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# Elevated noise power in gamma band related to negative symptoms and memory deficit in schizophrenia

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ABSTRACT

*Background:* There is an increasing consideration for a disorganized cerebral activity in schizophrenia, perhaps relating to a synaptic inhibitory deficit in the illness. Noise power (scalp-recorded electroencephalographic activity unlocked to stimuli) may offer a non-invasive window to assess this possibility.
*Methods:* 29 minimally-treated patients with schizophrenia (of which 17 were first episodes) and 27 healthy controls underwent clinical and cognitive assessments and an electroencephalographic recording during a P300 paradigm to calculate signal-to-noise ratio and noise power magnitudes in the theta and gamma bands.
*Results:* In comparison to controls, a significantly higher gamma noise power was common to minimally-treated and first episode patients over P3, P4, T5 and Fz electrode sites. Those high values were directly correlated to negative symptom severity and inversely correlated to verbal memory scores in the patients. There were no differences in signal-to-noise ratio magnitudes among the groups. Gamma noise power at Fz discriminated significantly between patients and controls. No significant differences were found in theta noise power or in gamma noise power over the other electrode sites between the groups of patients and controls.
*Limitations:* We have not assessed phase-locked and non-phase locked power changes, a complementary approach that may yield useful information.
*Conclusions:* Gamma noise power may represent a useful and non-invasive tool for studying brain dysfunction in psychotic illness. These results suggest an inefficient activation pattern in schizophrenia.


## 1. Introduction

Synchronized oscillations in the brain play a role in coordinating cerebral activity (Uhlhaas et al., 2010). In particular, theta and gamma rhythms seem involved in coordinating local neural circuits underlying higher cerebral functions, probably in relation to their capacity to subtend transient functional assembly formation (Singer, 1993; Tallon-Baudry et al., 1998). These frequency bands may contribute to coherent percept construction by the brain and to the strengthening and weakening of synaptic links (Buzsáki, 2006) and, in the case of gamma oscillations, to neural activity integration within and between regions in a range of cognitive functions (Singer, 1999). Thus, it seems relevant to study gamma and theta oscillations and their relation to the likely non-focal, dynamic cerebral dysfunction of schizophrenia.

Within that framework, the study of "noise power" may be of special importance. This term refers to the amount of scalp-recorded power not temporally locked to stimuli, quantified as the difference in each band between the mean power of single trials and the power magnitude in the averaged potential (Möcks et al., 1988; Winterer et al., 2000). This way, "noise power" is equivalent with spontaneous background activity and jittering of the event-related signal (Winterer et al., 2004), i.e. the power in each band that could be observed independently from the task in opposition to stimulus-evoked power. An overabundance of noise power may reflect an excessive extension of cortical activation at the expense of adequate selection of neural populations and cognitive performance.

*Abbreviations:* GABA, gamma-aminobutyric acid; EEG, electroencephalography; PANSS, Positive and Negative Syndrome Scale; BACS, Brief Assessment in Cognition in Schizophrenia Scale; WAIS-III, Wechsler Adult Intelligence Scale—Third Edition; SNR, signal-to-noise ratio; ANOVA, analysis-of-variance; GLM, general linear model; ROC, receiver operating characteristic curve; DMN, default mode network; BOLD, blood oxygen level-dependent.

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High-frequency noise power assessment can be useful to the study of schizophrenia for two reasons. First, GABA neurotransmission is relevant in the generation (Bartos et al., 2007) and modulation (Brown et al., 2007) of high-frequency rhythms in the brain. Since a synaptic inhibitory deficit seems likely in schizophrenia (Lewis et al., 2005), disorganized gamma oscillations and thus higher noise power magnitudes may be expected in this illness. Second, functional neuroimaging reveals a disorganized and/or excessive brain activity during cognitive tasks along with a hampered activation of regions usually involved in those tasks (Manoach, 2003). Therefore, the association between gamma band oscillations and modulation of cerebral blood flow seems stronger than the corresponding association of the latter with oscillations in other bands (Niessing et al., 2005; Scheeringa et al., 2011). Accordingly, functional alterations in schizophrenia (i.e., the disorganization described with functional neuroimaging) might also be evidenced as higher noise power in the gamma band over certain regions. In fact, higher noise power has been reported in schizophrenia in comparison to healthy controls (Winterer et al., 2004). Consistent with this, neuropshysiological data support a deficit of cortical inhibition of the gamma band in schizophrenia but not in bipolar disorder (Farzan et al., 2010). The higher temporal resolution of electroencephalographic (EEG) studies may yield complementary data to those of functional magnetic resonance concerning disorganization of cortical activity in schizophrenia.

To further validate noise power relevance in the study of schizophrenia, it seems suitable to examine its association with clinical and cognitive variables. In order to do so we planned the present study since, to our knowledge, these issues have not been addressed to date except for the relation between noise power and working memory performance (Winterer et al., 2004). We hypothesized an excessive amount of scalp-related noise power in the gamma band in schizophrenia patients during a simple cognitive odd-ball task associated to symptoms and/or cognitive deficit. We also studied theta noise power given the above mentioned role of these oscillations in coordinating neural circuits related to higher cerebral functions.

## 2. Methods and materials

We recruited 29 patients with schizophrenia who were drug-free before inclusion (of them, 17 first episode patients) and 27 healthy controls. All met the DSM-IV-R criteria for paranoid schizophrenia.

The patients had not received any previous treatment (first episode patients) or they had dropped their medications before inclusion for a period longer than one month.

Owing to an acute psychotic state of drug-free patients prior to inclusion, we administered a small amount of haloperidol (2 to 4 mg) the day before the EEG study, with a wash-out period of approximately 24 h before EEG. The objective was to minimize the likely bias of only including patients able to cooperate with the EEG recording during an acute psychotic episode without any treatment. Therefore, from here on we will refer to these patients as minimally-treated patients. In order to rule out the acute effects of haloperidol on noise power, five healthy controls gave their informed consent to be studied with EEG before and 24 h after a 2-mg dose of haloperidol, approximately reproducing the treatment conditions of minimally-treated patients.

We scored the clinical status of the patients by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Marital status was stratified into single (single, divorced, separated) or living in couple; employment status, as employed (currently studying or working) or unemployed (looking for a job or retired) and educational level, as completed academic courses.

We recruited healthy controls through newspaper advertisements and remunerated their cooperation. They were previously assessed by a semi-structured psychiatric interview by one investigator (V. Molina) to discard major psychiatric antecedents (personal or familial) and treatments.

The exclusion criteria included total IQ below 70; a history of any neurological illness; cranial trauma with loss of consciousness; past or present substance abuse, except nicotine or caffeine; the presence of any other psychiatric process or drug therapy and treatment with drugs known to act on the central nervous system. We discarded toxic use in patients and healthy controls with the information gathered in the interview and a urinalysis.

We obtained written informed consent from the patients, their families and healthy controls after providing full written information. The research board endorsed the study according to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

### 2.1. Cognitive assessment

We acquired cognitive assessment by the direct scores from the following subscales of the Spanish version of Brief Assessment in Cognition in Schizophrenia Scale (BACS) (Segarra et al., 2011), administered by trained researchers (V. Suazo, A. Díez): verbal memory (list learning), working memory (digit span), motor speed (token motor task), verbal fluency (categories), attention and processing speed (symbol coding) and executive function/problem-solving (tower of London). We used the Spanish version of the WAIS-III to assess IQ.

