 7.5, P < 0.005]. This difference was not apparent in the average ERP to easy targets that followed immediately after another target. This occurred infrequently and the waveforms from individual subjects were too noisy for reliable statistics. However, the ERP averaged over all subjects showed a small N1 (dotted line in Fig. 3). The peak amplitude of the auditory N1 response (left side of Fig. 3) along with visual and auditory peak amplitude latencies were not significantly different between target and standard stimuli nor were they affected by the difficulty or distraction manipulations. The target stimuli in both modalities elicited a large positive p300 wave that peaked at around 300–600 ms. The peak amplitude was significantly smaller in the auditory than the visual modality [4.8 μV vs. 7.8 μV, F(1,9) = 44.4, P < 0.001]. The peak latency was significantly earlier in the auditory than the visual modality [423 ms, SD = 17 vs. 484 ms, SD = 12, F(1,9) = 16.2, P < 0.003]. The P3 peak amplitude was significantly smaller in the difficult and distraction conditions relative to the easy condition [F(2,18) = 18.9, P < 0.009], with no significant difference in peak amplitude between the difficult and distraction condition. The peak latencies were significantly later in the difficult (491 ms, SD = 19) and distraction conditions (482 ms, SD = 19) than in the easy condition [400 ms, SD = 7, F(2,16) = 20.1, P < 0.001].
Figure 3. Event-related potentials. Grand-mean ERP waveforms (auditory on the left and visual on the right) are represented from each of the experimental conditions at selected scalp locations to illustrate the main ERP measurements. The auditory N1 was measured at the vertex (upward arrows on the left), whereas the visual N1 was measured at the occiput (upward arrows on the right). The target–target ERP for the easy visual target is superimposed on the other occipital recordings for the visual ERP (dotted line). The P300 wave was measured at parietal electrodes (downward arrows) for both modalities.

Spectral analyses

Fig. 4 shows how the time courses of activity in the theta frequency band for the target waveform was converted into a set of topographical maps over sequential 100-ms intervals. Fig. 5 shows the maps for all four frequency bands for the target waveforms. Rather than presenting the extensive results of the ANOVAs that looked at the changes in the timing, amount and topography of these maps, we shall simply describe the significant effects in narrative form in relation to the maps.
Figures 4. Conversion of spectrogram waveforms to scalp topographies. The upper part of this figure shows the spectrogram waveforms for the theta frequency band evoked by the target in the visual modality in each of the three experimental conditions. For simplicity, these waveforms are shown at only 19 of the actual 47 scalp locations. The full scalp topography of the waveforms was calculated sequentially every 100 ms and plotted using an equi-azimuthal polar projection that descends to 20° below the mid-temporal equator.

Theta band (4–7 Hz)

The ERS peaked earlier in the easy condition (300–400 ms) than in the difficult or distraction condition (400–500 ms) (TIME × CONDITION interactions at O1/O2, P3/P4, and F3/F4). The largest ERS occurred at around 300–400 ms (main effect of TIME at all electrodes). Overall, the visual response showed a larger effect than the auditory (main effects of MODALITY at P3/P4, C3/C4, and F3/F4). The ERS also reached its maximum value earlier in the auditory modality (at around 200–300 ms) than in the visual modality (300–400 ms) (TIME × MODALITY interaction at C3/C4 and F3/F4).
Figure 5. Scalp topographies for each frequency band. Topographic maps are plotted for each modality, for the target and standard stimuli in the easy experimental condition. The maps are for the time interval 0 to 600 ms.

The ERS was greater for the target stimulus than for the standard stimulus, with the difference occurring later in the visual than auditory modality (TIME × MODALITY × STIMULI interactions at P3/P4, C3/C4, F3/F4).

Alpha band (9–12 Hz)

An ERD began at around 200 ms after stimulus onset for the target stimuli and was larger for the targets compared to the standards (TIME and TIME × STIM interactions across O1/O2, P3/P4, C3/C4, and F3/F4). At O1/O2 both the visual target and standard stimuli caused an ERD, whereas the auditory standard stimuli did
not. For the visual target stimuli, the ERD continued for the rest of the epoch whereas in the standard stimuli, the ERD greatly diminished relative to the target stimuli after 400 ms. The ERDs initiated earlier (≈100 ms) and were larger in the occipital region for the visual target stimuli than the auditory target stimuli (≈400 ms) (main effects of MODALITY and STIMULI and a significant TIME × MODALITY and TIME × MODALITY × STIMULI interaction).

The spatial PCA results are seen in Fig. 6. Three spatial factors explaining 85% of the data were retained: a broad pattern present across all electrodes but maximal in frontal and posterior regions, a centro-parietal pattern, and an occipital pattern. The time course of the spatial factors as seen in the factor scores for each of the different stimuli showed that the first factor was specific to targets, the second opposite for targets and standards, and the third present for both types of visual stimuli.

In a subsequent temporal PCA (cf. Spencer et al., 2001), three temporal factors accounted for 91% of the data. The results of this analysis (not illustrated) showed that the first temporal factor (accounting for 50% of the variance) was an initial ERS, followed by a subsequent longer-lasting ERD that started at around 200 ms after stimulus onset and proceeded for the duration of the epoch. This likely represented the widespread ERD associated with target processing. The second temporal factor which accounted for 21% of the variance in the data was a brief transient ERD that started and ended between 200 and 400 ms. This likely represented the occipital ERD associated with processing of the visual stimuli. The third temporal factor which accounted for 9% of the variance in the data was a brief ERS that occurred 200–300 ms after stimulus onset. This was likely associated with the central ERS observed for the targets.
An ERD began around 200 ms for visual and 300 ms for auditory (main effects of TIME and STIMULI, and a significant TIME × STIMULI interaction across O1/O2, P3/P4, C3/C4, and F3/F4). The scalp topography of the beta ERD differed with the modality of the stimulus. There was a greater ERD to target stimuli in the visual modality than in the auditory at O1/O2 and P3/P4. Moreover, both the visual target and standard stimuli resulted in an ERD at O1/O2 and P3/P4 (the target ERD was larger in magnitude and duration than the standard) whereas the standard auditory stimuli resulted in little change at O1/O2 and P3/P4. These findings were shown in the main effect of MODALITY and the significant TIME × MODALITY interaction.
**Gamma band (35–46 Hz)**

The gamma band activity was only examined at three electrode sites (Cz, P3, P4). At the vertex, there was a significant ERD of the gamma band at 300–500 ms after the stimulus onset for the target stimuli, whereas an ERS occurred for the standard stimuli (TIME × STIMULI effect). There were no significant effects for the time course of the gamma band at P3 and P4.

**Phase locking**

The possible synchronization of phase was studied only for responses to the visual easy target stimulus. The analysis at 100 ms prior to the stimulus confirmed that the phase was usually random at that time. At the mean peak latency of the N1 wave,
there was clear evidence of phase locking at most frequencies (Fig. 7). Superimposed single trials and the average ERP are shown on the left of the figure. Phase locking was most prominent at 7–9 Hz where all subjects showed a significant departure from uniformity on the Rayleigh test (lower right of Fig. 7). The upper right part of Fig. 7 shows the phase distributions at 7 Hz at two time points for data illustrated on the left. At −100 ms, the distribution of phases from trial to trial was
approximately uniform and exhibited no evidence of coherence (Rayleigh test, $P = 0.79$). At 184 ms, the distribution exhibited significant phase coherence (Rayleigh test, $P = 0.0004$).

Fig. 8 shows the results of modeling the phase synchronization that occurs with an ERP. The upper left tracings show superimposed single-trial waveforms for the first 20 trials. The lower left tracing shows the average evoked potential for 100 trials. The phase distributions at a baseline period and at the midpoint of the modeled evoked potential are shown at the upper right. The lower right shows a histogram of the power changes. These were always less obvious than the phase-locking effects and when the ERP was similar in amplitude to the background, the power changes were often not significant (as shown in this example).

**Discussion**

*Behavioural data*

The manipulation of task difficulty resulted in longer RTs in the difficult and distraction conditions, indicating that these two tasks were harder to perform than the easy condition. The lack of any effect of distraction may be related to the youth of our subjects. For the auditory stimuli, contralateral competition affects the early physiological responses in elderly but not young subjects (Hymel et al., 1998).
Figure 8. Model of generation. The upper left of the figure shows 20 superimposed trials of a model evoked potential consisting of a single cycle of activity added to ongoing activity of the same frequency with variable phase and amplitude. Below is given the average evoked potential over 100 trials. At the upper right are the polar plots showing the phase distributions the frequency of the evoked potential (and background activity) during the baseline and at the middle of the evoked potential. There is significant phase synchronization at the time of the evoked potential. At the bottom is a histogram of the power measurements in the middle of the evoked potential across the 100 trials (because of the Morlet filtering effect this gives the maximum power). There is no significant change in power.

**ERP data**

In the visual modality, the N1 response was larger for target stimuli than standard, and larger for the easy condition than the difficult or distraction conditions. These effects are likely related to the specificity of the refractory period of the N1 generators. The neuronal population responding to a stimulus sharing few features with preceding stimuli is less refractory than the population responding to a stimulus that is similar to preceding stimuli (Näätänen and Picton, 1987) This is supported by the small N1 in the ERP to the target that occasionally follows another target (dotted line in Fig. 3). Following this logic, the auditory N1 should also have been significantly larger for the easy target than for the difficult target. The lack of such
an effect might have been caused by the easy–difficult differences being less perceptually salient in the auditory modality.

The P300 was earlier and larger for the easy target than the difficult target. These findings are consistent with previous literature that suggests the P300 latency is mainly determined by the time it takes to discriminate the target and its amplitude by the confidence with which the discrimination is made (Johnson, 1985; Picton, 1992).

*Spectral dynamics*

Event-related changes in the EEG are usually expressed as percentages of some baseline activity. Making the baseline equivalent across frequencies allows one to compare changes across frequencies. If the baselines are not equivalent, the changes in the higher frequencies will become invisible since the energy of the EEG decreases with increasing frequency. With a “jet” colormap, the spectrogram looks like a beach going down to light blue water, and the distant deep blue water shows no ripples. Although baselines are necessary, the interpretation of baseline-related data requires caution. First, the same absolute amount of ERS or ERD will be larger if the baseline is lower. This may have affected the theta ERS which did not change with task difficulty. If a higher level of background theta activity persisted throughout the task, the amount of theta activity during the baseline would have been higher and the percentage change when the target occurred would have been less. The conversion of the measurements to a percentage of baseline is typically performed after averaging the spectral-change waveforms to reduce the effect of the trial-to-trial variability of the baseline power. Second, converting to percentages differs for ERD and ERS because percentage scales are limited to −100 for ERD but can achieve large numbers (e.g., several hundred percent) for ERS, particularly if the baseline power is low. Logarithmic scales might attenuate (but not remove) this problem.
The choice of the bandwidth over which to track changes in the spectrum can be problematic. We selected bandwidths that were loosely based on the general frequency ranges used to study EEG. These bands may mix together activities that are independent and obscure some of the changes present in the EEG. For example, the main changes in the theta activity may be near 5 Hz and the activity at 7 Hz may react differently to the stimuli (cf. Fig. 1). Ultimately, bandwidths should be chosen on the basis of the patterns of change seen in individual subjects.

In recent years, numerous studies have reported event-related changes in the beta and gamma activity of the EEG. The possibility that this activity may represent evoked activity in the muscles of the scalp and skull has only occasionally been considered (Akay and Daubenspeck, 1999), (Goncharova and McFarland, 2003) and (Pulvermuller et al,1999). In this study, we looked only at electrode locations where there is little or no underlying musculature. As can been seen in the topographic maps of Fig. 6, there were large changes in gamma activity in the frontal and temporal regions. However, we could not be sure that these changes were not generated in the frontalis and temporalis muscles. Attention is often associated with a furrowed brow or clenched teeth. MEG recordings, particularly those that involve source projection, may be less affected by muscle activity, but this needs to be further investigated.

**Theta**

The theta activity was enhanced at 300–400 ms in response to the target stimuli but not the standards. These findings replicate previous studies which found greater theta ERS to targets than standards (Başar-Eroğlu, et al, 1997) and (Yordanova and V. Kolev, 1998). In addition, the theta ERS peaked earlier for easy than for difficult targets. This is consistent with studies that found the theta ERS to be sensitive to variables such as task difficulty and target probability (Başar-Eroğlu, et al, 1997; Cacace and McFarland, 2003; Spencer and Polich,1999)The theta ERS peaked
earlier in the auditory than in the visual modality with correspondingly different topographies in frontal and central sites. This is similar to other studies that found theta ERS to exhibit modality-specific effects with respect to its scalp topography and time course (Başar and Schurmann, 1994; Klimesch et al., 1994).

The theta ERS that we observed is partially related to the evoked theta activity that forms the P300 wave of the ERP, and partially related to the generation of theta EEG activity that is not phase-locked to the stimulus. This can be seen in Fig. 2 which shows both the averaged spectrogram (induced plus evoked) and the spectrogram of the average (evoked). The induced theta activity may be related to memory processes or attentional processes. In experiments designed to engage semantic or episodic memory, an increase in theta power at around 300 ms only occurred with episodic memory (Klimesch, H. Schimke, 1994). Recognition memory, which is likely involved in target discrimination, has also been found to result in the synchronization of the theta rhythm (Burgess and Gruzelier, 1997). Furthermore, a frontal midline theta ERS is observed during focused attention (Gevins et al., 1997; Ishii et al., 1999). Ishii et al. found that there was a significant frontal midline theta enhancement in subjects performing continuous mental calculations compared to a resting state. Several authors have noted frontal theta activity in association with response processing (Luu et al., 2004) and (Makeig et al., 2004). Several studies of human intracortical EEG have shown theta rhythms in the frontal and temporal regions during various cognitive tasks (Caplan et al., 2003; Raghavachari et al., 2001; Rizzuto et al., 2001). These rhythms may reflect the coordination of processes between different brain regions. The scalp topographical differences in the theta ERS that we found between the visual and auditory modalities might be due to different theta networks in the brain that facilitate the processing of the auditory and visual target stimuli.

The lack of any effect of difficulty of the target discrimination on the theta ERS argues against the idea that the theta activity is related to the amount of attention necessary for the task. The discrepancy between our finding and the results of
Cacace and McFarland (2003) might be due to the shorter interstimulus interval used in our experiment (1 as opposed to 3 s). There may have been a greater amount of theta activity from the preceding stimulus during our reference period for calculating the ERS.

**Alpha**

As predicted, processing the target stimuli was associated with a desynchronization of the alpha activity. The alpha ERD began at about 200 ms after stimulus onset for the target stimuli and was larger and more prolonged for the targets compared to the standards. This is consistent with the body of research that has found an alpha ERD to target stimuli (Spencer and J. Polich, 1999; Yordanova et al, 2001). However, neither the difficulty nor the distraction manipulations significantly affected the magnitude of the alpha ERD. The easy target actually had a greater alpha ERD than the difficult target although this was not statistically significant. The rapid stimulus rate may again have contributed to our findings since there may have been a sustained ERD throughout the block of stimuli when the task was difficult. An alternate explanation derives from the concept of diffuse and selectively distributed alpha systems in the brain (Başar et al, 1997). According to this view, the non-phase-locked alpha is minimized and the phase-locked alpha is maximized during cortical processing. The ERD/ERS time courses of the present study include both phase-locked and non-phase-locked activity. If the difficult targets resulted in an increase in phase-locked alpha activity but a suppression of the non-phase-locked activity, the two effects could roughly cancel each other out. This could then account for the failure to observe significant differences between the alpha ERD of easy and difficult targets.

