



Multiple gamma oscillations in the brain: A new strategy to differentiate functional correlates and P300 dynamics

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ABSTRACT

Brain oscillations in the gamma frequency band, – i.e. oscillations greater than 25 Hz – have attracted increasing attention over the last few decades in the research of sensory-cognitive processes. In the neuroscience research literature, a great number of reports aim to describe the functional correlates of oscillatory responses in the gamma frequency window. However, analysis using a broadband frequency window often leads to divergent functional interpretations and controversies.

In order to provide a more exact approach, we have used a strategy by defining multiple frequency and multiple time windows according to the combined analysis of conventional power spectral windows, frequency adaptive multiple filters, and inter-trial coherence. The analysis in frequency windows of 25–30 Hz, 30–35 Hz, and 40–48 Hz enables the investigator to provide a distinction of cognitive and/or sensory responses. Moreover, according to topological differentiation and the consideration of neuroanatomic pathways, more reliable interpretations of gamma responses are reached.

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1. Introduction

The present report is a fundamental step providing analyses of functional correlates of the gamma frequency window between 25 and 48 Hz in cortical recordings. In order to deepen our functional knowledge of gamma-band responses using sensory and cognitive stimulation an effective ensemble of mathematical methods as well as a systematic view considering cortical and subcortical signal transfer in the brain were applied.

Neuronal gamma-band oscillations, which can be recorded in many cortical and subcortical areas in the mammalian brain and in invertebrate ganglia, can be recorded spontaneously or evoked/induced by different stimuli or tasks. There are several views related to the role of gamma activity in the communication processes of the brain and opinions related to functional correlates of the gamma band responses (Başar-Eroğlu et al., 1996a, 1996b; Herrmann et al., 2004; Fries, 2009). The literature includes a number of reviews of cellular mechanisms and cognitive/behavioral correlates of gamma oscillations (Başar et al., 2001; Başar-Eroğlu et al., 1996b; Herrmann et al., 2004, 2010; Herrmann and Knight, 2001; Jensen et al., 2007; Singer, 1999; Tallon-Baudry and Bertrand, 1999).

The wide variety of results in a huge number of publications often leads to controversies. A recent review described the research beginning with the early days of Lord Adrian (1942). In this review, it was concluded that it is extremely difficult to derive a reliable general theory of gamma from the various results, models, and hypotheses. Instead, it was proposed that it would be more reasonable to present highlights, results, and exclusion principles with the aim of excluding somewhat controversial trends, at least in order to avoid errors. One of the possible errors is the consideration of a large frequency window in most publications (Başar, 2013).

In preliminary works related to the late gamma response we have demonstrated the existence of a 40 Hz response, which approximately occurs 300 ms after the cognitive input. The experiments have been carried with human subjects and additionally with freely moving cats. We used an omitted stimulation paradigm with repetitive auditory stimuli. Every fifth stimulation was omitted (Başar-Eroğlu and Başar, 1991). In the meantime, there have been several studies showing a 40 Hz response in the late time window.

Herrmann et al. (2004) distinguished the evoked gamma and induced gamma oscillations as follows: Oscillations in the brain can either occur *spontaneously*, that is, without relation to external stimuli, or they can be related to the processing of stimuli. In the latter case, a distinction is usually made between ‘evoked’ and ‘induced’ oscillations (Başar-Eroğlu et al., 1996b). If an oscillation appears with the same latency and phase after each stimulus, it is considered as *evoked activity*, which is usually the case for early gamma activity before 150 ms after

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stimulus presentation (peak latencies are typically around 50 ms for auditory and around 100 ms for visual stimuli) (see also Fig. 2).

Herrmann et al. (2004) also indicated that, if the oscillation varies in either latency or phase from trial to trial, it is called induced activity. This is typically the case for the late gamma activity that occurs 200–300 ms or later after stimulus presentation. Gamma activity appears in a wide frequency band between about 30 and 80 Hz. Evoked responses often oscillate around 40 Hz whereas induced responses might also reveal higher frequencies. When computing the average potentials across many experimental trials, as is usually done in electrophysiology to yield the event-related potential, evoked oscillations are summed because they are phase-locked to stimulation. Induced activity on the other hand, is almost canceled out completely in the averaged event-related potential. It should be commented that induced oscillations are highly reduced in the averaged curves but never canceled out if the number of epochs do not attain high numbers.

In the meantime, there have been a few studies in which gamma band oscillations were analyzed in a response time period between 50 ms and 100 ms (Castelhano et al., 2013; Martini et al., 2012). However, in none of those studies were systematic recordings and systematic applications of multiple methods performed. In most cases, a comparative baseline by application of simple sensory stimulation was omitted; responses to the complex visual or auditory stimulation were not compared with this baseline. Further, the application of system theory methods did not consider the basic “response power spectra” and only colored figures were globally analyzed.

Imaging methods have several advantages; however the exact descriptions of time and frequency boundaries are often confusing. Additionally to these critiques related to mathematical applications, we point out that all signal analysis methods must be interpreted with the knowledge of physiological electrical signal transfer under the skull.

According to these facts, descriptions of event related oscillations (EROs) in several frequency frames and broad time windows should be carefully analyzed to develop a true picture of the functional signals.

The oddball paradigm is one of the most applied cognitive experiments, and the response to cognitive input triggers attention, perception, remembering, and learning. Accordingly, in the analysis of the oddball paradigm, the brain is involved in several responses, also including sensory responses. The implication of these components will be discussed in Section 4.

The present report includes several steps for elucidation of functional correlates.

- 1) Comparison of gamma band responses upon pure sensory stimulation (simple light) and gamma response to a cognitive stimulation (sensory signal with cognitive load as in the oddball paradigm) will be performed. This comparison is often neglected in research on gamma oscillations.
- 2) Time frame analysis in four time windows between 25 and 48 Hz was analyzed. Topological changes in frontal, occipital and parietal areas are separately analyzed and compared. The rationale for this precaution is that: It has been shown that frontal and occipital areas react differently to the modality of sensory stimulation (Karakaş and Başar, 2000; Sakowitz et al., 2001) and modulation by cognitive load.
- 3) The neuro-anatomical structures and possible signal transmission along multiple structures following stimulation signals will be discussed. In the rule, simple light signals activate only the pathway directly converging on the occipital cortex, whereas cognitive inputs activate several loops that reach association cortices and the limbic system (see Fig. 10). This view has important consequences: We argue that in all cognitive paradigms related to brain responses, simple light responses provide an indispensable baseline in the design

of the experiment.

- 4) Several signal analysis methods will be applied, since a single method leads to a reduction of information, masking the true picture of gamma oscillations.

2. Methods

2.1. Rationale for application of several methods

In studies related to the analysis of brain oscillations, typically only one or two analytical tools are applied. This can often lead to shortcomings in interpretations. It is important to understand brain activity by analyzing EEG activity in time and frequency windows. Moreover, the analyses of phase locking and coherence in time, and coherence in space are important. In the application of statistical techniques, it is vital to choose regions of interest in the gamma frequency window. Gamma responses are very sensitive to the modality of stimulation and recording sites (Sakowitz et al., 2001). A cognitive signal target also contains a sensory input. Therefore, we should aim to differentiate effect of a light signal from the response elicited by a cognitive target. It is the reason why we aim to compare sensory and cognitive components of gamma responses. Section 4.2.1 tries to describe how these measures are correlated to different facets of neurophysiological function.

2.2. Subjects

Thirteen subjects (7 females, 6 males; age 19 to 29 years; mean = 22.62 ± 3.75 years) were included in this preliminary study. All subjects were students or staff of Istanbul Kultur University. All subjects completed at least 10 years of education and all were right-handed. The subjects were interviewed with a questionnaire about their family history, demographic characteristics, medical profiles, and drinking habits. None of the subjects reported any current or past neurological or psychiatric illnesses, and all had normal or corrected-to-normal vision. All subjects signed an approved consent form.

2.3. Stimulation

The participants sat in a dimly lit, isolated room during recordings. Two types of stimuli were presented: simple visual stimuli and visual oddball paradigm. First, the simple visual stimuli were presented in the form of a light (10 cd/m² luminance) with inter-stimulus intervals varying between 3 and 7 s. Then, a classical visual oddball paradigm was applied by using the simple 10-cd/m² luminance light as the standard and a 40-cd/m² luminance light as the target stimuli. The light appeared at full size on a 19-inch computer monitor with a refresh rate of 60 Hz. The duration of the stimulation was 1000 ms. The probability of the deviant stimuli was 0.33 and, in all paradigms, they were embedded randomly within a series of standard stimuli. These stimulation signals were applied randomly, with inter-stimulus intervals again varying between 3 and 7 s. In order to assess focused attention and working memory, the task required mental counting of the target stimuli.

2.4. Electrophysiological recording and analysis

EEG was recorded with 30 Ag/AgCl electrodes mounted in an elastic cap (Easy-cap) according to the international 10–20 system. Additionally, two linked earlobe electrodes (A1 + A2) served as references. The EOG from the medial upper- and lateral orbital rim of the right eye was also registered. For the reference electrodes and EOG recordings, Ag/AgCl electrodes were used. All electrode impedances were less than 10 k Ω . The EEG was amplified by means of a Brain Amp 32-channel DC system with band limits of 0.01–250 Hz. The EEG was digitized on-line with a sampling rate of 500 Hz.

Artifacts were eliminated manually off-line, taking into consideration the EOG recorded from the right eye. The sweep numbers were equalized randomly between the target and simple visual stimulation conditions.

2.4.1. Computation of evoked spectra

The epochs were extracted from continuous EEG files with Brain Vision Analyzer software (Brain Products GmbH, Germany). Single-trial epochs were extracted from –500 to 1000 ms relative to the stimulus.