### 2.2. EEG Methods

EEG recordings were performed while the participants underwent an odd-ball task. To elicit P3a and P3b components an oddball 3-stimulus paradigm was employed with a 500-Hz-tone target, an infrequent 1000-Hz-tone distracter and a 2000-Hz-tone standard stimulus (see Supplementary Data).

Accordingly, participants heard binaural tone bursts (duration 50 ms, rise and fall time 5 ms and intensity 90 dB) presented via speakers with random stimulus onset asynchrony of 1000 and 1500 ms. Random series of 600 tones consisted of target, distracter and standard tones with probabilities of 0.20, 0.20 and 0.60, respectively.

We asked the participants to press a button whenever they detected the target tones, to close their eyes and avoid eye movements and muscle artifacts.

#### 2.2.1. Electroencephalographic recording

The EEG was recorded by BrainVision (Brain Products) equipment from 17 tin electrodes mounted in an electrode cap (Electro Cap International). The electrode sites were Fp1, Fp2, F3, Fz, F4, F7, F8, C3, Cz, C4, P3, Pz, P4, T5, T6, O1 and O2 of the revised 10/20 International System. Electrode impedance was always kept under 5 kΩ. The online register was referenced over Cz electrode, the sampling rate was 250 Hz and the signal was recorded continuously.

#### 2.2.2. Data analysis

*2.2.2.1. Event-related potentials.* We divided the continuous recording into 650 ms epochs starting 50 ms before stimulus onset. We used an off-line 0.5 to 70 Hz filter. Artifacts were automatically rejected by eliminating epochs that exceeded a range of ±70 μV in any of the channels. Based on a visual inspection we eliminated any epochs that still presented artifacts. Individual data were included in the analyses if 50 or more useful epochs were available. Overall, the mean rate of rejected segments was of 49.4%.

Data were re-referenced to electrodes average activity (Bledowski et al., 2004). We defined baseline as the available 50 ms prestimulus recording. P3a and P3b components were respectively calculated from distracter and target stimuli and defined as the mean amplitude in the 300 to 400 ms interval (see Supplementary Data for details).

*2.2.2.2. Noise power.* For quantitative event-related EEG analysis, the recorded signals (−50 ms to 600 ms post-stimulus, target condition)

were submitted to specific band filtering and spectrum analysis by a fast Fourier transform yielding spectral values. The absolute magnitude (averaged total power) in each frequency band was computed expressed in μV². Frequency band partition was as follows: delta (0.5 to 4.0 Hz), theta (4.5 to 8.0 Hz), alpha (8.5 to 12.5 Hz), beta1 (13.0 to 18.0 Hz), beta2 (18.5 to 30.0 Hz) and gamma (35.0 to 45.0 Hz).

We calculated noise magnitude, which is subsequently denoted as "noise power", following the recommendations of Möcks et al. (1988) and Winterer et al. (2004). This calculation was based on the signal-to-noise ratio (SNR), a measure of the quality of the EEG signal applied to each band; it is calculated by the Brain Vision Analyzer (2006) for the time window from −50 to +600 ms for the target stimuli (see Supplementary Data for details).

For every individual participant, band and electrode, we calculated the averaged noise power from the already extracted averaged total power (the addition of the signal and noise power) and SNR (the average signal power quotient divided by the average noise power) by the following formula:

$$\text{Avg Noise Power} = \text{Avg Total Power} / (\text{SNR} + 1).$$

This way, a quantification of the noise part of the activity related to the event is approximated and "noise" is equivalent with activity that is not time-locked to the stimuli.

### 2.3. Statistical methods

We compared demographic, cognitive and clinical scores among the groups by using chi square or ANOVA test when appropriate.

In order to identify noise power patterns associated to schizophrenia, ruling out confounding factors, we looked for statistically significant differences between all patients and healthy controls in common with statistically significant differences between first episode patients and healthy controls. To this end, we used a repeated measures general linear model (GLM) with a between-subject factor (group) and two within-subject factors (electrode and band) to assess significance of global differences in noise power. If a significant effect for noise power was detected between patients and controls, we used a post-hoc analysis (Student's *t* test for independent samples) to identify which electrodes and bands displayed significant differences between the patients and controls. As planned, we repeated the comparisons displaying significant differences to corroborate that such differences also held for the first episode patients alone (Student's *t* test). Then, we compared SNR between patients and controls (*t* tests for independent samples) to investigate if noise power changes were accompanied by similar signal power changes. To rule out the effects of acute treatment on noise power and SNR values, we used the data from the specific control group before and after receiving haloperidol with a Wilcoxon test for related samples.

The following calculations (noise power relation with symptoms and cognition, and predictive capacity) would be restricted to electrode/band combinations reaching that threshold (i.e., significant differences common to both comparisons). We studied the association between noise power, symptoms, cognitive values and P300 amplitude by stepwise linear regression. Only noise power values with significant differences, as previously defined, were introduced in the model as independent variables and PANSS and cognitive scores and P300 amplitude as dependent variables, testing normal distribution and homoscedasticity of the residuals. We repeated the calculations in the first episode patients alone.

Finally, we assessed the predictive capacity of noise power differences common to all patients and FE patients in comparison to controls by a receiver operating characteristic (ROC) curve.

## 3. Results

There were no significant differences in sex distribution ($\chi^2 = 0.04$, df = 1, p = 0.95), completed education courses (t = 0.984; df = 20; p = 0.337) marital status ($\chi^2 = 3.714$, df = 1, p = 0.054) or age (t = 0.012, df = 54, p = 0.990) among the groups. Employment status ($\chi^2 = 4.339$, df = 1, p = 0.037) was significantly different among the groups. IQ was significantly lower in the patients (t = 5.090, df = 50, p < 0.001). These results are summarized in Table 1.

### 3.1. Noise power comparisons

#### 3.1.1. Patients vs. controls

Repeated measures GLM revealed significant effects for electrode (Wilk's λ = 0.136, F = 15.420, p < 0.001) and band (Wilk's λ = 0.191, F = 228.431, p < 0.001) and a significant interaction between group, band and electrode (Wilk's λ = 0.457, F = 2.894, p = 0.003).

Following analyses revealed a significantly higher noise power in the gamma frequency over P3 (t = 3.007, df = 54, p = 0.004), P4 (t = 2.391, df = 54, p = 0.02), T5 (t = 3.232, df = 54, p = 0.002) and Fz (t = 2.933, df = 54, p = 0.005) in patients (Table 2).

First episode patients showed similar significance levels of higher gamma noise power values at P3 (first episode mean = 0.012, sd = 0.006; t = 3.565, df = 42; p = 0.001), P4 (first episode mean 0.011, sd = 0.005; t = 2.363, df = 42, p = 0.023), T5 (first episode mean = 0.030, sd = 0.015; t = 4.349, df = 42, p < 0.001) and Fz (first episode mean = 0.008, sd = 0.002; t = 3.090, df = 42, p = 0.004) in comparison to controls.

There were no significant noise power differences in the minimally-treated or first episode patient's theta band. For further noise power comparisons see table S1.

Figs. S1 and S2 depict theta and gamma noise power comparisons at Fz between patients and controls respectively.

