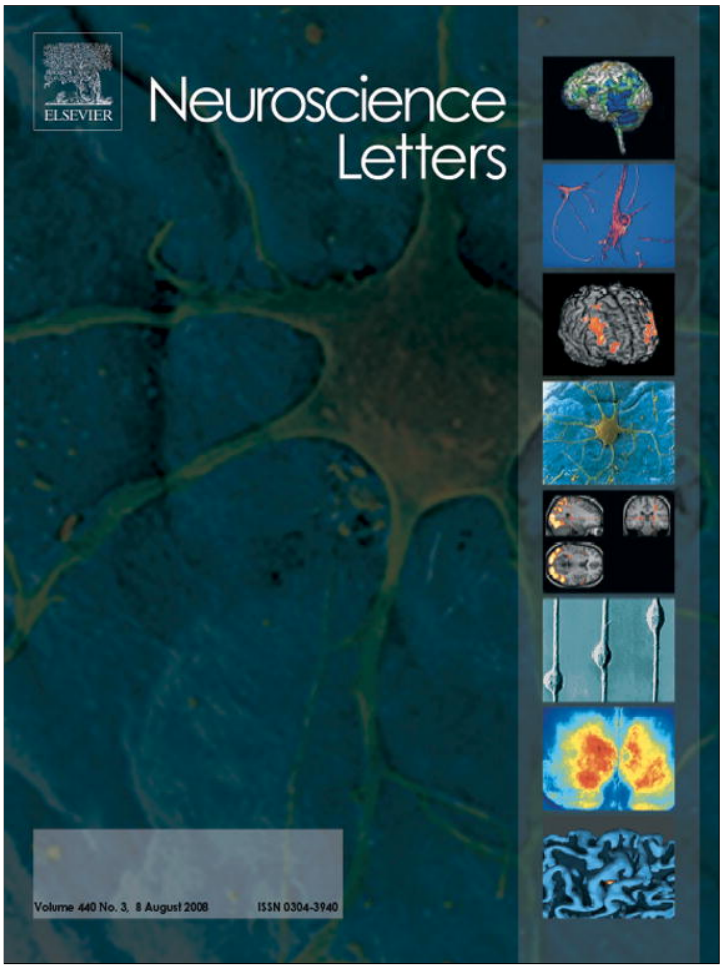

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# P3 and delta band responses in visual oddball paradigm in schizophrenia

Mehmet Ergen[a], Sonja Marbach[b], Andreas Brand[c], Canan Başar-Eroğlu[b], Tamer Demiralp[a,*]

[a] Department of Physiology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
[b] Institute of Psychology and Cognition Research, University of Bremen, Bremen, Germany
[c] Clinic Bremen-East, Center for Psychiatry and Psychotherapy, Bremen, Germany

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ABSTRACT

Amplitude reduction of the oddball P3 wave is a well-replicated but non-specific finding of schizophrenia. The time-frequency analysis of single-trial ERP data allows to specify in a reliable manner whether the P3 reduction in schizophrenia is due to the decreased P3 response in single trials or due to the inter-trial variability in the timing of the response. Since the delta response most strongly contributes to the P3 amplitude, we focused to the low frequency range of the time-frequency transformed data. EEG was recorded from chronic schizophrenia patients and matched healthy controls during a simple visual oddball task. The wavelet transforms of the averaged ERP and the single trials were computed to investigate the amplitudes of the evoked (phase-locked) and total (phase-locked + non-phase-locked) delta (1–3 Hz) responses, respectively. Evoked delta activity and P3 amplitude to target stimuli were both reduced significantly in patients with schizophrenia, whereas no such difference was obtained for the total delta activity. The significant reduction of the evoked delta response and the absence of such a difference in the total delta response of schizophrenia patients reveals that the delta band response is weakly phase-locked to stimulus in schizophrenia. This result suggests that the reduced P3 amplitudes in the averaged ERPs of schizophrenia patients result from a temporal jitter in the activation of neural circuits engaged in P3 generation.



Impairments of working memory and attention have been widely considered as crucial cognitive deficits in schizophrenia [3,14,27] and were associated with the functional outcome in this disease [15]. Event-related potentials (ERPs) time-locked to stimuli presented within the context of a cognitive task have been a common tool for investigating the substrates of mental processes and their disorders. The best known cognitive ERP component is the P3, which is a positive deflection with a parietal maximum occurring about 300–500 ms post-stimulus during target detection in an oddball task [23]. Reduction of the P3 amplitude is one of the most robust biological abnormalities found to reflect impaired attention and working memory capacity in schizophrenia [4,20], which is however not specific for this disease [22].

