

**Cognitive Network Interactions and Beta 2 Coherence in Processing Non-Target Stimuli in Visual Oddball Task**

M. Kukleta<sup>1,3</sup>, M. Brázdil<sup>2</sup>, R. Roman<sup>1</sup>, P. Bob<sup>1,3</sup>, I. Rektor<sup>2</sup>

<sup>1</sup>Department of Physiology and <sup>2</sup>First Department of Neurology, Medical Faculty, Masaryk University, Brno,

<sup>3</sup>Department of Psychiatry, First Medical Faculty, Charles University, Prague, Czech Republic,

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Processing Non-Target Oddball Stimuli

Corresponding author:

M.Kukleta, Department of Physiology, Komenskeho 2, 66243 Brno, Czech Republic

Tel. 00420 549495117

E-mail: [mkukleta@med.muni.cz](mailto:mkukleta@med.muni.cz)

## Summary

Spatiotemporal dynamics of event-related potentials (ERP) evoked by non-target stimuli in a visual oddball experiment and the presence of coherent oscillations in beta 2 frequency band of decomposed EEG records from peristimulus period were investigated by means of intracranial electrodes in humans. Twenty-one patients with medically intractable epilepsy participated in the study. The EEG signal was recorded using platinum electrodes implanted in several cortical and subcortical sites. Averaged 2s EEG records were analysed. Task-specific EEG changes were found in each patient; ERPs were derived from 92 electrodes used (96% of possible cases). In the majority of analysed cases, ERPs were composed of several distinct components, and their duration was mostly longer than 1 s. The mean onset of the first ERP component was  $158 \pm 132$  ms after the stimulus (median 112 ms, minimum value 42 ms, maximum value 755 ms), and large variability of these onset times was found in all the investigated structures. Possible coherence between neural activities of remote brain sites was investigated by calculating running correlations between pairs of decomposed EEG records (alpha, beta 1, beta 2 frequency bands were used; total number of correlated pairs was 662 in each frequency band). The record pairs exhibiting highly correlated time segments represented 23% of all the investigated pairs in alpha band, 7% in beta 1 band, and 59% in beta 2 band. In investigated 2s record windows, such segments were distributed evenly, i.e. they were also found before the stimulus onset. In conclusion, the results have implicated the idea that a lot of recorded ERPs was more or less by-products of chance in spreading a signal within the neuronal network, and that their functional relevance was somewhat linked with the phenomenon of activity synchronization.

**Key words:** Intra-cerebral EEG recording in humans; event-related potential; oddball task; beta coherence; binding in cognition.

## Introduction

In the cognitive brain research, the registration of event-related potentials (ERPs) continues to be a widely used method. Especially P3 wave, first described by Sutton and coworkers in 1965, has been attracting researchers' attention for decades. In the oddball experimental task used mostly for eliciting P3 wave, two kinds of stimuli are presented – rare, target ones signalling that the instructed response ought to follow, and frequent, non-target ones that are given no significance in the experiment. The P3 latency ranges from 250 to 600 ms after the stimulus onset, and this variability was shown to depend on the stimulus modality, task complexity and subject (Mertens and Polich, 1997; Comerchero and Polich, 1998). Other data indicate that this latency is sensitive to the response processing time. More generally, the P3 latency is positively correlated with the time required to identify the category membership of the stimulus, indicating that the processes associated with this waveform are subsequent to and contingent upon the stimulus identification (Kutas et al., 1977; McCarthy and Donchin, 1983; Verleger, 1997). A study of intracerebrally recorded P3 waves in the medial temporal lobe structures of epileptic patients demonstrated that besides simple auditory, somatic, and visual stimuli the task-dependent potentials were also reliably elicited by exemplars of semantic categories and by the stimulus omission (McCarthy et al., 1989). The finding of intracerebral P3-like waveforms, which were time-locked to the motor response, also suggested its linkage to the processes of response execution (Roman et al., 2005). In psychological terms, several explanations of P3 were proposed. The P3 waveform was mostly viewed as reflecting decision or cognitive closure of the stimulus identification; it has been also linked to orientation, attention mechanisms, and context updating (Squires et al., 1975; Desmet, 1980; Donchin, 1981; Verleger, 1988). The cited and numerous other studies using scalp EEG, intra-cerebral EEG, and MEG have shown that the ERP to a target stimulus (including its prominent component P3) is a complicated phenomenon involving many areas of the brain in space and time and a number of mental operations, which has not yet been delineated unequivocally.

