Eur Arch Psychiatry Clin Neurosci
DOI 10.1007/s00406-014-0525-5

ORIGINAL PAPER

Decreased entropy modulation of EEG response to novelty and relevance in schizophrenia during a P300 task

Alejandro Bachiller · Alba Lubeiro · Álvaro Díez · Vanessa Suazo · Cristina Domínguez · José A. Blanco · Marta Ayuso · Roberto Hornero · Jesús Poza · Vicente Molina

Received: 15 April 2014 / Accepted: 8 August 2014

Abstract The analysis of the interaction between novelty and relevance may be of interest to test the aberrant salience hypothesis of schizophrenia (SCH). In comparison with other neuroimaging techniques, such as functional magnetic resonance imaging, electroencephalography (EEG) provides high temporal resolution. Therefore, EEG is useful to analyze transient dynamics in neural activity, even in the range of milliseconds. In this study, EEG activity from 31 patients with SCH and 38 controls was analyzed using Shannon spectral entropy (SE) and median frequency (MF). The aim of the study was to quantify differences between distractor (i.e., novelty) and target (i.e., novelty and relevance) tones in an auditory oddball paradigm. Healthy controls displayed a larger SE decrease in response to target stimulus than in response to distractor tones. SE decrease was accompanied by a significant and widespread reduction of MF (i.e., a significant slowing of EEG activity). In comparison with controls, patients showed a significant reduction of changes in SE in response to both target and distractor tones. These differences were also observed in patients that only received a minimal treatment prior to EEG recording. Furthermore, significant changes in SE were inversely correlated to positive and total symptoms severity for SCH patients. Our findings support the notion that SCH is associated with a reduced response to both novelty and relevance during an auditory P300 task.

Keywords Schizophrenia · Shannon entropy · Positive symptoms · Saliency · Novelty · Relevance

Introduction

The analysis of bioelectrical changes from baseline to the processing stages of an auditory discrimination task using

Electronic supplementary material The online version of this article (doi:10.1007/s00406-014-0525-5) contains supplementary material, which is available to authorized users.

A. Bachiller · A. Lubeiro · R. Hornero · J. Poza
Biomedical Engineering Group, Department T.S.C.I.T., E.T.S. Ingenieros de Telecomunicación, University of Valladolid, Paseo Belén, 15, CP 47011 Valladolid, Spain

Á. Díez
Division of Psychiatry, Faculty of Brain Sciences, University College London, Charles Bell House, 67-73 Riding House Street, London W1W 7EJ, UK

V. Suazo
Neuroscience Institute of Castilla y León, University of Salamanca, Calle Pintor Fernando Gallego, 1, CP 37007 Salamanca, Spain

V. Suazo · R. Hornero · J. Poza · V. Molina (✉)
Institute of Biomedical Research (IBSAL), Salamanca, Spain
e-mail: vmolina@med.uva.es

C. Domínguez · J. A. Blanco · V. Molina
Psychiatry Service, University Hospital of Valladolid, Valladolid, Spain

M. Ayuso
Neurophysiology Service, University Hospital of Valladolid, Valladolid, Spain

R. Hornero · J. Poza
Instituto de Investigación en Matemáticas (IMUVA), University of Valladolid, Valladolid, Spain

V. Molina
Psychiatry Department, Faculty of Medicine, University of Valladolid, Avenida de Ramón y Cajal, 7, CP 47005 Valladolid, Spain

Published online: 28 August 2014

electroencephalographic (EEG) recordings may help to better understand the dynamic information processing abnormalities observed in schizophrenia (SCH) [43]. In particular, exploring aberrant salience correlates in psychosis might be useful [22]. Some studies suggest that salience could be altered in SCH [11]. Specifically, a heightened response to novel but irrelevant stimuli [11] and/or a decreased response to relevant stimuli [17] has been associated with this syndrome. Therefore, comparing the response to novelty and relevance between a group of patients with SCH and healthy controls should be of interest to the study of this illness. Salience detection is a short-lived process [28]. Both novelty [16] and salience [15] detection occur in the few hundred milliseconds following stimulus presentation. Thereby, due to its temporal resolution, EEG may be a useful tool to study their respective contributions to SCH.

Auditory event-related potential (ERP) oddball paradigms are adequate methods for studying novelty and relevance. For that purpose, they include standard (i.e., frequent), distractor and target (i.e., infrequent) tones. Target and distractor tones are randomly interspersed among a series of standard tones. Distractor tones usually have the same frequency as target tones and a pitch between the target and standard tones. Nevertheless, unlike target tones, distractor tones do not require a response. Hence, distractor tones only possess a novelty component, since they are irrelevant for the task. However, target tones possess both novelty and relevance. A classical approach to analyzing evoked ERP components is to perform the grand-average across trials in the time domain. In the widely used oddball paradigm, the participant is instructed to respond to the target and ignore the distractor tones. Event-related cerebral activity can be observed by averaging in the time domain, while cerebral activity not related to the event is canceled, allowing for the assessment of amplitude and latency of the corresponding ERP. The P3a ERP component is related to novelty. Thus, it is determined from the grand-average amplitude of the responses to the distractor stimuli. On the other hand, P3b is also elicited by infrequent tones but, unlike P3a, it is task relevant. Thereby, P3b is computed from the grand-average amplitude of the responses to the target stimuli [14, 31].

Previous studies indicate that salience detection may be impaired in SCH. This impairment should be reflected in a reduced response to the relevant stimuli of an oddball task (where the participant is instructed to respond only to the target stimuli). Indeed, during the performance of this task, a reduced cerebral activity has been found after the relevant stimuli onset in SCH [9]. That reduced activity was supported by a decrease in P3b (i.e., the response to the relevant stimuli) amplitude [9]. However, an overall reduced response to novelty may also contribute to salience detection impairment. In oddball tasks, the response to novelty but not relevance can be assessed by means of the P3a potential. This potential arises after the presentation of the distractor stimuli to which the participant should refrain from responding (i.e., irrelevant). A reduced P3a amplitude has also been found in SCH [20, 36]. It has been observed in first episodes [23] and high-risk participants [3, 27].