ERP P3 is based on averaging [31] and averaging neglects certain aspects of the data. In contrast, single trial analysis considers trial by trial variability of the electrophysiological response to a stimulus, hence reflects the fluctuating nature of the cognitive state of a subject during an experiment [16]. Only a few groups have analyzed P3 reduction in schizophrenia by the single trial approach. One of them reported that fewer trials with P3 results in amplitude reduction of the averaged ERP in schizophrenia [24]. Another group emphasized that besides fewer occurrence of P3 in single-trials, amplitude reductions, as well as a more variable P3 latency across the trials accounted for the smaller amplitude of the averaged ERP [10].

Analysis of the event-related oscillatory EEG activity, known as event-related oscillations (EROs), has become an important approach in understanding the dynamics of neural assemblies [1,2]. Wavelet transform, which optimizes the time-frequency representation of an ERP, is a powerful method for decomposing ERPs into oscillatory components hypothesized to be generated by different neural structures operating within different frequency ranges [7,25]. Several effects missing in the time domain but reflecting distinct functional aspects of a cognitive process could be revealed by this technique.

Delta band (1-3 Hz) response has been proven to be the most pronounced time-frequency component correlating with the P3 wave [7], such that the presence of P3 in single-trial ERPs can be efficiently detected by using a criterion based on the wavelet coefficients in the delta frequency range [8]. Recent studies on EROs in schizophrenia mostly concerned modulations in the gamma band activity [3,17,21]. Based on these findings, modern approaches suggest that the cognitive impairment in patients with schizophrenia

* Corresponding author at: Istanbul Tip Fakultesi, Fizyoloji Anabilim Dali, 34093 Capa-Istanbul, Turkey. Tel.: +90 212 635 26 31; fax: +90 212 635 26 31.
*E-mail address:* demiralp@istanbul.edu.tr (T. Demiralp).

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could be related to the disrupted integrative functions of local and distributed neural circuits, i.e. binding errors in the integration of cognitive domains [12,33]. Slow oscillatory components, shown to reflect long-range interactions of large-scale networks [26,32], however, have been rarely studied in schizophrenia [19]. Since the core cognitive domains affected in schizophrenia are the attention and working memory systems that involve the activation of large-scale networks, we assume that slow oscillations in the delta frequency range would show informative changes in schizophrenia. When the magnitudes of the time-frequency transform of each single trial are averaged, all the signal change in the post-stimulus period, often called total activity is captured regardless of phase-locking to the stimulus, whereas computing the wavelet transform of the averaged ERP represents only components that are phase-locked to the event, called evoked activity.

As P3 reduction is a solid but not a specific feature of schizophrenia, further characterization of this effect is needed. Carrying out single-trial analysis in the time-frequency plane may provide further information on P3 changes that are more specific to this disorder. Therefore, we tested several explanations for amplitude reduction of the P3 in the averaged ERP. In case of consistently low amplitudes in all single trials or normal amplitudes in a subset of single trials and attenuated waves in the others, delta response would decrease independent of the phase-locking effect, which means that both evoked and total delta responses would decrease. However, in case of a higher latency jitter among trials, the evoked delta response would decrease in line with the averaged P3 amplitude, whereas the total delta response might remain similar to that of the control group.

In the present study, our aim was to compare both evoked and total delta activities in schizophrenic patients and their matched controls in order to determine the mechanism of P3 reduction in schizophrenia more precisely.

Ten outpatients with chronic schizophrenia with a mean age of 31.5 (±8.5) diagnosed according to DSM-IV and 10 healthy controls with a mean age of 27.4 (±3.5), matched for gender (8 men/2 women) and with comparable education period ($16 \pm 4.16$ vs. $17.8 \pm 2.09$ years) participated in the study. Mean duration of illness was 6.7 years. The data from one male patient were excluded because of excessive movement and electro-oculogram (EOG) artifacts. All patients were in remission, receiving medication including atypical and classical neuroleptics. Psychopathologic signs were measured by the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS). The average SANS score of the patients was 10.5 (±3.29), whereas the SAPS score was 4.25 (±2.96). So, our patients showed predominantly negative symptoms. All participants were right-handed, had normal or corrected-to-normal vision, and gave informed consent.