#### 3.1.2. SNR comparisons

There were no significant gamma SNR differences between patients and controls over P3, P4, T5 or Fz, electrodes (Table 2).

#### 3.1.3. Changes with haloperidol in healthy controls

Gamma noise power lessened significantly with haloperidol over T5 (z = −2.02, p = 0.04). We did not find any other significant changes

**Table 1**
Clinical, cognitive and demographic data, P300 parameters and ERP task behavioral data in all patients and controls. No significant differences were found in the latter.

| | Patients (n = 29) | Controls (n = 27) |
|---|---|---|
| Age | 33.00 (9.81) | 33.04 (13.16) |
| Sex distribution (M:F) | 18:11 | 17:10 |
| Education (completed courses) | 12.53 (2.65) | 11.20 (2.68) |
| Marital status (% single) | 87.50* | 64.29 |
| Employment status (% employed) | 37.50** | 66.67 |
| Total IQ | 82.24 (16.51)# | 102.78 (12.44) |
| PANSS positive | 20.83 (4.01) | n/a |
| PANSS negative | 16.79 (4.77) | n/a |
| PANSS total | 75.96 (11.78) | n/a |
| BACS-verbal memory | 36.42 (12.03)# | 53.52 (8.96) |
| BACS-working memory | 17.35 (5.56)# | 22.26 (3.75) |
| BACS-motor speed | 54.00 (16.61)** | 63.85 (14.05) |
| BACS-verbal fluency | 16.26 (4.73)# | 25.11 (4.57) |
| BACS-processing speed | 16.08 (8.60)# | 57.85 (11.56) |
| BACS-problem solving | 39.35 (13.40)*** | 17.26 (3.01) |
| P300% correct responses | 70.50 (32.79) | 90.09 (21.95) |
| P3b reaction time (ms) | 617.95 (90.85)*** | 524.43 (53.73) |
| P3b N valid segments | 45.03 (20.69) | 56.96 (25.59) |
| Pz amplitude S1 (μV) | 0.241 (0.659) | 0.075 (0.635) |
| Pz amplitude S2 (P3a) (μV) | 0.899 (1.128) | 1.182 (1.179) |
| Pz amplitude S3 (P3b) (μV) | 1.172 (1.554)* | 1.818 (1.058) |

S1: standard; S2: distractor; S3: target.
*p = 0.07; **p < 0.05; ***p < 0.01; #p < 0.001 with respect to healthy controls (*t* test).

**Table 2**
Noise power values ($\mu V^2$) and SNR values per band and electrode. Band/electrode values were significantly different in the same direction in minimally treated patients as well as in first episode subgroup as compared to controls. See supplementary data and Section 3.1 in the text for other noise power differences.

| | Patients (n = 29) | | Controls (n = 27) | |
|---|---|---|---|---|
| | Noise power | SNR | Noise power | SNR |
| Gamma P3 | 0.011 (0.007)** | 0.857 (0.204) | 0.007 (0.004) | 0.953 (0.322) |
| Gamma P4 | 0.010 (0.005)* | 0.894 (0.279) | 0.007 (0.004) | 0.953 (0.251) |
| Gamma T5 | 0.025 (0.014)** | 0.886 (0.204) | 0.015 (0.009) | 0.963 (0.237) |
| Gamma Fz | 0.007 (0.003)** | 0.936 (0.205) | 0.005 (0.003) | 0.990 (0.200) |

*p<0.05; **p<0.01; ***p<0.001 with respect to healthy controls (*t* test).

with haloperidol in the gamma or theta noise power or SNR on T5, P3, P4 or Fz electrodes (Table S2). In all cases, post-haloperidol noise power values were lower than the corresponding basal values. There was no significant effect of haloperidol on P300 amplitude.

*3.1.4. Relation with symptoms and cognition*

A significant and direct correlation was found between noise power at Fz and negative symptom scores ($R^2 = 0.186$, $F = 5.022$, $p = 0.035$; $\beta = 0.431$; $t = 2.241$; Fig. 1). This association was not found in the first episodes considered alone.

Noise power in the gamma band over P4 in the patients was inversely related to verbal memory ($R^2 = 0.161$, $F = 4.598$, $p = 0.042$; $\beta = -0.401$; $t = -2.144$; Fig. 2). This association was also significant in the first episodes considered alone ($R^2 = 0.298$, $F = 5.513$, $p = 0.035$; $\beta = -0.546$; $t = -2.348$). This association was not present in the healthy controls group.

In all cases, regression residuals were normally distributed and homoscedastic.

*3.1.5. P300 comparisons*

There was a trend level difference in P300 amplitude only for target condition (P3b) between patients and controls at Pz, the amplitudes being smaller in patients ($t = 1.805$; $df = 54$; $p = 0.070$). P300 amplitude and percentage of correct responses in the oddball task were not related to P3, P4, T5 and Fz gamma noise power ($R^2 < 0.03$, $p > 0.2$ in all cases). Reaction time for correct target detection was positively and significantly related to P3b gamma noise power ($R^2 = 0.374$, $F = 5.370$, $p = 0.046$; $\beta = 0.611$; $t = -0.046$). Figs. S3 and S4 depict mean average waveforms and spatial distribution corresponding to distracter (P3a) and target (P3b) tones in patients and controls.

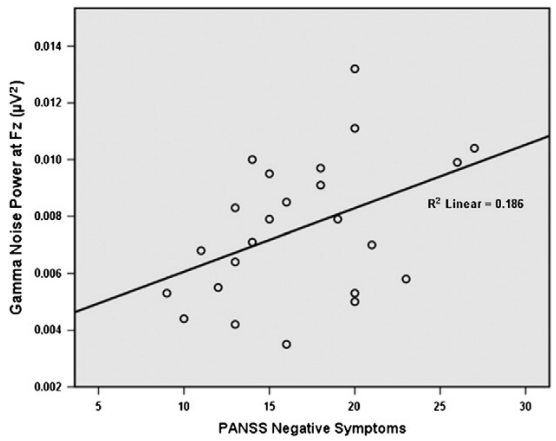


**Fig. 1.** Scatterplot showing the association between gamma noise power magnitude and severity of negative symptoms in the patients.

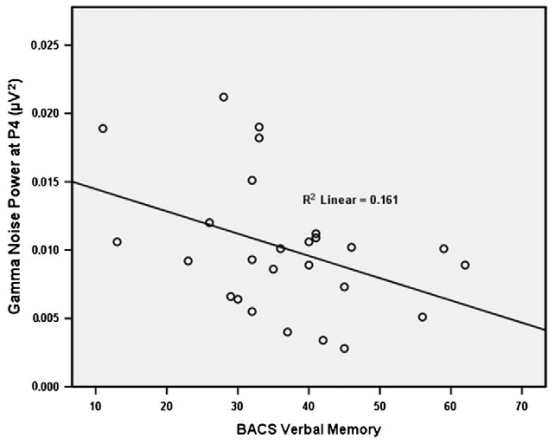


**Fig. 2.** Scatterplot showing the association between gamma noise power magnitude and performance in verbal memory test (BACS) in the patients.

There were no significant relationships between P3b amplitude and PANSS or cognitive scores.

*3.1.6. Classificatory capacity*

The ROC curve showed a significant predictive capacity for gamma Fz noise power as a predictive variable and for patient vs. control differentiation (Fig. 3). The area under the curve was 0.727 (asymptotic significance $p = 0.004$; 95% CI intervals 0.593 to 0.861).

