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A typical antipsychotics normalize low-gamma evoked oscillations in patients with schizophrenia☆

Manuel Alegre[a,c,1], Patricio Molero[b,1], Miguel Valencia[c], Guillermo Mayner[b], Felipe Ortuño[b], Julio Artieda[a,c,*]

[a] Clinical Neurophysiology Section, Clínica Universidad de Navarra, Pamplona, Spain
[b] Department of Psychiatry, Clínica Universidad de Navarra, Pamplona, Spain
[c] Neurophysiology Laboratory, CIMA (Centre for Applied Medical Research) Universidad de Navarra, Pamplona, Spain

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ABSTRACT

The symptoms of schizophrenia might be mediated by a cortical network disconnection which may disrupt the cortical oscillatory activity. Steady-state responses are an easy and consistent way to explore cortical oscillatory activity. A chirp-modulated tone (increasing the frequency of the modulation in a linear manner) allows a fast measure of the steady-state response to different modulation rates. With this approach, we studied the auditory steady-state responses in two groups of patients with schizophrenia (drug-naive and treated with atypical antipsychotic drugs), in order to assess the differences in their responses with respect to healthy subjects, and study any potential effect of medication. Drug-naive patients had reduced amplitude and inter-trial phase coherence of the response in the 30–50 Hz range, and reduced amplitude of the response in the 90–100 Hz range, when compared to controls. In the treated patients group, the response in the 30–50 Hz range was normalized to values similar to the control group, but the reduction in amplitude in the 90–100 Hz range remained as in the drug-naive group. These results suggest that gamma activity impairment in schizophrenia is a complex phenomenon that affects a wide band of frequencies and may be influenced by antipsychotic treatment.

1. Introduction

Synchronization seems to play a critical role in the information processing by neural networks (Singer, 1993). Current theories on the pathophysiology of schizophrenia suggest that some of the key findings of the disease might be mediated by a disconnection syndrome both within and between different cortical areas (Phillips and Silverstein, 2003; Uhlhaas, 2013). Changes in cortical oscillatory activity might be the functional correlate of this cortical network disco3nnection, and thus may be related with the cognitive dysfunction and psychopathological symptoms of the disorder (Uhlhaas and Singer, 2010). On the other hand, the functional disconnection of cortical networks might be the consequence of alterations in the anatomical connectivity, as suggested by the grey and white matter anomalies described in the disease (Kubicki et al., 2007;Crossley et al., 2009).

One way to study brain synchronization is through the analysis of the oscillatory activity in the EEG. There have been many reports of altered oscillatory activity in schizophrenia, in a wide band from slow (theta) to faster activities (gamma) (Uhlhaas and Singer, 2015; Kirihara et al., 2012). Gamma activity has raised special interest in this regard, as this band has been particularly involved in several aspects of cortical binding (Singer, 1993; Senkowski and Gallinat, 2015).

Steady-state responses are an easy and consistent way to explore cortical oscillatory activity. Steady-state responses are defined as oscillatory brain responses to the rhythmic stimulation of a sensory pathway (Stapells et al., 1984). The amplitude of the oscillatory response critically depends on the stimulation frequency and its modality. In the auditory pathway, the amplitude of the responses are highest around 40 Hz (Galambos et al., 1981), as well as between 80 and 120 Hz (Lins et al., 1995). The greater amplitude in the response observed at these stimulation rates may be related to the preferential working frequencies of the auditory pathway. Auditory steady-state responses were originally obtained with rhythmic clicks,

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* Correspondence to: Clinical Neurophysiology Section, Clínica Universidad de Navarra, Avda. Pío XII, 36, 31008 Pamplona, Navarra, Spain.
E-mail address: jartieda@unav.es (J. Artieda).

[1] These authors have participated equally in this paper.

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Table 1
Clinical and demographic characteristics of the patients.