A visual oddball paradigm with checkerboard stimuli was recruited as the cognitive task. Stimuli were presented on a computer screen with subjects seated 1.5 m in front of the monitor. They were instructed to mentally count the trials when the centrally located green circle's place was changed as the pattern is reversed. Green circle's radius was 25′, checks' sizes were 50′, and circle was shifted 25′ in terms of visual angle. Inter-stimulus interval was randomized between 2.5 and 3 s, and target probability was 25% within 150 trials (38 targets).

The EEG was recorded from F3, F4, C3, C4, P3, P4, O1, O2, T3, T4, T5 and T6 with a band pass filter of 0.1–70 Hz. Sampling rate was 512 Hz. Linked earlobes were used as the reference. The electro-oculogram (EOG) was recorded bipolarly between the electrodes placed above and on the right canthus of the right eye for monitoring the ocular artifacts. Data were processed in 2 s event-related epochs (1 s pre-stimulus/1 s post-stimulus). Epochs contaminated by eye or other artifacts were manually rejected. For each subject, approximately 30 epochs of target and standard presentations were randomly selected for further analyses in order to keep the S/N ratio at a comparable level across conditions and subjects. Epochs were baseline corrected to pre-stimulus 200 ms. Amplitude and latency of the positive maximum in the post-stimulus interval between 300 and 800 ms (P3 component) was measured in data digitally filtered at 0.1–10 Hz.

For the analysis of oscillatory activity, a continuous WT with complex Morlet wavelets of 3 cycles was applied both on single trials and on averaged ERPs. The absolute values of WT magnitudes of single trials were subsequently averaged to obtain the total oscillatory activity, which includes signal components that are phase-locked and non-phase-locked to the stimulus, whereas magnitudes of the WT of the averaged ERP were computed to obtain the evoked activity that reflects only phase-locked signal components. WT magnitude within the time interval between −300 and −100 ms preceding the stimulus was used to estimate the baseline activity. Evoked and total delta (1–3 Hz) responses were evaluated by measuring the mean amplitudes of this frequency range in the post-stimulus time window between 300 and 800 ms on the wavelet-transformed data.

Accuracy in mental count was analyzed by an independent samples *t*-test. Eight electrodes (F3, F4, C3, C4, P3, P4, O1 and O2) were included into the statistical analyses. Repeated measures analyses of variance (ANOVAs) with one between-subjects

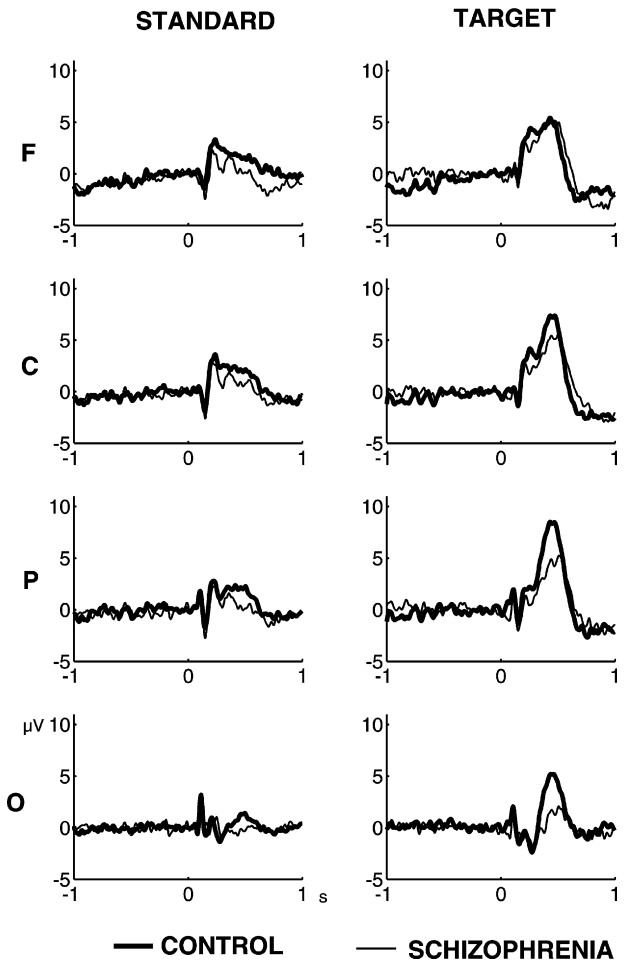


**Fig. 1.** Grand-average ERPs to standard (left column) and target stimuli (right column) from healthy controls (thick lines, $N = 10$) and schizophrenics (thin lines, $N = 9$) (F: frontal; C: central; P: parietal; O: occipital).

factor (group: schizophrenia, control subjects) and two within-subject factors (antero-posterior distribution: frontal, central, parietal, occipital and lateral distribution: left vs. right) were used. Greenhouse–Geisser correction was applied to the degrees of freedom, when the repeated measure factor contained more than two levels. Only corrected probability values are reported.

