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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)