We applied two different methods for evoked spectra, FFT and event-related spectral perturbation (ERSP). The analysis of evoked spectra by FFT was performed using the Brain Vision Analyzer, and the ERSP was analyzed using EEGLAB (Delorme and Makeig, 2004). The analysis of evoked spectra by FFT was performed in order to determine the filter limits for digital filtering of Event Related Potentials (ERPs) in different gamma frequency ranges. An example of FFT analysis is seen in Fig. 1. The analysis of evoked spectra by means of ERSP was performed and the ERSP values were used in the statistical assessment.

For the analysis of the event-related spectral perturbation (ERSP), a 'width' of six cycles of Morlet-based wavelet transform was applied (28 through 48 Hz) for a –500 to 1000 ms time period (EEGLAB, Delorme and Makeig, 2004). Baseline log spectrum (–300 to –50 ms) was subtracted from each spectral estimate to produce the baseline-normalized time–frequency distribution. The color at each image pixel indicates amplification (in dB) at a given frequency and latency relative to the time-locking event.

The peak amplitude/power at a 28–48 Hz individual frequency was extracted for statistical assessment (Herrmann et al., 2004; Lenz et al., 2010, 2011). The peak-frequency was defined as the frequency bin showing the highest response in four different time intervals (1) between 0 ms and 200 ms, (2) between 200 and 400 ms, (3) between 400 and 600 ms, and (4) between 600 and 800 ms, obtained via time–frequency plots of the average response for each electrode and each subject.

2.4.2. Inter-trial coherence (ITC)

Inter-trial coherence (ITC) is a frequency-domain measure for the synchronization of activity at a particular latency and frequency for a set of experimental events to which EEG data trials are time-locked (Delorme and Makeig, 2004; Tallon-Baudry et al., 1996). Here, we

calculated the ITC using EEGLAB (see Delorme and Makeig, 2004) as follows:

For $j = 1$ to N trials,

$$ITC(t, f) = \frac{1}{N} \times \left| \sum_j \left(\frac{W_j(t, f)}{|W_j(t, f)|} \right) \right| = \frac{1}{N} \times \left| \sum_j \exp(i\phi_j(t, f)) \right|$$

where $\phi_j(t, f)$ is the phase of the wavelet at time t and frequency f . ITC values range from 0 (indicating absence of phase-locking) to 1 (indicating perfect phase synchronization). All ITC values were computed for each participant; for a grand average ITC values were averaged across all participants. The individual peak phase locking value within 28–48 Hz range was extracted for statistical assessment in four different time intervals (1) between 0 ms and 200 ms, (2) between 200 and 400 ms, (3) between 400 and 600 ms, and (4) between 600 and 800 ms.

2.4.3. Digitally filtered event-related gamma oscillatory responses

Digital filtering of ERPs was performed with Brain Vision Analyzer (Brain Products GmbH). Averaged event-related potentials of each subject were digitally filtered in the 25–30 Hz, 30–35 Hz, and 40–48 Hz frequency range. The maximum peak-to-peak amplitudes for each subject's averaged gamma (25–30 Hz, 30–35 Hz, and 40–48 Hz) responses were analyzed for four time windows and for the F_3 , F_z , F_4 , P_3 , P_z , P_4 , O_1 , O_z , and O_2 electrodes. These time windows were as follows: 0–200 ms, 200–400 ms, 400–600 ms, and 600–800 ms.

2.5. Statistical analysis

All statistical analyses were calculated using SPSS and Statistica Software. The differences between modalities were assessed by means of repeated measures of ANOVA. The performed statistical analyses are as follows:

1. Analysis of ERSP measures by means of ANOVA; repeated measures of ANOVA included the within-subject factors of time window (time window 1 (0–200 ms); time window 2 (200–400 ms); time window 3 (400–600 ms); time window 4 (600–800 ms)), stimulation (target vs. simple light) $\times$ four locations (frontal, central, parietal, occipital) $\times$ two hemispheres (left, right). Greenhouse–Geisser corrected p-values were reported. Post-hoc comparisons were analyzed with Bonferroni test. The significance level was set to $p < 0.05$ for all comparisons.
2. Analysis of ITC measures by means of ANOVA; repeated measures of ANOVA included the within-subject factors of time window (time window 1 (0–200 ms); time window 2 (200–400 ms); time window 3 (400–600 ms); time window 4 (600–800 ms)), stimulation (target vs. simple light) $\times$ four locations (frontal, central, parietal, occipital) $\times$ two hemispheres (left, right). Greenhouse–Geisser corrected p-values were reported. Post-hoc comparisons were analyzed with Bonferroni test. The significance level was set to $p < 0.05$ for all comparisons.
3. Analysis of Region of Interest (ROI) for ITC measures. In order to see the direct effects of stimulation on phase locking factors for each time window (0–200 ms; 200–400 ms; 400–600 ms; 600–800 ms) and for frontal locations (F_3 , F_z , F_4), parietal locations (P_3 , P_z , P_4) and occipital locations (O_1 , O_z , O_2) we have performed separate ANOVA analysis for each time window and for each location as follows: (a) 0–200 ms frontal location: Repeated measures of ANOVA included the within-subject factors as stimulation 2 (target vs. simple light) $\times$ three sagittal locations (F_3 , F_z , F_4); (b) 0–200 ms parietal location: Repeated measures of ANOVA included the within-subject factors as stimulation 2 (target vs. simple light) $\times$ three sagittal locations (P_3 , P_z , P_4); (c) 0–200 ms occipital location: Repeated measures of ANOVA included the within-subject factors as stimulation 2 (target vs. simple light) $\times$ three

Healthy Subjects Visual Gamma Power Spectrum Grand Average

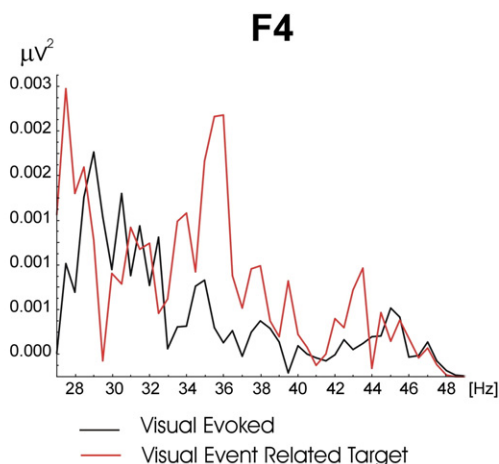


Fig. 1. Grand average of event related power spectrum upon presentation of target stimuli.

sagittal locations (O_1 , O_z , O_2). The same procedure was applied separately for each time window (200–400 ms; 400–600 ms; 600–800 ms) as it was applied to 0–200 ms time window. This means that 12 different ANOVA analyses were performed to see the direct effects of stimulation to each time window for the region of interest.

4. In the analysis of filtered oscillatory gamma responses, repeated measures of ANOVA was used. Three frequency windows (25–30 Hz; 30–35 Hz; 40–48 Hz) were analyzed separately for three different electrode locations (frontal electrodes, parietal electrodes, occipital electrodes). Repeated measures of ANOVA included the within-subject factors of time window (time window 1 (0–200 ms); time window 2 (200–400 ms); time window 3 (400–600 ms); time window 4 (600–800 ms)), stimulation (target vs. simple light) $\times$ three anterior-posterior (F_3 , F_z , F_4), (P_3 , P_z , P_4) or (O_1 , O_z , O_2). Greenhouse–Geisser corrected p-values were reported. Post-hoc comparisons were analyzed with Bonferroni test. The significance level was set to $p < 0.05$ for all comparisons.

3. Results

3.1. Results of event-related spectral measures

Fig. 1 illustrates the grand average ($N = 13$) of power spectra obtained by Fourier transform. The black curve is the average spectra of visual evoked potentials of healthy subjects. The red curve is the spectrum upon target stimulation. In the power spectrum of the target response, the maxima are around 26 Hz, 35 Hz and 43 Hz. There are also minor peaks which are not considered for defining cut off frequency of digital filters. The power spectra of simple visual responses are usually less ample other than a maximum at 20 Hz. We have also considered the individual peaks in order to confirm the cut-off frequencies of the digital filters. These types of filters are defined adaptive digital filters and are chosen according to the specific experimental paradigm. In this report, at the first step we use the same filter limits for all electrode locations.

We have had the experience that this approach was more informative in comparison to ERSP analysis because the overlap of different colors is somewhat masked when the more exact filters are chosen.

Fig. 2 illustrates the grand average of time–frequency planes showing the post-stimulus enhancement of gamma responses in both stimulations (target and simple light) at F_4 location. The grand average plots

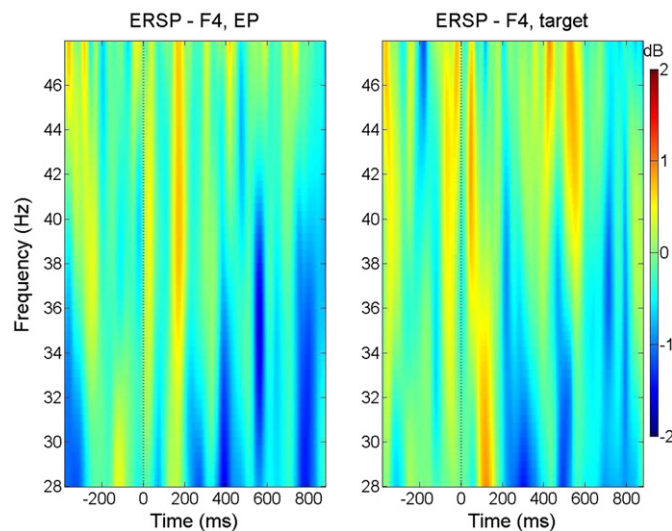


Fig. 2. Grand averages of ERSP measures showing event-related power of gamma responses in both stimulations (target and simple light) at F_4 location. EP on the left side, target response on the right side.

of ERSP analysis of targets and simple light revealed that in the early time window (0–200 ms), the target stimuli elicited two gamma peaks (28–34 Hz and 38–46 Hz) while the simple light stimuli elicited one gamma peak (36–48 Hz). In the first time window (0–200 ms) at 28–34 Hz, target stimulation had greater gamma power than the simple light stimuli; in the third time window (400–600 ms), the target stimuli elicited higher gamma power than simple light stimuli in the higher frequency range (38–48 Hz). As an example, location F_4 is presented in Fig. 2. In this illustration, the power of the 30 Hz response is increased in the first 200 ms. Further, around 40–44 Hz an additional power increase at 200 ms is recorded. Another power increase in the higher frequency window at 44 Hz is seen around 60 ms following stimulations in the target signal. The higher frequency in the target is not seen in the evoked oscillation (EP) upon simple visual stimulation.

