

## P50 potential-associated gamma band activity: Modulation by distraction

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We aimed to evaluate the effect of changing attentional demands towards stimulation in healthy subjects on P50 potential-related high-frequency beta and gamma oscillatory responses, P50 and N100 peak amplitudes and their gating measures. There are no data showing effect of attention on P50 potential-related beta and gamma oscillatory responses and previous results of attention effects on P50 and N100 amplitudes and gating measures are inconclusive. Nevertheless the variation in the level of attention may be a source of variance in the recordings as well as it may provide additional information about the pathology under study. Nine healthy volunteers participated in the study. A standard paired stimuli auditory P50 potential paradigm was applied. Four stimulation conditions were selected: focused attention (stimuli pair counting), unfocused attention (sitting with open eyes), easy distraction (reading a magazine article), and difficult distraction (searching for Landolt rings with appropriate gap orientation). Time-frequency responses to both S1 and S2 were evaluated in slow beta (13–16 Hz, 45–175 ms window); fast beta (20–30 Hz, 45–105 ms window) and gamma (32–46 Hz, 45–65 ms window) ranges. P50 and N100 peak amplitudes in response to both S1 and S2 and their ratio were evaluated. The phase-locked P50 potential-associated gamma activity was attenuated during distraction tasks as compared to focused attention and an unfocused attention condition. The amplitudes and gating measures of P50 and N100 waves and beta activity were not sensitive to the competing distraction task performance. The use of a distraction task is not favorable when phase-locked gamma range activity is a key interest in auditory potential studies.

Key words: P50, N100, gamma band activity, auditory, attention, multi-way matrix factorization

One of the most frequently investigated auditory evoked potentials – P50 potential – is widely applied in research practice. In the P50 testing paradigm, P50, N100, and P200 are distinguished components that serve different functions (Lijffijt et al. 2009a,b). In the time-frequency domain the major contributors to auditory P50 ERP responses appear to be in the gamma (35–45 Hz) and beta (13–30 Hz) frequency range (Haenschel et al. 2000). Both P50 and N100 are of clinical value as these waves and their gating measures are known to be affected in diseased state (Boutros et al. 1993, Erwin et al. 1998, Ghisolfi et al. 2004, 2006b,

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Received 12 December 2011, accepted 07 February 2012

Cancelli et al. 2006, Grootens et al. 2008, Brenner et al. 2009, Lijffijt et al. 2009a), by medication or chemical compounds (Light et al. 1999, Ghisolfi et al. 2002, 2006a, Hong et al. 2009, Knott et al. 2009) and by the level of arousal (Griskova-Bulanova et al. 2011a, Woods et al. 2011). The relationship between the P50-related gamma and beta oscillations and psychopathology of several disorders with impaired P50 gating has also been shown (Clementz and Blumenfeld 2001, Muller et al. 2001, Hong et al. 2004). Importantly, P50 recording conditions differ substantially by the level of attention/ distraction to the stimulation-starting with competing task performance and ending with paying direct attention to stimulation. Whereas effects of factors such as attention and psychological stressors on amplitudes and gating of the P50 and N100 have been previously examined in a number of studies in healthy subjects (Jerger et al. 1992, Guterman and Josiassen 1994, White and Yee 1997, Kho et al. 2003, Wan et al. 2008), results are inconclusive. Lijffijt and coauthors (2009c) and Wan and others (2008) showed that P50 and N100 gating are associated with attention-related processes, as assessed by different attention-related tasks (Wan et al. 2008, Liffijt et al. 2009c). Others showed that attention either had no effect (Jerger et al. 1992, White and Yee 1997), or a relatively small effect (Guterman and Josiassen 1994, Kho et al. 2003) on P50 amplitudes and gating. Likewise, N100 has been shown to have increased amplitude under selective attention in some studies (White and Yee 1997, Rosburg et al. 2009), while others report a lack of difference of N100 amplitude when attention level was manipulated (Lavoie et al. 2008). Attention effects on the P50-related oscillations has only been addressed in one study up to date, showing that attention increased only very low frequency (<3 Hz) event-related neocortical activity (Rosburg et al. 2009). Thus, it is interesting to investigate further how attention modulates P50-related oscillations.

