Neural Mechanisms of Evoked Oscillations: Stability and Interaction With Transient Events

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Abstract: There is increasing evidence that early event-related potentials are a result of phase alignment of ongoing background oscillations of the electroencephalogram rather than additive amplitude modulation. Steady state visual-evoked potentials (ssVEPs) can be recorded using an intensity modulated stimulus, resulting in an evoked brain response at a known frequency, i.e. the stimulation frequency. Given this property, the ssVEP is ideally suited for examining the relationship between single-trial fluctuations in phase/amplitude and the evoked brain potential resulting from averaging across trials. To address this issue, the current study investigated the contribution of single trial power and intertrial phase locking to ssVEP generation by presenting a peripheral flicker. Further, transient stimuli were presented during flicker and at three increasing latency lags following flicker offset to examine (1) to what extent a stimulus can disturb the ssVEP oscillation and (2) how phase alignment during P1-N1-P2 time windows is affected during presence of evoked oscillations. The former assessment evaluates the stability of ssVEPs and the latter the phase alignment processes to transient stimuli under experimentally induced background oscillations. We observed that ssVEPs are a result of phase alignment rather than single trial amplitude modulation. In addition, ssVEP oscillations were not disturbed by transient stimuli. Finally, phase alignment in P1-N1-P2 time windows was distorted during and shortly after steady state stimulation. We conclude that ssVEPs represent strongly phase locked oscillations sharing the same generation mechanisms as early evoked potentials. *Hum Brain Mapp* 28:1318–1333, 2007. ©2007 Wiley-Liss, Inc.

Key words: steady state visual evoked potentials; phase alignment; intertrial phase locking; single trial power; neural oscillations; electroencephalography

INTRODUCTION

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Traditional views about the generation of event-related potentials (ERPs) in the electroencephalogram (EEG) consider the waveforms (e.g. the P1-N1-P2 complex) obtained by stimulus-locked averaging of single trials to be additive activations distinct from the ongoing EEG background. According to this perspective, background EEG activities independent of stimulus onset are filtered out by averaging and, as a result, the scalp potentials of temporally distinct neuronal generators for specific ERP components (e.g. P1, N1, P2) become visible. Recently, another theoretical perspective has emerged that is contrary to the traditional view. In particular,

it is proposed that ERP components arise from stimulus-induced alignment (or “resetting”) of the phase of ongoing EEG oscillations in the theta and alpha bands [Basar and Stampfer, 1985; Brandt, 1997; Gruber et al., 2005; Jansen et al., 2003; Klimesch et al., 2004; Makeig et al., 2002].

Support for the phase alignment theory of ERP generation (i.e., pure phase resetting without additive amplitude components) requires demonstrating that reorganization of background EEG oscillations with respect to stimulus onset occurs without amplitude changes in the single trials. It has been shown that early ERPs (within the first few hundred ms after stimulus onset) coincide with phase alignment processes without [Sayers et al., 1974] or with only small amplitude increases [Jansen et al., 2003; Klimesch et al., 2004] in the ongoing EEG. Gruber et al. [2005] supplied additional evidence for the phase alignment model by showing that oscillations in the theta and alpha band align their phases within the N1 time window. In the alpha band, phase alignment actually coincides with amplitude decreases on single trials within the N1 time window [Gruber et al., 2005; Klimesch et al., 2004]. This observation cannot be reconciled with additive amplitude modulation because only increases in amplitude are possible in this model. These findings suggest that phase alignment accounts for early ERP generation (the P1-N1-P2 complex), although later components might be accompanied by event-related activations distinct from the ongoing EEG [Fell et al., 2004].

Steady state visual-evoked potentials (ssVEP) also have been used to track sensory processing. The ssVEP is a response of sensory cortex to flickering stimuli, whereby an oscillatory brain response at the frequency of the flickering stimuli evolves. Possible advantages of ssVEPs over transient ERPs are that the experimenter can select the flicker rate (frequency) of the intensity-modulated stimulus and stimulus-driven evoked power changes take place at the fundamental frequency of the flicker rate [Regan, 1989]. Most importantly, ssVEPs are characterized by high signal-to-noise ratios [Mast and Victor, 1991], and, in contrast to ERPs where changes occur at many frequencies, changes in ssVEPs occur predominantly at a known frequency of interest. Of course, at the onset of steady-state stimulation there is an ERP (P1-N1-P2) onset response [Müller and Hillyard, 2000]. After a few hundred milliseconds, however, the highest signal-to-noise ratio response is primarily at the steady-state flicker frequency with neural sources in, or close to, visual cortex [Di Russo et al., 2006; Müller et al., 1997; Pastor et al., 2003], making it likely that basic sensory processes primarily determine neuronal oscillations at the stimulation frequency.

Steady-state stimulus delivery has facilitated knowledge acquisition in a variety of areas. For instance, steady-state responses are sensitive to attention manipulations [Morgan et al., 1996; Müller and Hillyard, 2000; Müller and Hubner, 2002; Müller et al., 1998], the emotional content of stimuli [Keil et al., 2003, 2005; Moratti and Keil, 2005; Moratti et al., 2004, 2006], and tonic changes in brain state [Picton et al., 1987; Plourde and Picton, 1990; Silberstein et al., 1990]. Attention-related changes in N1 ERP amplitudes also correlate

with attention-related modulations of ssVEP amplitudes, suggesting a functional link between these two measures [Müller and Hillyard, 2000]. In addition, although the relationship between ssVEP and the ongoing EEG is presently uncertain, it is reasonable to hypothesize that the same neural architecture supports both activities [Picton et al., 2003].