Although the ERSP analysis depicts a global similarity to the analysis of power spectra in Fig. 1, the comparative analysis of the visual response power and event-related power can be seen in a more detailed manner in the spectral analysis.

At first glance, these figures are useful to show globally the existence of superposition and of large responses, for example the existence of 45 Hz responses at approximately 600 ms in the target signal. However, the exact frequencies and the time windows are extremely difficult to define compared with the component analysis based on power spectral and time window analysis, which will be explained in Section 3.2., shows.

Within-subjects repeated measures of ANOVA revealed a significant difference for window $\times$ stimulation-type $\times$ location $\times$ hemisphere [$F(9,108) = 3.141$; $p < 0.03$]. Post-hoc comparisons showed that the difference between different time windows were mostly significant at the F_4 location for the first time window and for the target stimulation. The gamma power at F_4 location for the first time window was greater than the second ($p < 0.04$) and fourth time windows ($p < 0.0003$).

3.2. Results on phase-locking

Fig. 3A illustrates the grand average of time–frequency planes showing the inter-trial coherence of gamma responses in both stimulations (target and simple light) at the F_4 location. The grand average plots of ITC analysis of targets and simple light revealed that, in the early time window (0–200 ms), target stimulation elicited greater gamma-phase locking than simple light stimulation. Furthermore, upon target stimulation, there are phase-locked components at 400 and 600 ms in addition to phase locking at around 100 ms; moreover, the frequency of phase-locked oscillations was shifted to frequencies higher than 40 Hz (200 ms) periodicity, indicating a superposition with the 5 Hz frequency band.

Fig. 3B shows ITC analysis for the occipital location in principal; again, there are multiple phase-locked responses upon target stimulations.

Fig. 4 illustrates the inter-trial coherences for five different subjects. In single subjects, the number of phase-locked gamma responses is increased upon presentation of target stimulation in comparison to simple visual stimulation.

3.3. Statistical interpretation of results on phase-locking

ANOVA of gamma phase-locking responses revealed significant results for time window [$F(3,36) = 4.160$; $p < 0.03$]. The post-hoc comparisons revealed that gamma phase locking was significantly greater for the first time window (0–200 ms) than for the second (200–400 ms; $p < 0.0001$), third (400–600 ms; $p < 0.0001$) and fourth (600–800 ms; $p < 0.0001$) time windows. Furthermore, the gamma phase-locking of the third time window (400–600 ms) was greater than the second time window (200–400 ms) ($p < 0.05$). ANOVA of gamma phase-locking responses revealed significant results for paradigm [$F(1,12) = 5.445$; $p < 0.04$]. Post-hoc comparisons showed that gamma phase-locking was greater for the target stimulation than for the simple light stimulation ($p < 0.0001$). ANOVA of

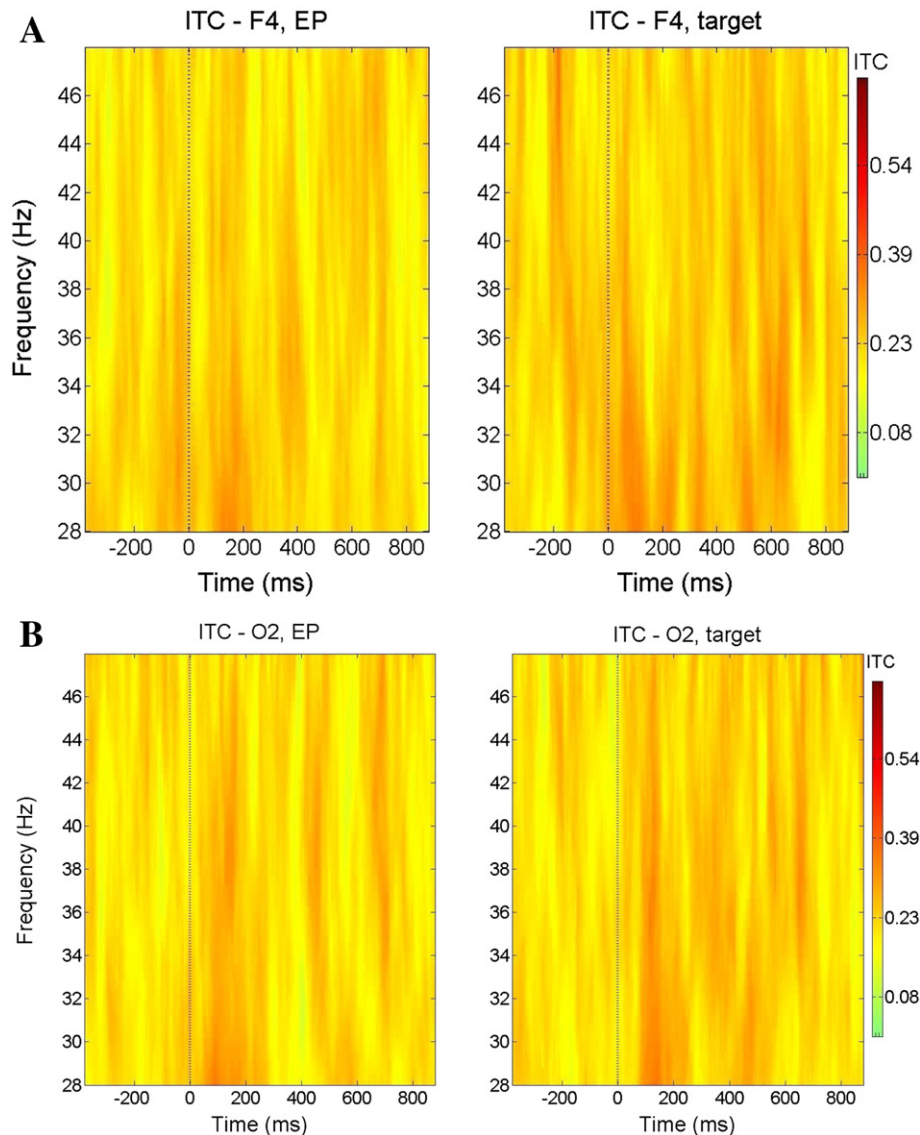


Fig. 3. A: Grand average of time–frequency planes showing the inter-trial coherence of gamma responses in both stimulations (target and simple light) at F_4 location. EP on the left side, target response on the right side. B: Grand average of time–frequency planes showing the inter-trial coherence of gamma responses in both stimulations (target and simple light) at O_2 location. EP on the left side, target response on the right side.

gamma phase-locking responses also revealed significant results for time $\times$ paradigm $\times$ location $\times$ hemisphere [$F(3,36) = 3.581$; $p < 0.05$]. The post-hoc comparisons revealed that the difference between target and simple light stimulation was most pronounced at the right frontal electrode site; gamma phase-locking of right frontal (F_4) was significantly greater for target stimulation in comparison to simple light stimulation ($p < 0.0001$). There were no significant differences between gamma phase-locking of target stimulation in comparison to simple light stimulation for occipital locations.

3.4. Results of region of interest (ROI) analysis of ITC

The most significant results were observed in the frontal locations. In order to compare distant and functionally different areas, we also analyzed the parietal and occipital locations. Therefore, frontal locations (F_3 , F_z , F_4), parietal locations (P_3 , P_z , P_4) and occipital locations (O_1 , O_z , O_2) were analyzed separately for each time window (0–200 ms; 200–400 ms; 400–600 ms; 600–800 ms) and for 28–48 Hz frequency range. ANOVA was used for statistical analysis.

Four time windows (0–200 ms; 200–400 ms; 400–600 ms; 600–800 ms) were analyzed separately.

3.4.1. Frontal locations

Fig. 5 shows the phase locking values for F_3 , F_z and F_4 electrode locations for the 0–200 ms, 200–400 ms, 400–600 ms, and 600–800 ms time windows. Statistical analysis showed that target stimulation elicited higher gamma phase-locking values than the simple light stimulation in the 200–400 ms [$F(1,12) = 13.75$; $p < 0.003$] and 400–600 ms [$F(1,12) = 13.91$; $p < 0.003$] time windows. There were no significant differences between target and simple light stimulation for the 0–200 ms and 600–800 ms time windows. These results show that the difference between the cognitive stimulation and sensory stimulation is seen mostly in the 200–400 ms and 400–600 ms time windows.

