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Frontal gamma noise power and cognitive domains in schizophrenia

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ABSTRACT

The cognitive deficit profile is different among individuals with schizophrenia. We quantified the amount of electroencephalographic activity unlocked to stimuli onset (noise power) over frontal regions regarding deficit in cognitive domains. Forty-six patients with schizophrenia and 27 healthy controls underwent clinical, cognitive and electrophysiological assessments. Noise power studies may be considered complementary but not equivalent to induced power studies. We compared gamma and theta noise power magnitude during a P300 paradigm between subsets of patients divided according to cognitive deficit in key domains and controls. Patients displayed higher gamma noise power activity at Fz site and significantly lower performance in all cognitive domains when compared to controls. The subset of patients with cognitive deficit for working memory and problem solving/executive functions domains displayed significantly higher frontal–lateral noise power values in comparison to the subset of patients without cognitive deficit and controls. Patients with significant cognitive deficits in domains with greater frontal contribution are also characterized by an abnormally higher gamma band noise power over the frontal region. Our data may endorse various biological subsets within schizophrenia, characterized by the presence or absence of a significant cognitive deficit in frontal domains.

1. Introduction

The schizophrenia phenotype varies in terms of biological underpinnings (Honea et al., 2005) and cognitive profile (Dickinson et al., 2007), which lead researchers to propose distinct pathological pathways within the disorder (Tandon et al., 2009).

One replicated biological finding in schizophrenia is a hyperactive pattern in regions not involved in the task being performed while areas expected to be functional appear hypoactive (Manoach, 2003; Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009). Such a pattern can be a possible substrate for the cognitive deficit that many patients exhibit and seems coherent with the extant data that suggests a lower synaptic inhibitory activity in schizophrenia (Lewis et al., 2005; Uhlhaas et al., 2010). Interestingly, recent data support the existence of a subset of patients with schizophrenia with clear frontal GABA neuron-related deficits (Volk et al., 2012).

Since GABA neurotransmission seems relevant in the generation (Whittington et al., 1995; Bartos et al., 2007) and modulation (Brown et al., 2007; Teale et al., 2008) of high-frequency oscillations in the brain, a deficit in normal inhibition could lead to an impaired selection of neural assembly related to task that may hamper performance.

The relevance of GABAergic system for these oscillations cannot be isolated from its interaction with other neurotransmission systems. First, parvalbumin-positive interneurons possess NR2A and NR2B type NMDA receptors (Kinney et al., 2006), making them susceptible to changes in glutamatergic conduction that may in turn contribute to an inhibitory cortical dysfunction, in particular in a hypo-NMDA state (Cull-Candy et al., 2001; Loftis and Janowsky, 2003). The administration of NMDA antagonists to animal models has been demonstrated to lead to gamma activity decrease (Cunningham et al., 2006; Zhang et al., 2008), albeit with some contradictory data (Pinault, 2008; Roopun et al., 2008) probably reflecting the complexity of the neurotransmission processes involved. Moreover, cholinergic (Rodriguez et al.,

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2004; Wespatat et al., 2004) and dopaminergic (Ito and Schuman, 2007; Andersson et al., 2012) activities are also involved in the modulation of gamma oscillations and response synchronization.

An approach to assess in vivo that pattern of cortical activity plausibly associated to inhibition deficits is therefore to quantify the amount of electroencephalographic (EEG) activity unrelated to a given task's performance. In this respect, the study of theta and gamma oscillations seems accurate considering these bands are involved in local neural circuits coordination underlying higher cerebral functions, probably in relation to their capacity to subtend transient functional assembly formation (Singer, 1993). These frequency bands may contribute to coherent percepts construction by the brain and to the strengthening and weakening of synaptic links (Buzsáki, 2006b) and, in the case of gamma oscillations, to neural activity integration within and between regions in a range of cognitive functions (Singer, 1999). Higher baseline auditory steady-state response in the 40 Hz (i.e., gamma) band has been reported in schizophrenia (Spencer, 2011).

Among the possibilities to assess collective neural activity organization stands quantifying the amount of bioelectrical activity not related to the task being performed by employing a "noise power" measurement (Möcks et al., 1988). Noise power is quantified as the averaged electrical power in each band of the EEG resulting from the difference between the power of the averaged signal, which is related to the task being performed, from the corresponding power of the averaged total signal (which is comprised of the background EEG activity, unrelated to task processing, and the task-related signal).