## 4. Discussion

Higher gamma band noise power over P3, P4, T5 and Fz electrodes was found in patients with schizophrenia (most of them were first episode patients) during a P300 paradigm and was directly related to negative symptom severity and inversely related to verbal memory performance. There were no SNR differences between patients and controls.

Our data partially agree with the excess of noise power, including gamma band, previously reported in schizophrenia during a similar

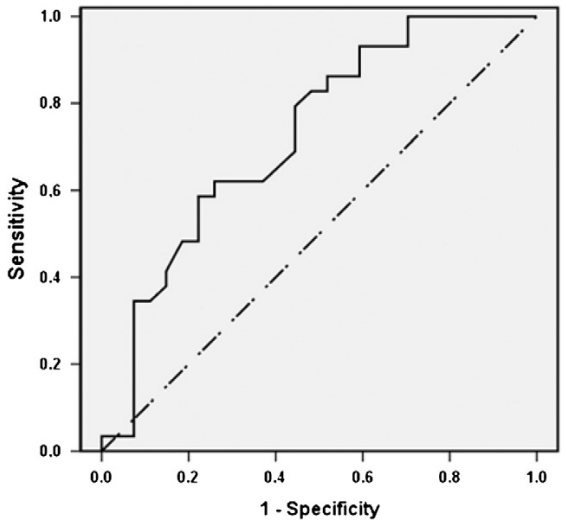


**Fig. 3.** ROC curve using Fz gamma noise power magnitude as a predictor of diagnosis (patient/control).

P300 paradigm and inversely related to working memory performance (Winterer et al., 2004). EEG noise power measurement is not usual in schizophrenia studies, which makes our results difficult to directly compare to others. However, excessive evoked gamma power has been reported in schizophrenia over frontal electrodes during the 3-back condition of an N back test (Barr et al., 2010), positively related to negative symptom scores and without any differences in other bands, which is consistent with our results, although background ("noise") and signal power were not discriminated. In that report, evoked gamma power changed in the control group but not in the patients between cognitive load conditions, suggesting a deficient regulation of gamma oscillations in schizophrenia syndrome. Similar high gamma band power has been reported with higher working memory loads in healthy controls but not in patients, whose gamma activity remained constant with overall impaired test performance (Basar-Eroglu et al., 2007), suggesting a deficient regulation of fast oscillatory mechanisms in the brain in schizophrenia that may relate to the higher noise power in the gamma band. Also supporting this possibility, gamma power was related to reaction times and amplitude during a P300 task in healthy controls but not in patients with schizophrenia (Reinhart et al., 2011). From these data, it could be speculated that an elevated gamma power independent of stimulus perception or processing may be detrimental to cognitive functions in schizophrenia.

Nevertheless, other groups measured evoked activity and did not find higher evoked (i.e. in-phase) gamma band power in schizophrenia. Significantly less power in the auditory evoked gamma-band response (30–100 Hz) over Cz (Leicht et al., 2010) was described when subjects had to distinguish between two equally frequent tones of different pitches and consequently press one of the two buttons. However, in-phase evoked responses that tend to survive averaging and responses that are not in-phase cancel out in this process. Therefore our "noise" magnitude (that represents the difference between averaged total and signal power) is likely to relate to the non-evoked part of the response, thus our higher noise power in the gamma band is compatible with the lower evoked response reported by other studies in the same band. Indeed, the trend-level lessened P3b amplitude (that results from averaging and may relate more directly to the evoked response) in our patients may result from a lower global evoked response (not restricted to the gamma band).

The higher gamma band noise values in our patients were not accompanied by significant SNR differences. This may indicate that background (noise) and task-related gamma-band activities (signal) were higher in patients as compared to controls, since taken together higher noise and normal SNR magnitudes imply an elevated signal power in the corresponding band. However, the nearly significant lessened P3b amplitude in our patients, coherent with the usual reduction of this potential in schizophrenia, suggests that the cortical hyper-activation underlying higher noise power and normal SNR is inefficient in the patients. In other words, patients seem to use more neural activation yet they achieve worse outcome. Similar findings (higher activation to achieve normal or lower cognitive performance) have been reported using functional magnetic resonance (Manoach, 2003).

Such inefficiency would be also consistent with the results obtained with other techniques used to distinguish between resting/background and task-related patterns of brain activity in schizophrenia. Among them, considerable attention was paid using functional magnetic resonance to the default mode network (DMN) (Broyd et al., 2009), a set of regions more active at rest whose activity decreases with engagement in a task, allowing the corresponding activation of other regions. Higher gamma noise power distribution (medial frontal, lateral parietal) is congruent with the topography of that DMN in our patients. Since the neuronal firing rate was reportedly associated with power modulation in the gamma band (Whittingstall and Logothetis, 2009) and, as already noted, there seems to be a strong association between gamma band oscillations and modulation of cerebral blood flow (Niessing et al., 2005; Scheeringa et al., 2011), the impaired task-related deactivation of DMN in schizophrenia (Pomarol-Clotet et al., 2008) could be accompanied by higher gamma activity during a cognitive task on the corresponding DMN regions. Therefore, it could be speculated that the higher gamma noise power in our patients derived from a failure to deactivate their DMN during the odd-ball task. This is to be taken cautiously, since DMN is characterized by very slow oscillations (0.1 to 1 Hz) of the BOLD signal (Broyd et al., 2009).

The basis for the elevated noise power in our patients might have to do with synaptic inhibitory deficits, since gamma band oscillations are influenced by cortical GABA function (Bartos et al., 2007) and gamma band alterations in schizophrenia might relate to GABA dysfunction (Haenschel et al., 2009; Uhlhaas and Singer, 2010). Since EEG signals are thought to be dominated by synaptic currents rather than action potentials, the higher noise power in patients with schizophrenia seems consistent with an inefficient and/or disorganized excess of excitatory activity that can result from an inhibition deficit.

We did not find elevated noise power in the theta band, which can relate to task requirements. Theta power is consistently related to episodic memory tasks (Klimesch, 2003), while gamma oscillations are associated with top-down attentional processes, being the latter but not the former prominent requirements in the P300 paradigm. Even so, the lack of higher noise power in theta band is discrepant with that reported by Winterer et al. (2004), which may be in part explained by our inclusion of first episode and minimally treated patients, as chronicity (Galderisi et al., 2009) and long-term treatment (Galderisi et al., 2009; Knott et al., 2001) have a significant effect on higher theta power in patients with schizophrenia. An association between cognitive impairments and gamma but not theta power has been reported in medicated and unmedicated patients with schizophrenia (Minzenberg et al., 2010).

Our study has limitations. Our patients had received an acute treatment with haloperidol by the moment of their inclusion, but this is not a likely explanation for the findings here reported, since we did not detect higher noise power in controls after the haloperidol administration and a wash-out period similar to those of acute patients. If any, the effect of haloperidol was to lessen the magnitude of noise power in the short-term and thus is unlikely to justify its elevation in the patients. The number of electrodes hampers source localization but the presence of noise power differences limited to any small region seems unlikely. Indeed, the GABA dysfunction in schizophrenia that may underlie gamma dysregulation may be present across cortical areas (Hashimoto et al., 2008). We have not assessed phase-locked and non-phase locked power changes, a complementary approach to the problem here studied that may yield useful information. Finally, we have not considered the possible contribution of other bands to alterations in cognition, due to a priori hypothesis and sample size limitations.