The P300 has often been attributed to post-perceptual processing since its peak latency is often after (or at the same as) the RT (Duncan-Johnson and Donchin, 1977) Since the alpha ERD preceded the peak latency of the P300, it may be a
correlate of the actual perceptual processing. However, the duration of the ERD lasts beyond what is necessary to process the target discrimination suggesting that the alpha ERD is also involved in factors other than perceptual processing such as context-updating and maintenance of working memory.

The topographical ANOVAs and the spatial PCA both found a posterior alpha desynchronization specific for the visual task and a more widespread desynchronization for both auditory and visual targets. According to the classical interpretation, the simultaneous existence of alpha ERD in distinct scalp areas means that there are separate areas of activation (Pfurtscheller and Klimesch, 1992) This is consistent with the idea that alpha ERD during a cognitive task is topographically localized over the corresponding brain area involved with a specific task (Pfurtscheller and F.H. Lopes da Silva, 1997) For example, the alpha ERD may be composed of a visual ERD in posterior regions (spatial component 3 in Fig. 6) and a more widespread ERD that occurs when targets are presented. The physiological interpretation of the more widespread ERD (spatial component 1 in Fig. 6), which actually shows a maximum distribution in both occipital and frontal areas is not clear. The view that the ERD topography maps the locations of activation is not always correct since the fields generated by neurons can show complex topographies with maxima at some distance from the generators. The ERD of the first spatial component may represent a dipolar generator in the central regions (perhaps associated with response processing) rather than simultaneous ERD in both the front and back of the brain. Evaluation of these different models would require concomitant consideration of the sign (or phase) of the activity, a value lost in the power calculations. The second spatial component in Fig. 6 likely represents some ERS in the alpha frequency band that is part of the alpha and theta ERS associated with the evoked potentials to the target.

Although it can provide some insight into the different topographies of the alpha ERDs, spatial PCA has limitations. If changes occur at different latencies in different conditions, the PCA may show components that are related to the latency shift rather
than to specific underlying processes. We found this out when comparing the ERDs across modalities since the ERD is later in the visual modality than in the auditory. Combined spatial and temporal PCAs (e.g., Spencer et al., 2001) may be difficult to interpret unless each spatial component is specifically associated with a distinct temporal component.

**Beta**

A beta ERD was seen in both modalities for the target stimuli. Since only the target stimuli required motor responses, this finding is similar to studies showing beta ERD during voluntary movement (Pfurtscheller and Berghold, 1989). However, we did not find a significant asymmetry in the beta activity related to the side of motor preparation. Furthermore, the beta ERD began earlier in the visual task than in the auditory task, although RTs were shorter in the latter. Moreover, the task difficulty manipulation, which affected RTs, did not have an effect on the beta band. These findings suggest that the beta ERD was not purely movement-related. The different scalp topographies of the beta ERD in the visual and auditory modality suggest at least two types of beta. The posterior beta ERD elicited by the visual task may in part represent a visual alpha harmonic or “fast alpha variant” which has an activity at twice the frequency of the main alpha rhythm (International Federation of Societies for Clinical Neurophysiology, 1974). ERD of this posterior beta activity may represent visual processing in much the same way as the ERD of the posterior alpha rhythm.

**Gamma**

The gamma band showed ERD at 300–500 ms after the target but ERS for the standard stimuli. This finding is consistent with some studies (Fell et al., 1997; Marshall et al., 1996; Muller et al., 1994, Tomberg and Desmedt, 1998) but not with others (Haig et al., 1999; Watanabe et al., 2002; Gurtaby, 2001) who found an
increase in gamma activity for targets. Several studies have found an enhancement of gamma activity during movement preparation (Pfurtscheller and Neurper, 1992; Salenius et al., 1996) but this would have been opposite to what we observed. However, if the P300 indicates the perceptual erasure that follows a cognitive decision (Verleger, 1988; Desmedt 1980), here may be an inhibition of the gamma activity. One way this might occur is by the hippocampal gamma activity (too distant to be recorded at the scalp) seen with the P300 somehow inhibiting cortical gamma activity (Fell et al., 1997). Another explanation of the P300 gamma inhibition is that a surface positive component like the P300 might reflect a hyperpolarization in the dendrites of the pyramidal neurons responsible for the gamma oscillations (Speckmann et al., 1984).

**Induced and evoked activity**

We initially derived the induced spectrogram by subtracting the ERP spectrogram from the averaged spectrogram of each individual EEG trial. Our rationale was that the ERP spectra contained phase-locked evoked components while the averaged spectra contained both phase-locked and non-phase-locked components. Theoretically, subtracting the ERP spectrogram from the averaged spectrogram would remove the phase-locked activity. However, after the subtraction, we often observed an ERD in the same time range of the maximum activity in the ERP spectrogram (Fig. 2). Latency variability of the ERP can subvert the assumptions of this subtraction since the spectrum of the average ERP may underestimate the spectrum of the ERP on a single trial. Subtracting the spectrum of the average from the single trial spectra (or from the average of these) does not fully remove the power of the ERP from the spectrum Truccolo et al., 2002; Trucco et al., 2003). However, we noticed the opposite effect. One explanation of our findings is that the background EEG rhythms did not actually decrease their amplitude after stimulus onset but rather became phase-locked to the stimulus. The subtraction of the ERP spectrogram from the averaged spectrogram of each individual EEG trial would then show an ERD of the non phase-locked rhythms.
These findings raise some intriguing issues. Two different theories account for the relationship between stimulus-evoked ERPs and the EEG (Klimesch et al, 2004; Makeig et al, 2002; Shah et al, 2004; Snyder and Large, 2004). One proposes that the two activities are independent and additive. The neuronal populations responsible for the ERP generate a waveform that is added to a background EEG that is unrelated to and unaffected by the stimulus. Stimulus-locked averaging attenuates the background EEG and leaves the ERP waveform. Since the stimulus-evoked ERP should be seen in the frequency analysis as a transient increase in amplitude, the theory can be considered the amplitude-modulation theory of ERP generation. A variant of this theory would allow the background EEG to be independently affected by the stimulus. Thus, ERS or ERD could occur simultaneously with the ERP.

The alternative theory proposes that following the presentation of a stimulus, the phases of ongoing EEG rhythms are shifted to lock to the stimulus (Gruber et al, 2004; Sayers and Beagley, 1974; Sayers et al, 1979; Tass and Haken, 1996). Following this rationale, during pre-stimulus intervals, the distribution of the phase at each EEG frequency would be random, whereas upon stimulus presentation, the phases would be set (or reset) to specific values (for each frequency). The resetting of the phases causes an ERP waveform to appear in the average. During the period of the ERP, the trial-to-trial phase coherence becomes significantly different from the random phases that occur before the stimulus (Fig. 7). This proposal can be considered the phase modulation theory of ERP generation.

Unfortunately, simple adding a signal to random background activity also causes an increase in trial-to-trial phase coherence, since the addition of an ERP waveform (with set phases for each of its component frequencies) to a randomly phased EEG causes the recorded phases to move toward the phases of the ERP waveform. A simple example would involve a stimulus evoking an additional single-cycle sine wave in the EEG at a latency time-locked to the stimulus, and the ongoing background EEG at the frequency of the sine wave being unchanged in amplitude or phase by the stimulus (Fig. 8). This aligns the post-stimulus phases to a degree that
varies with the ratio of the amplitudes of evoked to ongoing activity. When the stimulus-evoked sine wave is of the same order of magnitude as the ongoing background activity, the overall amplitude (or energy) of the recording might not change significantly. On the trials wherein the added signal is 180° out of phase with the background, the trial will show a decrease in energy. In the example shown in Fig. 8, the small increase in the amplitude of the signal during the evoked potential was not significant. The addition of a signal to an unchanging background can therefore look much the same as a phase locking of the background activity. A recent paper more extensively evaluating the effects of adding a waveform to the EEG on measures of synchronization has shown that methods presently used to demonstrate synchronization “may not effectively disambiguate between the competing views of ERP generation” (Yeung et al, 2004). Phase synchronization during the ERP is clearly not proof that the ERP is generated by phase-resetting of the EEG.

One key requirement of the phase modulation theory is the existence of ongoing EEG rhythms whose phases can be modulated. Intracortical animal recordings have shown the visual-evoked ERP can occur when there is little background EEG activity (Shah et al, 2004). It is possible that the visual-evoked ERP of these recordings might have triggered phase locking of EEG rhythms that were not recorded in the multi-electrodes but which might have been visible in the scalp recording, but this is unlikely. Human intracortical recordings of 7–16 Hz rhythms during cognitive processing show clear phase-resetting without any consistent increase in amplitude (Rizzuto et al, 2003)

Neither the phase modulation nor the amplitude modulation theory fully accounts for the available data. That amplitude modulation must occur in some conditions is clearly demonstrated when an ERP is recorded in the absence of any ongoing EEG oscillations at the frequency of the ERP (Shah et al, 2004). As yet the clear demonstration of phase resetting–increased phase synchronization in the absence of any stimulus-induced increase in signal power–is not common (Shah et al, 2004).
Even when phase synchronization occasionally occurs with a decrease in power (Gruber et al, 2004; Makeig et al, 2004a) it might be explained by a specific ERP occurring at the same time as a more general ERD and the two effects summing together.

Makeig and his colleagues have proposed that any stimulus (or cognitive event) will both activate a specific pattern of response and reset the phases of ongoing oscillatory activity Makeig et al, 2004a b). The full brain response can then be mapped in an “event-related brain dynamic state space” which has three dimensions: frequency, power, and degree of synchronization. Others have proposed that, although the predominant process underlying the recorded ERPs is a phase-resetting, there may also be a simultaneous amplification of the activity that is being synchronized to the stimulus (Gruber et al, 2004).

We suggest that the findings in the literature might be explained by a more unified view—that the ERPs and the EEG rhythms share neuronal generators. Most neurons in a particular region of cortex are involved in both the generation of EEG rhythms and in stimulus-evoked ERPs. In the words of Shah and his colleagues, “ongoing rhythms and evoked responses are generated by overlapping components of the same biophysical machinery” (Shah et al, 2004). A stimulus may thus cause several changes. First, the stimulus may activate cells that are relatively quiescent. The processes underlying neuronal activation and the ways in which these processes relate to local and far fields are complex. For the purpose of our discussion, we shall treat them in a relatively simplistic way as the changes in neuronal membrane currents that when added together cause fields that can be recorded at a distance. Activation may be precisely time-locked to the stimulus and show as a distinct evoked ERP, or it may be variably time-locked to the stimulus and shows as an induced ERS. This burst of activity within a limited frequency range is determined by the neuronal membrane properties of individual neurons and the functional connectivity between them. Second, the stimulus may cause neurons that are already active in some ongoing rhythm to lock themselves to the stimulus (phase-resetting).
Third, the stimulus may generally inhibit ongoing neuronal activity. This could be one mechanism for ERD. More likely than not, ERD is caused by multiple ERSs occurring at different times in different subgroups of neurons, such that their resultant rhythmic patterns cancel each other out in fields recorded at a distance.

The shared-generator hypothesis can explain several findings that do not readily fit with either amplitude or phase modulation. The occasional occurrence of an ERD in the induced activity at the same time as the evoked potential (Fig. 2) could occur when a subset of the neurons generating the ongoing rhythm becomes involved in the generation of the stimulus-evoked ERP. The shared-generator hypothesis can also explain why the stimulus-evoked ERP shows evidence of amplitude modulation in conditions where the background rhythmic activity is low and of no amplitude modulation when the background rhythmic activity is high (and all the ERP generators are involved in the generation of rhythms). Effects of background EEG phase on the ERP (e.g. Kruglikov and S.J. Schiff, 2003) could be explained by neurons that participate in the EEG being in a particular state of enhanced or depressed excitability when they are recruited to generate the ERP.

**EEG rhythms**

Over the past few years, the role of the EEG in cerebral processing has been extensively reconsidered. The EEG is no longer just relatively random background activity that must be removed in order to see the event-related potentials. Changes in the EEG rhythms can indicate the processing of information or the changing of cerebral state (Steriade et al, 1999). However, these changes cannot explain all of the brain's activity. ERPs are not simply the phase-resetting of EEG rhythms. Furthermore, changes in the EEG rhythms can be quite indirect in their relation to information processing. Alpha rhythms most likely reflect idling rather than processing, although in certain situations the idling may be subsequent to active inhibitory gating (Worden et al, 2000). The amount of ERD will depend as much on
the state of the cortex before the event as the amount of processing required by the event. ERS of the faster EEG rhythms may be related to processes that synchronize discharges between disparate neurons, acting to bind information and mediate attention (Engel et al, 2001) and (Singer, 1999). Unfortunately, these rhythms are particularly difficult to record from the scalp due to EMG contamination. Another point that needs to be considered is the distinction between temporal (trial-to-trial) and spatial (location-to-location) synchronization. The synchronization between spatially separate neurons that can facilitate processing of particular stimulus features and that can lead to rhythmic patterns in the ongoing EEG (a “synchronized” EEG as opposed to a “desynchronized” EEG) may occur without any necessary synchronization to an external event as it repeats from trial to trial. The EEG can tell us much about the human brain, but it has limitations. Our present study indicates that the detection of expected targets is associated with an increase in theta activity and an attenuation of alpha and beta activity, the topography of which varies with the modality of the target.
References


CHAPTER 3
Posterior alpha activity is not phase reset by visual stimuli

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Summary

There is currently a debate as to whether event-related potentials and fields measured using electroencephalography (EEG) or magnetoencephalography (MEG) are generated by ongoing oscillatory activity becoming phase-reset in response to a given stimulus. We performed a MEG study measuring brain activity in response to visual stimuli. Using a new measure termed the phase-preservation index (PPI) we investigated the phase of oscillatory alpha activity (8-13 Hz) before and after the stimulus. We found that in single trials the alpha oscillations after visual stimuli preserve their phase relationship with respect to the phase prior to the stimuli. This finding argues against phase-resetting of ongoing oscillations as being responsible for visually evoked responses. The event related field could be primarily explained by stimulus locked activity in the theta band which is absent prior to the stimulus. These findings suggest that different neuronal events are responsible for generating the ongoing oscillations and the visually evoked responses.
Introduction

Event related fields (ERFs) measured using MEG (analogous to the event related potentials, ERPs, using EEG) reflect, with high temporal resolution, neuronal activity associated with stimulus processing in a time-locked way (Picton and Mazaheri 2002). The event related responses are produced by neuronal synchronization over trials evoked by the stimuli. In addition to event related responses, spontaneous oscillations are also measured in the ongoing signals (Hari and Salmelin 1997). These oscillations are produced by intrinsic synchronization of large groups of neurons.