The present study analyses intra-cerebrally recorded ERPs elicited in a visual oddball experiment by frequent, non-target stimuli. In relevant literature these responses were mostly taken as reference data and were given deeper research attention in a few occasions only (Ritter et al., 1983; Lovrich et al., 1986). Following the study of Garcia-Larrea and collaborators (1992), several attempts appeared to use non-target ERPs

in clinical examinations of attention deficits (Amenedo and Diaz, 1998; Brown et al., 2002; Higashima et al., 2004). Our present attempt to investigate non-target ERPs as electrophysiological correlates of a simple cognitive task, was based on the following reasoning. The correct response to a non-target stimulus in the oddball experimental setting necessitates the detection of a stimulus, decoding its significance, and deciding “what to do” in the condition determined by the stimulus meaning. It essentially implicates that from the point of view of signal processing related to cognitive discrimination there is not a qualitative difference between target and non-target stimuli. Apparently, both stimuli have received significance before the experiment as a part of the experimental instruction. Encoded significances after instruction had been stored in verbally mediated working memory and recognized after the stimulus presentation in the course of the experiment. The instructed behavior, i.e. doing nothing, is then the final step of the trial. One undeniable advantage of this methodical approach in research of cognition relies on the fact that obtained data predominantly reflect the cognitive process as such and are not contaminated by efferent actions linked with overt behavioral response. Another advantage is a greater number of available responses (five-times greater in our case), which allows calculating the average curves with a more favorable signal/noise ratio. Further advantage is also a simpler experimental design, which does not mean any loss with respect to the methodical demands on a cognitive task.

The character of the study presented is explorative. Its aim was to investigate spatiotemporal dynamics of responses evoked by non-target stimuli, to describe their configuration, and to look for the presence of coherent oscillations in beta 2 frequency bands of decomposed EEG records during periods of the stimulus presentation, which are supposed to represent one of mechanisms underlying conscious awareness.

## **Methods**

### **Subjects**

Twenty-one patients (15 males, 6 females; aged 19 - 47 years; mean 28.6 years; all with medically intractable epilepsies; 1 left-handed) participated in the study. Standard MicroDeep semi-flexible electrodes (DIXI) with the diameter of 0.8 mm, length of each contact 2 mm, and inter-contact intervals of 1.5 mm were used for invasive EEG monitoring. Orthogonal depth electrodes were implanted in the frontal, temporal,

and/or parietal lobes using the methodology by Talairach et al. (1967) with the aim to localize the seizure origin prior to surgical treatment. In 7 patients, additional diagonal electrodes were inserted stereotactically into the amygdalo-hippocampal complex (via frontal approach, passing through the basal ganglia in 6 patients, via occipital approach in 1 patient). The electrodes were placed bilaterally in 14 patients and unilaterally in 7 patients (details are presented in Table 1). Contacts at the electrode (5-15) were always numbered from the medial to lateral sites. Their positions were indicated in relation to the axes defined by Talairach system using the 'x, z, y' format where 'x' is lateral, millimeters to midline, positive right hemisphere, 'y' is antero-posterior, millimeters to the AC (anterior commissure) line, positive anterior, and 'z' is vertical, millimeters to the AC/PC (posterior commissure) line, positive up. The exact positions of electrodes and their contacts in the brain were verified using post-placement magnetic resonance imaging (MRI) with electrodes in situ. The recordings from lesional structures and epileptogenic zones were not included into the analysis. No patient from the group examined has had bilateral hippocampal sclerosis or bilateral temporal lobe epilepsy. All the patients had normal or corrected-to-normal vision. Informed consent was obtained from each patient prior to the experiment, and the study received an approval from the Ethical Committee of Masaryk University.