The aim of the current study was to investigate the effect of different demands on attention towards auditory stimulation on P50 potential-related high-frequency beta and gamma oscillatory responses. We focused on early stimulus-locked activity as this is closest to stimulus-locked time-domain averaged waveforms and the measure of phase-locking index as it is the least sensitive to the noise (Kalcher and Pfurtscheller 1995, Klimesch et al. 1998, Griskova et al. 2007, 2009). Additionally, we aimed to assess attention modulation effects on P50 and N100 waveforms and their gating.

Nine healthy subjects (six females) were included into the study. Written informed consent was obtained, as approved by the Ethics Committee of the hospital. The mean age of the sample was 22.6 years [standard deviation (SD) 1.5].

Sixty stimulus pairs (500 ms between stimuli) were presented with inter-trial interval of 10 s. Tones were identical clicks of 3 ms duration delivered binaurally at peak SPL of 100 dB. One stimulation trial lasted about 8 minutes.

The experiment was designed to achieve modulation in attentional load (Griskova-Bulanova et al. 2011b). Four tasks that differed by the level of attentional demands towards stimulation were selected: counting of stimuli pairs, sitting with open eyes fixated at the cross in front of the subject, reading an article (enquiry after the run), performing a task – searching for Landot rings with appropriate orientation on the sheet of printed paper. The order of tasks was randomly counterbalanced across the subjects. Counting condition was referred to as "focused attention" with direct attention paid to auditory stimuli; sitting with open eyes fixated was referred to as "unfocused attention" condition as no specific attentional efforts were asked for; reading and performing a searching task were assigned as "easy distraction" and "difficult distraction" these conditions implied low attention to stimulation as the subjects were absorbed in the distraction task. The level of attention paid to auditory stimulation was diminishing in the following way: (1) "focused attention", (2) "unfocused attention", (3) "easy distraction", (4) "difficult distraction".

The ERPs were recorded with Galileo Mizar EEG device (EBNeuro, Italy) (passband 0.1-760 Hz) from F3, Fz, F4, C3, Cz, C4, and Pz sites (according to the 10/20 International system) using Ag/AgCl electrodes. Ear electrodes served as a reference for all electrodes and the ground electrode was attached to the forehead. Data was recorded at 512 Hz.

Off-line processing was performed in EEGLAB and ERPWAVELAB for MatLab<sup>©</sup> (Delorme and Makeig 2004, Griskova et al. 2007). Evoked potentials from Fz electrode for all conditions were created as follows: EEGs were cut into epochs from -100 to +400 ms separately for S1 and S2. Baseline correction was performed on -100 to 0 ms prior stimuli. Artifact rejection threshold was set at 70 µV. P50 and N100 components were identified blindly to the condition. For P50 peak measurements data was filtered at 10-50 Hz: P50 was the positive deflection at 40–80 ms. For the N100, data was low-pass filtered at 50 Hz and the peak was defined as the negative deflection at 60-170 ms. The amplitudes were measured from baseline to minimize the contribution of the preceding peak. Decrement of the amplitude from S1 to S2 was computed as S2/S1 ratio. Grand averaged evoked potentials for both conditions were created from 500 epochs.