There are two main views concerning the relationship between ERPs/ERFs and spontaneous oscillatory activity (Fell, et al. 2004; Gruber, et al. 2005; Klimesch, et al. 2004; Makeig, et al. 2002; Penny, et al. 2002; Sayers and Beagley 1974; Shah, et al. 2004). According to the first view, referred to as the additive model, ERPs/ERFs are a consequence of a neuronal response adding to the ongoing oscillations. When analyzing ERPs/ERFs, the spontaneous oscillatory activity is considered irrelevant and by stimulus-locked averaging the spontaneous oscillatory activity is attenuated while leaving the ERF waveform. Since the ERF should be seen in the frequency domain as a transient change in amplitude, the additive model is also referred to as the amplitude-modulation theory (Penny, et al. 2002). In the additive model the phase of the oscillatory activity is largely unaffected by external stimuli.

According to the second view, referred to as the phase resetting model, the phases of the ongoing background oscillations are aligned (phase-reset or partially phase-reset) to the stimulus (Gruber, et al. 2005; Klimesch, et al. 2004; Makeig, et al. 2002; Penny, et al. 2002). The resetting of the phases accounts for the emergence of the ERP/ERF in the averaged traces. Given that strong alpha oscillations often are present prior to the stimuli, it is believed that phase resetting of the alpha oscillations are particularly important for producing the ERPs/ERFs. A fundamental prediction of the phase resetting model is that at the time of the ERF the trial-to-trial phase
coherence increases after the stimuli. Typically measures such as inter-trial coherence (ITC) (Makeig, et al. 2002), and the phase-locking index (PLI) (Gruber, et al. 2005; Klimesch, et al. 2004) have been applied to provide support for phase-resetting. These techniques quantify the consistency in phase of the single trial evoked signal with respect to the stimulus. It should be noted that these measures do not speak to whether there is an oscillatory signal prior to the stimulus: for instance, an ERF/ERP with spectral power at 10 Hz emerging from white noise will also result in a detectable phase-reset in the 10 Hz band (Mazaheri and Picton 2005). The phase resetting model argues that the phase of the oscillatory activity is permanently changed as a result of the stimulus onset. In previous work Makinen et al., (2005) (Makinen, et al. 2005) have developed a measure for post-stimulus amplitude variance. They used this measure to argue in favor of an additive model for ERP/ERF generation. However, based on a model study, the conclusions drawn from the amplitude variance measure has recently been brought into question (Klimesch, et al.).

Recently Shah et al. (2004) (Shah, et al. 2004) defined a set of criteria for distinguishing between the phase-resetting and additive model. With respect to the phase-resetting model they argued that beyond an increase in trial-to-trial coherence also oscillatory activity : at the dominant frequency of the ERF/ERP should be present prior to the stimulus. Furthermore, in contrast to what would be expected in the additive model, no stimulus induced increase in oscillatory power would be expected. In addition to these criteria we will include arguments pertaining to the phase relationship between pre- and post-stimulus oscillatory activity. If the stimulus is able to reset the phase of the oscillatory activity, there would be no relationship between the pre- and post-stimulus phase. Thus, a fundamental prediction would be that the phase after the stimulus bears no relation to the phase of the oscillations prior to the stimulus. To quantify this phase relationship over time we have developed a tool that we term the phase preservation index (PPI). We have applied this measure to visual evoked signals acquired by MEG.
Methods

Participants

Eight normal young adults (3 females) with a mean age of 25 (range 20–29) years participated in the experiment. All participants had normal or corrected-to-normal (better than 6/8) vision. MEG signals were recorded with a 151 sensor CTF Omega System (VSM MedTech Ltd, Coquitlam, Canada) placed in a magnetically shielded room. In addition, the electrooculogram (EOG) was recorded to later discard trials contaminated by eye movements and blinks. The ongoing MEG and EOG signals were low-pass filtered at 200 Hz, digitized at 600 Hz and stored for off-line analyses.

Procedure

The standard visual stimuli were constructed from wedge shaped checker boards presented in the lower left visual field (Fig. 1). Deviant visual stimuli were similar to the standards, but the black checkers were marked with red dots. The width of the stimuli was 12° degrees and the screen was about 60 cm away from the subject. The fixation cross was constantly on. Each stimulus was displayed for 0.7 s. The stimuli were presented in 4 blocks of 150 trials in the lower left visual field. The inter-trial interval varied randomly from 1.5 to 4.0 s. Deviants occurred randomly with a probability of 0.2. To ensure that participants were attending they had to respond to the deviant stimuli by pressing a button with the right index finger. Given the length on the inter-stimulus interval, we were also able to extract epoch in which there was no stimulus (or motor response). We extracted as many unstimulated as stimulated trials for each subject (about 200 trials).
Figure 1. The visual stimuli used in the paradigm. The stimuli were presented in the lower left visual field for 0.7 s with a random intertrial interval (1.5–4.0 s). The standard (Left) and deviant (Right) stimuli were presented in 80% and 20%, respectively, of the trials.

Data analysis

In each subjects we used the data from the MEG sensor with the largest ERF (characterized by the N1m and P2m complex, (Portin, et al. 1999)) over the right visual cortex. Time-frequency representations (TFRs) were obtained using a wavelet transform according to the procedures of Tallon-Baudry, et al (1996) (Tallon-Baudry, et al. 1996). Single trials were convolved by a complex Morlet wavelet

\[ w(t, f_0) = A \exp\left(-\frac{t^2}{2\sigma_i^2}\right) \exp(2i\pi f_0 t), \]

where \( \sigma_i = m/2\pi f_0 \), and \( i \) the imaginary unit. The normalization factor was \( A = \left(\sigma_i \sqrt{\pi}\right)^{-1/2} \). The constant \( m \), which defines the compromise between time and frequency resolution was set to 7.

The wavelet transformation produces a complex time series for the frequencies \( f_0 \) of interest. The TFRs of power were calculated by averaging the squared absolute values of the convolutions over trials. The PLF (the phase-locking index) was defined as the modulus of the complex convolutions normalized to length 1 and averaged over trials (Tallon-Baudry, et al. 1996):

\[ PLF(f_0, t) = \frac{1}{N} \left| \sum_{k=1}^{N} e^{i\varphi_k(f_0, t)} \right| \]

Where \( \varphi_k(f_0, t_{\text{ref}}) \) represents the instantaneous phase resulting from convolving the trials with the complex Morlet wavelet and \( N \) is the number of trials. A PLF close to 0 reflects a high phase variability, whereas a PLF = 1 reflects all trials
having the same phase. The PLF measure is related to the ITC (Makeig, et al. 2002), the inter-trial phase locking (Fell, et al. 2004) and the PLI (Gruber, et al. 2005).

**Phase Preservation Index (PPI)**

To investigate the phase-stability of the oscillatory activity over time we quantified the relationship between phase before and after the stimulus. Phases were calculated by discrete Fourier transforms (DFTs) for the dominant alpha and theta frequencies identified in each subject. The alpha frequency (mean 10.1 Hz, SD=1) was identified in a 0.5 s time-window prior to stimulus onset and the theta frequency was identified in the post-stimulus PLFs (mean 6.6 Hz, SD=0.74). The DFTs were calculated using 3 cycles long data segments (e.g. 10 Hz resulted in a 0.3 s window; 180 samples long). Each data segment was multiplied by a Hanning taper prior to calculating the DFT. A reference phase \( \phi^k(f_o, t_{ref}) \) was calculated for a 3 cycle segment 0.25 s prior to stimulus onset for each trial, \( k \). For 10 Hz this resulted in a reference time window from -0.4 to -0.1 s (180 samples) and for 6 Hz a time-window from -0.5 to 0 s (300 samples), i.e. even for the lowest analyzed frequency the reference time window did not overlap with the stimulus. In the post stimulus interval the instantaneous phase \( \phi^k(f_o, t) \) was calculated every 0.1 s until 0.7 s.

For a given segment we calculated the difference between the instantaneous and the reference phase (Fig. 2). The modulus of the average of the complex representation of the phase differences resulted in a measure we termed the phase-preservation index (PPI):

\[
PPI(f_o, t) = \frac{1}{N} \left| \sum_{k=1}^{N} e^{i(\phi^k(f_o, t_{ref}) - \phi^k(f_o, t))} \right|
\]
Figure 2. A schematic illustration of the PPI. The ongoing oscillations of three trials have different phases before the stimulus as shown (Left) by the circles representing the reference phases. The arrow marks the time of the stimulus. Because of the following evoked response, the instantaneous phases become aligned and, thus, become random with respect to the reference phase [circles (Center)], yielding a small PPI. Later, if there is consistency in phase difference between the reference and instantaneous phase [circles (Right)] over trials, a high PPI will emerge.

The PPI is related to the PLF, however, rather than quantifying phase-locking over trials with respect to a stimulus, it quantifies the consistency in phase-stability as a function of time over trials. The measure yields a number between 0 and 1 quantifying the degree of phase-stability. The statistical significance of the PPI can be tested by calculating Rayleigh’s Z value (Fisher 1993), \( Z = nPPI^2 \), where \( n \) is the number of trials. The Z value provides a statistical measure with respect to the null-hypothesis that the phase differences across trials are randomly distributed. Rejecting the null hypothesis and establish that the phase differences between pre- and post-stimulus intervals are related. Across subjects the Z value was corrected to

\[
Z_{all} = \frac{\sum Z_{subject}}{\sqrt{M}}
\]

where \( M \) is the number of subjects. The statistical significance of the Z value can be established according to \( P = e^{-Z_{all}} \) for \( n > 60 \) (Fisher 1993).
For about 200 trials per subject and 8 subjects, PPI values greater than 0.088 could be considered statistically significant with respect to $p < 0.01$

In order to further characterize the PPI we calculated the measure for the data shuffled in time. The average PPI for the data shuffled a 100 times are shown in the figures. This randomization procedure provides an estimate for the change in PPI for data with no temporal correlations.

**The model**

In order to account for our experimental findings we constructed a simple model. A single trial ($k$) was defined as:

$$s^k(t) = s^k_{ERF}(t) + s^k_\alpha(t) + s^k_{noise}(t)$$

The ERF was modeled as using a sinusoid with frequency $f_{ERF} = 6Hz$ multiplied to an alpha-function.

$$s^k_{ERF}(t) = A_{ERF} \frac{t-t_0}{\tau} e^{-(t-t_0)/\tau} \sin(2\pi f_{ERF}(t-t_0))$$

for $t > t_0$

where $t_0 = 0.05$ s reflects time of the effect of the “stimulus” and $\tau = 0.05$ s. The amplitude of the ERF was set to $A_{ERF} = -0.2$. The alpha activity in each trial $k$ was created from sinusoidal function with random phase ($\varphi_k$) and a frequency ($f_k$) selected from a Gaussian distribution with a 10 Hz mean and standard deviation of 0.5 Hz. Additionally the oscillatory signals were multiple to an inverted sigmoid function representing the depression in alpha following the stimulus:

$$s^k_\alpha(t) = (1 - \frac{0.5}{1 + e^{-30(t-t_0)}}) \cdot \sin(2\pi f_k t + \varphi_k)$$

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Finally, \( s_{noise}^k(t) \) represented white noise with a standard deviation of 2.0. The parameters were set to match the experimental data qualitatively. The model was used to create 500 trials which were subjected to the same analysis as the experimental data.

**Results**

Fig. 3A shows the visual evoked field averaged over 8 subjects in sensors over the right hemisphere where the evoked fields were strongest. A time-frequency representation of the power averaged over trials and subjects demonstrated strong alpha activity before and after the stimulus (Fig. 3B). As seen in Fig.3C alpha activity was depressed but still present after the stimuli. In the theta band we observed a transient increase coinciding with the ERF at \( t = 0.1-0.2 \) s (see arrow). The power in the theta activity appeared to be depressed after the transient increase however this coincided with the depression of in the alpha band. Given the frequency resolution of the wavelets, the theta depression is most likely explained by effects in the alpha band into the theta band. This was supported by the fact that the theta depression ( \( >0.045 \) s) becomes less when longer wavelets decreasing the spectral bleeding were applied. Consistent with previous reports (Gruber, et al. 2005; Klimesch, et al. 2004; Makeig, et al. 2002), strong phase-locking was observed in the theta band from 0-0.3 s after the stimulus as measured by the PLF (Fig. 3D).

Fig. 4A shows the grand average of the PPI calculated at 0.1 s time steps with respect to a reference phase estimated 0.25 s prior to the stimuli. PPI values above the red line in the figures indicated a significant relationship between pre- and post-
stimulus alpha phase. The PPI remained significant up to 0.3 s after the stimulus. The PPI for time shuffled trials (temporally uncorrelated, dashed line) dropped a lot faster than the PPI for the alpha activity. The PPI for stimulated and unstimulated trials (Fig. 4B) could not be differentiated statistically. Had the stimulus resulted in a phase reset of the alpha activity, the phase differences from the pre- and post-stimulus intervals would have been random, i.e. the PPI would have been reduced at the time of the ERF. Thus, our findings show that pre-stimulus alpha phase is being preserved over time even following visual stimuli.
Figure 4. The PPI of the \( \alpha \) oscillations. (A) The PPI across time averaged over eight subjects for the \( \alpha \) frequency identified in individual subjects. Error bars indicate the SEM. The reference phase was determined at \(-0.25\) s. The PPI decays slowly, showing that the poststimulus phases are preserved with respect to the prestimulus phase, up to \( \approx 0.3\) s poststimulus. PPI values above the line are considered statistically significant (\( P < 0.01\); see Methods). The dashed line indicates the PPI for trials shuffled in time (temporally uncorrelated). (B) The PPI for the unstimulated trials. The PPI values between the stimulated and unstimulated trials were not significantly different across time. (\( t \) test, \( P < 0.05\)).

Given that phase-locking in response to the stimulus was observed in the theta band (Fig. 3D) we calculated the PPI in this band as well. As seen in Fig. 5A and B, the PPI for stimulated and unstimulated trials dropped as fast as the PPI for time shuffled trials indicating little phase stability in the theta band. Already at \( t = 0.05\) s the PPI values were below significance. This is most likely explained by little or no ongoing oscillatory theta activity. This is consistent with Fig. 3C showing that the power in the pre-stimulus alpha band is several magnitudes higher than the theta band power. Furthermore, there is an increase in theta band power at the time...
of the stimulus. We conclude that the ERF is an additive effect not explained by phase resetting of ongoing theta oscillations.

In order to account for our experimental findings we constructed simple model. Single trials data were produced by alpha oscillations ~10 Hz, white noise and an evoked response. The evoked response was an exponentially damped 6 Hz sinusoid.
Figure 6. The model constructed to account for the experimental data. Each trial was composed of white noise, an ≈10-Hz sinusoid, and a time-locked component constructed from a damped 6-Hz sinusoid. The ≈10-Hz sinusoids varied in phase and slightly in frequency. (A) An example of one trial. (B) The evoked component generated from 500 trials. (C) The TFR of power of the trials showing the oscillatory activity. (D) The PLF, demonstrating the contribution of the evoked component. (E) The PPI applied to the model data in the α (black) and θ (gray) bands.

Examples of individual trials are shown in Fig. 6A. The averaged evoked responses can be seen in Fig. 6B. The TFRs in Fig. 6C shows the power of the signals over time and reproduces the experimentally observed alpha activity being attenuated at the time of the stimulus (Fig. 3B). The PLF in Fig. 6D shows strong phase-locking in the theta band which is explained by the “evoked response”. The PPI in the alpha and theta band are shown in Fig. 6E. As in the experimental data, the PPI drops
rapidly in the theta band but remains high in the alpha band during the time of the “evoked response”.