Classical ERP components analyses have several limitations, like the lack of simultaneous information about the time and spectral dynamics of oscillatory components [37, 41]. For this reason, time–frequency analyses are carried out. Spectral parameters can yield additional information about time–frequency components of the response to novelty and relevance. Firstly, the median frequency (MF) is a classical technique that has been used to analyze the distribution of the spectral content of a signal. It summarizes the whole spectral content by means of a measure of the frequency that comprises 50 % of signal power [32]. Secondly, the Shannon spectral entropy (SE) has been computed to gain further insights into the characterization of the power spectrum. SE quantifies the degree of disorder of a signal. It is a measure derived from the original notion suggested by Shannon [41], who defined entropy as the average amount of information of a probability distribution. This concept was extended to EEG power spectral density (PSD) by Inouye et al. [21]. Thus, a high SE value implies a flat, uniform power spectrum with a broad spectral content (i.e., a more complex signal), whereas a low SE indicates a power spectrum with a narrower frequency range (i.e., a more regular signal). In an auditory oddball approach, SE is useful for assessing differences in information content and signal variability average across time. Hence, it can be helpful for the study of cognitive processing substrates. Likewise, SE may contribute to improve our understanding of the altered cortical processing mechanism in mental illness, especially when considering task-related differences between baseline and stimulus response conditions [5].

To date, MF and SE have been barely used in SCH research. In this regard, Sabeti et al. [39] assessed their discriminatory ability in comparison with other parameters. They did not find any differences in SE between a group of patients and controls during resting-state activity. However, using a SE-based method, an increased connection entropy in the gamma band was described in patients with SCH [40]. In a recent study, our group described a widespread decrease of SE across electrodes in response to the target tone of an auditory oddball task in healthy controls [5]. In that work, patients with SCH showed smaller changes in SE than controls in response to the target tone [5]. Moreover, changes in SE were associated to clinical severity [5].

In the present research, we further explored the alterations in stimulus processing, likely associated with aberrant salience in SCH. To that end, we studied the changes in SE between baseline and response to both distractor and target tones during a P300 task. Furthermore, we analyzed the responses to relevant (P3b) and novel but irrelevant (P3a) stimuli of participants from our previous study [5], in order to compare the differences in responses (i.e., changes in SE) to novelty and relevance.

Materials and methods

Participants

The cohort of participants enrolled in the study was formed by 31 patients with SCH and 38 healthy controls. Patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition [1] criteria and were divided into 20 chronic stably treated patients (CP) and 11 minimally treated patients (MTP). Prior to their inclusion, MTP did not receive any previous treatment (first episode patients, $n = 8$) or they had dropped their medications for longer than 1 month. Owing to an acute psychotic state of MTP group, a small amount of haloperidol (2–4 mg) was administered with a wash-out period of approximately 24 h before EEG acquisition. The objective was to minimize the likely bias of only including patients able to cooperate with the EEG recording during an acute psychotic episode and without any previous treatment. The stable patients were previously treated with atypical antipsychotics: risperidone (12 cases, 2–6 mg/day), olanzapine (5 cases, 5–20 mg/day), quetiapine (2 cases, 300–600 mg/day), aripiprazole (1 case, 10–15 mg/day) and clozapine (4 cases, 100–350 mg/day). Four patients received two different antipsychotics. Doses and drugs were unchanged during the 3 months preceding EEG recordings.

The clinical status of the patients was scored using the Positive and Negative Syndrome Scale (PANSS) [24]. The intelligence quotient (IQ) was acquired using the Spanish version of the Wechsler Adult Intelligence Scale 3rd edition (WAIS-III) [42]. Demographic and clinical characteristics for both groups are shown in Table 1.

The control group was composed of age- and gender-matched participants. They were recruited through newspaper advertisements and remunerated for their cooperation. To discard major psychiatric antecedents (personal or familial) and treatments, they were previously assessed by a semi-structured psychiatric interview by one researcher (V. Molina).

The exclusion criteria can be summarized as follows: (1) total IQ below 70; (2) a history of any neurological illness; (3) cranial trauma with loss of consciousness; (4) past or present substance abuse, except nicotine or caffeine; and (5) 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 urine analysis.

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

Electroencephalographic recording

EEG data were continuously recorded from 17 electrodes using a BrainVision® (Brain Products GmbH; Munich, Germany) amplifier system. Electrodes were mounted in an

Table 1 Demographic, clinical, cognitive and EEG parameters

	Patients		Controls
	CP	MTP	
Total participants (*N*)	20	11	38
Age (years)	40.37 (10.36)	33.53 (9.91)	33.65 (13.12)
Sex distribution (M:F)	12:8	7:4	23:15
School years*	6.62 (3.01)	12.47 (2.59)	13.00 (5.74)
PANSS positive	19.26 (5.29)	21.12 (3.99)	NA
PANSS negative	22.00 (4.80)	17.00 (4.69)	NA
PANSS total	76.26 (15.63)	76.27 (11.37)	NA
Total IQ (WAIS-III)**	86.31 (14.94)	82.19 (16.76)	101.94 (12.44)
Number of artifact-free epochs	78.65 (19.78)	69.90 (18.16)	84.47 (9.32)
P3a amplitude (Pz) in μV	2.26 (1.17)	2.63 (1.23)	2.53 (1.36)
P3b amplitude (Pz) in μV**	1.74 (1.21)	2.78 (1.28)	3.39 (1.59)

Values are shown as mean (standard deviation, *SD*)

P300 amplitudes are shown in microvolts (μV)

CP chronic stable patients, *MTP* minimally treated patients, *NA* not applicable, *M* male, *F* female