One theory considers changes in ssVEPs to be consequences of reentrant modulations at early sensory stages representing neural mass action that is influenced by higher order (top down) control processes [Silberstein et al., 1990]. Similar to early ERPs, however, phase alignment could play an important role in the generation of ssVEPs [Ding et al., 2006]. Addressing more clearly whether additive amplitude modulation, or intertrial phase alignment processes without amplitude modulation, accounts for the ssVEP could help clarify the theoretically important issue of the relationship between the ongoing EEG, ssVEPs, and early ERPs.

The present study had three goals: (1) to investigate the relationship between background EEG and the ssVEP by tracking changes in phase and amplitude on single trials before and after the onset of steady-state stimulation. Regression analyses were used to assess the predictive value of intertrial phase locking (ITPL) and single trial amplitude for the ssVEP. Under the phase alignment model, ITPL should account for the majority of variance in ssVEP with there being little or no change in proportion of variance accounted for by single trial amplitude; (2) to examine the role of phase alignment for the generation of early ERPs by systematically perturbing the visual system during steady-state stimulation. Transient visual stimuli were presented during the steady-state response at four time points in relation to steady-state offset. Neuronal oscillations induced by flickering stimuli linger after their offset [Clementz et al., 2004], and so it was expected that the phase locking engendered by the flickering stimuli would attenuate the amplitude of early visual ERPs to the transients presented either during or shortly after steady state stimulation. It was hypothesized that this effect would be accompanied by less ITPL in the theta and alpha band in response to transient stimulation because that frequency range contains the greatest power for early visual ERPs. This approach will provide a test of the phase alignment model of early ERP generation while providing strict control over ongoing EEG activity; and (3) to investigate the impact of a transient stimulus on the ITPL in relation to the flickering stimulus. Assuming that the ssVEP involves synchrony and resonance in widespread neural networks, we hypothesized that an already phase-locked system (at the steady-state flicker rate) would remain relatively undisturbed by transient stimuli. Thus, stronger changes in amplitude and phase-locking were expected in time ranges following ssVEP offset.

MATERIALS AND METHODS

Participants

Twelve paid native English speaking volunteers (6 females, 6 males; age range 24–55 years; 10 right handed [Oldfield,

1971)) were recruited from the University of Georgia to participate in the study. They had normal or corrected-to-normal vision and no family history of photic epilepsy or other serious medical problems (based on self-report). The study was approved by the Institutional Review Board (IRB) at University of Georgia according to the Declaration of Helsinki.

Stimuli and Procedure

Stimuli were presented on a 19-inch computer monitor with a refresh rate of 100 Hz positioned 80 cm distance from the subjects' eyes. Steady-state stimuli were pairs of red 8×8 checkerboards (4 red boxes and 4 boxes of background color in alternating sequence) located bilaterally in the left and right visual fields and synchronously luminance-modulated at a fixed oscillation rate of 12.5 Hz. The checkerboards' inner borders were 6.8° and their outer borders were 13.5° from central fixation. The checkerboards were $9.6 \text{ cm} \times 9.6 \text{ cm}$, with each check having a width and height of 1.2 cm. The luminance modulation was achieved by showing the checkerboards for 40 ms, followed by a 40 ms black screen (taking 10 ms retrace time of the monitor into account). This resulted in an 80 ms on/off cycle (12.5 Hz). The flashing checkerboards were shown for 2,000 ms by presenting 25 of the 80 ms on/off cycles.

Transient stimuli were filled boxes of the same red color and size as the checkerboards presented for 240 ms at central fixation. Transient stimuli were presented at four times relative to steady-state stimulation offset: 240 ms before its offset (during flickering of the checkerboards, exactly 3 flicker cycles before its offset), and 240, 480, and 720 ms after its offset, resulting in four experimental conditions (referred to as C1, C2, C3, and C4). Each condition consisted of 66 trials; 6 trials within each condition were target trials during which the box was pink instead of red. Subjects were requested to press, as quickly as possible, two buttons on a response pad simultaneously with their left and right index fingers upon appearance of the pink box. Target trials were not included in the analyses. The intertrial interval (ITI) varied randomly between 6 and 10 s (rectangular distribution) and was defined as the time period between offset of the transient stimulus and onset of the subsequent steady state stimulus train.

Before the experimental session, subjects were presented with examples of one target and one nontarget trial to ensure that they could discriminate the pink from the red boxes and understood the instructions. Participants were provided with one-minute breaks after 80 and 160 trials. After the experiment, subjects were paid \$10 US.

Electrophysiological Recordings

EEG was recorded continuously from 257 electrodes using an Electrical GeodesicsTM (EGI) system and digitized at a rate of 250 Hz, using Cz as the recording reference. Impedances were kept below 50 k Ω as recommended by the manufacturer. The electrodes located at the outer canthi as well as below and above both eyes were used to record the

vertical and horizontal electrooculogram. During data acquisition, an analog bandpass filter of 0.1–100 Hz was applied.

Electrodes located at the neck and cheeks were excluded, leaving 216 electrode sites for data analysis. EEG data were corrected for eye-blinks using an algorithm implemented in BESATM software [Berg and Scherg, 1994]. Movement artifacts were identified by visual inspection, and trials containing such artifacts were excluded from analysis. Before averaging trials for each of the four transient stimulation conditions, data were average referenced, high pass filtered at a frequency of 1.0 Hz (6 dB per octave, zero phase), and low pass filtered at a frequency of 20 Hz (48 dB per octave, zero phase). Artifact-free single trials with a 1,000 ms baseline and a 3,500 ms poststimulus interval with respect to onset of the flickering checkerboards were extracted for data analysis. The extracted single trials were averaged, yielding the ssVEPs to the flickering stimuli and the visual ERPs to the transient stimuli for each subject and for each condition.