## 5. Conclusion

In our study we describe elevated gamma band noise power over parietal–temporal areas in patients with schizophrenia, most of them first episode patients, in comparison to healthy controls during a P300 paradigm. These higher gamma noise power scores were directly related to negative symptoms severity and inversely related to verbal memory performance. These results support an elevated gamma power independent of stimulus perception or processing that may be detrimental to cognitive functions in schizophrenia. Patients with this disease seem to use more neural activation yet they achieve worse outcome.

## Disclosure

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All authors have approved the final manuscript. The authors have no conflicts of interest to declare.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.pnpbp.2012.04.010.

## References


Anonymous. Brain vision analyzer: user manual. Brain Products GmbH; 2006. p. 55–6.

Barr MS, Farzan F, Tran LC, Chen R, Fitzgerald PB, Daskalakis ZJ. Evidence for excessive frontal evoked gamma oscillatory activity in schizophrenia during working memory. Schizophr Res 2010;121:146–52.

Bartos M, Vida I, Jonas P. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. Nat Rev Neurosci 2007;8:45–56.

Basar-Eroglu C, Brand A, Hildebrandt H, Karolina Kedzior K, Mathes B, Schmiedt C. Working memory related gamma oscillations in schizophrenia patients. Int J Psychophysiol 2007;64:39–45.

Bledowski C, Prvulovic D, Hoechstetter K, Scherg M, Wibral M, Goebel R, et al. Localizing P300 generators in visual target and distractor processing: a combined event-related potential and functional magnetic resonance imaging study. J Neurosci 2004;24:9353–60.

Brown JT, Davies CH, Randall AD. Synaptic activation of GABA(B) receptors regulates neuronal network activity and entrainment. Eur J Neurosci 2007;25:2982–90.

Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ. Default-mode brain dysfunction in mental disorders: a systematic review. Neurosci Biobehav Rev 2009;33:279–96.

Buzsáki G. The gamma buzz: gluing by oscillations in the waking brain, rythms of the brain. New York: Oxford University Press; 2006. p. 231–61.

Farzan F, Barr MS, Levinson AJ, Chen R, Wong W, Fitzgerald PB, et al. Evidence for gamma inhibition deficits in the dorsolateral prefrontal cortex of patients with schizophrenia. Brain 2010;133:1505–14.

Galderisi S, Mucci A, Volpe U, Boutros N. Evidence-based medicine and electrophysiology in schizophrenia. Clin EEG Neurosci 2009;40:62–77.

Haenschel C, Bittner RA, Waltz J, Haertling F, Wibral M, Singer W, et al. Cortical oscillatory activity is critical for working memory as revealed by deficits in early-onset schizophrenia. J Neurosci 2009;29:9481–9.

Hashimoto T, Bazmi HH, Mirnics K, Wu Q, Sampson AR, Lewis DA. Conserved regional patterns of GABA-related transcript expression in the neocortex of subjects with schizophrenia. Am J Psychiatry 2008;165:479–89.

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–76.

Klimesch W. EEG, theta, memory and sleep. In: Polich J, editor. Detection of change: event-related potential and fMRI findings. Norwell: Kluwer Academic; 2003. p. 149–66.

Knott V, Labelle A, Jones B, Mahoney C. Quantitative EEG in schizophrenia and in response to acute and chronic clozapine treatment. Schizophr Res 2001;50:41–53.

Leicht G, Kirsch V, Giegling I, Karch S, Hantschk I, Moller HJ, et al. Reduced early auditory evoked gamma-band response in patients with schizophrenia. Biol Psychiatry 2010;67:224–31.

Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci 2005;6:312–24.

Manoach DS. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. Schizophr Res 2003;60:285–98.

Minzenberg MJ, Firl AJ, Yoon JH, Gomes GC, Reinking C, Carter CS. Gamma oscillatory power is impaired during cognitive control independent of medication status in first-episode schizophrenia. Neuropsychopharmacology 2010;35:2590–9.

Möcks J, Kohler W, Gasser T, Pham DT. Novel approaches to the problem of latency jitter. Psychophysiology 1988;25:217–26.

Niessing J, Ebisch B, Schmidt KE, Niessing M, Singer W, Galuske RA. Hemodynamic signals correlate tightly with synchronized gamma oscillations. Science 2005;309:948–51.

Pomarol-Clotet E, Salvador R, Sarro S, Gomar J, Vila F, Martinez A, et al. Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? Psychol Med 2008;38:1185–93.

Reinhart RM, Mathalon DH, Roach BJ, Ford JM. Relationships between pre-stimulus gamma power and subsequent P300 and reaction time breakdown in schizophrenia. Int J Psychophysiol 2011;79:16–24.

Scheeringa R, Fries P, Petersson KM, Oostenveld R, Grothe I, Norris DG, et al. Neuronal dynamics underlying high- and low-frequency EEG oscillations contribute independently to the human BOLD signal. Neuron 2011;69:572–83.

Segarra N, Bernardo M, Gutiérrez F, Justicia A, Fernández-Egea E, Allas M, et al. Spanish validation of the Brief Assessment in Cognition in Schizophrenia (BACS) in patients with schizophrenia and healthy controls. Eur Psychiatry 2011;26:69–79.

Singer W. Synchronization of cortical activity and its putative role in information processing and learning. Annu Rev Physiol 1993;55:349–74.

Singer W. Neuronal synchrony: a versatile code for the definition of relations? Neuron 1999;24(49–65):111–25.

Tallon-Baudry C, Bertrand O, Peronnet F, Pernier J. Induced gamma-band activity during the delay of a visual short-term memory task in humans. J Neurosci 1998;18:4244–54.

Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci 2010;11:100–13.

Uhlhaas PJ, Roux F, Rodriguez E, Rotarska-Jagiela A, Singer W. Neural synchrony and the development of cortical networks. Trends Cogn Sci 2010;14:72–80.

Whittingstall K, Logothetis NK. Frequency-band coupling in surface EEG reflects spiking activity in monkey visual cortex. Neuron 2009;64:281–9.

Winterer G, Coppola R, Goldberg TE, Egan MF, Jones DW, Sanchez CE, et al. Schizophrenia: reduced signal-to-noise ratio and impaired phase-locking during information processing. Clin Neurophysiol 2000;111:837–49.

Winterer G, Ziller M, Dorn H, Frick K, Mulert C, Wuebben Y, et al. Prefrontal broadband noise, working memory, and genetic risk for schizophrenia. Am J Psychiatry 2004;161:490–500.

# SUPPLEMENTARY DATA

**DATA ANALYSIS**

***P3a and P3b calculation***

Generation of ERP Grand Averages across montage and subsequent topographic EEG magnitude analyses were automatically performed using Brain Vision Analyzer Software® (Brain Products GmbH; Munich, Germany).

P3 amplitude corresponded to the averaged amplitude in the interval 300-400 ms following tones' onsets. The P3a and P3b waveforms were extracted respectively from the distracter-related and target-related Grand Averages.

Spline-interpolated topographical maps of scalp voltage and current source density (CSD) were automatically calculated at the respective 300 interval to distracter and target stimuli.