Results of between-groups statistical analyses are shown in the first column (Kruskal–Wallis test, * $p < 0.01$; ** $p < 0.005$)

electrode cap (Electro-Cap International, Inc.; Eaton, Ohio, USA) at Fp1, Fp2, F3, F4, F7, F8, C3, C4, P3, P4, O1, O2, T5, T6, Fz, Pz and Cz. They were placed according to the revised 10/20 international system. Electrode impedance was always kept under 5 kΩ. Participants were instructed to sit comfortably, relaxed and with their eyes closed to avoid muscle and eye movements. Thirteen minutes-length ERP recordings were acquired at a sampling rate of 250 Hz, while the participants underwent a three-stimulus auditory oddball task. The tones (duration 50 ms, rise and fall time 5 ms and intensity 90 dB) were presented with different frequencies: a 500 Hz-tone target; a 1,000 Hz-tone distractor; and a 2,000 Hz-tone standard stimulus. Random series of 600 tones consisted of target, distractor and standard tones with probabilities of 0.20, 0.20 and 0.60, respectively. The participants were asked to press a button whenever they detected the target tones. P3a and P3b components represent the evoked response, which is associated with event-related changes phase-locked to the stimulus onset [37]. They were defined as the mean of ERP grand-average amplitude in the 300–400 ms interval from distractor and target stimuli, respectively.

The recordings were referenced over Cz electrode. Data were re-referenced to the average activity of all active sensors [8], since common average reference is less sensitive to microsaccadic artifacts in high-frequency recordings [25]. Then, each ERP recording was filtered using a 1–70 Hz finite impulse response (FIR) filter and a 50 Hz notch filter. Artifact rejection was conducted following a two-steps approach. Firstly, an independent component analysis (ICA) was carried out to decompose ERPs in a total of 17 components [13]. After a visual inspection of the scalp maps and their temporal activation, the components related to eyeblinks were discarded. Secondly, artifacts were automatically rejected using an adaptive thresholding method to remove EEG segments that displayed amplitudes exceeding a statistically based local threshold criterion. EEG recordings were then segmented into 800 ms-length epochs from −250 ms to 550 ms with respect to the onset of the stimulus (200 samples per epoch). The average number of selected epochs for target condition is shown in Table 1.

Spectral analysis and definition of parameters

Electromagnetic brain recordings can be characterized by the analysis of their spectral content. Nevertheless, EEG recordings are nonstationary signals, whose characteristics may change over time [7]. Nonstationary signal analysis techniques, such as time–frequency distributions, may be appropriate to accurately describe their dynamic properties [4, 33]. In this work, the short-time Fourier transform (STFT) was used to assess the time–frequency maps of ERP signals. STFT is a sliding temporal window technique used to obtain the time evolution of the power spectral density (PSD). Each 800 ms-length ERP epoch ($M = 200$ samples) was divided into temporal segments of 168 ms-length ($L = 41$ samples) with a 90 % overlapping. Thus, we obtained 32 time intervals identified by i ($i = 1,\ldots,32$) [7]. Finally, the spectral content between 1 and 70 Hz was selected, and PSD was normalized to a scale from 0 to 1, leading to the normalized PSD (PSD_n).

$$\mathrm{PSD}_n^{(i)}(f) = \frac{\mathrm{PSD}^{(i)}(f)}{\sum_{f=1\,\mathrm{Hz}}^{70\,\mathrm{Hz}} \mathrm{PSD}^{(i)}(f)}, \quad i = 1,\ldots,32 \tag{1}$$

After the normalization, it follows that $\sum_{f=1\,\mathrm{Hz}}^{70\,\mathrm{Hz}} \mathrm{PSD}^{(i)}(f) = 1$, for each i. Consequently, PSD_n can be considered as a probability distribution in the band of interest [1 70] Hz. This representation provides a suitable tool for the application of several spectral parameters. Figure A1 shows four examples of normalized spectrograms for distractor and target conditions, corresponding to a healthy control and a patient with SCH. That figure depicts the stimulus response percent of change from baseline.

Spectral entropy (SE)

Entropy is a thermodynamic function whose original meaning involves uncertainty of information, in terms of disorder, discrepancy and diversity [6]. Entropy was adapted to the context of information theory by Shannon [41]. Hence, SE can be defined as a disorder quantifier. A uniform spectrum with a broad spectral content (e.g., white noise) yields a high SE value. On the contrary, a narrow power spectrum with only a few spectral components (e.g., a sum of sinusoids) gives a low SE value [21]. To calculate SE, we applied the definition of Shannon's entropy computed over PSD_n [33].

$$\mathrm{SE}^{(i)} = -\frac{1}{\log(L)} \cdot \sum_{f=1\mathrm{Hz}}^{70\mathrm{Hz}} \mathrm{PSD}_n^{(i)}(f) \cdot \log\left(\mathrm{PSD}_n^{(i)}(f)\right), \quad i = 1,\ldots,32, \tag{2}$$

where L is the number of spectral components in the [1, 70] Hz band.

Median frequency (MF)

Median frequency provides an alternative way to summarize the changes in the spectral content of EEG recordings. It is defined as the frequency that comprises 50 % of the

power [32]. MF is calculated from PSD_n between 1 Hz and 70 Hz.

$$\sum_{f=1Hz}^{MF^{(i)}} PSD_n^{(i)}(f) = 0.5, \quad i = 1, \ldots, 21 \tag{3}$$

Parameter baseline correction

Baseline correction was carried out in order to obtain a stimulus-independent characterization. The time–frequency analysis provides a SE and a MF value for each temporal segment. The baseline and the stimulus response were defined as the available [−250 0] and [150 550] ms intervals, respectively. The baseline correction was then carried out using the 'percent change from baseline method' [37]. For that purpose, a pre-stimulus parameter mean was firstly obtained as the average of baseline values. Then, the pre-stimulus parameter mean was subtracted from the stimulus response values, and the result was divided by the pre-stimulus parameter mean. Finally, values were averaged in order to obtain a baseline-corrected parameter for each participant.

$$SE = \left\langle \frac{SE^{(i)}\big|_{i\in \text{response}} - SE^{(i)}\big|_{i\in \text{baseline}}}{SE^{(i)}\big|_{i\in \text{ baseline}}} \right\rangle, \quad i = 1, \ldots, 32, \tag{4}$$

where $\langle\cdot\rangle$ denotes the temporal average in the baseline and response windows.