## Procedure

The patients were seated comfortably in a moderately lighted room with a monitor screen positioned approximately 100 cm in front of their eyes. During the examination they were asked to focus their gaze continuously on the point in the centre of the monitor screen and to respond, as quickly as possible, to a target stimulus (yellow letter X on the white background) by pressing a micro-switch button in the dominant hand and counting the number of these stimuli in their heads, and to ignore frequent stimuli (yellow letter O on the white background). Both stimuli were displayed on the black screen, subtended at the visual angle of 3°. Their duration was 200 ms. The minimal number of presented stimuli was 245 (median 310). The inter-stimulus intervals varied randomly between 2 and 5 s, the ratio of target to frequent stimuli was 1:5.

## EEG recording

The EEG signal was recorded simultaneously from various intra-cerebral structures using 64 channel Brain Quick EEG system (Micromed). All the recordings were monopolar with respect to a reference electrode placed on the right processus mastoideus in all the cases. EEGs were amplified with the bandwidth of 0.1 – 40 Hz at the sampling rate of 128 Hz. Further processing was performed with artifact-free EEG periods (selection was based on the visual inspection of the periods by an experienced person). EEG periods of 2 s were averaged off-line using the stimulus onset as the trigger (-500 and +1500 ms from the stimulus onset). ScopeWin software was used for the signal analysis, which included up to 44 channels recorded simultaneously.

## Data analysis

Responses to frequent stimuli occurring in series after the target ones were analysed only. In each series, the first two responses were excluded so that the responses to the third, fourth, and next ones, if any, were used for creating the average curves. The potential change after the stimulus has been considered as an ERP if its amplitude was greater than the twofold of the maximal potential change seen in the period prior to the stimulus onset. The agreement of two independent observers was necessary for including the data into analysis. One ERP from an electrode or two ERPs derived from remote contacts of an electrode were taken for the analysis only. As a rule, the largest response from similar ones was selected.

In looking for synchronous oscillations between remote brain sites, the frequency decomposition and running correlation techniques were used. At first, the whole-band EEG records from the whole experiment were decomposed into three frequency bands (alpha=8-12 Hz; beta 1=12-25 Hz; beta 2=25-35 Hz) via digital bandpass filters. The procedure comprised the spectrum computation using Fast Fourier Transformation, zeroing all the spectral components outside the selected frequency interval, and inverse complex Fast Fourier Transformation computation. Then the 2s periods were averaged off-line using non-target stimuli as the trigger and correlation coefficients were calculated in pairs of these averages. The length of a sliding window in the computation of running correlations was 30 points (234 ms) in the case of alpha

and beta 1 frequency bands, and 12 points (94 ms) in the case of beta 2 frequency band. The brain sites, from which ERPs have been obtained, were investigated only. The main steps of the procedure are illustrated in Figure 1.

## **Results**

### Data about the task performance

Lacking a control condition, the analysis of error responses to both target and non- target stimuli was taken as the demonstration that patients really processed non-target stimuli according to the experimental instructions. With the exception of two patients (percentage of their error responses were 9.2% and 7.5 %, respectively), the task performance was good. Taken across the remaining 19 patients, the mean percentage of errors was  $1.1 \pm 1.1$ . Considering the total number of stimuli presented (median 310, minimum 245 and maximum 397), this result was taken as sufficient evidence of the patient's active participation in the experiment. Two patients with high number of error responses were not included into the study.

### Configuration and onset time of event-related potentials elicited by non-target oddball stimuli

The mean number of averaged records in one patient was 89 (median 88, maximum 128 and minimum 56). Task-specific EEG changes elicited by the presentation of non-target stimuli were found in each patient; the ERPs were derived from 92 electrodes used (96% of possible cases). There was no obvious lateralization in their incidence. The ERPs from 144 sites located in various brain structures were taken into analysis of their configuration and onset time (see Table 2). In the majority of cases, these ERPs were composed of several distinct components and their duration was mostly longer than 1 s. Each of these ERPs was found to be the original, no identical ERPs were revealed (we used the number of components, their polarity and time parameters in the detailed comparison of these ERPs).