For the evaluation of the evoked responses, the whole averaged epoch (–1,000 to 3,500 ms) was baseline corrected by subtracting the mean of the 1,000 ms prestimulus interval. For single trial and evoked power estimations, however, the baseline correction was not applied as prestimulus activity was corrected after power estimations (see below). To compare latencies and amplitudes of the transient visual ERPs between the four conditions, epochs with a 100 ms prestimulus and 400 ms poststimulus interval relative to the onset of the transient stimuli (red boxes) were extracted from the baseline corrected and averaged epochs (see above).

Spectral Measures

Topographies of ssVEP power, single trial power, and ITPL values (Fig. 1) associated with the flicker alone were derived from an average across 2,000 ms flicker presentation time and all subjects at the corresponding 12.5 Hz component for each electrode (extraction of spectral measures see below). As the topographies of the spectral measures showed maxima at parietal electrode sites (see Results), a parietal electrode at the center of that maximum was selected for analysis (corresponding to Pz of the 10–20 system). To estimate the evoked spectral power in a frequency range of 1.25–20.0 Hz, including the 12.5 Hz of the steady-state stimulus, the averaged epochs were submitted to a moving window fast Fourier transformation (FFT) analysis. The real and imaginary parts of the Fourier components were estimated for 200 sample-point windows (corresponding to 800 ms) that were shifted point-wise across the averaged epochs for each condition and subject. This resulted in 1.25 Hz frequency steps and a time uncertainty of 400 ms in both directions with respect to time. Spectral power was determined from the Fourier components for each frequency step and each shifted time window leading to a time–frequency representation of the data. The power values were log transformed using the natural logarithm and the mean log power values of a prestimulus interval of 600 ms were subtracted for each frequency and time step. The ssVEP data were analyzed at

Figure 1.

(A) Averaged epochs across 1,000 ms preflicker-onset to 3,500 ms post-flicker-onset and across all subjects for each condition. The vertical dotted line at time 0 ms represents the flicker onset. The different line styles in different gray scales indicate the latencies of the transient stimuli to flicker offset (2,000 ms) for each condition. (B) Topographies of ssVEP power, intertrial phase locking (ITPL) and single trial power changes. Values were derived from the time frequency estimations at the 12.5 Hz flicker frequency that were averaged across 2,000 ms of flicker and all subjects. Gray color-bars indicate ssVEP power, ITPL, and single trial power values at each electrode.

this frequency resolution to allow discrimination between the 12.5 Hz ssVEP and changes in the alpha band.

To estimate single trial spectral power, the same moving window FFT approach described above was applied to the single trials. The baseline corrected time–frequency power estimations were averaged for each condition and subject. Intertrial phase locking (ITPL) was determined by normalizing the phase vectors spanned by the real and imaginary parts of the FFT components for each frequency and time step by the corresponding length of the vectors (amplitude). For each time and frequency step, the normalized phase vectors were added across trials of each condition and subject. Thereafter, the sum of the phase vectors was divided by the corresponding number of trials resulting in the Rayleigh statistic R [Jammalamadaka and SenGupta, 2001]. The R value is bound between zero and one. The higher the ITPL of an oscillatory response, the more unimodal is the distribution of the phase vectors, and the closer the R value will be one. Zero values of R represent uniform (random) orientations of the phase vectors.

Statistical Analysis of Spectral Measures

To evaluate significant single trial power increases for each subject and condition, t -tests were conducted at each frequency and time step comparing the single trial power

values to the mean baseline (–600 to 0 ms) across each subject's epochs per condition. This resulted in individual t -maps for each subject and each condition. To account for a group statistic at each frequency and time step, the number of subjects exceeding a t -value corresponding to a P value of 0.01 was counted and plotted (corresponding to a time–frequency map of the number of subjects) for each condition. A binomial statistic was then applied to estimate the minimum number of subjects that had to show significant single trial power increases to violate the assumption of chance occurrence ($P = 0.5$). This method has been used and described previously in the time–frequency analysis domain [Makeig et al., 2004].

To assess significant phase locking over trials for each subject and condition, R values (see above) were determined for each frequency and time step, resulting in a time–frequency representation of phase alignment. The significant R threshold was determined by the following formula:

$$R_{\text{crit}} = \sqrt{-\frac{1}{M} \log(p)}, \quad (1)$$

where R_{crit} is the critical R value, M is the number of trials, and P is the significance level. R values associated with a P value smaller than 0.01 were considered significant. Subjects exceeding the statistical threshold at each

Figure 2.

(A) Time frequency estimations of evoked power at electrode Pz when the transient stimulus was shown *during* (–240 ms relative to flicker offset) the peripheral stimulus train. Panels B–D repre-

sent the time frequency plots for conditions in which the transient stimulus was shown 240, 480, and 720 ms after offset of the 12.5 Hz peripheral flicker.

frequency and time step for each condition were counted. A binomial statistic was used to determine the minimum number of subjects necessary to exceed the threshold to reject the assumption of chance occurrence (see above). To obtain an overall R value across all subjects and conditions, the mean number of trials across all subjects within one condition was used in order to determine the critical R -value for each condition corresponding to a P level of 0.01. Subsequently, the mean of all critical R values (four

conditions) served as an overall threshold ($R = 0.33$) to enable condition comparisons. Before any averaging across subjects and conditions or statistical analysis, R values were Fisher z -transformed (these values were back-transformed for plotting purposes). To assess condition differences of phase alignment in the lower frequencies, we averaged across frequency windows of 1.25–2.5 Hz for the delta-, 3.75–6.25 Hz for the theta-, 7.5–8.75 Hz for the lower alpha-, and 10–11.25 Hz for the higher alpha band for each

Figure 3.