3.4.2. Parietal locations

Fig. 5 shows the phase locking values for P_3 , P_z and P_4 electrode locations for 0–200 ms; 200–400 ms; 400–600 ms and 600–800 ms time windows respectively. Statistical analysis showed that target stimulation elicited higher gamma phase-locking values than the simple light stimulation in the 600–800 ms [$F(2,24) = 3.8764$; $p < 0.04$] time

Healthy Subjects Visual Evoked Potential & Event Related Target Inter Trial Coherence

F4

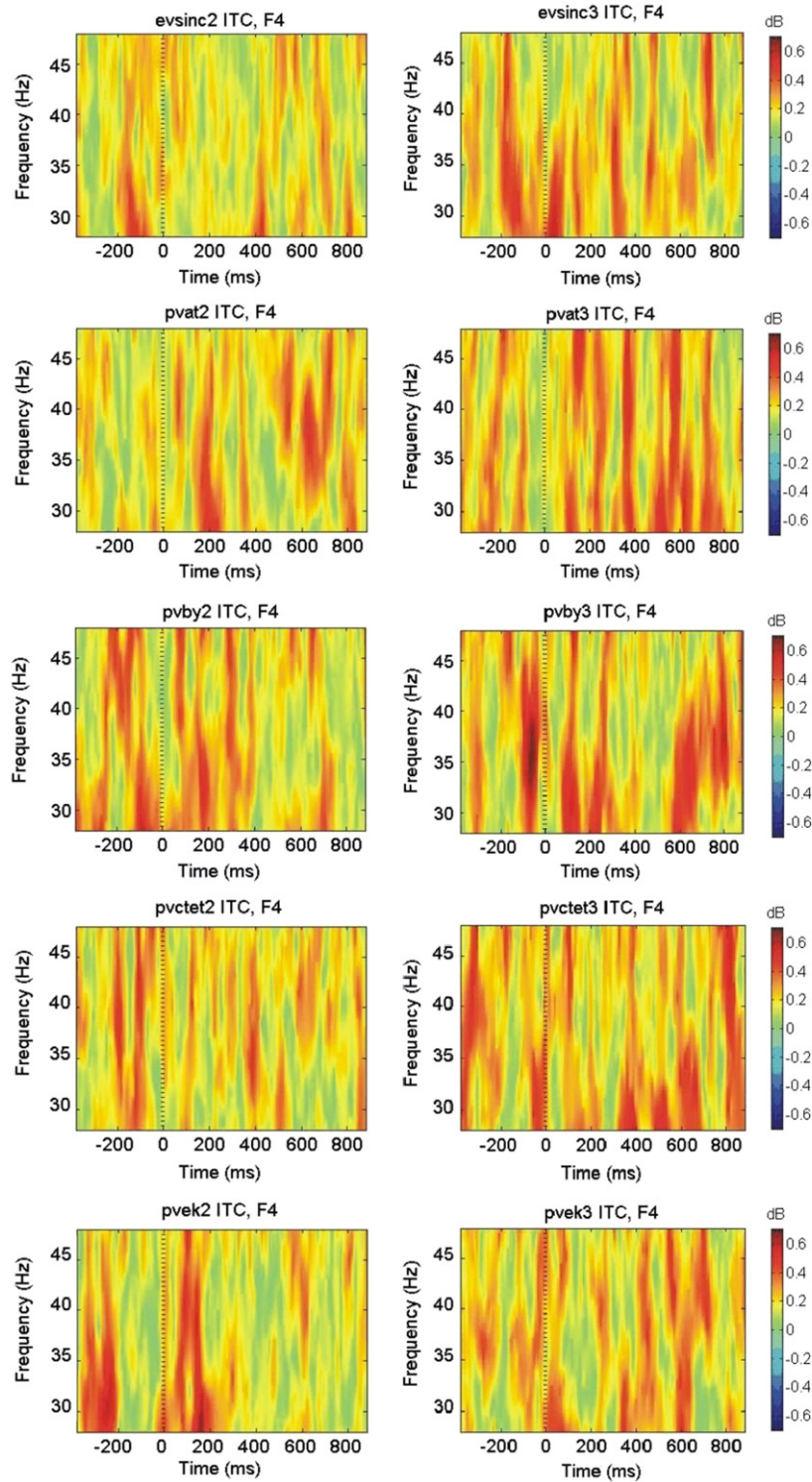


Fig. 4. Analysis of inter-trial coherences for five different subjects. In single subjects, the number of phase-locked responses is increased in target responses in comparison to simple visual responses in the gamma frequency range.

window. There were no significant differences between target and simple light stimulation for the 0–200 ms, 200–400 ms and 400–600 ms time windows.

3.4.3. Occipital locations

Fig. 5 shows the phase locking values for O_1 , O_z and O_2 electrode locations for 0–200 ms, 200–400 ms, 400–600 ms, and 600–800 ms

Visual Gamma (25–48 Hz) Phase Locking Values

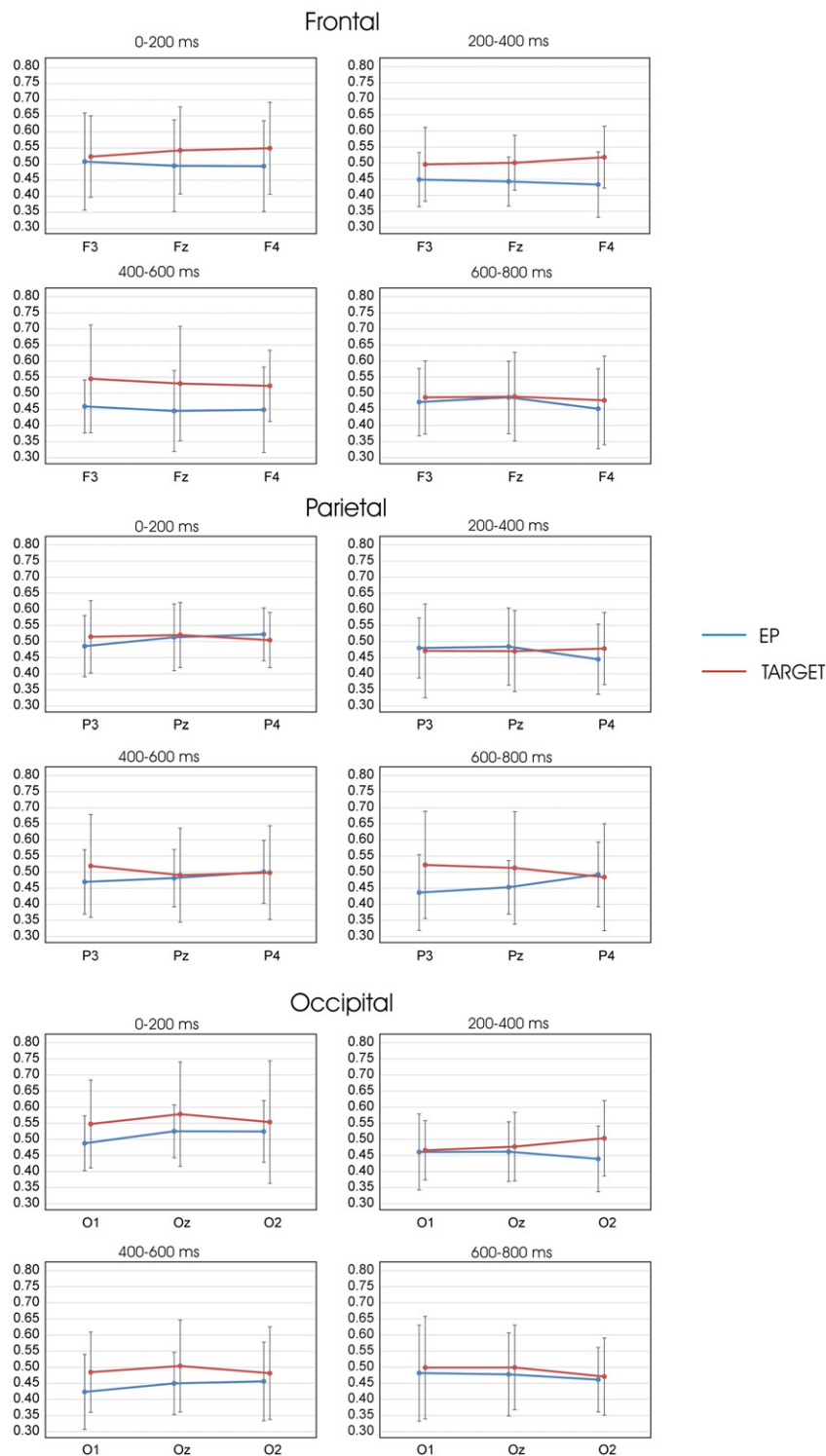


Fig. 5. The mean value of phase-locking values of 13 subjects for F₃, F_z, F₄, P₃, P_z, P₄, O₁, O_z and O₂ electrodes for target (red line) and simple light (blue line) for 0–200 ms, 200–400 ms, 400–600 ms and 600–800 ms time window.

time windows. As is seen in the figures, the target stimulation elicited higher phase-locking values than the simple light stimulation. However, this difference did not reach significant levels. There were no statistically significant differences between target stimulation versus simple light stimulation for occipital locations.

3.5. Results of digitally filtered event-related gamma1 (25–30 Hz) oscillatory responses

Fig. 6 represents the grand average of ERPs filtered at 25–30 Hz of 13 subjects for the F₄ electrode position. The red line represents the grand

Visual Evoked and Event Related Target Gamma Oscillation (25–30 Hz) Grand Average

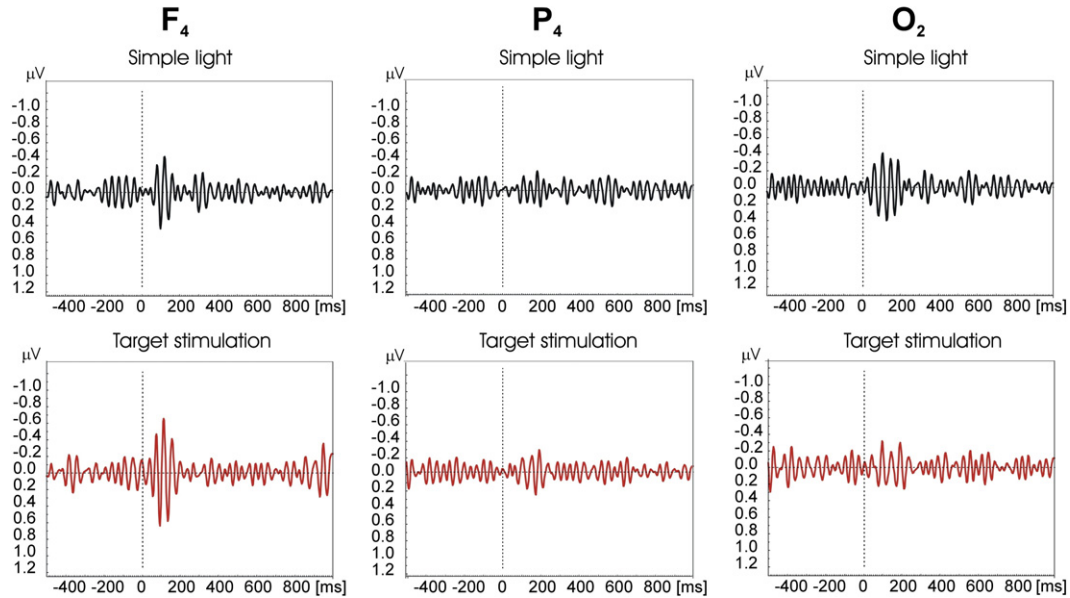


Fig. 6. Grand average of filtered (25–30 Hz) gamma oscillatory responses of 13 subjects for F₄, P₄ and O₂ electrodes upon application of target (red line) and simple light (black line) stimulation.

average of gamma oscillatory responses upon presentation of target stimulation, whereas the black line represents the grand average of gamma oscillatory responses upon simple light stimulation. As it is seen in the figure gamma oscillatory responses are 32.5% greater for target stimulation than for simple light stimulation in the 0–200 ms time window. Furthermore, the gamma oscillatory responses are greater in the first time window (0–200 ms) in comparison to the second (200–400 ms), third (400–600 ms) and fourth (600–800 ms) time windows.