Higher noise power in patients with schizophrenia in relation to healthy controls may be expected as a correlate of an excessive extension of cortical activation at the expense of adequate selection of neural populations and cognitive performance. In fact, an increase in broadband noise power has been reported in schizophrenia (Winterer et al., 2004). During a preparatory control task, gamma power was lessened in frontal electrodes in the high-control vs. low-control conditions in patients with schizophrenia while it was higher in healthy controls (Minzenberg et al., 2010), suggesting a hyperactive basal state at this level in the former. Recently, we reported a gamma noise power elevation in minimally treated patients with schizophrenia over frontal, central and parietal regions (Suazo et al., 2012). We also found similar results in a population of both chronic and minimally treated patients with schizophrenia when studying electrode clusters through principal component analysis, resulting in an elevated gamma noise power over a factor coherent with the default mode network (DMN) topography, and a significant inverse association between the same measure over a fronto-lateral factor and the working memory and problem solving outcome (Diez et al., 2013).

It would be of interest to investigate if such associations between frontal noise power and cognition are specific to a certain domain or whether this neurophysiological measure relates to a more widespread cognitive deficit. In the first case, the association between a plausible biological deviation and a clinically relevant deficit, also plausibly arising from the same region, might be a contributing step towards identifying a specific subtype within the schizophrenia syndrome. This hypothetical subtype might be contributed by significant inhibitory transmission alterations, since GABA function is essential for the brain's oscillatory activity (Buzsáki, 2006a) and may be altered in a proportion of schizophrenia cases (Volk et al., 2012).

In the present study, considering that the relevance frontal function alterations may have in schizophrenia we continue our earlier work, which associated frontal-like noise power elevation with worst cognitive outcome (Suazo et al., 2012; Diez et al., 2013). Using factor analysis we identified a distinct frontal factor, whose noise power values were associated to cognitive performance in patients (Diez et al., 2013). Therefore we presently address the specific hypothesis that patients with a clinically significant performance deficit during tasks with greater frontal involvement would be identified by a less efficient cortical function over frontal regions (i.e., abnormally high noise power values as compared to both non-deficit cases and healthy controls). This could be relevant as a step towards disentangling the phenotypic and biological variation within the schizophrenia syndrome. However, the mere demonstration of a noise power increase in patients with as compared to patients without deficit, in the absence of a significant elevation as compared to healthy controls, would not support the possibility of a distinct biological substrate for that kind of deficit.

2. Materials and methods

2.1. Participants

We included 46 patients with schizophrenia (DSM-IV-TR) and 27 controls; including 22 stable patients, treated in the long-term, and 24 untreated cases who received a minimal treatment prior to the EEG examination (minimally treated patients), of the latter 14 first episodes.

During the preceding year the stable patients had been treated with atypical antipsychotics (risperidone 11 participants (2–6 mg/d)), olanzapine six participants (5–20 mg/d), quetiapine two participants (300–600 mg/d) and clozapine five participants (100–350 mg/d). Two cases received two different antipsychotics in their treatment. Doses and drugs were unchanged during the 3 months preceding EEG recordings.

Prior to their inclusion minimally treated patients had not received any previous treatment (first episode patients) or they had dropped their medications for longer than 1 month. Owing to an acute psychotic state of these patients we administered a small amount of haloperidol (2–4 mg during 24 h or less, which amounted to three doses) 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, although cases suffering from agitation or severe behavioral problems were not included. Participants' level of cooperation was assessed by the number of correct responses during the P300 evocation task. We discarded significant haloperidol effects on gamma and theta noise power in five controls (Table SM1).

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 controls through newspaper advertisements and remunerated their cooperation. They were previously assessed by a semi-structured psychiatric interview to discard major psychiatric antecedents 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; any other psychiatric process or treatment and treatment with drugs known to act on the central nervous system. We discarded toxic use in all participants with the information gathered in the interview and a urinalysis.

We obtained written informed consent from all participants 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).

2.2. 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): 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 (Wechsler, 1997) to assess IQ.

To test our hypothesis we divided the patients into those less than or equal to −2 s.d. from the mean value of the controls for each neuropsychological test (cognitive deficit criterion) and those who did not fulfill this requirement. By doing so, we intended to segregate groups whose cognitive handicap was more likely to hamper real life performance.