Fig. 2 presents examples of these ERPs. In 47 of these ERPs, the signs of local generation of activity (the phase inversion or substantial decrease of amplitude in neighboring electrode sites) were observed in all the investigated structures except for basal ganglia. The beginning of evoked activity, i.e. the onset of the first ERP component, was  $158 \pm 132$  ms after the stimulus onset (median 112 ms, minimum value 42 ms, maximum value 755 ms). As evident from the data presented in Table 2, a large variability of these onset times was found in all the investigated structures.

#### Synchronization of oscillations of EEG activity recorded in remote cortical and subcortical areas

A possible coherence between neural activities of remote brain sites was investigated in 662 record pairs. In single patients, the number of correlated pairs varied according to the number of ERPs available (1-17 ERPs) from 0 to 136 pairs (median 21 pairs). The number of pairs exhibiting time segments with correlation coefficient higher than 0.95 (hc pairs; hc segments) represented 23% of all the investigated pairs in alpha band, 7% in beta 1 band, and 59% in beta 2 band. Statistical significance of these differences was ascertained by t-test for dependent samples ( $p < 0.007$  for the alpha/beta 1 difference;  $p < 0.030$  for the alpha/beta 2 difference;  $p < 0.014$  for the beta 1/beta 2 difference). The data presented in Table 3 show that the periods of highly synchronous EEG activity in beta 2 band were demonstrated between almost all the investigated brain sites. The relationship between level of coherence in beta 2 band and stimulus onset was investigated in 241 pairs, which were created from records from frontal and temporal sites. The hc segments were distributed within the evaluated record window evenly; no relationship between their location and the stimulus was obvious. Mean number of hc segments was  $0.7 \pm 1.0$  (max 4, min 0) in the 1s pre-stimulus epoch and  $0.7 \pm 1.0$  (max 5, min 0) in the 1s post-stimulus epoch ( $p > 0.43$ ; t-test for dependent samples). On the other hand, mean correlation coefficient was significantly higher in 1s post-stimulus epoch as compared with 1s pre-stimulus epoch ( $0.26 \pm 0.28$  and  $0.32 \pm 0.29$  respectively;  $p < 0.0004$ ; t-test for dependent samples).



## Discussion

The main results of the study are as follows:

1. Experimental task, which consisted in detecting a stimulus, decoding its significance and deciding “what to do” in the conditions determined by the stimulus meaning, evoked an undoubted event-related EEG response in almost all the investigated cortical and subcortical sites.
2. In the great majority of evaluated cases, the ERP was complex, relatively long-lasting, and unique in its configuration.
3. In all the investigated structures, the short-, middle- and long-latency ERPs were demonstrated.
4. Nearly perfect synchronization of segments on filtered EEG records from various remote sites was demonstrated in the 2s recording windows, which covered pre- and post-stimulus epochs (in approximately 60% of analysed record pairs in the beta 2 frequency band).

A starting point for the interpretation of obtained results is the statement that they describe the activity of high level neural network in executing a simple cognitive task or, more precisely, the activity during the comparison of a detected stimulus with memorized verbal instruction about its meaning and, based on the result of this comparison, in refraining from overt response. For this reason, the first problem to be addressed at this moment is the apparent lack of evidence that non-target stimuli really induced expected cognitive activity. The half of the question is easy to answer. The evaluation of any stimulus is obligatory; there are no a priori neutral stimuli. The remaining part of the question could be overcome by analysing error responses of patients collected during the experiment. In fact, the visible correct responding to target stimulus would not be possible without correct recognition of preceding non-target ones. As shown in results, the performance of our subjects was good; except for two patients, who were not included into the study, the mean number of all error responses was 1%.