**Discussion**

We have examined if the phase of ongoing activity is affected by visual stimuli. Here we report for the first time that the phase of the ongoing alpha oscillations is preserved up to 0.3 s after stimulus onset with respect to the phase prior to the visual stimuli. Our finding demonstrates that ongoing alpha activity is not phase reset by visual stimuli. This rules out phase-resetting of ongoing alpha oscillations as a mechanism for generation of ERPs/ERFs in the visual system. We did observe a power increase accompanied by a phase-alignment in the theta band following the stimulus, however, we found no support for ongoing theta oscillations prior to the stimulus. Our findings strongly argue in favor of an additive model for the generation of visual ERFs.

We have used MEG to investigate the relationship between alpha oscillations and event related responses while other studies have applied EEG (Gruber, et al. 2005; Klimesch, et al. 2004; Makeig, et al. 2002). EEG measures the potential on the scalp arising from the return currents of intracellular currents while MEG primarily detects the magnetic fields produced by the intracellular postsynaptic currents (Hamalainen M, et al. 1993). Even though EEG and MEG have different sensitivities with respect to current orientation, the two techniques essentially measure related electrophysiological activation. Thus we believe that our MEG findings apply to EEG data as well.

Our results support the view that ERFs/ERPs and ongoing oscillations are separate neuronal events. However, our findings do not discount that pre-stimulus alpha oscillations can modulate the generation of the ERFs/ERPs. A number of findings demonstrate that phase (Kruglikov and Schiff 2003) and amplitude (Barry, et al.
2000) of pre-stimulus oscillatory activity can influence the ERP. Additionally it has been shown that pre-stimulus alpha activity can modulate somatosensory detection (Linkenkaer-Hansen, et al. 2004). Even though our results speak against phase resetting of ongoing oscillations as being responsible for the generation of ERFs, our findings only pertain to visual ERFs/ERPs and do not exclude that phase resetting is responsible for evoked responses in other brain regions (Fell, et al. 2004; Rizzuto, et al. 2003).

How does the activity in the theta band relate to the generation of the ERF? Our findings show that there is no significant ongoing theta activity present before the stimulus and that the ERF produces a transient increase in theta power (Fig. 3C). As argued by Shah et al. (2004) (Shah, et al. 2004), the phase-resetting model requires that ongoing oscillations be present prior to the stimulus. As seen in Fig. 3D we observe a strong inter-trial phase-locking along with a transient power increase in the theta band which is a consequence of the ERF. In conclusion the event related response rather than phase-resetting of ongoing theta oscillations is a consequence of an additive transient neuronal response.

We constructed a simple additive model which could account for our experimental data. It was sufficient to assume 1) ongoing alpha oscillations were not perturbed in phase by the stimulus and 2) an additive evoked response with components in the theta band. We could find no simple model involving phase resetting in either the theta or alpha band that could account for our findings. The phase resetting models tested always resulted in a decrease in the PPI which was incompatible with our experimental data. (see Supplementary information on PNAS website).

Two schemes have been proposed with regards to the relationship between the ERF and the ongoing alpha oscillations: the shared generator and the dual generator hypothesis (Fig. 7).

According to the shared generator hypothesis, the generators of the ERFs and the ongoing oscillations share the same neuronal populations (Mazaheri and Picton...
2005; Shah, et al. 2004). During the time of the evoked field some of the neurons initially generating the ongoing rhythm participate in the production of the evoked field. An alternate view, also consistent with our observation, is that two different neuronal populations produce the ongoing oscillations and the ERF. The two generators might interact during and after the generation of the ERF. The dual generator model does not speak to whether the neuronal ensembles are macroscopically separable or intermixed. Distinguishing between these two models would require intracranial single cell measurements combined with local field potential recordings.

What is the role of ongoing alpha oscillations in visual processing? Since our findings speak against phase resetting of ongoing alpha oscillations as being responsible for generating the ERF, we will argue that the presence of alpha activity is not essential for generating visually evoked responses. Nevertheless, given the large signal size of the alpha activity and the sources in parieto-occipital areas, it is highly conceivable that alpha activity plays a modulatory role in perception and ERF/ERP generation. This has been supported by several studies (Barry, et al. 2000; Kruglikov and Schiff 2003; Linkenkaer-Hansen, et al. 2004). Future research is required in order to further determine how alpha phase and amplitude might modulate the generation of visual evoked responses.
Figure 7. Two models relating ERF and α oscillations. (A) In the shared-generator model, the generators of the ERF and α oscillations have the same neuronal populations in common. During the time period of the ERF, some of the neurons initially involved in generating the ongoing rhythm produce the evoked field. (B) In the dual-generator model, the ERF and the α oscillations have different generators. Before the stimulus, the ERF generators are quiescent and become active upon stimulus onset. The stimulus may modulate the power of the ongoing α rhythm. Likewise, the phase and/or amplitude of the α oscillations might modulate the ERF.
References


CHAPTER 4

Amplitude modulations of Brain Oscillations Generate Slow Evoked Responses

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Summary

Electrophysiological data measured by electroencephalography (EEG) and magnetoencephalography (MEG) are widely used to investigate human brain activity in various cognitive tasks. This is typically done by characterizing event-related potentials/fields (ERPs/ERFs) or modulations of oscillatory activity (e.g. event-related synchronization) in response to cognitively relevant stimuli. Here, we provide a link between the two phenomena by using MEG to demonstrate that slow ERFs are explained by asymmetric amplitude fluctuations of the oscillatory alpha rhythm in which peaks and troughs of the ongoing rhythm are differentially modulated. Further, we provide a physiological explanation for the observed asymmetric amplitude fluctuations. Given that in particular slow event-related components are modulated by a wide range of cognitive tasks, our findings provide new insight into the physiological basis of cognitive modulations of evoked brain activity.
Introduction

Event-related fields (ERFs) measured using magnetoencephalography (MEG) [analogous to the event-related potentials (ERPs) by using electroencephalography (EEG)] are often applied to investigate neuronal activity associated with the human brain’s processing of external events. ERPs/ERFs are calculated by averaging electrophysiological data time-locked to a given stimulus which is repeated multiple times. The averaging serves to attenuate external noise and oscillatory brain activity which is not time-locked to the stimulus. The early ERPs/ERFs (sometimes referred to as “exogenous components”) are transient components that occur within the first 100 ms of stimulus presentation, and are widely believed to index the arrival of information to the cortex (Coles and Rugg 1995). The later components of the ERPs/ERFs, (often referred to as “endogenous components”) emerges 100 ms after stimulus onset and are often sustained for hundred milliseconds or longer. Typically it is the slow late components that are modulated by cognitive tasks and as such these components are viewed as the link between electrophysiology and cognition. Examples are slow potentials reflecting working memory (Vogel, et al. 2005), long-term memory encoding and recognition (Rugg and Curran 2007; Sanquist, et al. 1980; Takashima, et al. 2006), action monitoring (Kilner, et al. 2004), language comprehension (Hagoort and Brown 2000; Kutas and Hillyard 1980), response preparation (Walter, et al. 1964) and novelty detection (Soltani and Knight 2000). While there have been some proposals, (Niedermayer and Lopes Da Silva 2004) the exact mechanism for how the slow responses are generated is not well understood.

In addition to ERPs/ERFs, electrophysiological signals from the brain have also been investigated by characterizing oscillatory brain activity. It is generally accepted that spontaneous neuronal synchronization is responsible for generating the oscillatory activity. While brain oscillations are present during rest, their magnitude is modulated by various tasks. These modulations are typically characterized using event-related synchronization (ERS) (Pfurtscheller and Lopes da Silva 1999),
temporal spectral evolution (Hari and Salmelin 1997) or time-frequency representations of power (Tallon-Baudry and Bertrand 1999). The posterior alpha rhythm (8-14 Hz), first observed ~80 years ago by Hans Berger (Berger 1929), is by far the strongest oscillatory signal measured by EEG or MEG. Alpha activity has been found to be attenuated by eye opening, visual stimuli and attention, while strengthened by internal tasks, such as mental arithmetic, visual imagery, and working memory (WM) retention (Jensen, et al. 2002; Palva, et al. 2005; Pfurtscheller and Lopes da Silva 1999; Salenius, et al. 1995). Beyond the alpha rhythm, oscillatory activity has been characterized in various other frequency bands as well (Hari and Salmelin 1997; Jensen, et al. 2007; Tallon-Baudry and Bertrand 1999). The physiological basis of oscillatory brain activity is better understood than for ERPs/ERFs. Essentially it is the kinetics of the membrane receptors which is thought to determine both synchronization properties and the frequency of the oscillations emerging in a network of coupled neurons (Jones, et al. 2000; Steriade 1999; Traub, et al. 1999).

What is the relationship between ERPs/ERFs and oscillatory brain activity? There is currently a debate in the literature as to whether the early exogenous evoked responses are due to additive neuronal responses elicited by the stimulus, or a stimulus-induced phase resetting of the ongoing oscillations (Fell, et al. 2004; Hanslmayr, et al. 2007; Makeig, et al. 2002; Makinen, et al. 2005; Mazaheri and Jensen 2006; Yeung, et al. 2004). With respect to the slower endogenous components very little is known on how they relate to modulations in oscillatory activity. The aim of this MEG study is to demonstrate that amplitude modulations of the ongoing oscillatory alpha activity can explain the generation of slow visual evoked components. A large component of MEG signals are thought to be produced by magnetic fields induced by dendritic intracellular currents in pyramidal cells (Hamalainen, et al. 1993) (Fig. 1A). The dendrites of inhibitory interneurons are not well aligned as those of the pyramidal cells and only indirectly contribute to the measured fields.
A key component of our hypothesis pertains to how peaks versus troughs of oscillatory activity fluctuate over time. Conventionally oscillatory activity from the brain is assumed to be symmetric with respect peaks and troughs (Fig. 1B). To generate such symmetric amplitude fluctuation it is required that intracellular currents of the same magnitude are propagating inward and outward the dendrites, producing the troughs and peaks respectively (Fig. 1B). For 10 Hz oscillations this means that first an inward current runs towards the soma. About 50 ms later it reverses to an outward current that runs away from the soma. Note that the outward propagating current should not be confused with the instantaneous extracellular return current. However, even though outward propagating dendritic electrophysiological events do contribute to the MEG signal (Ikeda, et al. 2005; Jones, et al. 2007; Murakami and Okada 2006), it would be a strange coincidence if the backpropagating outward currents exactly matched the synaptic inward propagating currents with a 50 ms delay. In line with the suggestion of (Nikulin, et al. 2007) we conjecture that inward dendritic currents are not necessarily matched by antiphase outward dendritic currents. As a consequence, oscillatory amplitude fluctuations are asymmetric such that peaks are modulated stronger than troughs (or vice versa) (Fig. 1C). In the case of alpha activity the signal to be measured is produced by bouts of excitatory synaptic inputs at the apical dendrites repeated every ~100 ms. Now consider the magnetic field measured by coils to the left and right of the current sources (Fig. 1A). If the amplitude modulations of the dendritic currents are asymmetric so are the measured fields. In the case shown, peaks would be modulated stronger that troughs in fields to the left of the current source and vice versa to the right (Fig. 1C). As a result, a measure of the asymmetry will form a bipolar topographic map as illustrated in Figure 1D. The asymmetric amplitude modulations have profound consequences when considering event related averages. Typically alpha activity is depressed in response to visual stimuli. According to our hypothesis, only the peaks are reduced in magnitude; not the troughs. When the single trials are averaged, the depression in the peaks will result in a negative shift in the calculated ERF (Fig. 1F). It is important to note that the amplitude fluctuations of the oscillatory activity can remain asymmetric throughout the trial; however, it is
primarily the asymmetric modulations in response to a stimulus which are important here. Had the magnitudes of the peaks and troughs been symmetrically decreased, no shift in the ERF would be generated (Fig. 1E). Specific to MEG, in the shown source orientation determined by the pyramidal dendrites primarily, the troughs are modulated to the left of the source whereas the peaks are modulated to the right (Fig. 1C and Fig. 5A).

In short, slow components of the ERFs can be generated by asymmetric amplitude modulations. In the following we experimentally establish 1) the existence of asymmetric amplitude modulations in human posterior alpha activity and 2) that these modulations can produce slow ERFs.

In the current study we developed a simple way to measure the amplitude fluctuation asymmetry (AFA) of a given signal termed the $AFA_{index}$. We first used simulated data to assess the properties of the $AFA_{index}$. We than applied the $AFA_{index}$ to MEG data recorded from subjects resting with eyes closed in order to quantify the amount and direction of the amplitude asymmetry present in spontaneous alpha oscillations. We then applied simple visual stimuli and tested how stimulus induced modulations in alpha activity correlated with the magnitude of slow ERFs. The direction of the modulation (polarity) was compared to the sign of the $AFA_{index}$. 
MEG signals measured outside the human scalp are primarily thought to be produced by magnetic fields induced by dendritic intracellular currents ($I_{dendrite}$) in pyramidal cells. The polarity of the field will be determined by the direction (inward or outward) of the currents in the dendrites. The two coils represent the sensors outside the head measuring the field to the left and right of the source ($F_{left}$, $F_{right}$). (B) The amplitude modulation of neuronal oscillatory activity is conventionally viewed as being symmetric around zero. This implies that inward and outward dendritic currents are of the same magnitude. As consequence the amplitude modulation measured by the sensors is symmetric as well. (C) We propose that the amplitude modulations of the oscillatory activity are asymmetric such that the peaks are modulated stronger than the troughs. For the 10 Hz alpha activity this is explained by bouts of inward dendritic currents every ~100 ms. As consequence amplitude modulations are positive (peaks modulated stronger than troughs) in magnetic fields measured to the left of the source and negative (troughs modulated stronger peaks) to the right. (D) The sign of the amplitude modulation as characterized by the amplitude fluctuation asymmetric index ($AFA_{index}$) will for a bipolar pattern. (E) The conventional view ignoring asymmetric modulations of oscillatory activity would mean that averaging across trials (the arrow representing the start of the evoked
response) would not result in the generation of slow fields. (F) As a direct consequence of the amplitude asymmetry a depression (or increase) in alpha activity in response to a stimulus will result in the generation of slow fields when multiple trials are averaged.

**Methods**

**Participants**
Eight normal young adults (3 females) with a mean age of 25 (range 23–28) years participated in the experiment. All participants had normal or corrected-to-normal (better than 6/8) vision.

**Recordings**
MEG signals were recorded with a 151 sensor CTF Omega System (VSM MedTech Ltd, Coquitlam, Canada) placed in a magnetically shielded room. In addition, the electrooculogram (EOG) was recorded to later discard trials contaminated by eye movements and blinks. The ongoing MEG and EOG signals were low-pass filtered at 300 Hz, digitized at 1200 Hz and stored for off-line processing.

**Procedure**

*Eyes-open/closed task.* Subjects were instructed to open and close their eyes according to auditory cues. The auditory cues for the eyes to open and close were respectively a single beep (233 Hz, 200 ms) tone and two consecutive beeps (500 ms part). The time between the two types of cues was 7.5 seconds. In order have the strongest possible alpha signal for the analysis we used only the data epochs in which the eyes were closed.