Figure A2 depicts MF and SE baseline-corrected values for distractor and target conditions, corresponding to a healthy control and a patient with SCH. This figure illustrates time-varying differences between the response to distractor and target stimulus.

Statistical analyses

The statistical analyses were carried out in a four steps approach: (1) demographic, clinical and EEG parameters analysis; (2) exploratory analysis; (3) electrode-level statistical analysis; and (4) clinical correlation analysis.

Initially, sex distribution, age, completed courses, IQ, and P3a and P3b amplitudes were compared between patients and controls.

Thereafter, data distribution was assessed by an exploratory analysis. The Kolmogorov–Smirnov and Levene tests were used to check for normality and homoscedasticity, respectively. The results indicate that parametric test assumptions did not hold.

To explore the electrode-level differences between patients and controls, both within- and between-groups significance maps were computed. In a first step, within-group differences were assessed using Wilcoxon signed-rank tests (Bonferroni corrected, $\alpha = 0.05/17$ electrodes $= 0.0029$) for the target and the distractor tones, comparing SE and MF values from baseline [−250 0] ms and stimulus response [150 550] ms windows. In a second step, between-groups differences for SE and MF baseline-corrected values were assessed by means of Mann–Whitney U tests (Bonferroni corrected, $\alpha = 0.05/17 = 0.0029$; trend $\alpha = 0.0058$). The analyses were complemented in a second step by further statistical comparisons between both groups of patients (i.e., CP and MTP) using Mann–Whitney U tests (uncorrected in this case, given the confirmatory purpose of this subtest). In order to minimize the possible influence of chronicity and treatment on spectral parameters, SE and MF were compared between patients and controls (p level corrected for multiple comparisons). Thereafter, we assessed whether: (a) the same pattern appeared in the comparison between MTP and controls, and (b) no differences were found between both patients groups. Additionally, stimulus responses to distractor and target tones were compared in a third step. Wilcoxon signed-rank tests (Bonferroni corrected, $\alpha = 0.05/17$ electrodes $= 0.0029$) were performed to assess within-group differences for baseline-corrected SE and MF responses to both stimuli.

Finally, correlations between spectral parameters and clinical relevance were evaluated by means of stepwise multivariate linear regressions. PANSS positive, negative and total scores were used as dependent variables and SE values at each sensor were introduced as predictive variables. In addition, the relationship between antipsychotic dose in mg of chlorpromazine (CPZ) equivalents/day, and change of MF and SE was assessed using Spearman's rho coefficients.

Results

Table 1 summarizes demographic, clinical and EEG parameters, as well as between-group comparisons. Non-significant differences were found in age or sex distribution between patients and controls. Total IQ and P3b amplitude was significantly lower in patients in comparison with controls. On the contrary, P3a amplitude did not differ significantly between patients and controls.

Within-group differences

Healthy controls

Healthy controls showed a global SE decrease (except at occipital electrodes) from baseline to target stimulus response (Fig. 1a). Likewise, controls displayed a statistically significant and global MF decrease in all electrodes (Fig. 2a).