Once the cognitive character of responding to non-target stimuli is accepted, the results can be considered within the framework of the long-lasting dispute between two opposing views on the relationship between the brain and cognitive functions. According to the first view, specific parts of the cerebral cortex are dedicated to specific functions, while the second one emphasizes that cerebral structures take part in all higher functions as a whole. The communication between neural constituents of the network rely preferentially on the precise connectivity (the

labelled line code) in the first case, and on the synchronization of activity between remote neuronal assemblies (the so-called neuronal assembly coding) in the second case. The results of the present study have demonstrated evoked electrophysiological activity within vast cortical and subcortical areas, which varied greatly in the onset and time course. This finding represents a strong argument in favor of the second view on the brain-cognition relationship. The lack of uniformity of the whole-band EEG responses evoked by a uniform and many times repeated elementary task can be understood as a manifestation of very complex neural connections of investigated sites. Great variability in ERP's onsets and time course can be explained in the same way.

In assessing decomposed whole-band records, the investigated loci exhibited synchronous oscillations in the investigated record window, which was especially frequent in the beta 2 frequency band. The synchronization of oscillations of neuronal activity between remote areas is considered to be the common way of long-range communication in cognitive networks (Woelf and Hameroff, 2001; Lee et al., 2003). The synchronization in the gamma band has been proposed as a candidate mechanism for it (Singer and Gray, 1995). The sampling frequency of analysed records in the present study did not allow investigating the gamma frequency band. However, some evidence is also available that synchronous activities in other frequency bands may participate in the integration of distributed neural activities into the coherent whole (Bressler et al., 1993; Lee et al., 2003). Our results corroborate these findings. The fact that highly synchronized activity was demonstrated without obvious relationship with the stimulus presentation is in good agreement with the opinion that neural synchronization may represent one of mechanisms underlying conscious awareness (Crick et al., 1990; Meador et al., 2002). On the other hand, the demonstrated increase of correlation coefficients in post-stimulus period may reflect also more direct implication of beta 2 synchronization in cognition per se.

Taken together, the results have necessarily implicated the idea that a lot of recorded ERPs are more or less by-products of chance in spreading a signal within the neuronal network, and that their functional relevance is somewhat linked with the phenomenon of activity synchronization.

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Table 1. The number of implanted electrodes and recording contacts across patients and structures (left/right hemisphere).

Structure Patient	Electrodes	Contacts										Total
		Dorsolat & basal prefrontal cortex	Cingulate gyrus	Motor cortices	Basal ganglia	Hippocampus	Parah, fusi & ling gyri	Amygdala	Lateral temporal cortex	Parietal cortex	White matter	
1	5/3	8/6	3/2			7/4			8/2			<b>26/14</b>
2	5/1		2/0			3/0	2/2		5/0	6/0		<b>18/2</b>
3	1/1				4/5	0/1	3/0	4/3			2/4	<b>13/13</b>
4	1/1					10/5	0/10	2/0				<b>12/15</b>
5	1/6	0/6	0/2		6/0	3/2	1/2	0/2	0/12		5/0	<b>15/26</b>
6	5/4	2/2				2/4	2/2	4/3	14/5		1/0	<b>25/16</b>
7	5/2	4/0	0/3	0/4			8/3	2/0	14/2		0/1	<b>28/13</b>
8	0/6	0/10				0/2	0/3	0/4	0/17		0/1	<b>0/37</b>
9	1/1				6/6	1/2		3/2			4/4	<b>14/14</b>
10	0/4		0/3				0/3		0/18	0/3	0/13	<b>0/40</b>
11	4/1	3/0	2/0		0/5	0/3	7/0	2/0	12/0		1/7	<b>27/15</b>
12	2/0		3/0	12/0							2/0	<b>17/0</b>
13	0/4					0/6			0/14		0/2	<b>0/22</b>
14	6/4	8/8	0/3			4/2		2/2	10/2			<b>24/17</b>
15	0/4		0/5			0/4	0/2		0/6	0/9	0/3	<b>0/29</b>
16	4/5	10/11	2/3			3/5			1/1		0/5	<b>16/25</b>
17	2/1				0/7	0/4		4/0	3/0			<b>7/11</b>
18	7/0	24/0	4/0			2/0		2/0	7/0		2/0	<b>41/0</b>
19	1/0				6/0		1/0	3/0			5/0	<b>15/0</b>
<b>Total</b>	<b>50/48</b>	<b>59/43</b>	<b>16/21</b>	<b>12/4</b>	<b>22/23</b>	<b>35/44</b>	<b>24/27</b>	<b>28/16</b>	<b>74/79</b>	<b>6/12</b>	<b>22/40</b>	<b>298/309</b>

Table 2. The onset values (ms) of event-related potentials across patients and structures.