	Antipsychotic drug naïve group (n=11)	Treated with antipsychotic drugs group (n=17)	*p*-values
Age Mean (sd)	32.6 (9.6)	38.5 (16.5)	*t*-test p > 0.05
Sex Male (%)	63.6	41.2	Chi-square p > 0.05
Completed educational level			Chi-square p > 0.05
Primary education (%)	9.1	11.8	
Secondary education (%)	45.5	58.8	
University/Professional education (%)	45,5	29.4	
Smoker Yes (%)	9.1	23.5	Chi-square p > 0.05
Cigarettes per day Mean (sd)	2.7 (9)	6.5 (15)	t-test p > 0.05
Chlorpromazine Equivalents (mg/day)[a] Mean (sd)	0 (0)	562.5 (380.7)	
Illness duration (mounths) Median (IQR)	0 (0)	24 (123.5)	

[a] Chlorpromazine Equivalents according to the International Consensus Study of Antipsychotic Dosing (Gardner et al., 2010).

but they can also be obtained using amplitude-modulated tones that produce *amplitude modulation following responses* (AMFR) (Picton et al., 1987).

A reduction in both amplitude and phase synchronization in 40 Hz AMFR has been described in patients with schizophrenia (Light et al., 2006). Previous studies carried out in different brain diseases suggest that abnormalities in oscillatory activity do not only affect the amplitude of the responses, but also their frequency (Pastor et al., 1996a; Arrondo et al., 2009). The use of a chirp-modulated tone (increasing the frequency of the modulation in a linear manner) instead of a constantly modulated tone allows to explore the auditory oscillatory response to a wide range of stimulation frequencies in a single test (Artieda et al., 2004). This technique allows a fast measure of the amplitude of the response to different modulation rates, which would otherwise require individual testing of every single click or modulation rate. The aim of our study was to assess the AMFR response in two groups of treated and untreated patients with schizophrenia using a chirp stimulus, in order to assess the differences in their responses to a wide range of frequencies with respect to healthy subjects, and study in detail any potential effect of medication.

2. Methods

2.1. Participants

Two kind of patients were recruited: i) patients acutely psychotic experiencing a first-episode schizophrenia who were antipsychotic drug-naïve at the moment of the study. And ii) patients already diagnosed with schizophrenia, under long-term treatment with antipsychotics and clinically compensated, with a documented history of good adherence to treatment, who were taking only one or two antipsychotics at the moment of the study. The determination of clinical compensation was done upon confirmation of each patient's attending psychiatrist, in addition to these criteria: (i) outpatient treatment with no need for hospitalization during the previous year and (ii) maintained Global Assessment of Functioning Scale (GAF, DSM-IV Axis V) of 60 or higher during the previous year. Exclusion criteria were alcohol and/or substance use (with the exception of tobacco) and other psychiatric or neurological comorbidities, and the use of all kinds of drugs other than antipsychotics at the moment of the EEG study for the treated group. Only right-handed participants were included in this study, given the important connotations of handedness in the EEG response. The whole analytical procedure (signal and statistical analyses) was blinded regarding the patient/control and treated/untreated conditions.

28 patients with diagnosis of Schizophrenia were included in the study. The demographic and clinical characteristics of the patients are presented in Table 1. Of them, 11 were acutely psychotic and antipsychotic drug-naive at the moment of the EEG recording, and 17 were patients already diagnosed with schizophrenia (median duration of illness of 2 years), clinically compensated and under long treatment with antipsychotics (mainly one single atypical antipsychotic). Treatment compliance was confirmed with close clinical monitoring during the 14 days prior to the EEG recording. There were no significant differences in age, gender distribution, completed educational level and nicotine consumption between treated and untreated patients (Table 1). 13 young healthy subjects recruited from the university staff (8 male, mean age 27.6 ± 3.3 years) were also included in the study. There were no significant differences in age and gender distribution between patients and healthy subjects. All of them were informed in detail about the experiment, and gave their written consent. The protocol was approved by the institutional ethics committee.

2.2. Recording procedure

The subjects were seated in an armchair in a dim-lit and sound-attenuated room during the whole procedure. They were told to remain at rest and listen passively to the sound. 64 EEG channels were recorded in monopolar montage referred to both earlobes, according to the 10-10 international system, using a commercial electrode cap (Electro-CAP, USA) and BrainAmps amplifiers (Brain Products, Germany). The signal was amplified x20000, filtered 1–300 Hz, digitized at 1000 Hz and stored in a PC for offline analysis, by means of Brain Vision Recorder software (Brain Products, Germany). A minimum of 500 sweeps were recorded per subject, synchronized with the beginning of the sound. The length of the sweep was 2 s, with a pre-stimulus period of 0.2 s.

2.3. Stimulus generation

The auditory stimuli were designed in the Matlab® environment