Left panels show time frequency estimations of single trial power changes at electrode Pz for each condition (different time latencies of transient stimulus depiction with respect to flicker offset). Color-bars indicate the power scale. Right panels

show time frequency distributions of the number of subjects demonstrating significant single trial power changes with respect to baseline (see Methods). Color-bars indicate the number of subjects.

Figure 3.

condition. These values were further averaged across time windows that comprised the P1, N1, and P2 (73–300 ms after onset of the transient stimulus) and were extended 400 ms in both directions to account for the time uncertainty (e.g., for condition C1: $t = (2,000 - 240 + 73 - 400)$ ms to $(2,000 - 240 + 300 + 400)$ ms). This resulted in time windows of 1,460–2,440 ms for C1, 1,916–2,940 ms for C2, 2,156–3,100 ms for C3, and 2,396–3,100 ms for C4 with respect to flicker onset. Note that time windows may overlap and time periods for the last two conditions (C3 and C4) were restricted to 3,100 ms due to the low time resolution (400 ms in both directions). Finally, the averaged Fisher z -transformed R values were submitted to statistical analysis for each frequency band (delta, theta, alpha low, alpha high) separately.

A linear mixed effects model (LME) with the fixed effect of *condition* (C1, C2, C3, and C4) and the random effect *subjects* was used, applying restricted maximum likelihood estimation (REML) for parameter estimation. A detailed introduction to LME models in psychophysiology can be found in Bagiella et al. [2000], and the REML method is described in Searle et al. [1992]. To account for dependencies of repeated measures across *conditions*, a general covariance structure estimating the correlations between observations across *conditions* was used. If significant main effects indicated condition differences, mean Fisher z -transformed R values were submitted to single comparisons using Fishers' PLSD. As single trial power changes in the high alpha band were close to significant (see Results), we applied the same procedure to this frequency band to assess condition differences.

To assess differences in the time course of phase reordering at the 12.5 Hz flicker rate of the checkerboards, Fisher z -transformed R values per time step for each condition and subject were submitted to a linear mixed effects model with a fixed effect of *condition* (C1–C4) and a random effect of *subjects*. A general covariance structure was applied in order to account for dependencies for the within measure condition (see above). As this kind of procedure involves many comparisons, we choose a P value of 0.001 as a threshold to indicate a significant condition effect (Bonferroni correction may be inappropriate as time series do not represent independent comparisons, while a threshold of 0.001 was a good compromise between accounting for multiple comparisons and not sacrificing statistical power, e.g., Pourtois et al., 2006).

To evaluate the relationship between the 12.5 Hz single trial and evoked power, the corresponding values derived from all electrodes were submitted to a linear model (regression analysis without intercept) for each time step of an epoch (–600 to 3,100 ms) and for each condition. The model was formalized

as followed:

$$\text{power(ssVEP)}_{i,e} = \text{siPower}_{i,e} + \text{ITPL}_{i,e} + \varepsilon_{i,e} \quad (2)$$

where i is the time index, e is the electrode number, power(ssVEP) is the evoked ssVEP power, siPower is the single trial power, ITPL is the inter-trial-phase-locking, and ε is the residual of the model. For each time step i , electrode e , and condition, the percentage of explained variance for the single trial power, ITPL , and residual were determined. The values derived from the Pz electrode were plotted for each time point and condition across the steady-state presentation time (2,000 ms). Further, the F statistic associated with the model fit for each time step i , electrode e , and condition was calculated. Finally, as ITPL explained most of the variance and the time course of the variance curves were similar for each condition (see Results), the explained variance in percentage was averaged across steady-state presentation time (2,000 ms) and all conditions for each electrode in order to depict the associated topography. The same procedure was executed with the F values to illustrate the topographical distribution of the model fit. The ssVEP power, single trial power, and ITPL values were also averaged across steady-state presentation time (2,000 ms) and submitted to the same linear model for each condition, and the t -statistics with their associated P values were derived.

Visual ERP Measures of Transient Stimulation Conditions

Measures of visual ERP amplitude and latency for the P1, N1 and P2 components in response to transient stimuli were obtained by averaging epochs with a 100 ms prestimulus to 400 ms poststimulus interval relative to transient onset (red boxes) across latency offset conditions. On the basis of grand averages and individual ERPs, three time segments were defined containing the P1 (73–125 ms), N1 (129–193 ms), and P2 (197–285 ms) components. Measures for the three components were obtained from the parietal electrode that captured the maxima in the ERP topographies (corresponding to Pz). The peak amplitude was defined as the maximum deflection in the respective time windows. The latency of the maximum amplitude within each time segment was determined following the procedure proposed by Mueller and Hillyard [2000].

Figure 4.

Left panels show time frequency estimations of intertrial phase locking values (ITPL) at electrode Pz for each condition (different time latencies of transient stimulus depiction with respect to flicker offset) above a threshold of 0.33 (see Methods). The color-

bars indicate the R statistic values. Right panels show time frequency distributions of the number of subjects demonstrating significant ITPL changes across trials (see Methods). Color-bars indicate number of subjects.

Statistical Analysis of VEP Measures of Transient Stimulation Conditions

Amplitudes and latencies of the P1, N1, and P2 components of the visual ERPs were entered in a LME model with fixed effect *condition* (C1, C2, C3, and C4) and random effect *subjects*. Parameter estimation was accomplished by the REML method (see above). To account for dependencies between measures in a repeated measures design (fixed effect), a general covariance structure estimating the correlations between observations across conditions was used. Post-hoc comparisons were evaluated by using the Fishers' PLSD test.