Although the schizophrenia patients performed slightly worse than the controls in terms of accurately detected number of target stimuli, the difference did not reach statistical significance ($t(17) = 2.06$, $p = 0.054$).

Fig. 1 presents the ERP grand-averages of the standard and target stimuli in schizophrenia patients and healthy controls. The target P3 amplitude was overall significantly reduced in patients ($F(1, 17) = 4.64$, $p = 0.046$), whereas the positive peak amplitude in the P3 latency range of the ERPs to standard stimuli was not significantly reduced ($F(1, 17) = 2.55$, $p = 0.128$). The antero-posterior distribution of the target P3 also differed between the groups. Control subjects displayed the typical P3 distribution with a parietal maximum, whereas the patients had a P3 with a central maximum, indicated by a significant antero-posterior distribution × group effect ($F(3, 51) = 3.52$, $p = 0.05$). The P3 seemed to peak slightly later in patients, however this effect did not reach significance neither for the target ($F(1, 17) = 4.00$, $p = 0.062$) nor for the standard ($F(1, 17) = 0.005$, $p = 0.94$) ERPs.

Although the amplitude difference was statistically significant only for the target P3s, we included both the EEG responses to target and standard stimuli in the time-frequency analyses. In the time-frequency plane the delta band showed the most pronounced effect. As the parietal channels display the effect most clearly, time-frequency data from parietal electrodes are illustrated in Fig. 2. Fig. 2a and b presents the grand-average wavelet transforms of the evoked and total activities obtained in response to standard and target stimuli.

To quantitatively analyze the time-frequency transforms, mean amplitudes of the delta responses were calculated for the time-frequency window of 300–800 ms and 1–3 Hz, where the peaks of the delta responses were commonly located. A clear difference between the control group and the patients could only be observed for the evoked delta response to targets ($F(1, 17) = 6.38$, $p = 0.022$). The evoked ($F(1, 17) = 0.008$, $p = 0.929$) and total delta responses ($F(1, 17) = 0.492$, $p = 0.493$) to standard stimuli, and the total delta response to target stimuli ($F(1, 17) = 1.39$, $p = 0.255$) did not show significant differences between the control and schizophrenic subjects. Fig. 3 shows the time courses of evoked and total delta responses to targets. The most prominent difference in the evoked delta response between the control and schizophrenia groups was observed in the parietal region, but this topography effect was statistically non-significant.

Although most studies have reported that the auditory rather than visual P3 is reduced in schizophrenia [11], there are several studies that also report a reduced P3 in visual target detection [5,28,29]. Reduced P3 to visual targets in schizophrenia was replicated in our study. Additionally, the typical topography of the P3 was changed in the patient group, which displayed a central rather than a parietal P3 maximum.

In the present study, P3 reduction during a visual oddball paradigm was examined by transforming the data to the time-frequency plane in order to further investigate the mechanism of this ERP effect in schizophrenia. The formalism of the time-frequency transform allows us to easily and efficiently determine the evoked (phase-locked) vs. total (phase-locked + non-phase-locked) activities within the ERPs by transforming either the averaged ERP onto the time-frequency plane or by averaging the magnitudes of the time-frequency transformed single ERP trials. Therefore, the wavelet transformed data reveals clearly, whether an effect in the averaged ERP is due to latency jitter among single