***Signal to Noise Ratio calculation by the Brain Vision Analyzer Software® (Brain Products GmbH; Munich, Germany)***

The SNR provides a measure of the quality of the EEG signal. Since neither the signal nor the noise in the EEG is known exactly, average total power must be estimated with statistical methods.

In this process it is assumed that noise will be eliminated by averaging. Thus average noise power for each channel is calculated from the total of the squares of the differences between the EEG value and the average value, divided by the number of points minus 1:

$$Avg\ Noise\ Power = \frac{\sum_{n=1}^{N}\sum_{k=1}^{K}(A_{kn} - \bar{A})^2}{K * N - 1}$$

Where N is the number of segments, K is the data point number in the segment, $A_{kn}$ is the amplitude of each point, and $\bar{A}$ is the average total amplitude (separately for each channel):

$$\bar{A} = \frac{\sum_{n=1}^{N}\sum_{k=1}^{K} A_{kn}}{K * N}$$

The average total power of a channel is a result of the mean of the squares for all data points of the channel before averaging:

$$Avg\ Total\ Power = \frac{\sum_{n=1}^{N}\sum_{k=1}^{K} A_{kn}^2}{K * N}$$

It can be assumed that the signal and noise are uncorrelated. Consequently the average power of the signal is equal to the difference between the average total power and the average noise power:

$$Avg\ Signal\ Power = Avg\ Total\ Power - Avg\ Noise\ Power$$

The SNR is then calculated from the quotient of the average signal power divided by average noise power.

$$SNR = \frac{Avg\ Signal\ Power}{Avg\ Noise\ Power}$$

| | **Patients (n=29)** | | **Controls (n=27)** | |
|---|---|---|---|---|
| | **Noise Power** | **SNR** | **Noise Power** | **SNR** |
| Theta Fp1 | 0.107 (0.061) | 0.601 (0.192) | 0.121 (0.055) | 0.574 (0.230) |
| Theta Fp2 | 0.108 (0.054) | 0.590 (0.192) | 0.130 (0.070) | 0.572 (0.185) |
| Theta F3 | 0.089 (0.051) | 0.600 (0.272) | 0.091 (0.050) | 0.572 (0.179) |
| Theta F4 | 0.096 (0.048) | 0.544 (0.202) | 0.079 (0.037) | 0.648 (0.315) |
| Theta C3 | 0.051 (0.023) | 0.542 (0.196) | 0.065 (0.034) | 0.515 (0.210) |
| Theta C4 | 0.053 (0.026) | 0.505 (0.184) | 0.050 (0.022) | 0.573 (0.232) |
| Theta P3 | 0.086 (0.042) | 0.488 (0.187) | 0.075 (0.048) | 0.588 (0.363) |
| Theta P4 | 0.088 (0.045) | 0.503 (0.214) | 0.069 (0.031) | 0.581 (0.282) |
| Theta O1 | 0.163 (0.078) | 0.574 (0.200) | 0.161 (0.109) | 0.626 (0.189) |
| Theta O2 | 0.175 (0.130) | 0.596 (0.210) | 0.152 (0.089) | 0.575 (0.140) |
| Theta F7 | 0.092 (0.046) | 0.539 (0.201) | 0.110 (0.054) | 0.524 (0.206) |
| Theta F8 | 0.098 (0.045) | 0.486 (0.171) | 0.103 (0.042) | 0.545 (0.149) |
| Theta T5 | 0.153 (0.093) | 0.513 (0.191) | 0.136 (0.094) | 0.638 (0.503) |
| Theta T6 | 0.164 (0.117) | 0.530 (0.205) | 0.146 (0.085) | 0.636 (0.352) |
| Theta Fz | 0.117 (0.060) | 0.520 (0.204) | 0.109 (0.058) | 0.622 (0.181) |
| Theta Pz | 0.077 (0.038) | 0.535 (0.239) | 0.078 (0.054) | 0.513 (0.148) |
| Theta Cz | 0.081 (0.046) | 0.549 (0.191) | 0.113 (0.068) | 0.565 (0.202) |
| Gamma Fp1 | 0.012 (0.007) | 0.922 (0.174) | 0.011 (0.006) | 1.016 (0.335) |
| Gamma Fp2 | 0.011 (0.005) | 0.938 (0.140) | 0.012 (0.006) | 0.892 (0.152) |
| Gamma F3 | 0.009 (0.007) | 0.914 (0.168) | 0.009 (0.014) | 1.041 (0.281) |
| Gamma F4 | 0.010 (0.011) | 1.017 (0.600) | 0.009 (0.009) | 0.870 (0.234) |
| Gamma C3 | 0.010 (0.015) | 0.834 (0.165) | 0.008 (0.007) | 0.817 (0.246) |
| Gamma C4 | 0.009 (0.008) | 0.777 (0.218) | 0.009 (0.010) | 0.829 (0.341) |
| **Gamma P3** | **0.011 (0.007)*** ** | 0.857 (0.204) | 0.007 (0.004) | 0.953 (0.322) |
| **Gamma P4** | **0.010 (0.005)** ** | 0.894 (0.279) | 0.007 (0.004) | 0.953 (0.251) |
| Gamma O1 | 0.048 (0.054) | 0.882 (0.199) | 0.029 (0.038) | 1.068 (0.566) |
| Gamma O2 | 0.037 (0.039) | 0.955 (0.210) | 0.029 (0.028) | 0.972 (0.315) |
| Gamma F7 | 0.021 (0.019) | 0.760 (0.222) | 0.024 (0.032) | 0.856 (0.220) |
| Gamma F8 | 0.019 (0.014) | 0.762 (0.209) | 0.019 (0.028) | 0.875 (0.215) |
| **Gamma T5** | **0.025 (0.014)*** ** | 0.886 (0.204) | 0.015 (0.009) | 0.963 (0.237) |
| Gamma T6 | 0.019 (0.012) | 0.914 (0.265) | 0.021 (0.023) | 0.960 (0.270) |
| **Gamma Fz** | **0.007 (0.003)*** ** | 0.936 (0.205) | 0.005 (0.003) | 0.990 (0.200) |
| Gamma Pz | 0.008 (0.005) | 0.875 (0.235) | 0.006 (0.004) | 0.883 (0.228) |
| Gamma Cz | 0.006 (0.003) | 1.093 (0.777) | 0.005 (0.003) | 1.186 (0.376) |

**Table S1. Noise power ($\mu V^2$) and SNR values per band and electrode. Band/electrode noise power values significantly different in the same direction in both groups of patients as compared to controls are highlighted.**