Wavelet transformation (WT; complex Morlet wavelet from MatLab® Wavelet Toolbox; frequencies represented from 10 to 80 Hz, 1 Hz intervals between each frequency) was performed. Phase locking index (PLI), that is best conceptualized as phase precision or synchronization of the evoked oscillations from trial to trial ranging from 0 (random phase) to 1 (nearly identical phase) was selected as the measure of interest (Morup

Table I

Means and standard deviations of peak amplitudes and gating measures

	Focused attention		Unfocused attention		Easy distraction		Difficult distraction	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
P50								
<b>S</b> 1	1.65	0.75	1.78	0.52	1.87	0.89	1.26	0.62
S2	1.21	0.85	1.27	0.64	1.39	0.79	1.03	0.62
S2/S1	0.69	0.27	0.71	0.33	0.76	0.32	0.82	0.33
N100								
S1	-7.29	2.53	-8.71	3.92	-7.87	4.01	-5.29	4.55
S2	-3.17	2.74	-2.70	2.69	-2.85	2.17	-2.82	2.78
S2/S1	0.57	0.72	0.46	0.60	0.38	0.22	0.92	1.09

(SD) standard deviation; (S1) first stimulus of the pair; (S2) second stimulus of the pair; (S2/S1) gating measured as the ratio of the amplitudes S2 to S1

et al. 2006). Individual time-frequency representations of phase locking index across nine channels were created and then decomposed through non-negative multiway factorization (NMWF) to obtain topographical signature that best describes the activity of interest and to quantify how the measure varies with experimental manipulation for all the subjects in all conditions (Morup et al. 2006, Griskova et al. 2007). This has proven being useful in the analysis of wavelet transformed event-related potentials (Arnfred et al. 2007, 2008). Prior to NMWF analysis, random phase synchronization activity, estimated by calculating the mean of an artificially generated random samples, was extracted (Morup et al. 2006) and baseline correction was performed based on -100 ms prior to stimuli. The primer window for mathematical decomposition of ERPs was set at 10-80 Hz and -100 to +400 and based on grand averaged TF plots activity of interest was defined for three frequency bands: slow beta (13–16 Hz, 45-175 ms window); fast beta (20-30 Hz, 45-105 ms window) and gamma (32-46 Hz, 45-65 ms window).

Obtained peak amplitudes and PLI measures were subjected to repeated measures ANOVA (r. m. ANOVA) separately to evaluate the effects of stimulus, task and their interaction. Gating of P50 and N100 were evaluated in univariate ANOVA for effect of task. *Post hoc* analyzes were performed using Least Significant Difference (LSD) test. Bivariate Pearson correlation

analysis was performed for amplitude and PLI measures.

Decomposition of the PLI distinguished the following time-frequency components: a slow beta component (peaking at 13 Hz, 111 ms and maximal over Fz), a fast beta (peaking at 26 Hz, 75 ms and maximal over Fz) and a gamma component (peaking at 36 Hz, 56 ms, maximal over Fz electrode). The grand averaged time-frequency plots of PLI at Fz site of all conditions for both S1 and S2 are given in Figure 1B.

R.m. ANOVA revealed significant effect of stimulus for slow beta ( $F_{1,8}$ =5.857, P=0.04), fast beta ( $F_{1,8}$ =22.053, P=0.002) and gamma ( $F_{1.8}=9.075$ , P=0.02) activities, pointing to lower PLI values in response to S2. No effect of task and interaction of the factors occurred for both slow beta and fast beta. The effect of task had significant impact on gamma activity ( $F_{3,6}$ =12.969, P=0.005). Stronger phase locking was observed during unfocused attention as compared to both easy distraction task (P=0.004) and difficult distraction task (P=0.001), while no difference was observed between unfocused and focused attention. Higher PLI values were obtained during focused attention (P=0.003) and easy distraction (P=0.02) as contrasted to the difficult distraction task. Although the interaction of stimulus and task factors was non-significant, separate analyses for S1 and S2 were made for illustration purpose. Univariate ANOVA indicated significant task effect

separately for S1 gamma PLI ( $F_{3,36}$ =3.259, P=0.034) and for S2 gamma PLI ( $F_{3,36}$ =4.175, P=0.013). Post hoc testing indicated that during difficult distraction task S1 gamma PLI was lower as compared to focused attention (P=0.033) and to unfocused attention conditions (P=0.006). S2 gamma PLI was significantly higher in unfocused attention condition as contrasted to easy distraction (P=0.025) and difficult distraction (P=0.002) tasks, and nearly significantly higher in comparison to unfocused attention condition (P=0.067). Means and SDs of gamma band PLI are given in Figure 1C.