Fig. 6 also represents the grand average of ERPs filtered at 25–30 Hz of 13 subjects for O₂ electrode position. The red line represents the grand average of gamma oscillatory responses upon presentation of target stimulation, whereas the black line represents the grand average of gamma oscillatory responses upon simple light stimulation. As seen in the figure, gamma oscillatory responses are 32.5% greater for simple light stimulation than target for stimulation in the 0–200 ms time window. Furthermore, the gamma oscillatory responses are greater in the first time window (0–200 ms) in comparison to the second (200–400 ms), third (400–600 ms) and fourth (600–800 ms) time windows.

3.5.1. Results of digitally filtered event-related gamma1 (25–30 Hz) oscillatory responses for frontal locations

ANOVA revealed significant results for paradigm [$F(1,12) = 6.701$; $p < 0.03$]. Post-hoc comparisons showed that target stimulation elicited greater gamma response than simple light stimulation. ANOVA revealed significant results for time window [$F(3,36) = 19.376$; $p < 0.0001$]. The post-hoc comparisons revealed that gamma responses were significantly greater for the first time window (0–200 ms) than for the second (200–400 ms; $p < 0.0001$), third (400–600 ms; $p < 0.0001$) and fourth (600–800 ms; $p < 0.0001$) time windows.

3.5.2. Results of digitally filtered event-related gamma1 (25–30 Hz) oscillatory responses for parietal locations

There were no significantly different results between target stimulation and simple light stimulation in parietal locations. ANOVA revealed significant results for time window [$F(3,36) = 16.296$; $p < 0.000$]. The post-hoc comparisons revealed that gamma responses were significantly greater for the first time window (0–200 ms) than for the second

(200–400 ms; $p < 0.000006$), third (400–600 ms; $p < 0.000013$) and fourth (600–800 ms; $p < 0.000013$) time windows.

3.5.3. Results of digitally filtered event-related gamma1 (25–30 Hz) oscillatory responses for occipital locations

There were no significantly different results between target stimulation and simple light stimulation in occipital locations. ANOVA revealed significant results for time window [$F(3,36) = 18.929$; $p < 0.0001$]. The post-hoc comparisons revealed that gamma responses were significantly greater for the first time window (0–200 ms) than for the second (200–400 ms; $p < 0.0001$), third (400–600 ms; $p < 0.0001$), and fourth (600–800 ms; $p < 0.0001$) time windows.

3.6. Results of digitally filtered event-related gamma2 (30–35 Hz) oscillatory responses

Fig. 7 represents the grand average of ERPs filtered in 30–35 Hz of 13 subjects for F₄ electrode position. The red line represents the grand average of gamma oscillatory responses upon presentation of target stimulation, whereas the black line represents the grand average of gamma oscillatory responses upon simple light stimulation. As seen in the figure, gamma oscillatory responses are 30.7% greater for target stimulation than for simple light stimulation in the 0–200 ms time window. Furthermore, the frontal gamma oscillatory responses are greater in the first time window (0–200 ms) in comparison to the second (200–400 ms), third (400–600 ms) and fourth (600–800 ms) time windows.

Fig. 7 also represents the grand average of ERPs filtered at 30–35 Hz of 13 subjects for O₂ electrode position. The red line represents the grand average of gamma oscillatory responses upon presentation of target stimulation, whereas the black line represents the grand average of gamma oscillatory responses upon simple light stimulation. As seen in the figure, gamma oscillatory responses are 33.3% greater for simple light stimulation than for target stimulation in the 0–200 ms time window. Furthermore, the gamma oscillatory responses are greater in the first time window (0–200 ms) in comparison to the second (200–400 ms), third (400–600 ms) and fourth (600–800 ms) time windows.

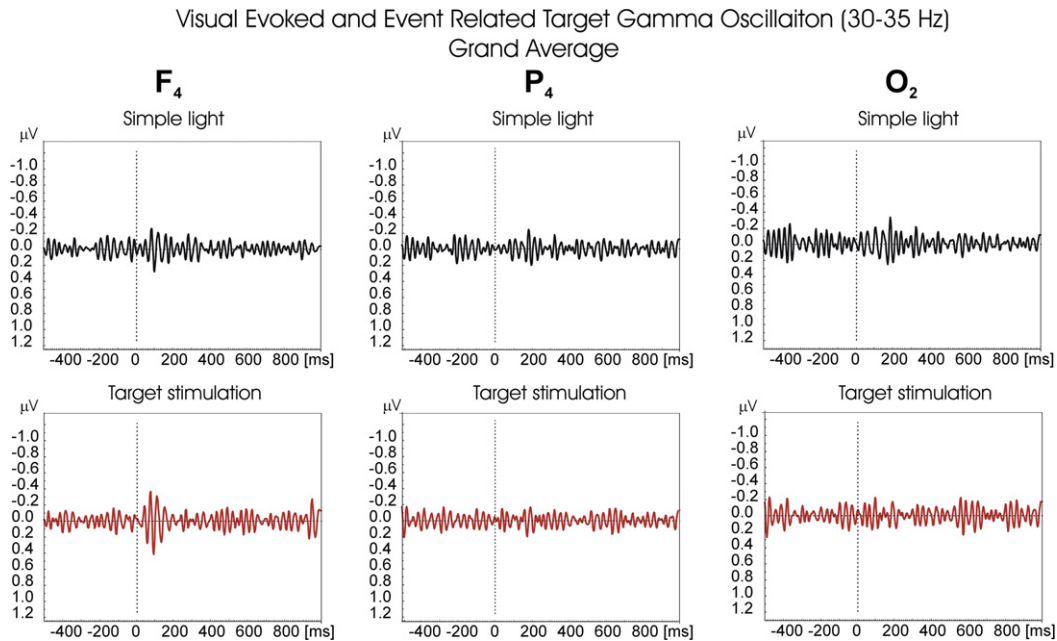


Fig. 7. Grand average of filtered (30–35 Hz) gamma oscillatory responses of 13 subjects for F₄, P₄ and O₂ electrodes upon application of target (red line) and simple light (black line) stimulation.

3.6.1. Results of digitally filtered event-related gamma2 (30–35 Hz) oscillatory responses for frontal locations

In this frequency window there were no significant differences between target stimulation versus simple light stimulation. The ANOVA revealed significant results for time window [$F(3,36) = 6.096$; $p < 0.008$]. The post-hoc comparisons revealed that gamma responses were significantly greater for the first time window (0–200 ms) than for the second (200–400 ms; $p < 0.0001$), third (400–600 ms; $p < 0.0001$) and fourth (600–800 ms; $p < 0.0001$) time windows.

3.6.2. Results of digitally filtered event-related gamma2 (30–35 Hz) oscillatory responses for parietal locations

There were no significantly different results between target stimulation and simple light stimulation in parietal locations. ANOVA revealed significant results for time window [$F(3,36) = 16.296$; $p < 0.000$]. The post-hoc comparisons revealed that gamma responses were significantly greater for the first time window (0–200 ms) than for the second (200–400 ms; $p < 0.000006$), third (400–600 ms; $p < 0.000013$) and fourth (600–800 ms; $p < 0.000013$) time windows.

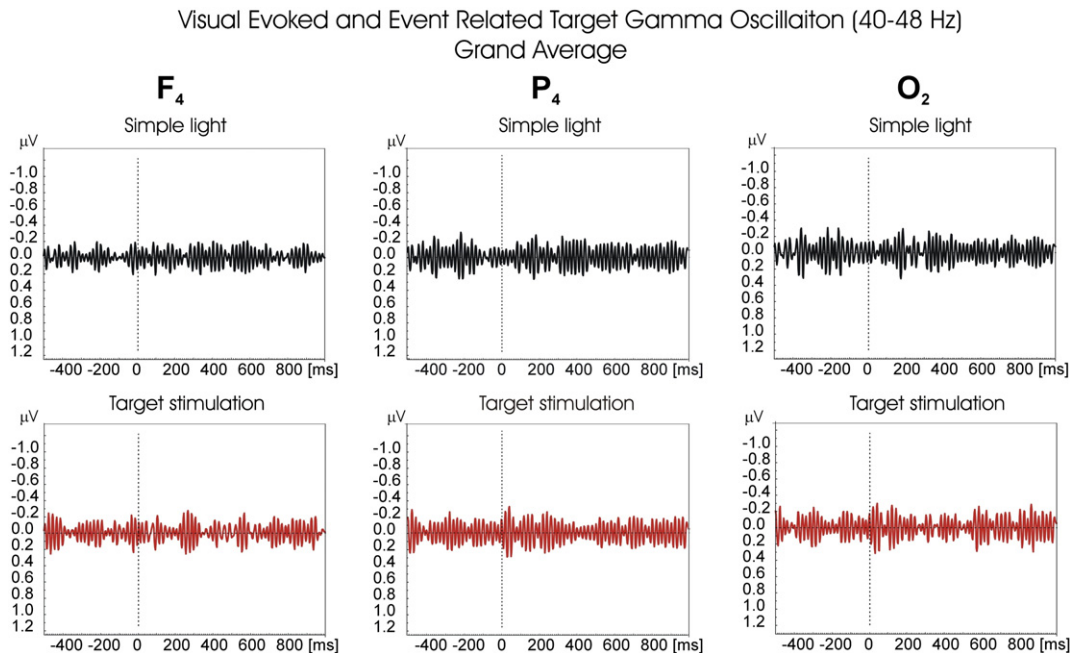


Fig. 8. Grand average of filtered (40–48 Hz) gamma oscillatory responses of 13 subjects for F₄, P₄ and O₂ electrode upon application of target (red line) and simple light (black line) stimulation.