Behavioral Measures

Reaction times to target stimuli were averaged across trials for each condition and subject. Mean reaction times exceeding 1,000 ms were excluded from analysis. This led to the exclusion of the reaction time of condition C3 of one subject. Mean reaction times were entered into a linear mixed effects model with *condition* (C1, C2, C3, and C4) as a fixed effect and *subject* as a random effect. To account for dependencies within subjects across conditions, a general covariance structure estimating the correlations between observations was applied. Effect parameters were estimated using the REML method. Note that by applying this method, we could include mean reaction times of one subject with excluded reaction time in one condition (see degrees of freedoms in Results). Throughout the whole report means are reported with their associated standard errors.

RESULTS

Behavioral Results

Mean reaction time of the subjects did not differ between conditions, $F(3, 32) = 1.62$, $P = 0.20$, indicating that subjects detected the color difference of the transient stimulus (pink versus red box) equally effectively regardless of when the transient was presented (reaction time C1: 535.9 ± 55.9 ms; C2: 483.9 ± 41.1 ms; C3: 466.5 ± 41.8 ms; C4: 499 ± 46.1 ms). It should be noted, however, that the behavioral task was used primarily to maintain subjects in an alert, attentive state throughout the experiment.

Contributions of Single Trial Power Changes and ITPL to the Generation of the ssVEPs

Figure 1A shows the grand mean ssVEPs and visual ERPs at the parietal electrode Pz across all subjects of the four different conditions (C1: -240 ms, C2: +240 ms, C3: +480 ms, and C4: +720 ms latency relative to steady-state offset). Pz is the electrode where the ssVEP, ITPL, and single trial power topographies showed maximal values (Fig. 1B). The topographies show averages of corresponding values across the 2,000 ms steady-state presentation time. As can be

seen in Figure 1B, the single trial power changes with respect to baseline were small.

Inspection of grand mean evoked time-frequency power estimations at electrode Pz across subjects for each condition demonstrated that the oscillatory response during steady-state stimulation was characterized by power changes with respect to prestimulus baseline at 12.5 Hz (Fig. 2). During onset of the ssVEPs and during visual ERPs elicited by transient stimuli, there were also power changes in the delta (1.25–2.5 Hz), theta (3.75–6.25 Hz), and lower alpha bands (7.5–8.75 Hz).

To determine the origin of the evoked power changes at 12.5 Hz driving frequency (flickering checkerboards), single trial power changes over time under each condition were evaluated. Figure 3 depicts the time-frequency estimation of the single trial power for each condition averaged across subjects (see Fig. 3A–D, left column). Single trial power changes at 12.5 Hz were rather weak compared to evoked power changes. The right column of Figure 3 depicts time frequency plots of the number of subjects that exceeded their critical *t*-values associated with an alpha level of 0.01, which was used to estimate the significant single trial power changes across trials from an individual subject. More than 9 out of 12 subjects need to demonstrate a significant single trial power change to reject the null hypothesis of chance occurrence (exact binomial test, $P < 0.05$). At 12.5 Hz, only 4 subjects showed significant single trial power increase and therefore the minimum number of subjects necessary to violate chance occurrence was not reached.

By applying a Rayleigh statistic to estimate ITPL across single trials, significant phase alignment (*R* values exceeding the overall threshold of 0.33 corresponding to a 0.01 significance threshold) at the 12.5 Hz driving frequency was observed (see left column of Fig. 4A–D and Fig. 6). This was also demonstrated by the exact binomial test ($P < 0.05$) as more than 9 subjects out of 12 exceeded their critical *R* values estimated for each individual subject (see right column Fig. 4A–D). This was observed in all conditions (C1, C2, C3, and C4).

To complement the analysis on contributions of single trial power changes and phase alignment, we used both single trial power and ITPL values as predictor variables in a linear model to determine their corresponding variance components on the ssVEP power changes. Figure 5A–D shows the time courses of explained variance of the ssVEP power by single trial power and ITPL during steady state stimulation under each condition (C1, C2, C3, and C4) at electrode Pz. ITPL explained most of the variance whereas the variance explained by single trial power was at the level of the residual. Figure 5E depicts the topography of the explained variance by ITPL averaged across flickering stimuli presentation time and all conditions. To evaluate the model fit of the regression analysis, we also calculated the *F* values of the linear model during the same time course. Figure 5F shows the topography of the *F* values averaged across time and conditions. The high *F* values indicated that the fit of the linear model was sufficient. To further illustrate contributions of

Figure 5.

Panels **A–D** depict the explained variance of ssVEP power by intertrial phase locking (ITPL), single trial power, and the residual of the linear model fit for each condition. The different line styles in different gray scales indicate the variance components of ITPL, single trial power and the residual. Panel **E** shows the topography

of the explained variance by ITPL. The grayscale-bar indicates percent of explained variance. Panel **F** depicts the topography of the model fit. The grayscale-bar indicates the associated *F* values of the linear model fit.

ITPL and single trial power to ssVEP generation, we submitted the mean of the ssVEP, ITPL, and single trial power at Pz (across steady state stimulation time) to the same linear

model for each condition. For each of the four conditions, only ITPL predicted ssVEP power (C1: ITPL: $t(9) = 9.6$, $P < 0.0001$, single trial power: $t(9) = 0.8$, $P = 0.45$, $R^2 = 0.93$; C2:

Figure 6.