*Visual stimulation.* The visual stimuli were contrast gratings (4 cycles/degree) presented in the lower left visual field with an eccentricity of 3.2°. The width of the circular stimuli extended from 5° by 5° degrees and the screen was about 70 cm away from the subject. The fixation cross was constantly on. Each stimulus was displayed for 0.7 s and they were presented in 4 blocks of 150 trials. The inter-trial interval
varied randomly from 2.5 to 3.5 s. To ensure that participants were attending, they had to respond to a change in the color of the fixation cross by pressing a button with the right index finger. Trials with changes in the fixation cross were ignored in the analysis. Four different contrasts were randomly presented (16, 23, 32 and 64) but only one contrast (32) was used in the analysis.

**Data analysis**

Data were analyzed using the Fieldtrip software package (http://www.ru.nl/fedonders/fieldtrip/), a Matlab-based toolbox for the analysis of electrophysiological data that has been developed locally. Data were checked for artifacts using a semiautomatic routine that helped detecting and rejecting eye blinks, muscle artifacts, and jumps in the MEG signal caused by the SQUID electronics. Independent Component analysis (ICA) (Bell and Sejnowski 1995) was used to remove any heart artifacts, and eye movements not rejected by the semi-automatic routines (Jung, et al. 2000).

The *amplitude fluctuation asymmetry index* ($AFA_{index}$).

To investigate the amplitude asymmetry of the oscillatory activity over time we developed a measure which quantifies the ratio of the variance of the peaks of an oscillatory activity and the troughs

$$AFA_{index} = \frac{Var(S_{peaks}) - Var(S_{troughs})}{Var(S_{peaks}) + Var(S_{troughs})}$$

First the data were band-passed at the specific frequency for which the $AFA_{index}$ was to be calculated (e.g. 8 – 12 Hz). The time-points for the peaks and troughs of the band-passed data were then identified. These time-points were used to obtain the signal values of peaks and troughs in the raw data. To reduce high frequency noise, the signal values around peaks and troughs were smoothed using a 10 ms boxcar kernel (corresponding to a ~100 Hz low pass filter). These values were the used to
calculate the AFA\textsubscript{index}. An AFA\textsubscript{index} close to zero would mean that the peaks and troughs are modulated similarly, and as such the signal’s amplitude fluctuations are symmetric. A positive AFA\textsubscript{index} would indicate that the peaks are modulated stronger than the troughs and vice versa. When applying MEG measurements, we predicted that the AFA\textsubscript{index} for fields measured on one side of the current dipole would be positive and negative on the other side (Fig. 1C); i.e. it would yield a bipolar topography (Fig. 1D). This bipolar topography is dependent on the orientation of the dipole and specific to the MEG. Since the AFA\textsubscript{index} is a quantification of the ratio between peaks and troughs the zero level (baseline) is of no consequence.

*Time-frequency analysis of power.*

Time-frequency representations (TFRs) were obtained using a wavelet transform according to the procedures of Tallon-Baudry *et al.* (Tallon-Baudry, et al. 1996). Single trials were convolved by a complex Morlet wavelet

\[ w(t, f_\circ) = A \exp(-t^2 / 2\sigma^2_i) \exp(2i\pi f_\circ t), \]

where \( \sigma_i = m / 2\pi f_\circ \), and \( i \) the imaginary unit. The normalization factor was \( A = \left(\sigma_i \sqrt{\pi}\right)^{-1/2} \). The constant \( m \), which defines the compromise between time and frequency resolution, was set to 7. The wavelet transformation produces a complex time series for the frequencies \( f_\circ \) of interest. The TFRs of power were calculated by averaging the squared absolute values of the convolutions over trials. In each subject we sorted trials according to alpha modulation (power post-stimulus minus power pre-stimulus) based on the data from the MEG sensor with the largest pre-stimulus alpha amplitude (always a sensor over occipital cortex). The pre- and post-stimulus intervals were respectively -600 to -100 ms and 300 to 800 ms with respect to stimulus onset.
Results

Simulations
In order to ensure that our measure was not a consequence of a slow DC offset interacting with the alpha rhythm we investigated various principles of actions using constructed surrogate signals. This first type of interaction was designed to produce the hypothesized amplitude asymmetry:

\[ s_1(t) = A(t)(1 + \sin(2\pi ft)) + \text{noise} \]

where \( f = 10 \text{ Hz} \) and the noise was normal distributed with a standard deviation of 0.2. Note that for illustrative purposes the noise level of the simulated signal is lower than the noise in the measured MEG data. The actual waveform of the slow modulations \( A(t) \) is inconsequential but was constructed from a sinusoid with frequency 0.8 Hz and amplitude 0.5. The length of the signal was 4 seconds and sampling frequency 300 Hz. Fig. 2A shows the resulting signal in which the peaks (red dots) are stronger modulated than the troughs (blue dots). Applying the \( AFA_{\text{index}} \) to this signal yield 0.96, i.e. strongly supporting the amplitude asymmetry. We then constructed a signal in which the slow modulations affected the alpha rhythm in a multiplicative manner (Fig. 2B):

\[ s_2(t) = A(t)\sin(2\pi ft) + \text{noise} \]

As a consequence the amplitude of the alpha oscillations is modulated symmetrically over time yielding an \( AFA_{\text{index}} \) close to 0. Finally, we constructed a signal in which the slow modulation affected the DC-offset of the signal in additive manner (Fig. 2C):

\[ s_3(t) = A(t) + \sin(2\pi ft) + \text{noise} \]

This resulted in slow modulations of peaks and troughs in the same direction producing an \( AFA_{\text{index}} \) close to 0. These simulations demonstrate that the \( AFA_{\text{index}} \) successfully can detect true asymmetric amplitude fluctuation while being immune to slow multiplicative or additive modulations.
Amplitude asymmetry of ongoing alpha activity

We performed a whole-head MEG study measuring brain activity during rest and in response to simple visual stimuli. The $AFA\text{index}$ was calculated for 20 epochs of 5s for MEG data when subjects were resting with their eyes closed. The topography of alpha power during the eyes closed task can be seen Fig. 3A.

The topography of the $AFA\text{index}$ in 3 representative subjects can be seen in Fig. 3B. All the subjects demonstrated a bipolar like topography of the $AFA\text{index}$ which was particularly pronounced over occipital areas. This pattern was consistent with was predicted based on simulations we performed in the next section.

Figure 2 Various simulations in which surrogate signals were used to test the $AFA\text{index}$.

(A) The signal, $s_1(t)$, was designed to have an amplitude asymmetry. The amplitude modulation was determined by a slower signal $A(t)$. Clearly the peaks (black dots) are more modulated than the troughs (grey dots) yielding a strong $AFA\text{index}$.

(B) The signal, $s_2(t)$, was designed such that the slow modulations, $A(t)$, affected the alpha rhythm in a multiplicative manner. Thus peaks and troughs are modulated symmetrically over time yielding an $AFA\text{index}$ close to 0.

(C) In signal $s_3(t)$ slow modulations added to the alpha oscillations (DC-like offset of the signal). This affected peaks and troughs in the same direction producing an $AFA\text{index}$ close to 0.
Figure 3. Asymmetry of the alpha amplitude fluctuations. (A) The topography of alpha power during eyes closed in 3 representative subjects. (B) The AFA$_{\text{index}}$ applied to the eyes closed data in three representative subjects. The topography of the AFA$_{\text{index}}$ resembles a bipolar distribution as predicted (see Fig. 5). Note that the bipolar distribution suggests a posterior to anterior oriented current dipole in the first subject and anterior to posterior current dipoles in the other two subjects. (C) The grand average of the absolute AFA$_{\text{index}}$ across 8 subjects. Note the largest values over posterior brain areas consistent with where the alpha power was dominant. (E) The absolute AFA$_{\text{index}}$ for frequencies from 5 to 40 Hz for occipital sensors averaged over the subjects. The AFA$_{\text{index}}$ peaked at the alpha (~10 Hz) and beta (~23 Hz) frequencies (error bars denotes standard errors of mean).

*Simulation producing the bipolar topography of the AFA$_{\text{index}}$.*

We have hypothesized that the bipolar topography of the AFA$_{\text{index}}$ reported in Fig. 3 is explained by fields arising from a dipole in the posterior brain. To test this we...
performed a simple simulation using a forward model \((G)\) calculating the fields \((F)\) in the sensors given a dipolar sources \((q)\) at location \(r\):

\[
F = G q_r
\]

For the forward model we used spherical head model where the source was located at \(r = (-5,0,1)\) with respect to head coordinates and pointing in the posterior direction. We used a sensor configuration matching that of the CTF151 system. Next, we produced a surrogate signal with the hypothesized amplitude asymmetry:

\[
q_r(t) = A(t)(1 + \sin(2\pi f t)) + \text{noise}
\]

and applied it to the forward model. The peak amplitude \(A(t)\) was 5.7 nAm. The \(AFA_{\text{index}}\) was then calculated for the field data \((F)\) and the resulting topography (Fig. 5A). Note the clear bipolar distribution also observed in the data. When using a similar analysis for a signal without amplitude asymmetry

\[
q_r(t) = A(t)\sin(2\pi ft) + \text{noise}
\]

no bipolar pattern was observed (Fig. 5B). We conclude that topographies of the \(AFA_{\text{index}}\) in Fig. 3A are well accounted for by a posterior dipole producing an oscillatory signal being asymmetric with respect to current amplitude.

The orientation of the \(AFA_{\text{index}}\) topography (determined by the direction of the magnetic flux, i.e. the magnetic field rotating the current determined by the ‘right-hand rule’.) for two subjects suggest a dominant anterior to posterior current direction (Fig. 3B middle and right panel; as predicted in Fig. 1D and Fig. 5). This means that peaks were stronger modulated than troughs to right of the dipole and vice versa to the left (see Fig. 1C and D). In one other subject, the topography was reversed suggesting a posterior to anterior current direction (Fig. 3B, left panel). For this subject, it implied that peaks were stronger modulated than troughs to left of the dipole and vice versa to the right. Averaging the absolute \(AFA_{\text{index}}\) over the subjects revealed the strongest magnitude of the \(AFA_{\text{index}}\) over posterior brain areas where alpha power was strongest (Fig. 3C). In order ensure that the amplitude asymmetry
Figure 5. The $AFA_{index}$ was applied to two simple simulations using a forward model. A current dipole was placed in the posterior region of the head. (A) When the posterior dipole is generating an asymmetric amplitude signal, $q_r(t) = A(t)(1 + \sin(2\pi ft))$, the $AFA_{index}$ produces a bipolar pattern. (B) When the posterior dipole is generating an symmetric amplitude signal, $q_r(t) = A(t)\sin(2\pi ft)$, the $AFA_{index}$ produces a pattern with no structure.

was specific to the alpha band, we calculated the $AFA_{index}$ for frequencies from 5 to 40 Hz for occipital sensors over all the subjects (Fig. 3D). The $AFA_{index}$ was largest at the alpha frequency range, with a smaller peak associated with more variance in the beta band (20–24 Hz). We focused our subsequent analysis on the alpha band activity since it was the dominant rhythm in the posterior areas and had the greatest amplitude asymmetry. None of the analysis done on the beta band came out significant.

Relationship between amplitude asymmetry, amplitude modulation and ERFs

We then set out to test if the sign and magnitude of the $AFA_{index}$ at rest was consistent with the modulations in the visually evoked ERFs with respect to modulations in alpha power as hypothesized in Fig. 1. Using a wavelet approach (Tallon-Baudry, et al. 1996) we calculated time-frequency representations (TFRs) of power during a simple visual stimulation task. The modulation in alpha power with respect to a pre-stimulus baseline ($P_{modulation} = P_{post} - P_{pre}$; $P_{pre} \cdot -0.6 < t_{pre} < -0.1$; $P_{post}$)}
Following the visual stimulus was calculated for each trial. The trials were then sorted in three bins according to the magnitude of the modulation. Fig. 6A shows the TFRs for the bins with the lowest and highest alpha modulations for a representative posterior sensor. We then characterized the modulation in ERF amplitude with respect to alpha modulations. This was done by sorting the trials in three bins according to the magnitude of alpha modulation. The ERFs were then calculated for the trials in each bin. Linear fits of ERF amplitude (0.3–0.8 s) versus the alpha modulation ($P_{\text{modulation}}$) for the three bins were then calculated for all sensors. The slope of the fitted lines represented the rate and direction of ERF modulation as a result of alpha power modulation. The slopes were normalized between -1 to 1 by dividing by the largest absolute slope in each subject. A negative slope means that the ERF amplitude is decreasing with alpha modulation; a positive slope means that the ERF amplitude is increasing with alpha modulation (please refer to Fig. 4B for the slope topography of all 8 subjects). Note, that what is essential here are the signs of the slopes when relating the modulations in alpha power to the ERFs. A discussion on the signs of the actual deflections of the ERFs in relation to alpha power please is in the next section (Fig. 8, 9 and 10). Topographic representations of the slopes are shown for the three representative subjects in Fig. 6B (same subjects as in Fig. 3). An important clue is that the modulation is reversed for the first subject compared to the last two as was the case for the $AFA_{\text{index}}$ (Fig. 3B). The grand average of the absolute inflections in the slow component of the ERF is clearly constrained to the posterior part of the brain (Fig. 6C). These findings demonstrate a strong correlation between the slow components of the ERFs and stimulus induced modulation of alpha power.

We then asked if the $AFA_{\text{index}}$ could account for the correlation between modulation in alpha power and the slow components of the visual evoked responses. To statistically quantify this, we did a binomial sign test between the direction of the $AFA_{\text{index}}$ and the sign of the ERF inflection with alpha modulation. The topography of consistency (quantified by a sign test) between the $AFA_{\text{index}}$ calculated during eyes closed and the direction of ERF inflection with alpha modulation is shown in Fig. 7A.
Figure 6. (A) Time-frequency representations (TFRs) of the trials with the 30% lowest and 30% highest modulations of alpha power (TFRs baseline corrected; -0.6 < t < -0.1 s) in a representative subject. The respective ERFs (right panel) reveal a clear difference in the sustained modulation with respect to low (thin line) and high alpha power changes (thick line). (B) The topography of the ERF modulation with respect to post-stimulus alpha power from the TFRs. The color represents the slope resulting from linear fit between ERF (0.3 – 0.8 s) alpha power (0.3 – 0.8 s). The bipolar distributions are consistent with Fig. 1A. (C) The grand average of absolute ERF modulations with alpha power averaged across 8 subjects.