**p<0.05; ***p<0.01; with respect to healthy controls (t test for independent samples).

| | **Mean (sd)** | **Z (p)** |
|---|---|---|
| Gamma noise power P3. Basal<br>Gamma noise power P3. Halop | 0.007(0.007)<br>0.004(0.002) | -1.43(0.14) |
| Gamma noise power P4. Basal<br>Gamma noise power P4. Halop | 0.010(0.014)<br>0.007(0.007) | -0.67(0.50) |
| Gamma noise power Fz. Basal<br>Gamma noise power Fz. Halop | 0.006(0.005)<br>0.005(0.003) | -0.14(0.89) |
| Gamma noise power T5. Basal<br>Gamma noise power T5. Halop | 0.014(0.011)<br>0.009(0.005) | -2.02(0.04) |
| SNR gamma P3. Basal<br>SNR gamma P3. Halop | 0.940(0.136)<br>1.021(0.097) | -1.75(0.08) |
| SNR gamma P4. Basal<br>SNR gamma P4. Halop | 1.008(0.158)<br>0.995(0.117) | -0.13 (0.89) |
| SNR gamma T5. Basal<br>SNR gamma T5. Halop | 0.669(0.175)<br>0.990(0.234) | -0.67 (0.50) |
| SNR gamma Fz. Basal<br>SNR gamma Fz. Halop | 1.127(0.308)<br>1.074(0.225) | -1.21(0.22) |
| p3b amplitude Pz. Basal<br>p3b amplitude Pz. Halop | 2.894(1.995)<br>3.008(1.56) | -0.67 (0.50) |

**Table S2. Noise power ($\mu V^2$), SNR and P3b amplitude ($\mu V$) values in healthy controls (n=5) before and 24 hours after receiving 2 mg of haloperidol, following the procedure undergone by the patients (Wilcoxon test).**