3.6.3. Results of digitally filtered event-related gamma2 (30–35 Hz) oscillatory responses for occipital locations

There were no significantly different results between target stimulation and simple light stimulation in occipital locations for the 30–35 Hz gamma oscillatory responses. ANOVA revealed significant results for time window [$F(3,36) = 6.845$; $p < 0.005$]. The post-hoc comparisons revealed that gamma responses were significantly greater for the first time window (0–200 ms) than for the second (200–400 ms; $p < 0.0001$), third (400–600 ms; $p < 0.0001$) and fourth (600–800 ms; $p < 0.0001$) time windows. ANOVA revealed significant results for hemisphere [$F(2,24) = 4.66$; $p < 0.05$]. Post-hoc comparisons showed that left hemisphere (O_1) has higher gamma responses than right hemisphere (O_2) ($p < 0.02$).

3.7. Results of digitally filtered event-related gamma3 (40–48 Hz) oscillatory responses

Fig. 8 represents the grand average of ERPs filtered at 40–48 Hz of 13 subjects for F_4 electrode position. The red line represents the grand average of gamma oscillatory responses upon presentation of target stimulation, whereas the black line represents the grand average of gamma oscillatory responses upon simple light stimulation. As seen in the figure, gamma oscillatory responses are greater for target stimulation than for simple light stimulation in the late time windows (200–400 ms, 400–600 ms, and 600–800 ms) but almost unchanged in the first time window. In this frequency range, the gamma oscillatory responses are not greater in the first time window (0–200 ms) in comparison to other time windows as it was at 25–30 Hz and 30–35 Hz.

Fig. 8 also represents the grand average of ERPs filtered at 40–48 Hz of 13 subjects for O_2 electrode position. The red line represents the grand average of gamma oscillatory responses upon presentation of target stimulation, whereas the black line represents the grand average of gamma oscillatory responses upon simple light stimulation. In this frequency range, the gamma oscillatory responses are not greater in the first time window (0–200 ms) in comparison to other time windows as it was at 25–30 Hz and 30–35 Hz.

3.7.1. Results of digitally filtered event-related gamma3 (40–48 Hz) oscillatory responses for frontal locations

In this frequency window there were no significant differences between target stimulation and simple light stimulation; there were also no significant differences between the four different time windows. ANOVA revealed significant results for paradigm $\times$ window $\times$ hemisphere [$F(6,72) = 2.552$; $p < 0.05$]. The post-hoc comparisons revealed that gamma responses were significantly greater for right frontal (F_4) location for the third time window (400–600 ms) upon application of target stimulation in comparison to simple light stimulation.

Table 1 summarizes the most essential results that were described in detail in the above sections.

3.7.2. Results of digitally filtered event-related gamma3 (40–48 Hz) oscillatory responses for parietal locations

There were no significant results found for 40–48 Hz gamma filter analysis in parietal locations.

3.7.3. Results of digitally filtered event-related gamma3 (40–48 Hz) oscillatory responses for occipital locations

There were no significant differences between target stimulation and simple light stimulation in occipital locations for 40–48 Hz gamma oscillatory responses. ANOVA revealed significant results for hemisphere [$F(2,24) = 5.33$; $p < 0.03$]; post-hoc comparisons showed that left hemisphere (O_1) has higher gamma responses than right hemisphere (O_2) ($p < 0.02$). ANOVA revealed significant results for paradigm $\times$ time $\times$ hemisphere [$F(6,72) = 2.961$; $p < 0.04$]. Post-hoc

comparisons showed that in the first and second time windows upon target stimulation, the left occipital location (O_1) has greater gamma response than the right (O_2) and central (O_z) locations.

4. Discussion

4.1. Necessity of analysis in multiple frequency windows

A first superficial eyeball analysis of Fig. 9 shows the following: In the analysis of the parietal wide range gamma frequency window, the detection of a general response or responses is not possible. The superposition of multiple gamma responses in different time windows leads to the masking of multiple responses. Statistical analysis also does not indicate significant results. On the contrary, in the frequency window of 25–30 Hz, a significant response is detected in the early time window. Accordingly, the detailed results of the present paper suggest that analysis in multiple time windows is highly recommended, since in most cases vague interpretations are possible. This fact partly shows the source of divergent opinions in publications on gamma oscillations.

4.2. Physiologic and anatomic descriptions

In order to achieve a more progressive view of multiple gamma band responses, it is important to globally consider the flow of neural information and the major connections in the brain. Moreover, we will recapitulate some earlier findings from animal experiments and intracranial human recordings that will contribute to a deeper understanding of gamma responses, thus opening the way to separately analyze sensory and cognitive activations.

4.2.1. Connections of the sensory-cognitive systems in the brain

Flohr (1991) described the anatomical connections in the brain in a simplified and transparent manner as illustrated in Fig. 10.

1. *Specific afferents from sense organs reach specific thalamic nuclei before going to the primary cortical areas.* For instance, auditory information is transmitted through the medial geniculate nucleus to the primary auditory area; visual afferents are transmitted through the lateral

Table 1
Summary of the results.

Evoked power spectrum
The gamma power at F_4 location for the first time window upon application of target stimulation was greater than the second and fourth time windows.
Phase locking
Gamma phase-locking was greater for the target stimulation than for the simple light stimulation.
The difference between target and simple light stimulation was most pronounced at the right frontal electrode site (F_4).
The difference between the cognitive stimulation and sensory stimulation in the frontal locations is seen mostly in the 200–400 ms and 400–600 ms time windows.
The difference between the cognitive stimulation and sensory stimulation in the parietal locations is seen mostly in the 600–800 ms time window.
Gamma phase locking was significantly greater for the first time window (0–200 ms) than for the second (200–400 ms), third (400–600 ms) and fourth (600–800 ms) time windows.
Gamma phase-locking of the third time window (400–600 ms) was greater than the second time window (200–400 ms).
Digitally filtered event-related gamma oscillations
Target stimulation elicited greater 25–30 Hz gamma response oscillations than simple light stimulation.
40–48 Hz gamma response oscillations were significantly greater for right Frontal (F_4) location for the third time window (400–600 ms) upon application of target stimulation in comparison to simple light stimulation.

Healthy Subjects Event Related Target Gamma Filters (25–30 Hz and 25–48 Hz) Grand Average (N=13)

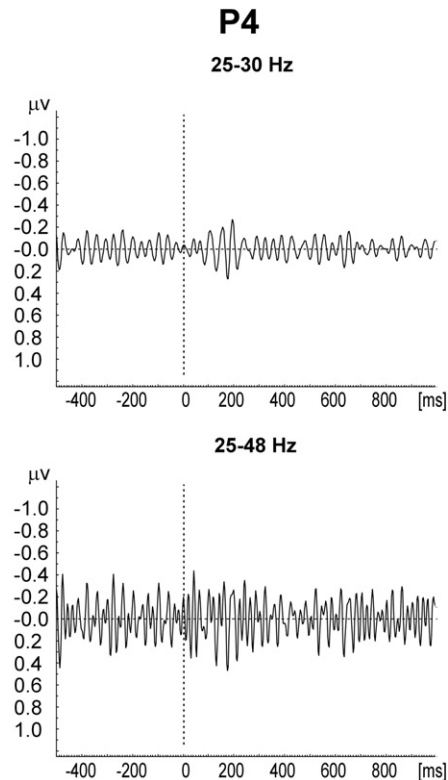


Fig. 9. Grand average of filtered oscillatory gamma responses upon stimulation of target stimuli. The upper part of the figure illustrates the filtered gamma responses at 25–30 Hz for P₄ location and the lower part of the figure illustrates the filtered gamma responses at 25–48 Hz for P₄ location.

- geniculate nucleus to area 17 of the occipital cortex.
2. *Non-specific afferents reach the cortex from the mesencephalic formation.* It has now been established that reticular formation is connected to different nuclei with specific afferent connections. There is a second site where the reticular formation influences the processing

of primary afferents: the thalamic relay nuclei. The nucleus reticularis thalami, a thin sheet of neurons, surrounds the dorsal thalamus and inhibits the thalamic relay nuclei. Its control function is, in turn, affected by collaterals of thalamo-cortical pathways, by collaterals from cortico-thalamic projections, and by inhibitory afferents from the mesencephalic reticular formation.

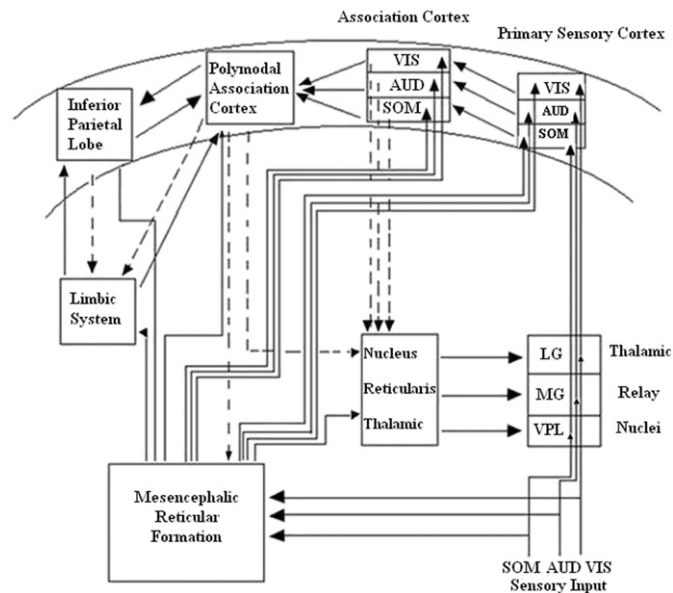


Fig. 10. Flow of information in the auditory, somatosensory and visual pathways, reticular formation, limbic system and association areas of the cortex (sensory and cognitive neural pathways in this figure are modified from Flohr (1991 Theory and Psychology 1: 245–262) and Başar (2004)).