Using the binomial test we determined the probability of observing matching signs of the ERF modulation and the $AFA_{index}$ under the null-hypothesis that the signs were unrelated. Matching signs in more than 6 of the 8 subjects were
Figure 7. Correlation between alpha amplitude asymmetry and the modulations of slow ERFs with alpha power. (A) The consistency between the sign of the $AFA_{\text{index}}$ (from eyes closed data) and the sign of the modulation in slow visually evoked ERF with alpha power. The color code represents the number of consistent signs over the 8 subjects. More than 6 consistent signs are considered significant (binomial test). Note the clustering of adjacent sensors with significant effects over posterior areas. (B) The correlation between the $AFA_{\text{index}}$ and the slope of slow ERF modulation with alpha power (the seven posterior sensors with the largest $AFA_{\text{index}}$ in Fig. 3C). The strong correlation strongly suggests that the slow modulations in the ERFs are produced by changes in asymmetric amplitude changes of alpha power.

considered significant ($p < 0.035$). Note the two clusters of significant sensor locations over posterior areas – the clustering makes it unlikely that the significant effect is due to multiple comparisons. Finally, when relating the $AFA_{\text{index}}$ to the magnitude of the ERF modulation we found a very strong correlation (7 posterior sensors, $r = 0.80$, $p = 0.018$). The data subjected to the same analysis in the beta band (~23 Hz) did not reveal a significant relationship between the slow ERF components and modulations in the beta power. We demonstrate that that amplitude fluctuations of the alpha activity are asymmetric (as seen in the resting eyes closed data) and consequently the stimulus induced amplitude modulations of such activity generate slow components of the event-related fields that are correlated in sign and magnitude to the asymmetric amplitude fluctuations observed during rest.
Simulating changes in ERFs with alpha modulation

In order to study the relationship between changes in power and how they modulate the ERFs we constructed a set of surrogate data. A set of 200 trials with amplitude asymmetry were constructed to emulate a signal in sensors to the right of a posterior dipole (see Fig. 1D):

\[
S^R_i(t) = A(t)(1 + \sin(2\pi 10t + \varphi_i))
\]

where \( \varphi_i \) denotes a random phase value between 0 and \( 2\pi \). For left sensors, \( S^L_i = -S^R_i \).

The amplitude modulation was determined by the expression:

\[
A(t) = a - \frac{b}{1 + e^{t/0.2}}
\]

which is a sigmoidal function approaching \( a-b \) for \( t \to -\infty \) and \( a \) for \( t \to \infty \). The stimulus is assumed to come on at about \( t = 0 \) s. The trials were constructed according to these equations. Subsequently we calculated the time-frequency representations of power (TFRs) and the event-related fields (ERFs). These equations were used for producing the results in Fig. 8 and Fig. 9.
Figure 8. An alpha increase relative to pre-stimulus baseline. Trials with low (a=1.2 and b=0.7) and high (a=1.5 and b=1) alpha modulation were constructed. Examples are shown in (A). The TFRs (B,C) show the changes in alpha power for the low and high modulations. (D) The ERFs for low and high alpha modulations. The “slope” (poststim ERF\textsubscript{high} minus ERF\textsubscript{low}) is negative for left and positive for right sensors. The “slope” is consistent with Fig. 6A. Note that the increase alpha power (B) for low trials is not consistent with the decrease in power in Fig. 6A (top panel).
Figure 9. An alpha decrease relative to pre-stimulus baseline. Trials with low 
\((a=0.5 \text{ and } b=-1.1)\) and high \((a=1.2 \text{ and } b=-0.4)\) alpha modulation were 
constructed. Examples are shown in (A). The TFRs (B,C) show the changes in alpha 
power for the low and high modulations. (D) The ERFs for low and high alpha 
modulations. The “slope” \((\text{poststim } ERF_{\text{high}} \text{ minus } ERF_{\text{low}})\) is negative for left and 
positive for right sensors. The “slope” is consistent with Fig. 6A. Note that the 
decrease alpha power (C) for high trials is not consistent with the decrease in power 
in Fig. 6A (bottom panel), nor is the deflection of the ERFs.
The simulations in Fig. 8 show the consequences of an increase in alpha in response to the stimulus. While the slope of the ERF modulation with respect to high and low alpha modulations is correct, the simulation is not compatible with the decrease in alpha power seen in Fig. 6A (top panel). In Fig. 9 we show the consequences of a decrease in alpha power. Again the slope of the ERF modulations is correct, however, the simulations cannot account for decrease (bottom panel) in power seen in Fig. 6A.

To fully account for our findings in Fig. 6A it was necessary to assume the mixing of two sources with opposite amplitude asymmetry:

\[
S_i^{R1}(t) = A^1(t)(1 + \sin(2\pi 10t + \phi_i^1))
\]
\[
S_i^{R2}(t) = -A^2(t)(1 + \sin(2\pi 10t + \phi_i^2))
\]

The signals in right and left sensors are then:

\[
S_i^R(t) = S_i^{R1}(t) + S_i^{R2}(t)
\]
\[
S_i^L(t) = -S_i^R(t)
\]

The outcome of simulating 200 trials is seen in Fig. 10 (see caption for parameters). Initially both source 1 and 2 are active together. After the stimulus, source 1 turns off. Source 2 has high and low prestimulus power for respectively the low and high trials. Given that the sources have opposite orientations they somewhat cancel each other prior to the stimulus. This allows for the summed power to actually increase with the stimulus for the ‘high’ trials while it decreases for the ‘low’ trials. In conclusion, the findings in Fig. 6A are qualitatively reproduced.

Note that in all simulations the ‘slope’ of the ERF changes with respect to alpha modulation is correct. This means that the topography of the $AFA_{index}$ predicts the slope of the ERF change independent of whether the total power modulations increase or decrease.
Figure 10. Mixing two sources with opposite AFA\textsubscript{index}. The low alpha modulations were defined by the parameters $a_1 = 0$ and $b_1 = -0.85$ (defining $A_1(t)$) and $a_2 = 1$ and $b_2 = -0.25$ (defining $A_2(t)$) and high alpha modulations by $a_1 = 0$ and $b_1 = -0.85$ and $a_2 = 1$ and $b_2 = -0.65$. This effectively means that source 1 turns off with the stimulus. Source 2 is weakened by the stimulus but is having different pre-stimulus levels thus defining the high and low alpha modulations. Examples are shown in (A). The TFRs (B,C) show the changes in alpha power for the low and high modulations. (D) The ERFs for low and high alpha modulations. The “slope” (poststim ERF\textsubscript{high} - ERF\textsubscript{low}) is here negative for left and positive for right sensors. Both the “slope” and TFRs are qualitatively consistent with Fig. 6A.
**Discussion**

In this study we have identified a mechanism by which event-related fields can be produced from oscillatory brain activity. We demonstrated that amplitude fluctuations of ongoing oscillations with respect to peaks and troughs are not symmetrically modulated. Due to this asymmetry, slow ERFs are produced from the amplitude modulations of the ~10 Hz alpha activity in response to visual stimuli. Note that while our analysis was based on MEG data, the basic assumptions hold for EEG/ERP data as well. In various cognitive tasks it is typically the slower components of the ERF that are modulated by different conditions. Thus, the proposed mechanism can provide a unified account for both evoked responses and oscillatory activity in the context of cognitive research.

Our current study focused on posterior alpha activity and how it relates to the modulation of the slow component of visual ERFs. Posterior alpha activity has been shown to be modulated by cognitive manipulations in a wide variety of tasks. This includes working memory operations (Jensen, et al. 2002; Jokisch and Jensen 2007; Klimesch, et al. 1996; Krause, et al. 1996; Medendorp, et al. 2007), long-term memory retrieval (Babiloni, et al. 2004; Klimesch 1999), directed attention (Worden, et al. 2000), and language comprehension (Bastiaansen and Hagoort 2006). In future work it would be interesting to relate the modulations in alpha activity the slow components which have been found to be modulated in related tasks (Hagoort and Brown 2000; Kutas and Hillyard 1980; Rugg and Curran 2007; Sanquist, et al. 1980; Takashima, et al. 2006; Vogel, et al. 2005). It is possible that the formation of these ERFs are due to changes in the alpha band activity.

We have proposed a simple physiological mechanism which is responsible for generating the amplitude asymmetry. The key element of the mechanism is that the dominating dendritic currents producing the magnetic fields primarily are inward, i.e. running from the distal synapses to the soma (Fig. 1). While there might be outward dendritic currents as well due to depolarization around the soma, it is unlikely that these currents would have the same magnitude as the inward currents.
Thus the measured oscillatory activity is most easily explained by bouts of inward dendritic currents produced every ~100 ms. Note that we do not mean to imply the inhibitory input are unimportant for generating the alpha rhythm. Indeed Jones et al. (2000) has proposed a physiologically realistic model for alpha oscillations in which GABAergic inhibition plays a crucial role for the rhythm generation. Likewise thalamic input to granular and intragranular layers have also been shown to play an essential role in generating the neocortical alpha rhythm (Hughes and Crunelli 2005). While these elements are important for rhythm generation, our arguments on amplitude asymmetry pertain to the inward dendritic currents directly producing the magnetic fields.

Human intracranial recordings will be needed directly observe this and gain further insight into this phenomena. While we focused the analysis on the posterior alpha activity, the proposed mechanism might generalize to other frequency bands and brain regions. For instance using the $AFA_{index}$ we did identify amplitude asymmetry in the beta band as well (Fig. 3C). Nikulin et al. (Nikulin, et al. 2007) demonstrated a correlation between low frequency drifts and the ~10 Hz somatosensory mu-rhythm. In line with our work, they interpreted their findings as a consequence of amplitude asymmetry and proposed that resulting 'baseline' shifts could play a role in the formation of somatosensory evoked responses. It would be highly relevant to investigate if asymmetric amplitude modulations exist in the gamma band as well (30-100 Hz). Oscillatory gamma activity in humans has been shown to be modulated by a wide range of cognitive tasks (Jensen, et al. 2007). Given that the period of a gamma cycle is 10-30 ms it is possible that asymmetric amplitude modulations can account for some of the faster modulations in ERFs (e.g. the N1, P1, N2, P2). Future work is required in order to investigate if the principle of amplitude asymmetry and generation of ERFs generalized to frequency bands beyond the alpha range.
References


CHAPTER 5

Pre-stimulus alpha and mu activity predicts failure to inhibit motor response

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Summary

Do certain brain states predispose humans to commit errors in monotonous tasks? We used MEG to investigate how oscillatory brain activity indexes the brain state in subjects performing a Go-noGo task. Elevated occipital alpha and sensorimotor mu activity just prior to the presentation of the stimuli predicted an upcoming error. An error resulted in increased frontal theta activity and decreased posterior alpha activity. This theta increase and alpha decrease correlated on a trial-by-trial basis reflecting post-error functional connectivity between the frontal and occipital regions. We propose that after an error, a top-down drive serves to set the state of the brain such that the likelihood of committing an error on subsequent trials is reduced. Our findings have the potential of being applied in brain-computer interfaces designed to prevent human errors. The measure of functional connectivity can be used to investigate patients groups with problems in executive control such as ADHD.
Introduction

To be able to sustain attention is of great importance in our daily life. Momentary lapse in attention could be fairly benign such as over pouring coffee but could also have more serious consequences such as traffic accidents. Despite how common these lapses of attention are in daily life, there has yet to be developed a system-wide understanding of the brain mechanisms underlying them (Weissman et al., 2006). The central questions of this paper is 1) can we identify states of the brain which predisposes a lapse in attention and 2) how do errors change the brain state in order to avoid future lapses in attention.

Brain states which might predict behavioral errors can be investigated by various techniques. One option is to use fMRI; however, due to the temporal smearing of the hemodynamic response function it is difficult to separate pre- from post-stimulus activity (Weissman et al., 2006). Another possibility is to apply electrophysiological measures such as EEG and MEG. The EEG and MEG signals are often analyzed using event-related potentials and fields (ERPs and ERFs). This approach is problematic since it requires a baseline interval which is difficult to define when investigating pre-stimulus signals. Characterizing brain states by analyzing oscillatory activity is however possible since there is little temporal smearing and no baseline interval required. Several recent studies do point to visual and somatosensory perception being modulated by pre-stimulus oscillatory activity. In particular activity in the alpha band has been shown to predict failures in perception (Ergenoglu et al., 2004; Linkenkaer-Hansen et al., 2004; Thut et al., 2006; van Dijk et al., 2008). In this study we have investigated how oscillatory brain activity is modulated before and after errors in a Go-noGo task requiring sustained attention (the sustained attention response task: SART).

We have chosen the Go-noGo task since it is well suited to investigating both response-inhibition and error-processing (Manly et al., 2002; Manly et al., 2003; Manly et al., 1999; Robertson et al., 1997). In the paradigm participants respond by
pressing a button to a frequent Go stimulus (digit 1-4 and 6-9) but must withhold responses to an infrequent noGo stimulus (digit 5). Since the Go stimuli are much more probable than the noGo stimuli, the paradigm lulls the participant into responding automatically to all stimuli. Preventing this automatic behaviour severely taxes the sustained attention system, and errors are often elicited.

The present study compared the pre-stimulus and post-response oscillatory activity recorded using MEG from subjects performing the Go-noGo task. We used MEG since the technique allows us to both measure and localize oscillatory brain activity. Our aim was to identify brain states characterized by oscillatory activity that prior to the onset of a noGo stimulus predicted the subject’s failure to inhibit a motor response. We also analyzed oscillatory activity after erroneous motor responses in order to investigate the cognitive processes initiated to prevent future mistakes. Such processes might include a top-down drive to perceptual areas. This we have characterized using a measure of functional connectivity based on power correlations in different frequency bands.

**Methods**

**Participants**

Fourteen normal young adults (3 female) with a mean age of 27 (range 23-33) years participated as subjects. All subjects were right-handed and all had normal or corrected-to-normal vision.

**Experimental Procedure**

The visual stimuli were single digits between 1 and 9 presented in the lower left visual field with an eccentricity of 3.2°. The width of the stimuli extended 5° by 5° degrees and the screen was about 70 cm away from the subject. The fixation cross at the centre of the screen was constantly on. Each stimulus was displayed for 0.2 s and the inter-trial interval was 1.5 s. The stimuli were presented in 12 blocks of 151 trials. Participants were asked to respond to all digits except ‘5’ by pressing a button
with the right index finger. Digits ‘1-4’ and ‘6-9’ are thus the ‘Go stimuli’ and digit ‘5’ the ‘noGo stimulus’. The presence or absence of a button-press was assessed for each trial. Trials were then categorized as ‘Hits’ (response to any digit except 5), ‘Correct Withholds’ (no response to the digit 5), and ‘False Alarms’ (response to the digit 5). All trials which were preceded by a noGo trial were excluded from further analysis. In all our analysis the amount of Correct Withhold and Hit trials were matched to those of False Alarms. We found that on average subjects were unable to inhibit their response to digit 5 in 40% of the trials. After artifact rejection there were on average about 40 False Alarm trials per subject.

Data acquisition
The MEG data were acquired with a 151-sensor axial gradiometer system (CTF systems Inc., Port Coquitlam, Canada) placed in a magnetically shielded room. In addition, the horizontal and vertical electrooculogram (EOG) were recorded to later discard trials contaminated by eye movements and blinks. The ongoing MEG and EOG signals were low-pass filtered at 300 Hz, digitized at 1200 Hz, and stored for off-line analyses. Prior to and after the data acquisition, the subjects’ head position relative to the gradiometer array was determined using coils positioned at the subject’s nasion, and at the left and right ear canal.

High-resolution anatomical images (voxel size = 1 mm³) of the whole brain were acquired using a 1.5-T Siemens Sonata whole-body scanner (Erlangen, Germany). These images were used for reconstruction of individual head shapes to create forward models for the source reconstruction procedures described later.