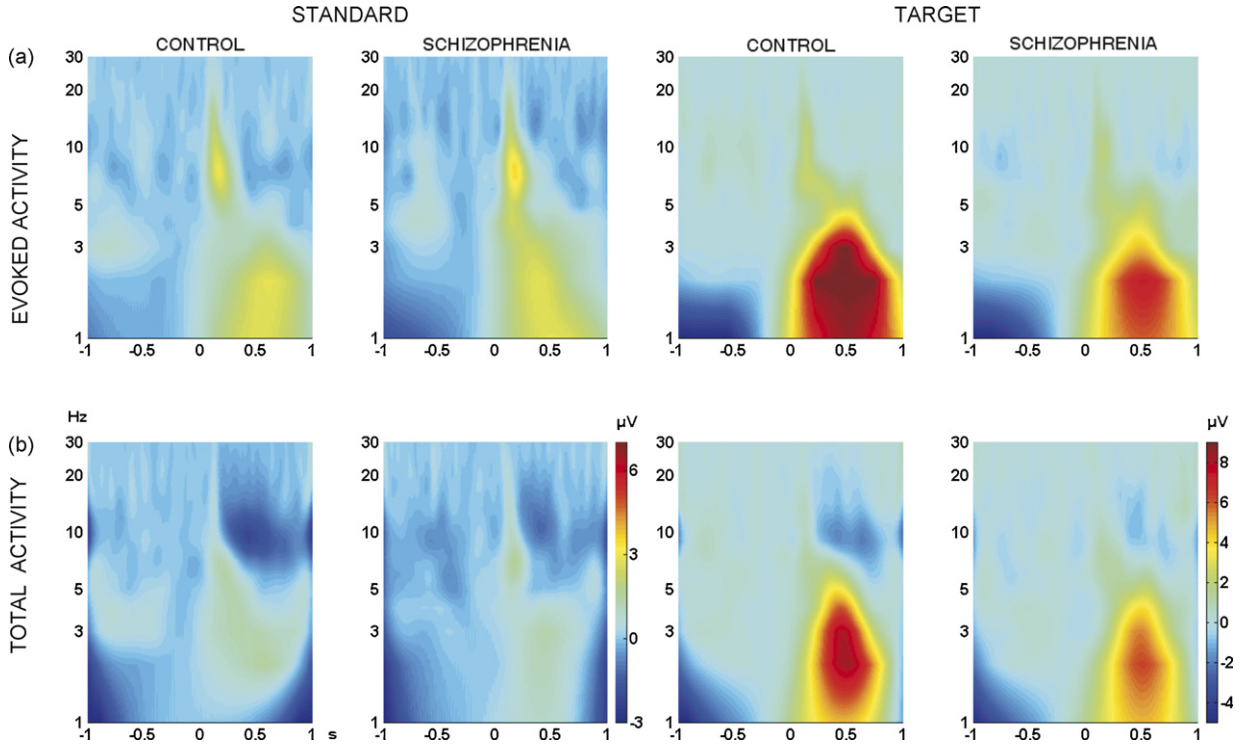


**Fig. 2.** Grand-average time-frequency plots of evoked (a), and total activity (b) in parietal region (P3 and P4 electrodes are averaged) of control subjects and schizophrenia patients in response to standard and target stimuli of the visual oddball paradigm. Frequency axis is displayed in logarithmic scale.

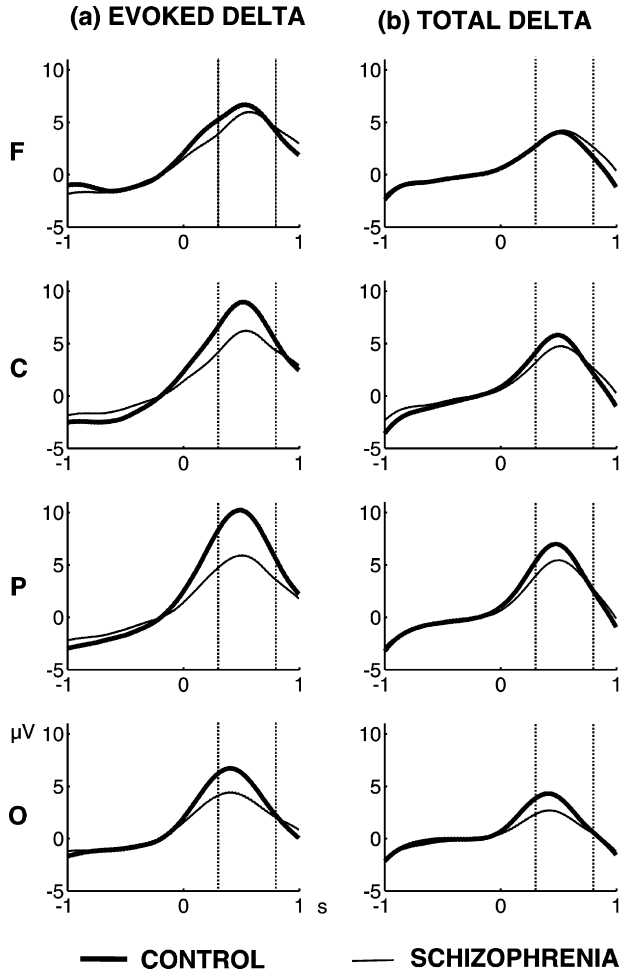


**Fig. 3.** Grand-average time courses of evoked (a) and total delta responses (b) to target stimuli from control subjects (thick lines) and schizophrenia patients (thin lines) (F: frontal; C: central; P: parietal; O: occipital). Vertical lines indicate the time window of mean amplitude measurement.