There are important connections within the cerebral cortex involving the association areas. Primary auditory, somatosensory, and visual fields each project to adjacent unimodal association areas, which, in turn, project to secondary unimodal association fields. The unimodal association areas project to a number of polymodal sensory areas, lying in the cingulate gyrus, parietal, temporal and frontal lobes. The functions of these areas are vaguely described as crossmodal association and synthesis. The polymodal association areas project to the inferior parietal lobe, which has been termed a “supramodal” area. Polymodal and supramodal regions have connections to the limbic system; these connections provide the anatomical substrate by which motivational states influence cortical processing of sensory stimuli.

Every sensation in the brain also induces cognitive loading, at least for matching processes. Furthermore, all the presented cognitive targets also evoke sensations; the respective neural processes.

There are, in summary and globally:

1. “Purely sensory connections” to the cortex over the thalamic nuclei.
2. “Secondary connections” to the cortex over the reticular formation.
3. “Secondary connections” over the limbic system.
4. “Connections within the cortex” between association areas.

According to the anatomic description above, we can track the transmission of an electrical signal from the retina over the thalamic system to the occipital cortex. However, a light signal including a cognitive load does not only use the simple visual pathway. The target signal

information is certainly processed over one of the other bottom-up connections. The attention-command signal reaches the higher cortical centers over the mesencephalic reticular formation to the limbic system and higher association areas in the cortex. It is therefore to be expected that cognitive signal processing requires more time and cognitive responses occur with a delay in comparison to sensory responses.

The results of the present study showed that there are multiple gamma windows in time and frequency domain. This multiple gamma windows may vary according to the functionality. Although it is not yet possible to definitely demonstrate that multiple networks in the brain are represented with multiple gamma windows in the frequency and time domain, we think that the results of the present study may highly justify this hypothesis. Our previous research on cat brain showed that gamma oscillations exist in different parts of the brain (Başar-Eroğlu and Başar, 1991; Başar, 1998, 1999, 2011). The new experiments in animals are needed to prove this hypothesis.

4.2.2. Cortico–cortical interplay from the rat and human brain: reverberations

Several studies using intracranial recordings from rat brain (Miller, 1991) and from human brain (Dastjerdi et al., 2011) indicated that cortico–cortical interplay occurs after sensory-network and hippocampal–cortical network activation. Miller (1991) estimated a hippocampal–cortical loop time in the range of 120–200 ms post-stimulus from rat intracranial recordings. In human intracranial recordings, upon a cognitive task, Dastjerdi et al. (2011) demonstrated occurrence of a cortical activation in the lateral parietal cortex after approximately 300 ms. Therefore, it is reasonable to assume that the beginning of the cortico–cortical interplay starts around 300 ms post-stimulus, taking these intracranial recording findings into consideration. One also has to consider that there are possibly several reverberations between association areas and the limbic system. These reverberations may also cause considerable delays and late responses.

4.3. Gamma responses to omitted stimuli from hippocampus recordings from the cat brain. A case when occipital cortex is not directly activated with the cognitive stimulation

The target signal does not include a sensory cue. The tone is omitted and the cat is already trained to “the attend” (the omitted) signal. The superposition of theta and gamma is in Fig. 11 and is a pure compound cognitive response manifested with the superposition of a late (300 ms) gamma and 4–5 Hz theta response.

During the application of the omitted stimulus paradigm, at the time of the omitted stimulus no gamma responses are seen since a physical stimulation does not exist. Thus the response at around 250–300 ms is a purely cognitive response. The cognitive input signal is most probably directly conveyed to the limbic system and frontal cortex over the mesencephalic reticular formation, with the pathway between the retina and occipital cortex over the thalamus not being activated.

4.4. Interpretation of gamma responses in the oddball P300 paradigm

During the application of the oddball paradigm, the stimulation consists of an attention (cognitive) task and a sensory signal (light). Accordingly, it is clear that the stimulation should directly activate the occipital cortex over the thalamus; also, in parallel, the limbic system and the cognitive network (i.e. association areas, frontal lobes and the limbic system). Once the limbic system is activated reverberations in all association cortices and the Papez circuit might be also activated (see also the anatomy in Fig. 10). In other words, the target signal (attend signal) will certainly give rise to excitation (activations) of a greater number of cortical structures with more delays in comparison to occipital recordings. Are these type of responses also recorded in scalp electrodes?

In fact, according to the presented results, this is most probably the case: The analysis of ITC analysis demonstrates the existence of more

P300 - 40 Hz RESPONSE IN HIPPOCAMPUS

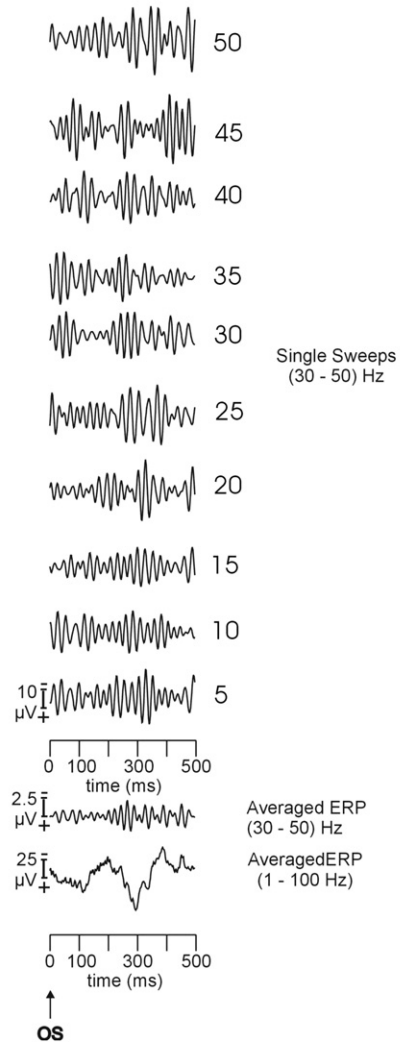


Fig. 11. Event-related potentials of the lower pyramidal layer (CA3) of the hippocampus (one cat). Top: Single ERP sweeps (epochs) filtered at 30–50 Hz. Middle: Averaged ERP filtered at 30–50 Hz. Bottom: Unfiltered ERP, average of 50 artifact-free epochs (modified from Başar-Eroğlu et al., 1991; Başar (2013)).

significant time-locked responses in frontal areas to cognitive target (attend) stimuli in comparison to the occipital cortex, which is activated with simple light (see the next section). Moreover, late responses starting at approximately 400 ms are more significant in frontal areas in comparison to a simple light response in the occipital cortex (compare Fig. 3A and B; Section 3.2). According to Kastner et al. (1999), the attended location is the fronto-parietal-network (see also Fig. 11).

The experiments with omitted stimuli (Fig. 11) clearly demonstrate an intracranial cognitive response that occurs at 250–300 ms, most probably following a subcortical interplay in the fronto-parietal–hippocampal circuit.

4.5. Results of event-related inter-trial coherence

Fig. 3A illustrates the grand average of time–frequency planes showing the inter-trial coherence of gamma responses in both stimulations (target and simple light) at F₄ location. The grand average plots of ITC analysis of targets and simple light revealed that, in the early time-window (0–200 ms), target stimulation elicited greater gamma-phase locking than simple light stimulation. Furthermore, upon target

stimulation there are phase-locked components at 400 and 600 ms in addition to phase-locking at around 100 ms. Moreover, the frequency of phase-locked oscillations was shifted to frequencies higher than 40 Hz occurring in packets with a periodicity of 200 ms, indicating a superposition with the 5-Hz frequency band.

These results show that there are more than two phase-locked responses and that cognitive inputs trigger more phase-locked responses in comparison to simple light.

Accordingly, there are induced late responses as described by Başar-Eroğlu and Başar (1991) and Herrmann et al. (2004). However, the multiple window new results indicate that late responses can be also phase-locked responses, depending on modality of the stimulation and the recording site. In occipital recordings and upon light stimulation the late responses are only time locked as in Fig. 3B.

4.6. Grand average of time–frequency planes showing the inter-trial coherence of gamma responses in both stimulations (target and simple light) at F_4 and O_2 location

The post-hoc comparisons revealed that the difference between target and simple light stimulation was most pronounced at the right frontal electrode site; gamma phase-locking of right frontal (F_4) was significantly greater for target stimulation in comparison to simple light stimulation ($p < 0.0001$). There were no significant differences in gamma phase-locking to target stimulation than to simple light stimulation in occipital locations.

This shows that, most probably, more structures in the cortical association areas and the limbic system are adequately stimulated upon target in comparison to occipital location (primary sensory cortex) during an attention and working memory process.

4.6.1. Frontal locations

There were no significant differences between target and simple light stimulation for the 0–200 ms and 600–800 ms time windows, thus indicating that the difference between the cognitive stimulation and sensory stimulation is seen mostly in the 200–400 ms and 600–800 ms time windows.

4.6.2. Occipital locations

As seen in the figures, the target stimulation elicited higher phase-locking values than the simple light stimulation. However, this difference did not reach significant levels. There were no statistically significant differences between target stimulation versus simple light stimulation for occipital locations (Fig. 5).