Preprocessing
The data analysis was performed using the FieldTrip which is an open source Matlab toolbox developed at the F. C. Donders Centre for Cognitive Neuroimaging (http://www.ru.nl/fcdonders/fieldtrip). Data segments contaminated with artifacts, eye movements, eye blinks, muscle activity and jumps in the superconducting quantum interference devices (SQUIDS), were detected with a semi-automatic
routine and discarded. An estimate of the planar gradient was calculated for each sensor using the signals from the neighboring sensors. The horizontal and vertical components of the planar gradient were combined using the root mean square \( \sqrt{\left( \frac{dF}{dx} \right)^2 + \left( \frac{dF}{dy} \right)^2} \). The planar field gradient simplifies the interpretation of the sensor-level data because the maximal signal power typically is located above the source (Hämäläinen et al., 1993). Furthermore, activation is produced in a contiguous set of sensors which is advantageous for the cluster-randomization algorithm described later. (A similar approach was used in (Nieuwenhuis et al., 2008; Bauer et al., 2006; Jokisch and Jensen, 2007; Osipova et al., 2006). For source reconstruction, we used the data from the true axial sensors and not the planar gradient estimate.

**Pre-stimulus frequency analysis**

The oscillatory activity was characterized by calculating the power spectra using one second intervals of data preceding the stimulus. A 1200 data points Hanning taper (1 s long) was applied to the data prior to calculating the spectra. The spectra were calculated for the individual trials and the averaged.

**Post response time-frequency representations of power.**

Time-frequency representations (TFRs) of power were calculated for each trial using a taper approach applied to short sliding time windows (Percival and Walden, 1993). The data in each time window were multiplied with a Hanning taper having the length of the time window for the frequencies 2-30 Hz. The power values were calculated for the horizontal and vertical components of the estimated planar gradient and summed. The planar gradient power estimates were subsequently averaged over trials for a given condition. We applied an adaptive time window of three cycles for each frequency (\( \Delta T = 3/f \)).
**Statistical analysis**

The difference in frequency power between conditions was first quantified within each subject over all trials by means of t-values which subsequently were converted to z-values (SPM2, http://www.fil.ion.ucl.ac.uk/spm). The variance was estimated over trials. This procedure served to normalize the power values and to reduce the contribution of subjects with large variance in the power estimates. The significance of the difference in z-values between conditions over subjects (random effects analysis) was tested by means of the randomization test proposed by Maris and Oostenveld (Maris and Oostenveld, 2007) also incorporated in the FieldTrip software. This test controls the Type-1 error rate in a situation involving multiple comparisons (e.g. multiple sensors and/or time-frequency tiles). Based on the grand-average data, frequency and time intervals were chosen for statistical testing. From those frequency-bands and time windows, the z-values were subjected to a cluster-level test. In the second step the Monte Carlo estimate of the permutation p-value of the cluster is obtained by comparing the cluster-level test statistic to a randomization null distribution assuming no difference between conditions. This distribution is obtained by 1000 times randomly swapping the conditions in subjects and calculating the maximum cluster-level test statistic. Using 1000 random draws the Monte Carlo p-value is an accurate estimate of the true p-value. The same procedures were followed for the statistical analysis of the frontal theta-alpha topography of correlations except that it was the raw correlation values at each sensor which was subjected to a cluster-level test.

**Source reconstruction**

Source reconstruction was performed using a frequency-domain beam-forming approach [Dynamic Imaging of Coherent Sources (DICS)]. The DICS technique uses adaptive spatial filters to localize power in the entire brain (Gross et al., 2001; Liljeström et al., 2005). A realistically shaped single-shell description of the brain-skull interface was constructed, based on the individual anatomical MRIs (Nolte, 2003). The brain volume of each individual subject was discretized to a grid with a 0.8 cm resolution and the lead field was calculated for each grid point. Using the
cross-spectral density matrices and the lead-field, a spatial filter was constructed for each grid point (Gross et al., 2001), after which the power at each grid point was estimated for both conditions separately in every subject. One filter was calculated for all conditions and then applied for the data divided over the individual conditions. Sources were estimated on time-frequency tiles that were pre-selected from the sensor level analysis. As a first step, z-values of the source estimates were calculated over trials, comparing the conditions within each subject. Prior to averaging the source estimates of the individual subjects’ functional data, the individual anatomical MRI images were spatially normalized to the MNI brain [Montreal Neurological Institute (MNI), Montreal, Quebec, Canada: http://www.bic.mni.mcgill.ca/brainweb] using SPM2 (http://www.fil.ion.ucl.ac.uk/spm). The z-values displayed for the source plots are uncorrected for multiple comparisons.

Results

Fourteen subjects performed a Go-noGo task in which they had to respond to a frequent Go stimulus (digit 1-4 and 6-9) but had to withhold responses to an infrequent noGo stimulus (digit 5).

Behavioral data

The grand average of mean reaction times (RTs) for False Alarms was significantly shorter than for Hits (296 ms versus 336 ms; p<0.001, two-sided t-test). This replicates previous studies showing that errors are more likely for short RTs (Manly et al., 1999; Robertson et al., 1997). This speeding is likely to reflect a temporary inattention as participants are lulled into an ‘automatic’ response mode (Robertson et al., 1997).

High pre-stimulus alpha activity predicts response errors

We set out to investigate if pre-stimulus oscillatory activity reflected states in which subjects were more prone to committing errors. This was done by comparing the pre-stimulus power spectra for False Alarms to Correct Withholds. Statistical
comparison revealed significantly greater alpha activity (10-11 Hz) preceding False Alarms than preceding Correct Withholds at sensors over posterior and left central regions (p<0.008; Fig. 1A). To identify the sources accounting for the difference in alpha we applied a beamforming technique. When contrasting False Alarms to Correct Withholds we identified the sources in occipital cortex and left and right primary sensorimotor cortex (Fig 1B). Note the sources were slightly more central than the hand area of primary motor cortex. The location of the occipital source and the left sensorimotor sources were consistent with differences in 10-11 Hz power observed at the sensor level (Fig. 1). We conclude that alpha activity in occipital cortex and ~10 Hz mu activity in sensorimotor areas are predictive of response errors.

*Increase in frontal theta and decreases in alpha and beta activity follow response errors*

In order to investigate changes in brain states after an error was committed we analyzed the post-response interval aligned to the button press. Between 0-600 ms after the button press theta power (3-7 Hz) was higher for False Alarm responses than for Hits in a cluster comprising frontal sensors (p<0.001; Fig. 2A,B). The beamforming technique allowed us to localize the difference in theta activity to the left superior frontal gyrus, left superior medial gyrus, and right middle frontal gyrus (Fig. 2C). Between 100-800 ms after the button press alpha activity (10-11 Hz) was lower for False Alarms than for Hits in central and posterior sensors (Fig. 2A; central panel; p<0.01). The sources responsible for this decrease in alpha activity were localized in occipital cortex (Fig. 2C). Between 500-1000 ms after the button press mu activity (10-11 Hz) was lower over central areas for the same comparison (p<0.01; Fig. 2B). The sources of the mu rhythm were localized to the left and right sensorimotor regions extending into pre-motor areas (Fig. 2C). Finally between 500-850 ms after the button press beta power (18-24 Hz) was lower for False Alarms compared to Hits constrained to left central sensors (p<0.0001; Fig. 2A,B). The primary source of the difference in the beta band was localized to sensorimotor cortex (Fig. 2C). In sum, when comparing erroneous to correct button presses, we
found that errors were followed by an immediate increase in theta activity produced in frontal cortex, followed by a decreases in occipital alpha and sensorimotor mu and beta activity.

*Errors generated a response-locked ERNm over frontal regions*

Planar gradient representations (see Methods) were calculated for the ERFs time-locked to the button press (Fig. 3A). As baseline we used a 100 ms interval prior to the button press. During the first 0.5 s the ERFs were larger for False Alarms than Hits. This effect was significant in a large left-lateralized cluster dominated by frontal sensor (p<0.001; Fig. 3B). Due to the topography and time-course of the difference in the ERFs between False Alarms and Hits, we consider it to be the magnetic equivalent (ERNm) of the error-related negativity (ERN) identified using EEG (Coles et al., 2001; Falkenstein et al., 2000). Next we calculated the time frequency representations (TFRs) of the ERFs. The difference in ERFs for False Alarms versus Hits in the 3-7 Hz theta band was significant in a cluster over frontal sensors (p < 0.001; Fig. 3C, D). This demonstrates that the ERNm to a large extend can be represented as theta activity phase-locked to the button press. We also conclude that a larger proportion of the frontal theta increase reported in Fig. 2A is likely to be phase-locked to the button press.
Figure 1. The power calculated in pre-stimulus interval (time -1– 0 s) for False Alarms compared to Correct Withholds. (A) Topography of the 10-11 Hz power of the difference between False Alarms and Correct Withholds averaged over subjects (planar gradient). The cluster of sensors showing significantly stronger alpha power for False Alarms than Correct Withholds is marked with dots (p < 0.008; cluster randomization routine). (B) Grand average of the spectra calculated (-1–0 s; red line: False Alarms; blue line: Correct Withholds). The spectra were averaged over the cluster of sensors that showed a significant difference. (C) Using a beamforming approach we identified the regions accounting for the difference in alpha power between False Alarms and Correct Rejections to occipital and sensorimotor cortex.
Figure 2. The power of oscillatory activity characterized in the post-response interval for False Alarms compared to Hits. (A) Grand average of the difference TFRs (False Alarms – Hits) of representative frontal, posterior and central sensors (sensors marked in white). The button press occurred at t = 0 s. No baseline correction was applied. (B) Grand average of the topography of theta (3-7 Hz), alpha (10-11 Hz), mu (10-11 Hz) and beta (18-24 Hz) activity. The dots denote clusters representing significant differences (cluster randomization routine). (C) A beamforming technique was applied to localize the regions responsible for producing the difference in the power shown in B. The theta increase was localized to frontal regions. Decrease in alpha and mu activity was localized to occipital cortex and extended sensorimotor areas. The beta decrease was localized to primary sensorimotor areas.
Functional coupling between frontal theta and posterior alpha activity

Do the changes in frontal theta activity following an error have consequences for the activity in posterior areas? To address this question we conducted an analysis quite similar to the psychophysiological interactions (PPI) approach often applied to fMRI data (Friston et al., 1997). Rather than investigating cognitive modulations in BOLD signal correlations between different regions, we investigated correlations in powers changes in various frequency bands. Specifically we asked if there were error-related interactions between the post-response frontal theta activity (0-500 ms) and posterior alpha activity. We chose two frontal sensors displaying a strong difference in the theta band (False Alarms – Hits). For both Hits and False alarms the trial-by-trial theta power from the seed sensors was anti-correlated with the alpha power across all other sensors to create topographies of the correlation. The statistical significance of these topographies were assessed at the group level with a one-sample t-test of the correlations at each sensor and then subjected to a cluster-level randomization test (see Methods) to correct for multiple comparisons. We found significant cross-frequency coupling expressed as anti-correlations between frontal theta and alpha power in a cluster of right occipital sensors for False Alarms (p<0.028, Fig 4, left panel), but not Hits (Fig 4, middle panel). Moreover, the anti-correlations of these right occipital sensors were significantly greater in magnitude for False Alarms compared to Hits (pair-wise t-test ,p<0.026, Fig 4, right panel). This is also displayed in Fig. 4B where we plot the correlation between frontal theta and occipital alpha power for Hits versus False Alarms. Note that most of the data points fall above the diagonal. In sum, we found that after erroneous button presses, the frontal theta activity became significantly anti-correlated with occipital alpha activity.
Figure 3. The time-locked signals in the post-response interval. (A) The ERFs with respect to False Alarms (red) and Hits (blue) for representative frontal sensors (marked in white). Button press was at $t = 0$ s. (B) The topography of the ERF difference between False Alarms and Hits (0-0.5s). Even though the difference was dominated by frontal sensors, the cluster of sensors representing the significant difference ($p < 0.001$; cluster randomization routine) was large. (C) The difference in TFRs of the ERFs for False Alarms and Hits. (D) The topography of the difference in TFRs of the ERFs. Note the frontal distribution of the significant cluster ($p < 0.001$; cluster randomization routine)

Discussion

We have investigated oscillatory brain activity in a Go-noGo task. We found that increases in pre-stimulus 10-11 Hz alpha and mu activity produced in occipital and sensorimotor regions were predictive of errors. After an error was committed we found that 10-11 Hz alpha activity was reduced in occipital and sensorimotor regions including pre-motor regions. That was in contrast to frontal theta activity which was stronger for errors than correct trials. The frontal theta activity was phase-locked to the button press and reflects to a large degree the frequency domain representations of the magnetic ERN (ERNm). Following errors we observed a correlation between the increase in frontal theta activity and the suppression of posterior alpha activity. This functionally connectivity suggests a top-down drive to perceptual areas setting the state of the brain to minimize errors in subsequent trials.
Figure 4. Correlations between the frontal theta increase and the posterior alpha decrease. Two frontal sensors (marked with stars) were used as a reference for the correlation analysis. The correlations between theta power in the reference sensors and the alpha power in all the other sensors were calculated on a trial-by-trial basis (0-500ms after response). (A) Left panel: Grand average of the theta-alpha correlation for False Alarms. Note the strong anti-correlation in an isolated region over posterior regions ($p<0.028$, one sample t-test, cluster randomization routine). Middle panel: Grand average of the theta-alpha correlations for Hits. There were no significant correlations. Right panel: the difference in theta-alpha power correlations between False Alarms and Hits. (B) The theta-alpha power correlation of the 14 subjects for False Alarms (x-axis) and Hits (y-axis). They were calculated for the two frontal sensors (marked by stars) and the posterior significant sensors (A, right panel). The correlations over the right posterior sensors were significantly more negative for False Alarm than Hits ($p<0.026$, pair-wise t-test).
Alpha activity reflects a state of reduced perception

In order for subjects to perform the Go-noGo task several steps are required. First, the visual stimulus has to be perceived. After perceiving the stimulus a decision has to be made on the action. Finally the decision should be transformed into a motor operation or not. One might expect that errors would be reflected in brain areas directly involved in decision making (Bray and O'Doherty, 2007; Bray et al., 2007; O'Doherty et al., 2007); we found that ~10 Hz activity in visual and sensorimotor areas was predictive of errors. It has been suggested that posterior alpha activity reflects functional inhibition of the visual stream. This is supported by covert attention and working memory tasks demonstrating a stimulus specific alpha decrease of the specific visual stream engaged in a given task (Jokisch and Jensen, 2007; Medendorp et al., 2007; Rihs et al., 2007; Romei et al., 2007; Romei et al., 2008; Thut et al., 2006; Thut et al., 2003). Moreover, alpha activity in the visual stream not required for the task is often increased. Additionally it has been shown that visual discrimination abilities are reduced with an increase in posterior alpha activity (van Dijk et al., 2008). In the current study, the increase in posterior alpha activity and thus functional inhibition might result in longer times for perceiving the stimuli. The longer processing time makes it more difficult for the subject to suppress the motor response in time to the noGo stimuli. This partly also explains why reaction times are shorter for erroneous responses. The stronger 10 Hz mu activity in sensorimotor areas predicting response errors is more difficult to explain. The 10 Hz mu activity has been associated with functional inhibition of sensorimotor areas. This is among others clear from studies showing a clear depression in the central ~10 Hz rhythm during motor execution and somatosensory stimulation (e.g. Hari and Salmelin, 1997; Salmelin et al., 1995a; Salmelin et al., 1995b; Salmelin and Hari, 1994). We posit that when subjects are in the automatic response mode the central ~10 Hz mu activity is relatively high even though motor responses are executed. The relatively high ~10 Hz activity makes the motor system less responsive to external inputs such as signals serving to inhibit an automatic
motor action. In conclusion, increased activity at ~10 Hz in both occipital and sensorimotor regions defines a brain state suitable for automatic responses but prone to commission of errors.