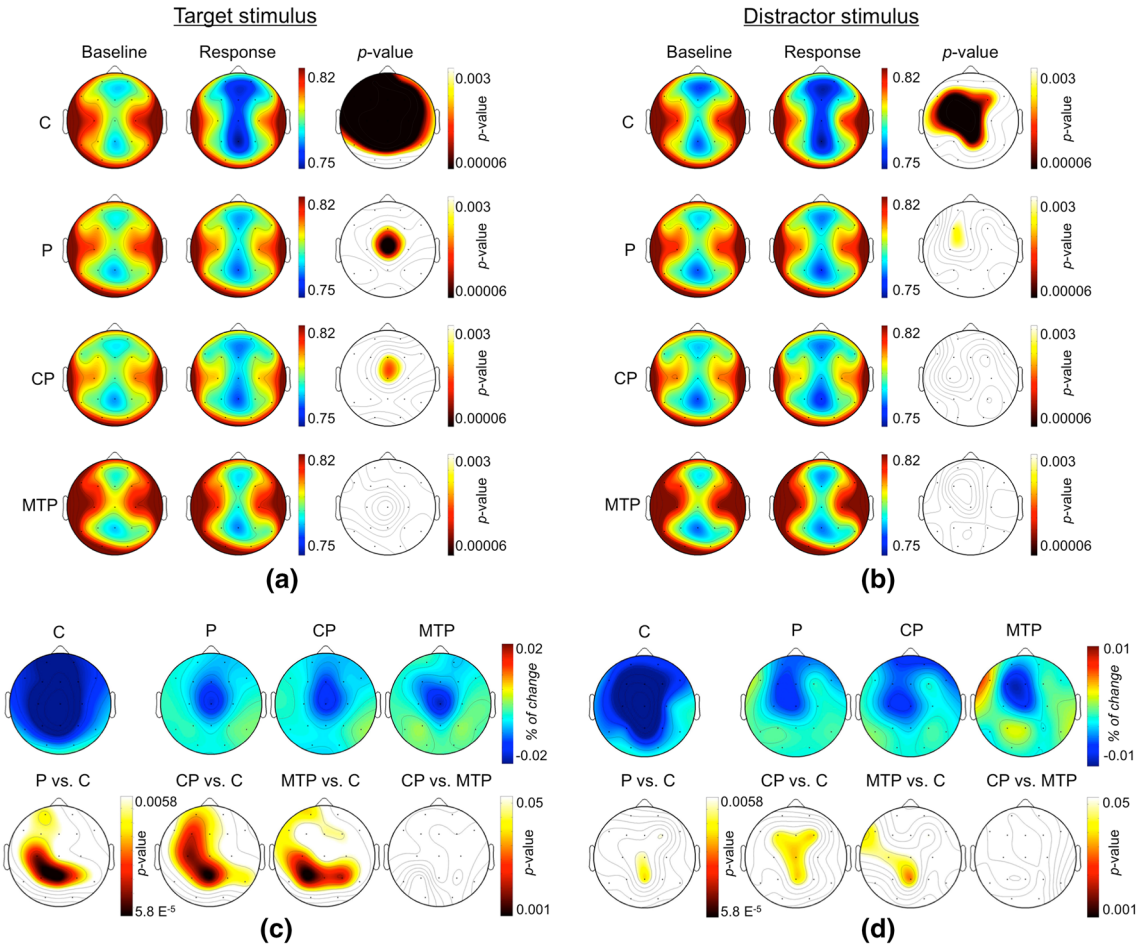

Fig. 1 SE topographic maps for target (**a**, **c**) and distractor (**b**, **d**) stimuli. **a** SE topographic maps at baseline, active response to target tone and within-groups statistical analyses; **b** SE topographic maps at baseline, active response to distractor tone and within-groups statistical analyses; **c**, **d** topographic maps depicting the difference between active and baseline SE values for each group and between-groups statistical analyses for target and distractor tones, respectively. *SE* spectral entropy, *P* patients, *CP* chronic patients, *MTP* minimally treated patients, *C* controls

In response to the distractor tone (Fig. 1b), controls showed a statistically significant SE decrease, localized over central, left parietal and posterior frontal regions. In addition, controls displayed a statistically significant and widespread MF decrease (Fig. 2b).

In this group, the assessment of the differences between responses to distractor and target tones revealed a statistically significant larger SE and MF decrease in response to target (Fig. 3), including central, frontal and parietal sensors.

Patients

Patients showed a statistically significant SE decrease from baseline to target response, mainly localized around Pz (Fig. 1a). A SE decrease was not observed in the MTP group considered alone. A MF decrease was observed in response to target over central and right frontal sensors, but not in the MTP group considered alone (Fig. 2a).

In response to the distractor tone (Fig. 1b), patients did not show any statistically significant difference in SE (not for all patients or for the MTP group considered alone). On the other hand, patients with SCH exhibited a MF decrease over anterior central sensors, though this result was not observed in the MTP group considered alone (Fig. 2b).

In the patients group, statistically significant differences between target and distractor responses were observed when analyzing changes in SE. Distractor SE was significantly smaller than target SE over a localized region around Pz (similar results were obtained for both CP and MTP groups). The MF decrease in patients was significantly larger in the target response than in the distractor response over parieto-central and right frontal electrodes (Fig. 3).

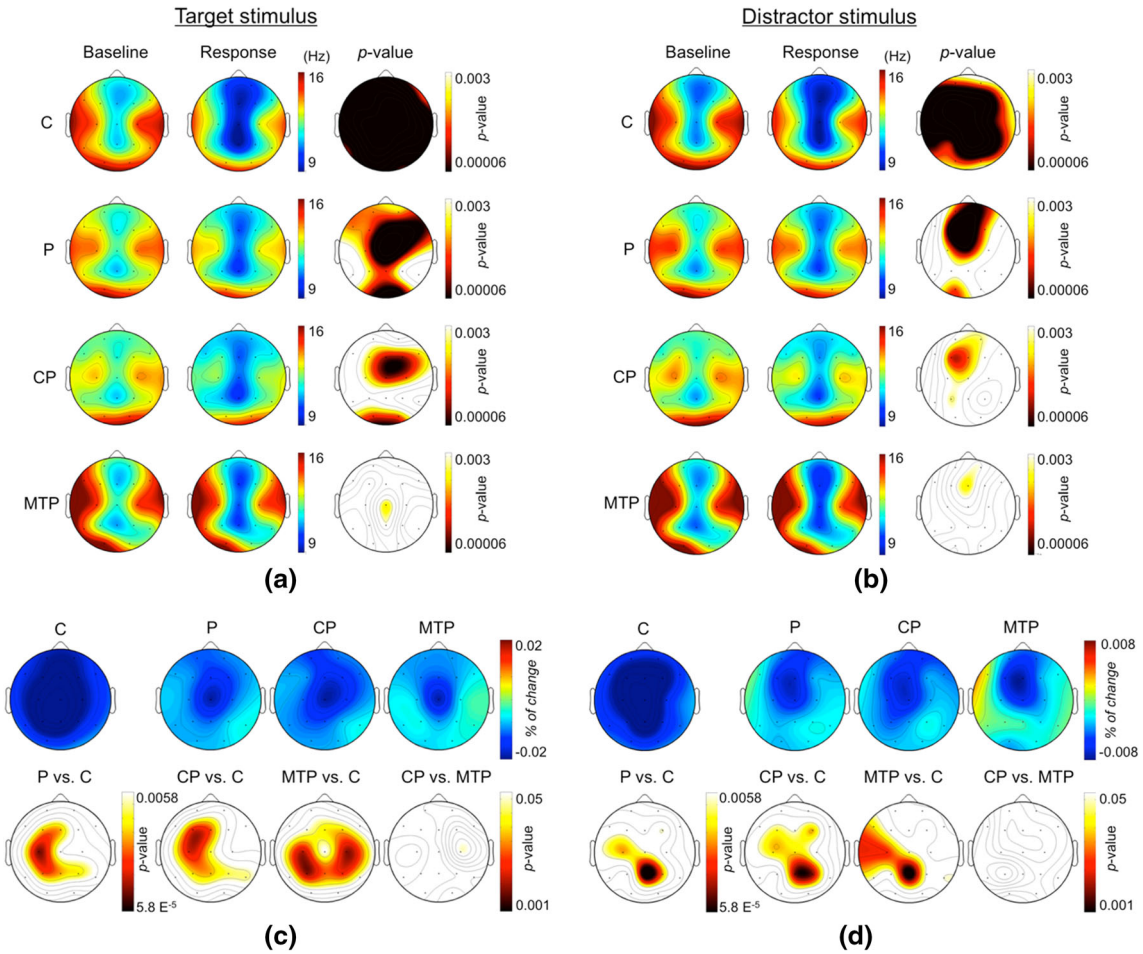

Fig. 2 MF topographic maps for target (**a**, **c**) and distractor (**b**, **d**) stimuli. **a** MF topographic maps at baseline, active response to target tone and within-groups statistical analyses; **b** MF topographic maps at baseline, active response to distractor tone and within-groups statistical analyses; **c**, **d** topographic maps depicting the difference between active and baseline MF values for each group and between-groups statistical analyses for target and distractor tones, respectively. *MF* median frequency, *P* patients, *CP* chronic patients, *MTP* minimally treated patients, *C* controls

Differences between patients and controls

The between-group analyses of SE response to target revealed a significantly smaller SE response in patients with SCH than in controls (both for CP and for MTP groups assessed separately), over posterior and central regions, and extending to left parietal and left frontal sensors (Fig. 1c).