Structure Patient	Dorsolat & basal prefrontal cortex	Cingulate gyrus	Motor cortices	Basal ganglia	Hippocampus	Parah, fusi & ling gyri	Amygdala	Lateral temp cortex	Parietal cortex	Total ERPs
1	r546	r131, 131			54, r124			85, r109		7
2		93			85	109, r233		69, 76, 78		7
3				47, r131		242	r94			4
4					67, r85	r54	192			4
5	r69, r78, r381	r124		304	116, r171	r105	r130	r62, r136, r240, r483		13
6	r340, 671				104, r445	r61, 109	r195, 324	85, 140, 324, r430, r468, 507		14
7	69	r54	r56			r62, 69, 71, 109	93	107, 109, 123, r130		12
8	r67, r109, r110				r100	r85	r169	r116, r171, r171, r171		10
9				116, r116			146, r228			4
10		r109				r45		r47, r69	r115	5
11	85	62		r61	161	45, 45	257	100, 114, 611		10
12		109	107, 116							3
13					r109, 440			r109, r142		4
14	r54, 54, r107, r116, 116	r116			54, r54, 107		67, r93	47, 93, 411		14
15		r114			r55			r69, r116	r190, r273	6
16	42, 45, r186, 211, r211, r248, r328, r335, 755	42, r186			r71, r71, 78			r171, 248, r398		17
17				r110			135			2
18	115, 115, 217	115					171	124, 272		7
19				60						1
Total ERPs	28	13	3	8	20	15	14	40	3	144

- *r* before the number designates the origin in the right hemisphere



Table 3. Location of recording sites, which yielded EEG activity with highly correlated segments ( $r$  greater than 0.95) in the beta 2 frequency band. Pairs with less than three independent observations were not included to the list.

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Dorsolateral and basal prefrontal cortex – Gyrus cinguli
Dorsolateral and basal prefrontal cortex – Hippocampus
Dorsolateral and basal prefrontal cortex – Parahippocampal, lingual or fusiform gyri
Dorsolateral and basal prefrontal cortex – Amygdala
Dorsolateral and basal prefrontal cortex – Lateral temporal cortex
Gyrus cinguli – Hippocampus
Gyrus cinguli – Parahippocampal, lingual or fusiform gyri
Gyrus cinguli – Amygdala
Basal ganglia – Parahippocampal, lingual or fusiform gyri
Basal ganglia – Amygdala
Basal ganglia – Lateral temporal cortex
Hippocampus – Parahippocampal, lingual or fusiform gyri
Hippocampus – Amygdala
Hippocampus – Lateral temporal cortex
Amygdala – Lateral temporal cortex
Lateral temporal cortex – Parietal cortex
Parahippocampal, lingual or fusiform gyri – Amygdala
Parahippocampal, lingual or fusiform gyri – Lateral temporal cortex