Mean R values across all subjects over time at 12.5 Hz flicker frequency derived from electrode Pz. The different line styles in different grayscales indicate the condition of transient stimulation time latency with respect to the flicker offset. The dotted horizontal line marks the overall critical R value 0.33 (see Methods). The black filled circles show time points in which the linear mixed effects model indicated condition differences ($P < 0.001$).

ITPL: $t(9) = 9.2$, $P < 0.0001$, single trial power: $t(9) = 1.0$, $P = 0.33$, $R^2 = 0.93$; C3: ITPL: $t(9) = 8.2$, $P < 0.0001$, single trial power: $t(9) = 0.4$, $P = 0.68$, $R^2 = 0.90$; C4: ITPL: $t(9) = 9.8$, $P < 0.0001$, single trial power: $t(9) = 0.7$, $P = 0.53$, $R^2 = 0.93$).

After the 12.5 Hz steady state presentation (about 2,000 ms), the R values dropped below 0.33, indicating uniformity of phase angles except in conditions in which the transient stimuli were shown 480 and 720 ms after steady state stimuli offset (see Fig. 6). In these conditions, R values increased to the 0.33 threshold at 12.5 Hz in time windows of transient stimulus presentation. Further, statistical analysis of the R values at every time point (-600 to $3,100$ ms) revealed that R values differed about time ranges between 2,680 and 3,100 ms between conditions (linear mixed effects, $P < 0.001$, see Fig. 6). During steady state stimulation (0–2,000 ms), however, ITPL at 12.5 Hz did not differ among conditions, indicating that the transient stimulus presented during steady state stimulation did not alter phase locking.

Visual ERPs With Respect to Steady State Stimulus Train Offset (Condition Effects)

Figure 7A shows the visual ERPs averaged across all subjects for each condition (C1, C2, C3, and C4) at Pz normalized with respect to the different latencies of the transient stimulus onsets (see Methods). All results with respect to the visual ERPs of transient stimulation are summarized in Figure 7B. The P1 amplitudes and latencies of all conditions did not differ.

The N1 amplitudes generated by transient stimulation differed as a function of steady-state offset ($F(3, 33) = 6.5$, $P < 0.01$). Transient stimuli presented during (C1: -240 ms offset) and briefly after (C2: 240 ms offset) steady state stimulation generated a smaller N1 than transient stimuli that were presented later (C3: 480 ms offset and C4: 720 ms offset) with respect to the steady state termination (C1 vs. C2: n. s., C3 vs. C4: n. s., C2 vs. C4: $P = 0.05$, all other comparisons: $P < 0.05$; N1 amplitude C1: $-1.95 \pm 0.36 \mu\text{V}$, C2: $-2.15 \pm 0.37 \mu\text{V}$, C3: $-2.75 \pm 0.46 \mu\text{V}$, C4: $-2.62 \pm 0.44 \mu\text{V}$, see Fig. 7). The latencies of the N1 components also differed among conditions ($F(3, 33) = 6.1$, $P < 0.01$); N1 latencies of the very late transient stimulation (720 ms) were shorter than those of transient stimulus presentation during and shortly after steady state offset (single comparisons: C1 vs. C4: $P < 0.05$, C2 vs. C4: $P < 0.05$, all other comparisons: n. s.; N1 latency C1: 167.3 ± 5.15 ms, C2: 167.0 ± 4.9 ms, C3: 161.3 ± 4.2 ms, C4: 154.3 ± 3.7 ms).

The P2 amplitudes also differed among conditions as a function of steady-state offset ($F(3, 33) = 10.0$, $P < 0.0001$). The P2 amplitudes increased with greater distance from steady-state stimulation offset (single comparisons: C2 vs. C3: n. s., all other comparisons: $P < 0.05$; P2 amplitude C1: $0.65 \pm 0.25 \mu\text{V}$, C2: $1.46 \pm 0.25 \mu\text{V}$, C3: $1.69 \pm 0.25 \mu\text{V}$, C4: $2.12 \pm 0.37 \mu\text{V}$). Latencies of the P2 component did not differ among conditions.

ITPL and Single Trial Power Changes in the Lower Frequency Bands (Condition Effects)

Besides strong ITPL at 12.5 Hz in relation to the flickering checkerboards, significant phase locking was also observed in the delta, theta, and lower alpha band during presentation of the transient stimuli (C1, C2, C3, and C4, see Fig. 4). In the delta band, there was no difference among conditions with respect to ITPL. However, in the theta band less phase alignment was observed when the transient stimulus was presented during the flickering checkerboards ($F(3, 33) = 4.5$, $P < 0.01$; single comparisons C1 vs. C2 and C4: $P < 0.05$, C1 vs. C3: $P = 0.05$, all other comparisons: n. s.; theta ITPL C1: 0.34 ± 0.09 , C2: 0.43 ± 0.12 , C3: 0.41 ± 0.13 , C4: 0.45 ± 0.16). ITPL in the lower alpha band was affected by condition ($F(3, 33) = 8.5$, $P < 0.0001$), with phase alignment being lower in this band in the early (C1 and C2) than in the late (C3 and C4) transient conditions (single comparisons C1 vs. C3 and C4: $P < 0.05$, C2 vs. C3 and C4: $P < 0.05$, all other comparisons: n. s.; ITPL C1: 0.32 ± 0.07 , C2: 0.32 ± 0.11 , C3: 0.37 ± 0.12 , C4: 0.41 ± 0.14). The results with respect to ITPL in the lower frequency bands are summarized in Figure 8.