Patients also showed a significantly smaller MF change in response to target than controls over posterior, central and left parietal regions (also including right parietal sensors in the MTP group; Fig. 2c).

A slight SE change in response to distractor was observed. Although statistically significant differences were obtained, the change in SE was smaller in patients with SCH than in controls, over posterior and central regions. MF decrease in response to distractor was significantly smaller for patients than controls over Pz (Figs. 1d, 2d).

Clinical relevance

Changes in SE from baseline to target were associated with positive and total PANSS scores (i.e., the smaller the SE decrease from baseline to target, the higher the clinical scores). This finding was in agreement with the results reported in a previous study [5].

A similar pattern was observed when the SE response to distractor was analyzed. Hence, the difference in SE between distractor and baseline segments at C3 was chosen as a direct predictor of positive ($R^2 = 0.263$; $p = 0.021$; $\beta = 0.513$, $t = 2.53$) and total ($R^2 = 0.242$; $p = 0.028$; $\beta = 0.492$, $t = 2.39$) PANSS scores in the stepwise regression (Fig. 4).

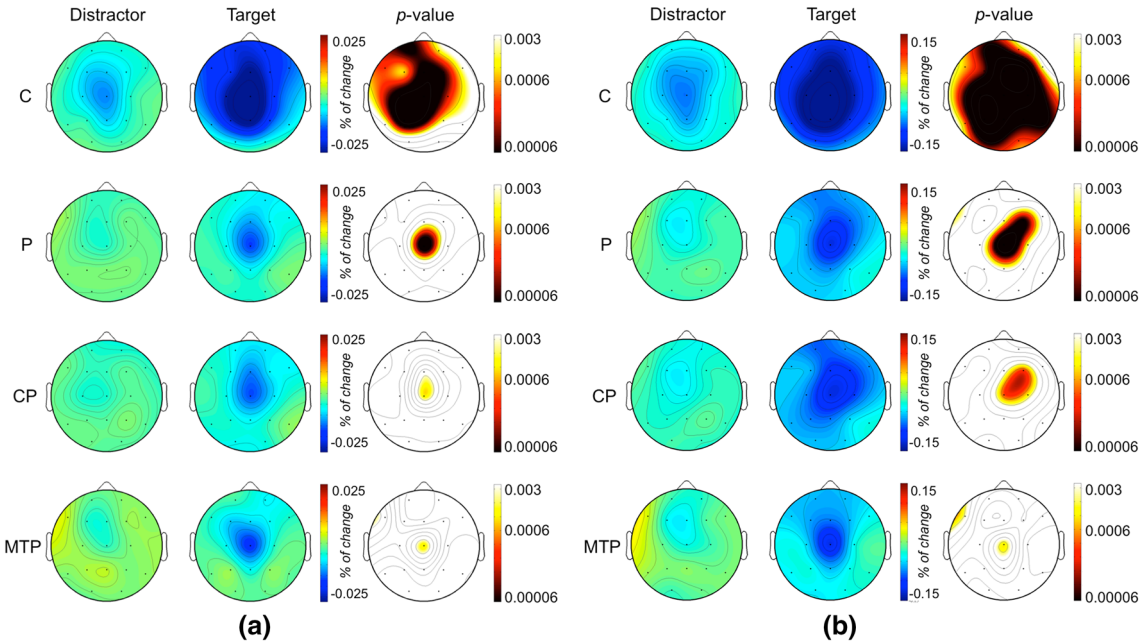

Fig. 3 Comparison of the percent of change in SE (**a**) and MF (**b**) from baseline to active window for each group. Each row depicts the percent of change from baseline for distractor and target tones, as well as the within-group differences between both conditions. *SE* spectral entropy, *MF* median frequency

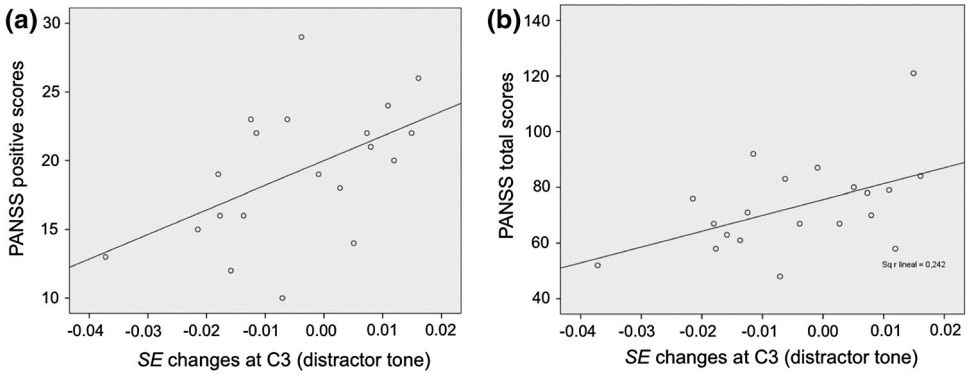

Fig. 4 Scatterplots showing the association between SE changes in response to distractor tones during a P300 task and positive (**a**) and total (**b**) PANSS scores. SE changes represent the proportion of change (SE active-SE baseline/SE baseline). Thereby, more positive values imply less entropy decrease during the active condition (target or distractor). These associations are similar to those found with the responses to target tones in a previous study [5]. *SE* spectral entropy

Finally, the relations between mean dose, and change in SE and MF were not statistically significant ($\rho < 0.15$).