trials or due to a consistent change of the amplitudes in all single trials. For this reason, the delta response in the time-frequency transformed data, which is the strongest contributor to the P3 wave, was analyzed instead of using less efficient single-trial analysis approaches in the time-domain.

Here, we investigated whether the P3 reduction can be explained by (1) consistently low amplitudes in all trials, (2) normal amplitudes in a subset of single trials and attenuated or absent waves in others, and (3) a higher latency jitter among trials leading to reduced amplitudes in the averaged response. Our results on the delta response, the strongest time-frequency component of the P3 wave [7,8], showed that evoked delta, which is sensitive to phase-locking, was lower in patients with schizophrenia. In contrast, no significant difference between healthy controls and patient group was observed in the total delta activity, which is sensitive to amplitude modulations that are not phase-locked to the event. Therefore, the third explanation mentioned above, i.e. the higher latency jitter among single trials is plausible for the P3 reduction in schizophrenia. In both other cases, the total delta activity should also be reduced.

Whereas the enhancement of single-trial delta amplitudes after a stimulus might reflect the synchronous activation of a larger neural assembly compared to baseline, precise phase-locking of ERO to the stimulus may reflect the activation of neural networks exactly at the right time point within the required sequence of neural processing [9]. Therefore, a possible explanation of our findings could be a looser organization of the activation timing of neural assemblies responsible of the P3 generation rather than their lower activation in schizophrenics. As slower oscillations are considered to be related to the long-range interactions in large-scale networks [32], our results in line with few other studies on changes of slower oscillations in schizophrenia [19,27] suggest that impaired timing of long-range interactions might contribute to the pathological process.

Previous studies suggested that the combination of fewer trials with a P3, a latency jitter among trials and consistently lower P3 amplitudes through all trials [10] or a combination of lower single-trial P3 amplitudes and fewer number of single-trials with a P3 [24] were responsible of the lower P3 amplitudes in schizophrenia. Two likely explanations for the different results of our study are the different sensory modalities and methodological differences. The other two studies employed auditory oddball paradigm and used either a template fitting procedure [10] or amplitude density functions [24] in the time domain for detecting P3 in single trials, while we employed a visual oddball paradigm and compared amplitudes of the evoked vs. total delta activity in the time-frequency plane. The mechanism of the P3 reduction in schizophrenia might be different for the visual modality, which was not studied before in the single-trial level. On the other hand, the methodological difference may also play an important role in the different results. Both earlier approaches classified single-trials with and without a P3 based on the assumption, that an amplitude threshold at either a fixed time interval or of a positive deflection of the signal, which fits to a 2 Hz half-sine wave template, would reliably detect the single-trial P3. The wavelet transform is a more sophisticated method to reflect the P3 related signal components on the time-frequency plane using all single-trials without an assumption related with a measure to detect the presence of P3 in any trial. Therefore, we believe that present results are more robust compared with the previous reports.

An important point to consider is that our results might represent mostly patients with negative symptomatology, as our patient group mainly displayed negative symptoms. With a larger group of subjects, possible correlations of the decrease of the delta phase-locking with the symptomatology could be tested. Another possible confounding factor could be pharmacological treatment of the patients. However, many studies reported that cognitive deficits are attributable to schizophrenia itself rather than medication [6,13,18,30].

In conclusion, evoked delta activity and P3 amplitude, which are both measures of the averaged ERP response, were significantly reduced in the visual oddball ERPs of patients with schizophrenia. However, total delta power, which is mostly sensitive to amplitude changes, and insensitive to the sharp timing of delta band activity, did not differ between patients and healthy controls. This dichotomy between evoked and total power implies weakly phase-locked delta responses during visual target detection in schizophrenia. Consequently, our results indicate that, higher variability in latencies across single trials, rather than the attenuation of delta oscillations and P3 component in each single trial, accounts for the lower P3 amplitude in the visual ERPs of schizophrenia patients.

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