Single trial power changes in the higher alpha band approached significance during transient stimulus presentation 720 ms after the flicker (C4) as 8 out of 12 subjects demonstrated single trial power enhancements (see Fig. 3D, right column). Therefore, power changes in that frequency band were compared among conditions. Single trial power differed among conditions ($F(3, 33) = 6.8$, $P < 0.001$); pre-

Figure 7.

Panel **A** shows the visual ERPs averaged across all subjects for each condition (indicated by different line styles and grayscales) at Pz, normalized with respect to the different latencies of the transient stimulus onsets (see Methods). The vertical dotted line indicates the transient stimulus onset. Panel **B** shows the means and standard errors of the N1 amplitude/latency and the P2 amplitude for each condition. * < 0.05; # not significant; for single comparisons see Results.

sensation of a transient stimulus during and shortly after offset of the flickering stimuli (C1 and C2) produced less power decrease in the high alpha band compared to the two late offset (C3 and C4) conditions (single comparisons C1 vs. C3 and C4: $P < .05$, C2 vs. C3: $P = 0.10$, C2 vs. C4: $P < 0.05$, all other comparisons: n. s.; power C1: -0.49 ± 0.11 , C2: -0.54 ± 0.16 , C3: -0.67 ± 0.14 , C4: -0.75 ± 0.17 , see also Fig. 8).

DISCUSSION

Steady State VEPs and Its Relationship to Single Trial Power and Phase Alignment

One of the main goals of the present experiment was to investigate whether additive amplitude modulation or phase alignment without amplitude modulation account for ssVEP generation. The relationship between ongoing background EEG and ssVEPs was investigated by tracking

changes of amplitude and phase before and after the onset of flickering stimuli. Single trial power changes during ssVEP generation were weak, with only 4 of 12 subjects demonstrating reliable increases in single trial power with respect to baseline (see Fig. 3). Changes in ITPL values, however, indicated phase alignment reliably exceeding baseline in more than 9 of 12 subjects suggesting that increased phase alignment after onset of the flickering checkerboards was present in nearly all subjects (see Fig. 4). These findings were corroborated by applying a linear model to assess the explained variance of the ssVEP by single trial power and ITPL changes. Phase alignment explained most of the variance of the ssVEP, whereas single trial power was not a better predictor than the residual of the model fit. The model fit also resulted in high F values throughout steady state stimulation, indicating the appropriateness of the linear model.

Phase alignment seemed to be the main mechanism for ssVEP generation while increases in single trial power

Figure 8.

Panel **A** shows intertrial phase locking values for each condition in the theta band (3.75–6.25 Hz) in P1–N1–P2 time windows. The same information for the lower alpha band (7.5–8.75 Hz) is shown in panel **B**. Panel **C** displays the single trial power changes with respect to baseline in the high alpha band (10–11.25 Hz). * < 0.05, ~ < 0.10; for single comparisons see Results.

played a less important role. This result parallels studies investigating the generation of early visual ERPs, where it has been demonstrated that phase alignment rather than additive amplitude changes account for early evoked components [Basar and Stampfer, 1985; Brandt, 1997; Gruber et al., 2005; Jansen et al., 2003; Klimesch et al., 2004; Makeig et al., 2002]. In the field of visual spatial attention it has been speculated that ssVEPs and early VEPs such as the N1 component may share the same neuronal mechanism [Müller and Hillyard, 2000]. Steady state VEPs are as sensitive to attentional changes [Morgan et al., 1996; Müller and Hillyard, 2000; Muller and Hubner, 2002; Müller et al., 1998] as the P1 and N1 components [Hillyard and Anllo-Vento, 1998] further suggesting a functional link between the visual steady-state and early event-related responses. The present data add evidence to the thesis of a common neural basis for ssVEPs and early visual ERPs given that both responses appear to be generated primarily by phase alignment at least at early sensory stages.

The synchronization of neural activity by phase alignment of the ongoing EEG at the driving stimulus frequency during presentation of intensity modulated stimuli may be a mechanism to gate the information flux associated with the frequency tagged stimulus [Steinmetz et al., 2000]. Phase alignment also could be serving a filtering function that enhances the signal to noise ratio in neural systems. Such mechanisms have been proposed in the field of visual spatial attention where they have been referred to as “sensory gating” mechanisms [Hillyard and Anllo-Vento, 1998]. Interestingly, enhancement of the signal-to-noise ratio does not seem to be achieved by simply adding more signals (single trial power) but by synchronizing neural activity to the stimulus train via phase alignment.

A possible complication for extending this interpretation to inferring a relationship between spontaneous EEG and the ssVEP relates to our use of raw scalp voltage data. It may be the case that raw scalp data are biased towards large scale steady state oscillatory activity and may underestimate the contribution of local neuronal networks [e.g., Nuñez and Srinivasan, 2006]. Addressing this issue in a systematic fashion will require using (1) paradigms that allow for examination of spontaneous EEG recordings with and without periods of steady-state stimulation [see, e.g., Clementz et al., 2004], and (2) Laplacian-transformed EEG data or source analysis with single trials. Future studies, therefore, should consider more systematically examining the relationship between spontaneous EEG and the ssVEP with appropriate paradigms and source localization techniques (although reliable localization methods for single trial data are still in development).

A possible limitation of our study is that we only used a single stimulation frequency (12.5 Hz), and so the present findings could be specific to stimulation only in that frequency range. When using high stimulation frequencies with peripheral flickering stimuli, Ding et al. [2006] reported increased ITPL with ssVEP power enhancement during an attention task. When using a flicker frequency in

the lower alpha band, however, Ding et al. [2006] observed a ssVEP power increase without changes in phase locking when subjects directed attention away from the flicker. It is possible that under these special circumstances a different neural mechanism is active. This finding, however, is inconsistent with previous work investigating visual spatial attention using ssVEPs [Morgan et al., 1996; Müller and Hillyard, 2000; Müller and Hubner, 2002; Müller et al., 1998], and so additional studies investigating this issue could be important.