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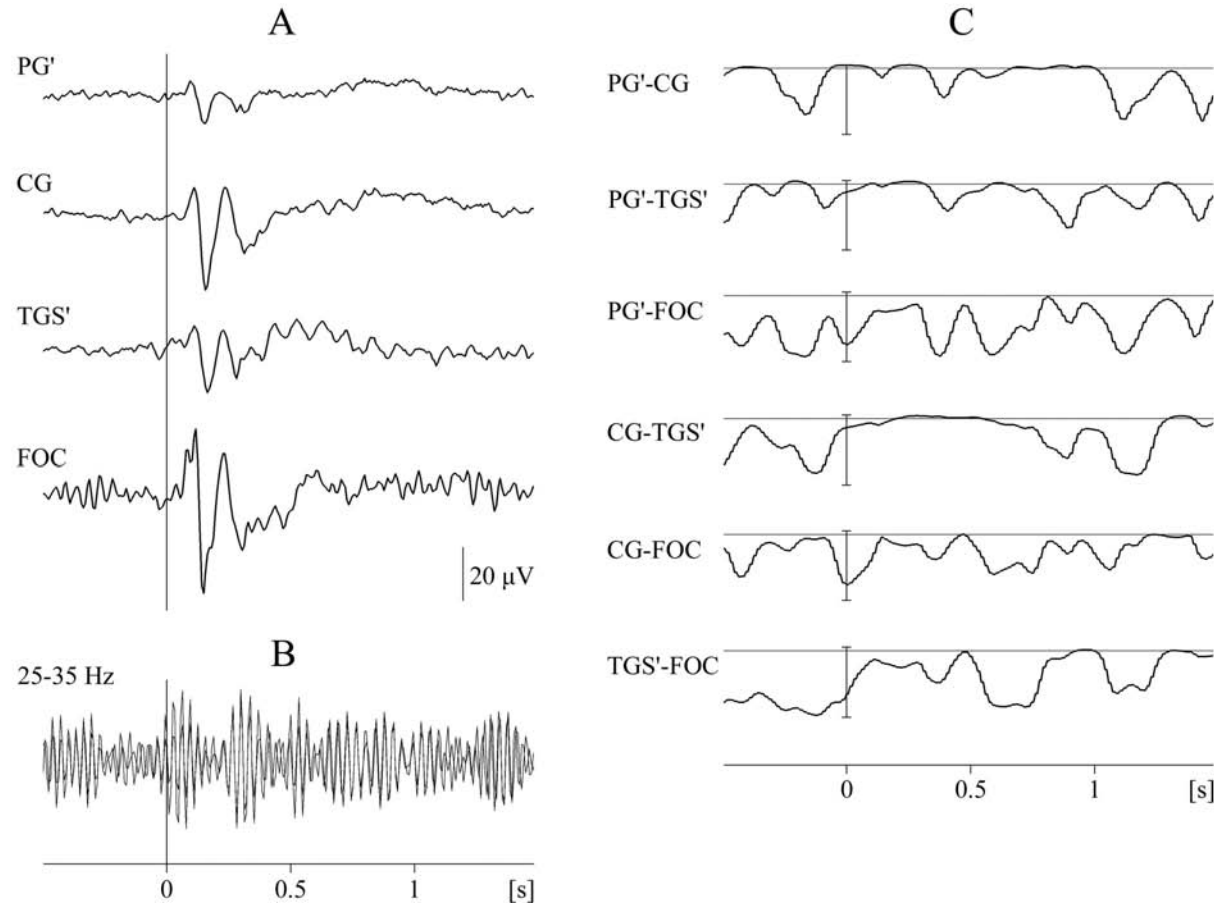


Figure 1. Left part of the figure presents four whole-band ERPs of patient No 7 (section A) and their beta 2 frequency components from CG and TGS' sites, which are overwritten (section B). Curves in the right part of the figure (section C) represent correlation coefficients computed between six possible pairs of beta 2 frequency components of records presented in section A. Vertical line at the stimulus onset (0) represent values of correlation coefficients from 1 to -1. Horizontal lines over curves are positioned at  $r=0.9$ . PG – parahippocampal gyrus; CG – cingulate gyrus; TSG – temporal superior gyrus; FOC – frontoorbital cortex. (') indicate the left hemisphere location.

Figure 2. Examples of event-related potentials induced by non-target visual stimuli in various brain structures: CG –cingulate gyrus, DLPFC – dorsolateral prefrontal cortex, MC – motor cortex, MFG –middle frontal gyrus, BG– basal ganglia, PC – parietal cortex, LTC –lateral temporal cortex, FG – fusiform gyrus, HP – hippocampus, AMY – amygdala. (‘) indicate the left hemisphere location; numbers in parentheses identify the patient; vertical lines (0) indicate the stimulus onset. Scaling was separately done for each waveform, to optimize amplitude.