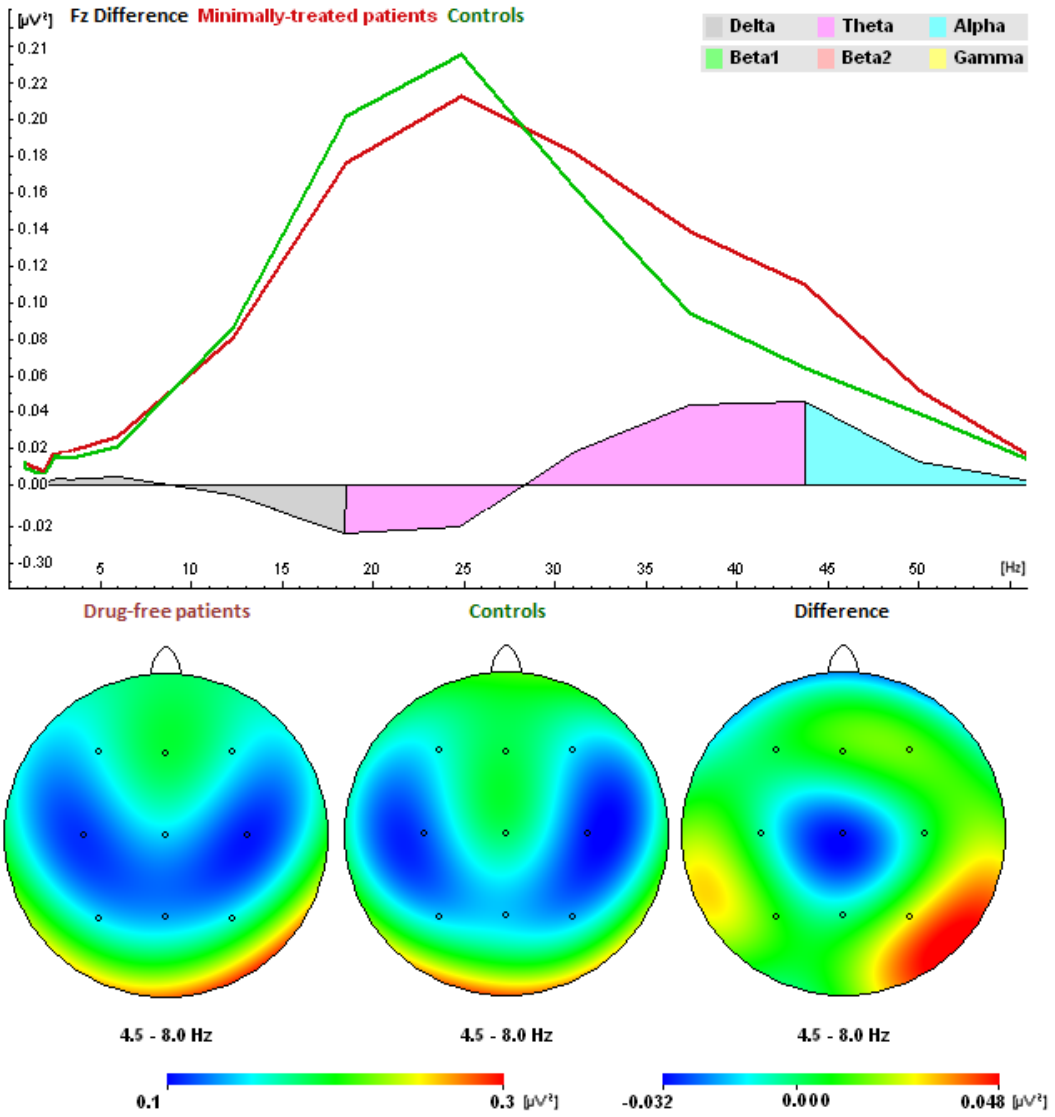


**Figure S1. Theta total power (μV²) differences between minimally-treated patients and healthy controls at Fz site.**

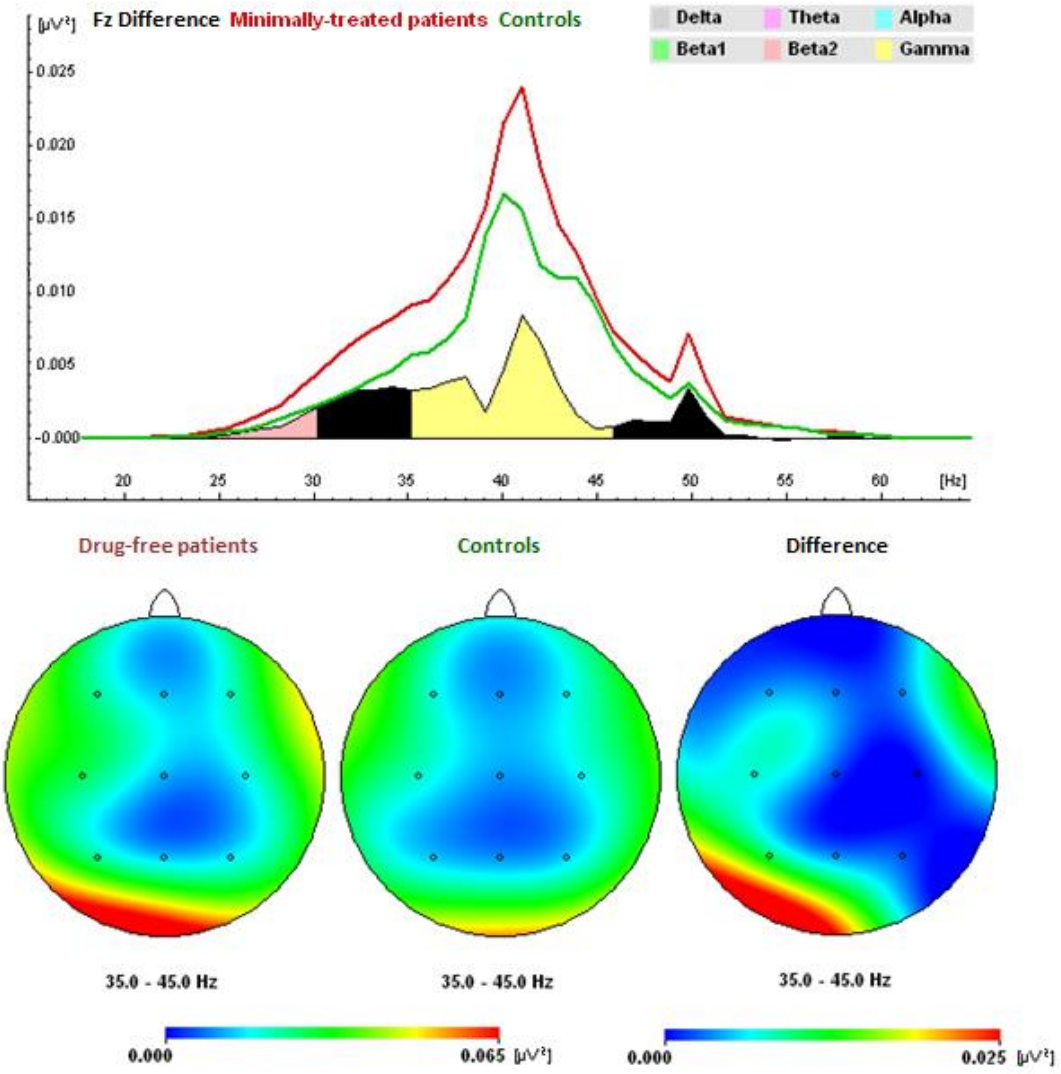


**Figure S2. Gamma total power (μV²) differences between minimally-treated patients and healthy controls at Fz site.**

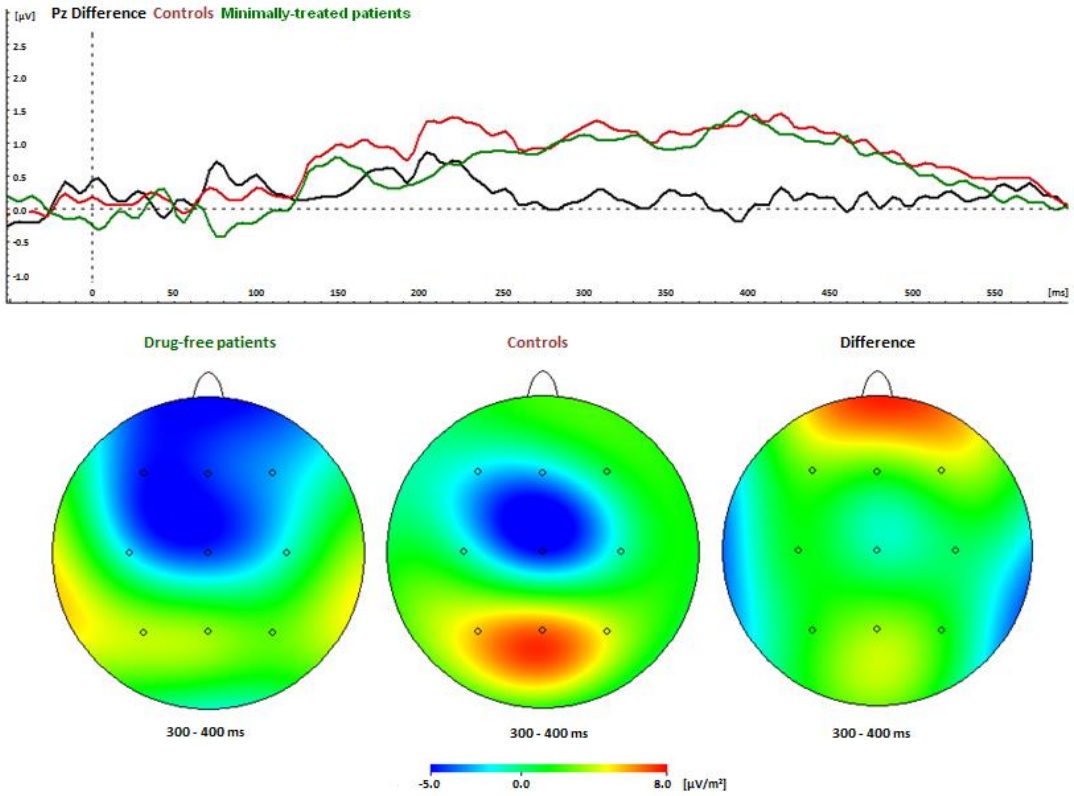


**Figure S3. P3a amplitude (µV) differences between minimally-treated patients and healthy controls at Pz site.**

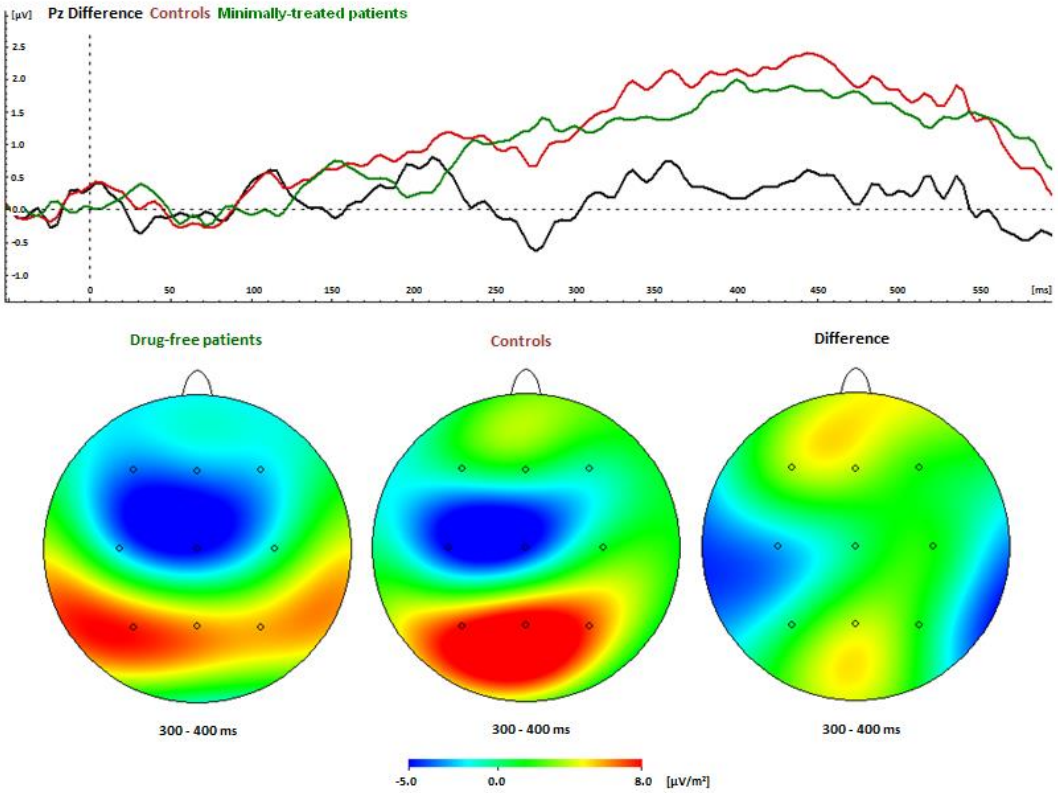


**Figure S4. P3b amplitude (µV) differences between minimally-treated patients and healthy controls at Pz site.**