Grand averaged ERPs from Fz site are given in Figure 1A. Significant effect of stimulus was obtained for both P50 ( $F_{1.8}$ =35.544, P<0.001) and N100 ( $F_{1.8}$ =13.063, P=0.007) amplitudes, pointing to lower amplitudes in response to S2. The task had no effect on P50 ( $F_{3.6}$ =0.784, P>0.05) and N100 ( $F_{3.6}$ =0.667, P>0.05) amplitudes, as well as on gating of both P50 ( $F_{3.36}$ =0.279, P>0.05) and N100 ( $F_{3.36}$ =0.962, P>0.05). Means and SDs of P50, N100 and their gating are presented in Table I. We failed to show any correlation between PLI of time-frequency components and peak measures.

We showed that P50 potential-associated gamma activity is attenuated during distraction task performance. We did not find any effects of attention manipulation on P50 and N100 amplitudes, P50 and N100 gating or beta frequency range activity.

Presently, we showed that gamma component in response to S1 and S2 is larger during unfocused attention condition than during distraction tasks. Although there is evidence that gamma ativity increases with selective attention (Tiitinen et al. 1993, Gurtubay et al. 2001), in the study by Rosburg and coworkers (2009) attention-related task effects on phase-locked activity were limited to low frequency components. Nevertheless, our results are in line with the observation of Kallai and colleagues (2003), who showed that evoked 40-Hz response to auditory stimuli was more prominent while subjects were lying awake in bed than while they were sitting and reading. Moreover, recently we showed the similar pattern of modulation by attenttion for steadystate response associated gamma band activity: the evoked gamma activity was attenuated during reading and performing a searching task, while there were no differences between attention to stimulation and no task conditions (Griskova-Bulanova et al. 2011b).

Recently, gamma band activity was shown to be seriously confounded by saccades (Yuval-Greenberg et al. 2008, Yuval-Greenberg and Deouell 2009).

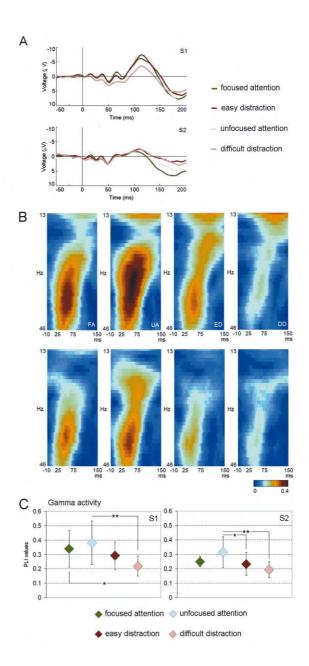


Fig. 1. (A) Grand averaged evoked potentials from focused attention, unfocused attention, easy distraction and difficult distraction conditions. Each potential is an average of 500 epochs.

(B) Time-frequency plots of phase locking index from Fz site for focused attention (FA), unfocused attention (UA), easy distraction (ED) and difficult distraction (DD) conditions in response to S1 (upper row) and in response to S2 (lower row). (C) Means and SDs of phase locking index for gamma band activity in focused attention, unfocused attention, easy distraction and difficult distraction conditions for S1 and S2. \* P<0.05, \*\* P<0.01.

However, this was true for the late induced gamma responses and not for the early evoked gamma (Yuval-Greenberg et al. 2008, Yuval-Greenberg and Deouell 2009) that was analyzed in the current study. Moreover, in our study the largest gamma activity was observed during the task that produced least saccades (in contrast to reading and searching tasks). Thus, it is not likely that the observed pattern of P50-related gamma modulation can be affected by saccades.