4.7. What does P300–40 Hz responses say in multiple frequency windows? Tentative explanations

The manifold results in the three frequency bands and four time windows in different locations can yet be only tentatively discussed, but it is fruitful to start with this kind of interpretation. The analysis of the time course of EROs in Figs. 8, 9, and 10 must be extended under the light of results obtained by the ITC-method, which demonstrated the existence of four time windows depicting significant phase-locking results in 0–200 ms, 200–400 ms, 400–600 ms and 600–800 ms time windows, and also in light of the physiologic-anatomical flow chart in Fig. 10.

Further, an exact description of functional correlates can be only achieved after application of diverse sensory/cognitive paradigms and especially by gathering results on cognitive impairment. Our results extend the recent view by Başar (2013), who indicated multiple gamma band responses, extending the conventional view only with a second induced response. In the following, we describe a first tentative physiological interpretation for the identification (separation) of sensory and cognitive gamma responses in the response time window of 800 ms.

4.8. The light signal and the cognitive “attend command (target)” are transmitted through different pathways

The target stimulation of the oddball paradigm is a compound stimulation: It elicits a sensory response and a cognitive load including a working memory task. This target, in turn, induces an “attend” order.

- The EROs in the lower 25–30 Hz frequency range show higher phase locked p–p amplitudes in the first 50–150 ms both in occipital and frontal locations upon light. As to the occipital response, it is clear that the shorter segment of the visual pathway between the retina and primary visual cortex does not need a longer transmission time of 300 ms. The occipital gamma response in the first 100 ms does not correlate with the duration needed for cognitive processing through association areas and the limbic system. Therefore it can be considered to be the sensory gamma component.
- In frontal areas the simple light also evokes an ample response in the first 100 ms, which is possibly due to the first direct connection over the reticular formation. Possibly, this manifests a superposition of responses to pure light stimulation and the “attend” comment included in the target stimulation.
- The statement of Karakaş et al. (2000) attributing only a sensory component to the early response should be extended: In fact, the frontal gamma response in the first 200 ms contains a sensory response; however this response is most probably superimposed (or elicited in parallel with the light stimulation) with the “attend” response manifested as the most ample frontal target (cognitive) response. This view is supported by the fact that the ITC of Fig. 3A clearly shows that this early response is a compound response consisting of two oscillatory components.
- The post-hoc comparisons revealed that the difference between target and simple light stimulation was most pronounced at right frontal electrode site; gamma phase locking of right frontal (F_4) was significantly greater for target stimulation in comparison to simple light stimulation ($p < 0.0001$). There were no significant differences between target gamma response and simple light gamma response in occipital locations. These results support the working hypothesis that frontal areas are reached in responsiveness during attend (cognitive) stimulation, whereas the occipital areas being more directly stimulated over lateral geniculate nucleus are not highly responsive to attend input. The gamma response occurs immediately upon stimulations in all frequencies. Further, according to statistical results, the difference between the cognitive stimulation and sensory stimulation is seen mostly in the 200–400 ms and 600–800 ms time windows.
- All other evoked and event-related 40–48 Hz responses to parietal locations have a delay of approximately 150–200 ms. It is possible that the attend signal directly reaches the parietal lobes in that frequency band whereas, in lower frequency gamma bands, the signals reach the parietal lobes over longer paths and over frontal areas (see Fig. 10); in P_4 it is noteworthy that the target response at 40–48 Hz has no delay and occurs in the first 50 ms following the stimulation.

A visual inspection of ITC plots in Fig. 3A and B and the statistical analysis in Section 3 show that the phase-locking peak occurs with almost regular intervals of around 200 ms, which corresponds to a cycling of 5.7 Hz, i.e. theta frequency range.

4.9. Fundamental remarks on the complex gamma frequency window

4.9.1. Brain's complex gamma responses

As described in Section 4.2, upon visual/cognitive stimulation, the neural signals elicited in the retina are conveyed or transferred from the retina to the thalamus, primary sensory cortices, association areas of the cortex, and finally to the frontal cortex and parietal cortex by

means of three/four neuronal pathways. Different structures are excited along this complex pathway, with the transmission being impossible to describe exactly. However, Figs. 3 and 4 show that there are preferred time windows with distinct phase-locking intervals of gamma responses in spite of this great complexity.

As a preliminary work we have previously analyzed the ERSP and ITC of gamma response oscillations for five subjects (Başar, 2012). This study confirms the results of the previous study with an increased number of subjects and with an increased amount of analysis.

In summary:

- 1) There are at least three transfer lines from sensory receptors to the frontal cortex (Fig. 10): 1) Direct transmission over thalamus, 2) longer connections over reticular formation, 3) connection over limbic system. There are also reverse transmissions of signals and possible reverberations. There are approximately 3–4 sub-gamma band responses in 25–30 Hz, 30–35 Hz and 40–45 Hz frequency windows. Accordingly, cognitive responses need longer time courses or latencies and a higher number of discrete phase-lockings (the amount of time locked responses is increased in target responses in comparison to sensory evoked oscillations).
- 2) Comparison of Figs. 8, 9 and 10 shows that cognitive stimulation elicits late responses, usually with higher frequencies. These late responses cannot be considered as after discharges or prolongation of the early responses. Responses at 300 ms, 600 ms, and 800 ms have mostly shown higher frequency behavior, thus indicating possible activation of different sources along the complex pathway. However, the early time window is often a superposition of multiple frequencies including 45 Hz responses (compare Tallon/Bouhassira).
- 4) Late responses starting around 300 ms are probably responses that are conveyed over the reticular formation, hippocampus etc., whereas the early response in the primary occipital cortex O₁ starting at 100 ms is most probably the direct response over the short pathway over the lateral geniculate nucleus.
- 5) Possibly, there are reverberations during the sensory-cognitive pathways, thus being the causality of multiple frequency responses, especially between the limbic system and all association areas.
- 6) It appears that the event related oscillations in the gamma band undergo an increasing frequency modulation. The time course in the first 200 ms has lower frequencies of approximately 25–30 Hz. With increasing time, the frequency of oscillations reaches values up to 46 Hz.
However, this frequency modulation does not occur in an analog way; there are almost discrete frequency jumps with periodicities of around 10 Hz (in the beginning) and 5 Hz with progressing time longer than 300 ms following stimulation. Interplay or incorporation with alpha response and theta responses is possible (see the periodicities in Fig. 3 and 4).
- 7) The discrete oscillatory packages are separable or can be dissected by application of different stimulation modalities. These separations can be observed also by topographic changes. For example, simple visual stimulation triggers at the occipital cortex a 30 Hz oscillatory response at the first 200 ms upon stimulation. Other secondary or tertiary oscillatory responses were usually not recorded at the occipital cortex upon simple visual stimulation (Fig. 3B). On the contrary, cognitive inputs (target stimulation) elicit secondary and tertiary responses around 400 ms, 600 ms and sometimes also around 800 ms. These late oscillatory responses are probably due to longer signal transmission over the pathways described in Fig. 10.
- 8) The late gamma responses in the 400–800 ms time window are also often phase-locked responses. Few neural structures in the cortex or in the limbic system could be excited later following stimulation onset (say 600 ms), but react with strong phase-locked responses (manifested with high inter-trial coherences). The successive response firing in neural structures along different neural connections can be also the cause for the existence of different gamma

responses.

- 9) It will be not simple to exactly describe the correlations of responses in cortical areas and time courses of phase-locking processes. This type of analysis will most probably be very important for the understanding of electrophysiology in cognitive impairment.

5. Concluding highlights

According to Başar (2013), it is presently extremely difficult to establish a reliable general theory of gamma from the various results, models, and hypotheses. Accordingly, we propose that it would be more reasonable to present highlights, results, and exclusion principles from the results with the aim of excluding somewhat controversial trends, at least in order to avoid errors in describing functionality.

- 1) In the present report we described globally separated sensory and cognitive responses. More precise statements related to specific functions can be performed by modification of the function related to stimulus in the future. It is almost imperative to use a pure sensory stimulation (with the same luminance or sound level) as a baseline to separate sensory components from more complex functional responses.
- 2) There are at least 3–4 phase/time-locked gamma responses in the frequency window of 25–45 Hz. Phase-locking analysis confirms our earlier results related to gamma cognitive responses at 300 ms following omitted stimuli in the cat hippocampus and human scalp recordings (see Fig. 11). Therefore, for optimal determination of functional correlated gamma, the analysis should be performed in the computed (per spectral analysis) separate windows. Otherwise controversial or erroneous statements are to be expected.
- 3) In most cases, cognitive responses are late; moreover, they depict higher frequencies. The analysis of Figs. 8, 9, and 10 show that there are two frequency responses in the first 200 ms. ITC or ERPS plots cannot show this fact in a clear manner. Accordingly, time frames in different frequency windows should be compared to ITC. Several superimposed gamma responses with various frequencies in the first 200 ms can be recorded. Without this joint analysis, it is not possible to perform a reliable analysis of functional correlates in the gamma band.
- 4) Gamma oscillations in the first 200 ms time window depict superposition of at least two frequency components. It is necessary to discuss the neuroanatomy and possible flow of neural impulses to understand functional correlates: sensory order or cognitive order.
- 5) The multiple gamma component analysis by interpretation of conventional event-related spectra, EROs in separate time frames and ITC may open a major new avenue for understanding of functional correlates. This strategy is time consuming, but it opens a serious possibility for eliminating controversies and better approaching functional correlates of gamma responses.
- 6) In earlier conclusions, Başar (1980, 1999) and Başar-Eroglu et al. (1996a, 1996b) used the expression *universal operator* for gamma activity. Further, gamma is induced by different stimuli or tasks and is related to several cognitive functions. Fries (2009) stated that neuronal gamma-band synchronization is found in many cortical areas. According to Fries, it appears as if many different gamma-band synchronization phenomena sub-serve many different functions. Thus, this author also argues that gamma-band synchronization is a fundamental process that sub-serves an elementary operation of cortical computation, which is in accordance with the findings of Başar (1980, 1998, 1999). However, Başar (2006) indicated that gamma band synchronization was also measured in many sub-cortical areas due to many cognitive processing strategies during whole-brain operation.

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