Perturbation of the Visual System by Transient Stimuli During and After Steady State Background Oscillations

A second goal of the present experiment was to examine the role of phase alignment on ssVEP generation by systematically perturbing the visual system through presentation of transient stimuli during or after steady state stimulation. By controlling background brain activity with visual flicker the phase alignment model of early visual ERPs could be tested under more strict experimental control. The amplitude of the N1 component was smaller when the transient was presented during or briefly after the steady state stimulus train offset, and N1 latency was shortest when the transient was presented 720 ms after steady state offset. The P2 amplitude linearly decreased with proximity to the steady state flicker, whereas its latency did not differ as a function of condition. These observations indicate an impact of the background flicker on visual ERP generation not only during the flicker but also for some time after steady state stimulus train offset. This is in line with previous results [Clementz et al., 2004], demonstrating that oscillatory responses persist after stimulus train offset.

Despite the effects of background stimulation on the N1 and P2 components, P1 amplitude and latency were unaffected. In addition, although the effect of different presentation time lags relative to flicker offset was greatest for P2 amplitudes, P2 latency was unaffected by this manipulation. If all early visual ERPs were a product of distinct, latency-fixed neural discharges added on the background EEG, one might have expected that P1 would be delayed and reduced and that this effect would propagate to subsequent components. In contrast to these predictions, the present findings indicate that condition effects on the P1-N1-P2 components are independent of each other. This effect points to a dynamic and nonlinear sequence of neural mass activities.

Early visual ERPs are sensitive to attentional changes [Hillyard and Anllo-Vento, 1998], and so it should be considered whether the observed condition effects are a function of divided attention (more attention on the peripheral checkerboards during steady state stimulation) rather than a consequence of highly synchronized background oscillations. In the attention literature, P1 and N1 are both typically modulated by attention. In the present study, however, P1 was unaffected by condition. In addition, subjects

were equally adept at detecting color changes of the transient stimuli regardless of when those targets occurred with respect to stimulus train offset. It seems unlikely, therefore, that divided attention effects are accounting for the observed condition-related differences in N1 and P2 amplitudes and latencies, and more likely that the effects were a function of differences in synchronized background oscillations evoked by the flickering checkerboards.

There was also less phase alignment in the lower alpha band associated with transient stimulus presentation during and shortly after the steady state flicker whereas phase alignment in the theta band was only affected during the flickering stimulus train. N1 and P2 visual ERP components, therefore, were affected in a similar way as the ITPL in the theta and lower alpha band. Phase alignment in these frequency bands theoretically has been considered crucial for early visual ERP generation [Basar and Stampfer, 1985; Brandt, 1997; Gruber et al., 2005; Jansen et al., 2003; Klimesch et al., 2004; Makeig et al., 2002]. The results of the present experiment, therefore, provide independent and novel support for this theory, especially given that single trial power changes in these frequency bands were not observed.

Single trial power reduction with concurrent phase alignment at transient stimulus onset in the alpha band was not prominent in the present data as compared to other studies [Gruber et al., 2005; Klimesch et al., 2004]. The higher alpha band was restricted to below 12.5 Hz in the present study, however, because this was the flicker rate of the steady state stimulus. Curiously, ITPL at 12.5 Hz tended to increase when transient stimuli were presented 480 and 720 ms after 12.5 Hz flicker offset. Perhaps this 12.5 Hz ITPL increase represented extended higher alpha band synchronization that was not possible during and shortly after the flicker because oscillations at that frequency were already highly synchronized. As phase alignment and power reduction has been reported to co-occur [Gruber et al., 2005; Klimesch et al., 2004] a blocking of 12.5 Hz phase alignment with respect to transient stimulus onset by the flicker may have led to less alpha power reduction by the transients during and briefly after the steady state stimulus train. This explanation is highly speculative, however, but this effect may be fruitfully investigated in future experiments.

The impairment of theta and lower alpha band phase alignment during and briefly after the flickering checkerboards is consistent with the hypothesis that a highly synchronized neural system (oscillations triggered by the flicker) will not allow further phase alignment to a new stimulus (the transient). The ability of the neural system to align the phases of the ongoing EEG was also impaired shortly after the steady state stimulus train because synchronization tends to linger after flicker offset [Clementz et al., 2004]. This observation adds further support to the phase alignment model of early visual ERPs, and supports the notion that a neural system must be decoupled before synchronizations with respect to a new stimulus can occur [Rodriguez et al., 1999]. Indeed, the degree of phase align-

ment at the 12.5 Hz flicker frequency across conditions did not change when the system was confronted with a transient stimulus indicating that an already established oscillation aligned to stimulus onset is quite stable.

CONCLUSION

The present study demonstrated that the underlying process of ssVEP generation is primarily phase alignment of the ongoing background EEG; additive amplitude changes contributing less to the evoked response. Second, an already established oscillation phase locked to the stimulus train onset of a steady state flicker is quite stable, as a transient stimulus presented during flicker depiction does not disturb the phase alignment of the flicker. Further, a phase locked neuronal oscillator does not have enough degrees of freedom left such that a transient stimulus can reorder the phases of the oscillations to its own onset. This resulted in less phase alignment in the theta and alpha band accompanied by reduced N1 and P2 amplitudes and prolonged N1 latencies in conditions in that the transient stimulus was presented during or briefly after a steady state flicker. This observation adds further support to the phase alignment model of early evoked brain responses.

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