Discussion and conclusions

In the present study, we found that bioelectrical responses to both novelty and relevance during an auditory oddball task were attenuated in patients with SCH, especially in the MTP group. In addition, we observed that the amount of modulation with both target and distractor tones was correlated with clinical symptoms. Specifically, patients with SCH with slight SE changes in response to both distractor and target tones exhibited increased severe positive and total symptoms.

On the one hand, the response to the distractor stimuli involves novelty detection. On the other hand, the response to the target stimuli is associated with novelty and relevance detection, as well as with response to relevance. Healthy controls showed a larger modulation of the oscillatory activity in response to the target than patients, which suggests a more intense and/or widespread activation of cerebral resources in response to relevance. In this group, both MF and SE displayed a larger response to target in

comparison with distractor, over central, parietal and frontal regions (Fig. 3). This result would indicate that relevance detection was associated with a slowing of the spectrum in these areas. In particular, both MF and SE showed a significant change with target, but not with distractor tones, over orbitofrontal sensors. This finding seems coherent with the proposed role for inferior frontal areas in relevance detection in healthy participants [18]. Moreover, the large response to target tones for healthy participants would agree with an increased coherence of relatively distant regions underlying salience detection, which is in turn consistent with functional magnetic resonance imaging (fMRI) data [2, 10]. However, the activity modulation was significantly smaller in patients under both conditions (in particular in the MTP group) than in controls, which would suggest that response to both novelty and salience is flattened in SCH. Nevertheless, this attenuated response may still contribute to aberrant salience (i.e., by conferring less relevance to those stimuli that under normal conditions should be perceived as more salient). Other researchers reported reduced connectivity in distributed networks underlying salience processing in SCH [38], which is in agreement with the reduced response observed in our patients. Orbitofrontal and anterior cingulate areas are key components of the salience network [30]. In our study, sensors over these regions were conspicuously inactive in response to target tones, indicating a salience detection malfunction in SCH.

The large and extended entropy decrease in controls for both conditions can be associated with an irregularity decrease of the EEG signal during the processing of target and (to a lesser degree) distractor tones. SE decrease was accompanied by a similar MF decrease, which suggests an increasing contribution of low-frequency bands to the EEG spectrum. The absence of significant P3a amplitude differences between patients and controls could be related to the weak statistically significant results obtained by SE for distractor tones. In addition, it may be associated with an improved ability of SE and MF to detect relevant neural activity differences when compared to amplitude-based methods. In healthy participants, P3a has been associated with a transitory increase of theta oscillations [14, 31], which seems consistent with the observed MF decrease. Transitory coordination of EEG activity among distant regions could be mediated by theta rhythms [44]. The observed MF decrease may support this fact, as well as previous fMRI studies that obtained a correlation between target detection in auditory oddball tasks and a spatially distributed cortical and subcortical activation [2, 10].

In a previous fMRI study, brain activity from CP with SCH was acquired during a three-tone auditory oddball task [26]. Their findings indicated that perfusion was increased in both patients and controls during novel stimuli as compared to nontarget baseline over limbic–paralimbic and association cortices, as well as subcortical structures [26]. These results are in agreement with the EEG spectrum modulation across all electrodes observed in our study. Moreover, also in accordance with our findings, the results obtained by Laurens et al. [26] showed a widespread hypoactivation in response to novelty in patients. Nevertheless, they did not detect statistically significant differences in target versus novel stimuli processing, which may be due to the limited temporal resolution of fMRI. Certainly, if any differences between target and distractor processing are circumscribed to a short temporal window, they could go undetected with fMRI.

Dopamine signals novelty [34] and relevance [35] in the cortex. Therefore, the reduced response observed in our study is consistent with a hypodopaminergic state in the cortex, as proposed in SCH [12, 29]. Indeed, met/met homozygotes for the catechol-*O*-methytransferase (COMT) gene (with smaller efficacy in degrading synaptic dopamine and, thus, with a longer duration of dopamine in the synapses) showed an enhanced P3a amplitude at Fz [19]. It could be possible that a cortical hypodopaminergia underlies the reduced response to relevance and novelty in our patients. Nevertheless, this does not imply that hypodopaminergia is common to all patients with SCH.

Potential limitations of the study merit further discussion. All patients with SCH were receiving antipsychotic treatment that may have flattened their response. Clearly, our data need to be replicated in untreated and preferably neuroleptic-naïve patients. However, medication is unlikely the only reason for the present findings, since: (1) SE and MF modulation was smaller in MTP than in CP, and (2) in our previous study [5], we found that the administration of single doses of haloperidol did not modify SE or MF response to target in a group of healthy participants. Likewise, it is noteworthy that the cohort of subjects enrolled in the study was limited. The statistical power analyses indicated that this sample size is sufficient for obtaining statistically significant results. Nevertheless, a large database would be helpful to confirm our findings.

In summary, patients with SCH showed less SE change in response to both distractor and target tones than healthy controls. Furthermore, changes in SE were related to clinical symptoms. These results support the notion that SCH is associated with a decreased response to both relevance and novelty, which in turn might contribute to the aberrant salience in this syndrome through a hampered differentiation between background and salient stimuli.

Acknowledgments The present work was supported in part by: 'Ministerio de Economía y Competitividad' and FEDER under project TEC2011-22987 and by the 'Project Cero 2011 on Ageing' from 'Fundación General CSIC,' 'Obra Social La Caixa' and CSIC; 'Fondo de Investigaciones Sanitarias (Instituto de Salud Carlos III)' (FIS

PI1102203) and the 'Gerencia Regional de Salud de Castilla y León' (GRS 613/A/11) Grants; a Marie Curie Intra European Fellowship within the 7th European Community Framework Programme (330156-CODIP) to A. Díez; a predoctoral scholarship from the University of Salamanca and Santander Bank to V. Suazo; and a PIF-UVA grant from the University of Valladolid to A. Bachiller.