After error the brain state is altered to prevent subsequent errors
How do we explain the decrease in occipital and sensorimotor alpha and beta band activity following erroneous button presses? Our interpretation is that the occipital alpha activity is reduced after an error in order to engage the visual system stronger to prevent subsequent errors. The decrease in occipital alpha is likely to increase the processing accuracy or speed in the visual stream thus allowing for a faster inhibition of a wrongly initiated button press. The decrease of the central mu and beta activity after a wrong key press might reflect that the sensorimotor system is becoming further engaged. This stronger engagement can facilitate the inhibition of the motor system if needed in subsequent trials. In sum, the decrease in occipital and sensorimotor alpha, mu and beta activity defines a more alert brain state facilitating visual processing and control of the motor system.

Frontal theta and ERNm provides a top-down drive setting the state of the brain
Following errors we observed a stronger evoked frontal theta activity associated with frontal ERNm (Coles et al., 2001; Falkenstein et al., 2000). The theta activity was localized to the frontal regions of the cortex such as left superior frontal gyrus, left superior medial gyrus, and right middle frontal gyrus which overlaps with areas found in a EEG-fMRI study localizing the ERN (Debener et al., 2005). Interestingly a recent fMRI study found that activation in the regions corresponding to the default mode brain network predicted the likelihood of an error (Eichele et al., 2008). This is consistent with our hypothesis on the role of error related theta activity modulating maladaptive brain activity, given that there is evidence that frontal theta is negatively correlated with the default mode network (Scheeringa et al., 2008).

After erroneous button presses, the frontal theta activity became significantly anti-correlated with occipital alpha activity. This suggests that the frontal theta activity
after an error reflects top-down modulation by suppressing oscillatory alpha activity in the visual areas. This serves to alter the state of the brain to prevent subsequent errors.

*Functional connectivity can be studies by cross-frequency power correlations*

It has been proposed that communication or functional connectivity between different brain areas can be studied by means of phase-synchronization between different brain regions (Varela et al., 2001). While there is some theoretical and empirical support for this notion, the examples where this approach has been successful are scarce. We here use the approach calculating the trial-by-trial correlation between different frequency bands. As for the psychophysical interaction approach (Friston et al., 1997) we were able to identify significant changes in correlation with respect to a cognitive modulation (Fig. 4B). It should be mentioned that our results cannot be explained by spurious correlations due to cross-talk or volume conduction. The correlations were identified between different frequency bands and they were long-range between frontal and posterior (Fig 4A). Thus, our simple approach provides a novel but powerful method for investigating functional connectivity in human electrophysiological data.

**Conclusion**

In summary, by examining the state of the brain before a stimulus we were able to show that it is possible to predict lapses of attention before they actually occur. This supports the case that the state of the brain is important for how incoming stimuli are processed and for how subjects respond. Thus the ‘resting state’ of the brain cannot be ignored when developing a complete picture of neuronal processing (Raichle, 2006). Our findings also have practical applications. A lot of effort is being devoted to develop brain computer interfaces (BCIs, Lebedev and Nicolelis, 2006). We suggest that pre-stimulus activity in the alpha band can be applied online to predict if subjects are in a state where errors are more likely to be committed. Our findings are also relevant for investigating the neuronal substrate of attention deficits in clinical groups such as ADHD. Certainly patients with ADHD make more errors in the Go-
noGo task (e.g. Aron and Poldrack, 2005; Suskauer et al., 2008). It would of great interest to investigate if the impaired execute control is reflected as a decrease in functional connectivity as assessed by reduced correlations between frontal theta and posterior alpha power.
References


CHAPTER 6

Conclusion

If one simply places electrodes on the scalp of a human volunteer performing no particular task and measures the voltage, a dizzyingly array of seemingly random fluctuations will be recorded. These fluctuations in neural activity seem to suggest that the brain’s neuronal state is continuously changing. Most studies focus on the neuronal activity related to information processing after a presentation of a particular event such as visual or auditory stimuli. The aim of the studies presented in this thesis were to understand how these seemingly random fluctuations, referred to as the brain’s ongoing activity, were related to the brain’s averaged stimulus evoked response and the subject’s behavioural response.

One view of the brain’s evoked response and the ongoing activity is that they are distinct and independent neuronal events. According to this view encompassed by the additive model, the onset of a stimulus elicits a transient additive neuronal response which is phase-locked to the stimulus onset. After averaging many stimuli locked trials the seemingly random fluctuations of the ongoing activity cancel out to reveal the brain’s evoked activity. An opposing view (called phase-resetting) proposes that the brain’s stimulus evoked response is in fact the random ongoing activity now becoming phase-locked to the onset of the stimulus. The additive and phase-resetting theories have been found to be notoriously difficult to disambiguate (Klimesch, et al. 2006; Makinen, et al. 2005). In chapter 2 a model was proposed that endeavored to unify the additive and phase-resetting theories of how evoked activity emerged from the ongoing activity: the ongoing and evoked activity might share neuronal generators. According to this ‘shared generator’ model some neurons may only generate ongoing activity and some may only generate transient evoked activity. A stimulus induced change in neuronal activity may be precisely time-locked to the stimulus and show as a distinct evoked component, or it may be variably time-locked to the stimulus and shows up as a transient increase in
oscillatory activity. This burst of activity within a limited frequency range is determined by the neuronal membrane properties of individual neurons and the functional connectivity between them. The shared-generator hypothesis can explain several findings that do not readily fit with either amplitude or phase modulation. The occurrence of a decrease in oscillatory activity (most often in the alpha band) at the same time as the evoked components could occur when a subset of the neurons generating the ongoing activity becomes involved in the generation of the stimulus-evoked activity.

In chapter 3, additive and the phase-resetting models were disambiguated with the development of a new tool called the phase preservation index (PPI). The PPI tested if the phase of the ongoing activity BEFORE the stimulus is preserved AFTER the event related response. The fundamental point here was that if a stimulus resets the phase of the ongoing activity, there would be no relationship between the pre- and post-stimulus phase. This measure was applied to visual evoked signals recorded from humans acquired with MEG. The ongoing alpha activity (8-13 Hz) after visual stimuli preserved their phase relationship to the activity prior to the stimuli. This strongly speaks against phase-resetting of ongoing oscillations in the alpha band as a mechanism for generation of ERPs/ERFs in the visual system. There was a power increase accompanied by a phase-alignment in the theta (4-6 Hz) band following the stimulus, however, there was not any ongoing theta activity prior to the stimulus. This argues against a phase-resetting model for the generations early visual ERFs.

The debate on additivity versus phase-resetting has mainly focused on the early ERPs/ERFS (sometimes referred to as “exogenous”), which are transient components that occur within the first 100 ms of stimulus presentation and are widely believed to index the arrival of information to the cortex (Coles and Rugg 1995). The late component ERPs/ERFs, (often referred to as “endogenous”) occur later than 100 ms after stimulus onset and are often sustained for a hundred milliseconds or longer. In essence, these are the components that link electrophysiology with cognition (e.g. (Hagoort, et al. 2004; Johansson and...
Chapter 4 presents theoretical and empirical evidence of a third mechanism accounting for the generation of slow components. Fundamental to this hypothesis is the idea that amplitude fluctuations of activity with respect to peak and troughs are not symmetrically modulated as is conventionally viewed. As a consequence of this “amplitude asymmetry” slow evoked components will be produced by simple trial by trial changes in the amplitude of the brain’s ongoing activity. Using a new measure termed the amplitude fluctuation asymmetry index (AFA\text{index}) we were able to show that the amplitude modulations in posterior alpha activity were asymmetric. As a consequence of this asymmetry, slow ERFs were produced from the amplitude modulations of the \(\sim 10\) Hz alpha activity in response to visual stimuli. The slow ERFs were correlated in sign and magnitude to the asymmetric amplitude fluctuations observed during rest. The proposed mechanism can provide a unified account for both slow evoked responses and oscillatory activity in the context of cognitive research.

The study in chapter 5 endeavored to go beyond the conventional event-locked ‘averaging’, that is commonly used to examine the neuronal activity after an event. Instead, the interest here was using the ongoing activity to identify brain states which could predict erroneous responses. We found that pre-stimulus alpha activity (10-11 Hz) in occipital and motor areas were higher for errors than correct responses. This suggests that high pre-stimulus alpha activity is reflective of a state prone to lapses in attention. This lapse in attention could reflect functional inhibition of visual and motor regions preventing proper execution of the task. The alpha activity in occipital and motor were reduced following erroneous compared to correct button presses along with beta activity in sensorimotor areas. Only frontal evoked theta activity and the ERNm were stronger for erroneous compared to correct responses. The post-response reduction in oscillatory activity after errors could reflect changes in the brain state such that errors are less likely to be committed in the next trials. The changes in oscillatory brain states following errors
could be a consequence of a top-down modulation reflected by the frontal theta activity and/or the ERNm.

All this taken together suggests that the state of the brain is important for how incoming stimuli are processed and for how subjects respond. Thus the ever changing state of the brain cannot be ignored when developing a complete picture of neuronal processing.

**Future work:**

Understanding the relationship between the brain’s ongoing oscillations and evoked activity is quite important to the field of human electrophysiology since it leads to fundamentally better understanding of how the signals measured by MEG/EEG link to cognition. Moreover understanding this relationship can extend beyond the realm of EEG and MEG research because evoked components provide a critical link between the hemodynamic response measured by the fMRI and the underlying temporal dynamics of neuronal activity. Although there are some suggestions about the relationship between ongoing alpha activity and the BOLD response (Goldman, et al. 2002), the relationships between ERPs and BOLD have thus far been little investigated. If indeed event-related changes in the amplitude of ongoing oscillatory activity can account for the slower components of evoked fields, this would provide important understanding for the relationship between the BOLD responses and ERPs.

In this thesis the PPI was used to examine the phase stability of posterior alpha activity after a visual stimulus. The specific goal was to investigate if the mechanism behind the early visual response was due to phase-resetting, which it was found not to be. However, this does not rule out that phase-resetting in other modalities or cognitive tasks. Thus it would be interesting to apply the PPI to other frequency ranges and data during higher cognitive tasks. We found that the phase
stability of the ongoing alpha oscillations across time dissipates after about 1 sec. It might be interesting to see if pharmacologically the duration of phase-preservation in spontaneous oscillatory activity could be modulated. Perhaps this measure might reveal some new dimension to intrinsic properties of the cortical neurons that might provide potential insights into pathologies of the neocortex (e.g. Alzheimer’s, schizophrenia).

We were able to prove using the AFA$_{index}$ that the amplitude fluctuation of the posterior alpha activity are asymmetric. Thus any event-related modulation of alpha activity would produce slow evoked fields. It would be interesting to take this a step further and if some of the widely reported higher cognitive slow evoked components (e.g. Vogel and Machizawa 2004, Rugg and Curran 2007) could be accounted for by amplitude modulations of ongoing activity. While we focused the analysis on the posterior alpha activity, the proposed mechanism might generalize to other frequency bands and brain regions. For example it would be highly relevant to investigate if asymmetric amplitude modulations exist in the gamma band as well (30-100 Hz). Oscillatory gamma activity in humans has been shown to be modulated by a wide range of cognitive tasks (Jensen, et al. 2007). Given that the period of a gamma cycle is 10-30 ms it is possible that asymmetric amplitude modulations can account for some of the faster modulations in ERFs (e.g. the N1, P1, N2, P2). The idea then would not be to replace ERPs with ERDs or ERS but rather to use what is already known about the neurophysiologic basis of oscillatory activity to get better understanding of the physiological link between cognition and neuronal processing. Modulations in the spectral dynamics of the oscillatory activity can indicate the processing of information or the changing of cerebral state. The strength of studying oscillatory activity lies in its temporal dynamics, since it provides a direct instantaneous measure of synchronized neural activity.

The large fluctuations in neuronal activity during rest suggest our brain state is continuously changing and perhaps updating. It is likely that there are states in these neural fluctuations prior to the arrival of stimuli that either facilitate or inhibit the
perception and processing of the stimuli (Fries, et al. 2001; Medendorp, et al. 2007; Romei, et al. 2008; Thut, et al. 2006; Worden, et al. 2000). Moreover there also studies which indicate that perceptually relevant shifts in ongoing activity can be voluntarily driven but can also occur spontaneously without experimental modulation of the attention focus (Ergenoglu, et al. 2004; Linkenkaer-Hansen, et al. 2004; van Dijk, et al. In press) it would be interesting to find a top-down source of these changes in brain state. Such a source would be intimately related to attentional processes that might modulate sensory processing by biasing the state and variability of the neural fluctuations as to inhibit some events while facilitating the processing of others.

Changes in oscillatory brain states following events are often characterized by increases and decreases in activity at specific frequency bandwidths and spatial locations. It would be possible to take this further and use a correlation analysis of frequency bands at different spatial locations to examine changes in the functional connectivity of the brain related to specific cognitive tasks. In this case functional connectivity refers to the coordination of activity between different neural assemblies in order to facilitate a perceptual or cognitive process. For example in the particular case of Go-Nogo study presented in this thesis one could see if the increase in frontal theta was correlated (or anti-correlated) with any oscillatory change in the posterior alpha or sensory-motor mu. This could in turn provide a top-down mechanism of how oscillations modulate sensory processing. Such lines of research can provide potential insights into disorders such as autism, attention deficit disorder, dementia, spatial neglect and schizophrenia where the brain is unable to properly process the information from the outside world.

From an applied standpoint using the brain’s ongoing activity could have implications into the development of brain-computer interfaces in the future, that can perhaps be used to monitor performance and brain-state of individuals in highly attentionally demanding jobs (pilots, air traffic controllers). Even more ambitious, perhaps there will one day be a re-interpretation of the role the brain’s intrinsic background activity plays in how we perceive the world every day. In such a
reinterpretation the brain would be viewed as an active system where the spontaneous variability of neuronal activity does not represent noise but rather transient looking glasses through which we perceive the world.
References


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CURRICULUM VITAE

Ali Mazaheri was allegedly born on September 6th, 1976. In 1995 he started his undergraduate studies at the University of Toronto (Canada) majoring in neuroscience and psychology with a minor in biology. In 2001, after obtaining his bachelor’s degree he went on to complete his master’s degree at the University of Toronto’s Institute of Medical Science program under the supervision of Terry Picton. His master’s degree involved quantifying the spectral and evoked changes in the EEG after visual and auditory stimuli. Some of the works done during that time are featured in parts of this thesis. After obtaining his master’s degree he, on the advice a very good friend, decided to go the F.C Donders Centre for his PhD in May 2004. The work at the F.C Donders Centre done between May 2004 and 2008, under the supervision of Ole Jensen, manifested in the formation of this thesis.

Currently Ali is a NWO-Rubicon post-doctoral scholar at the University of California, Davis.
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