The observed pattern of attention modulation could be the result of at least two processes. First, lower gamma phase precision during the distraction task could reflect a sensory cortical inhibition to promote stimulus-unrelated task performance. This interpretation is based on the assumption that the strong attention focus required by a difficult visual task does not allow subjects to process the irrelevant auditory input; whereas during no task, attention resources are available for this purpose (Muller-Gass et al. 2006, Wronka et al. 2007). Secondly, the high level of phase synchronized gamma activity during unfocused attention condition could be a manifestation of increased focal cortical activity due to induced shifts of involuntary attention. This could be substantiated by the fact that the gamma phase synchronization did not differ between focused attention and unfocused attention conditions and gamma activity is known to increase with selective attention (Tiitinen et al. 1993, Gurtubay et al. 2001). Also, most notably, during the condition in which subjects were not required to perform any specific task, their attention might have been focused on their thoughts (instead of re-directed to the to-be ignored auditory stimuli) (Muller-Gass et al. 2005).

Previously, increased stimulus saliency as manipulated by ISI (Kisley and Cornwell 2006) and/or expectancy (Clementz et al. 2002) has been associated with increased beta activity in healthy controls and thus beta along with gamma was considered a candidate for modulation by attention-related demands. However, we did not find any modulation of beta by changing the level of attention demands. The lack of beta activity modulation is in line with our earlier observations on beta frequency range steady-state responses (20 Hz), that were not affected by the task (Griskova-Bulanova et al. 2011b).

Based on previous reports, we expected N100 to be largest in focused attention condition, when attention was paid to the stimulation (White and Yee 1997, Kho et al. 2003, Gjini et al. 2011). However, we failed to

show any significant effect of attention modulation on N100 response either to S1 or to S2. Although the N100 data could be assumed to assist in interpreting whether attention was successfully manipulated or not, our result is in line with the study of Lavoie and coauthors (2008). They compared several experimental conditions, including focused attention condition and distraction tasks and did not observe the largest N100 during the focused attention (Lavoie et al. 2008). Neither did they find any effect of their distraction tasks (reading or watching a movie) on the amplitudes of any ERP component as compared to counting and sitting without any task with eyes open. Their explanation was that the counting task was the most boring part of the experiment causing the subjects' interest and alertness to drift. This might also be the case in our experiment as the subjects counted tone pairs delivered in a regular order. The task did not require much concentration or cognitive activation (Lavoie et al. 2008). Lawrence and Barry (2009) also did not observe N100 increment when their subjects were counting auditory stimuli and considered this observation to be a supportive of the general notion of the N100 as an index of stimulus registration or stimulus detection.

There are several reports pointing to a significant modulation of P50 response by attention. Guterman and Jossiasen (1994) reported reduced P50 gating when subjects were instructed to pay attention to the stimuli. In the study by Gjini and others (2011) P50 amplitudes to S1 were significantly increased by auditory attention to S1. Kho and colleagues (2003) showed that both P50 S1 and S2 were higher in the attend condition, whereas distraction had no effect on P50. Nevertheless, the lack of attentional modulation on P50 component has also been shown before (Jerger et al. 1992, White and Yee 1997, Rosburg et al. 2009). The reasons for the variable results reported in the literature are unknown. It seems that attention effects are highly task-dependent and study sample-sensitive and additional studies are necessary to uncover a solid relationship.

The main limitation of the current study is the small number of participants. It might be that some potential attention effect on any of the measures was missed. However, it is shown for the first time that phase-locked P50 potential-associated gamma activity is modulated by the distraction tasks.

The phase-locked P50 potential-associated gamma activity is attenuated during distraction tasks as compared to focused attention and an unfocused attention

condition. The amplitudes and gating measures of P50 and N100 waves and beta range activity were not sensitive to the competing distraction task performance in the current study. The use of a distraction task is not favorable when phase-locked gamma range activity is a key interest in auditory potential studies. It might be valuable in future studies to examine the difference between distraction and the unfocused condition in certain neuropsychiatric populations, i.e. attention deficit/hyperactivity disorder.

We would like to thank all the participants of the study. We also thank Ignat Iljinych and Jevgenij Paskevic for the help with data collection.

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