Conflict of interest All authors have approved the final manuscript. On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standard The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

1. American Psychiatric Association APA (2013) Diagnostic and statistical manual of mental disorders: Dsm-v. American Psychiatric Association, Washington, DC
2. Ardekani BA, Choi SJ, Hossein-Zadeh GA, Porjesz B, Tanabe JL, Lim KO, Bilder R, Helpern JA, Begleiter H (2002) Functional magnetic resonance imaging of brain activity in the visual oddball task. Brain Res Cogn Brain Res 14:347–356
3. Atkinson RJ, Michie PT, Schall U (2012) Duration mismatch negativity and p3a in first-episode psychosis and individuals at ultra-high risk of psychosis. Biol Psychiatry 71:98–104
4. Aviyente S, Brakel LA, Kushwaha RK, Snodgrass M, Shevrin H, Williams WJ (2004) Characterization of event related potentials using information theoretic distance measures. IEEE Trans Biomed Eng 51:737–743
5. Bachiller A, Diez A, Suazo V, Dominguez C, Ayuso M, Hornero R, Poza J, Molina V (2014) Decreased spectral entropy modulation in patients with schizophrenia during a p300 task. Eur Arch Psychiatry Clin Neurosci 264:533–543. doi:10.1007/s00406-014-0488-6
6. Berezianos A, Tong S, Thakor N (2003) Time-dependant entropy estimation of eeg rhythm changes following brain ischemia. Ann Biomed Eng 31:221–232
7. Blanco S, García H, Quiroga RQ, Romanelli L, Rosso OA (1995) Stationarity of the eeg series. IEEE Eng Med Biol Mag 14:395–399
8. Bledowski C, Prvulovic D, Hoechstetter K, Scherg M, Wibral M, Goebel R, Linden DE (2004) Localizing p300 generators in visual target and distractor processing: a combined event-related potential and functional magnetic resonance imaging study. J Neurosci 24:9353–9360
9. Bramon E, Rabe-Hesketh S, Sham P, Murray RM, Frangou S (2004) Meta-analysis of the p300 and p50 waveforms in schizophrenia. Schizophr Res 70:315–329
10. Casey BJ, Forman SD, Franzen P, Berkowitz A, Braver TS, Nystrom LE, Thomas KM, Noll DC (2001) Sensitivity of prefrontal cortex to changes in target probability: a functional mri study. Hum Brain Mapp 13:26–33
11. Cortinas M, Corral MJ, Garrido G, Garolera M, Pajares M, Escera C (2008) Reduced novelty-p3 associated with increased behavioral distractibility in schizophrenia. Biol Psychol 78:253–260
12. Davis KL, Kahn RS, Ko G, Davidson M (1991) Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry 148:1474–1486
13. Delorme A, Makeig S (2004) Eeglab: an open source toolbox for analysis of single-trial eeg dynamics including independent component analysis. J Neurosci Methods 134:9–21
14. Demiralp T, Ademoglu A, Comerchero M, Polich J (2001) Wavelet analysis of p3a and p3b. Brain Topogr 13:251–267
15. Gralewicz S, Lutz P, Wiaderna D, Tomas T (2003) Alteration in behavioral sensitivity to amphetamine after treatment with oxotremorine. Effect of dose and test environment. Behav Brain Res 147:163–173
16. Grondin R, Cass WA, Zhang Z, Stanford JA, Gash DM, Gerhardt GA (2003) Glial cell line-derived neurotrophic factor increases stimulus-evoked dopamine release and motor speed in aged rhesus monkeys. J Neurosci 23:1974–1980
17. Gur RE, Turetsky BI, Loughead J, Snyder W, Kohler C, Elliott M, Pratiwadi R, Ragland JD, Bilker WB, Siegel SJ, Kanes SJ, Arnold SE, Gur RC (2007) Visual attention circuitry in schizophrenia investigated with oddball event-related functional magnetic resonance imaging. A J Psychiatry 164:442–449
18. Hattori S, Li Q, Matsui N, Nishino H (1993) Treadmill running test for evaluating locomotor activity after 6-ohda lesions and dopaminergic cell grafts in the rat. Brain Res Bull 31:433–435
19. Heitland I, Kenemans JL, Oosting RS, Baas JM, Bocker KB (2013) Auditory event-related potentials (p3a, p3b) and genetic variants within the dopamine and serotonin system in healthy females. Behav Brain Res 249:55–64
20. Hermens DF, Ward PB, Hodge MA, Kaur M, Naismith SL, Hickie IB (2010) Impaired mmn/p3a complex in first-episode psychosis: cognitive and psychosocial associations. Prog Neuropsychopharmacol Biol Psychiatry 34:822–829
21. Inouye T, Shinosaki K, Sakamoto H, Toi S, Ukai S, Iyama A, Katsuda Y, Hirano M (1991) Quantification of eeg irregularity by use of the entropy of the power spectrum. Electroencephalogr Clin Neurophysiol 79:204–210
22. Kapur S (2003) Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 160:13–23
23. Kaur M, Battisti RA, Ward PB, Ahmed A, Hickie IB, Hermens DF (2011) Mmn/p3a deficits in first episode psychosis: comparing schizophrenia-spectrum and affective-spectrum subgroups. Schizophr Res 130:203–209
24. Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrome scale (panss) for schizophrenia. Schizophr Bull 13:261–276
25. Keren AS, Yuval-Greenberg S, Deouell LY (2010) Saccadic spike potentials in gamma-band eeg: characterization, detection and suppression. Neuroimage 49:2248–2263
26. Laurens KR, Kiehl KA, Ngan ET, Liddle PF (2005) Attention orienting dysfunction during salient novel stimulus processing in schizophrenia. Schizophr Res 75:159–171
27. Mondragon-Maya A, Solis-Vivanco R, Leon-Ortiz P, Rodriguez-Agudelo Y, Yanez-Tellez G, Bernal-Hernandez J, Cadenhead KS, de la Fuente-Sandoval C (2013) Reduced p3a amplitudes in antipsychotic naive first-episode psychosis patients and individuals at clinical high-risk for psychosis. J Psychiatr Res 47:755–761
28. Monville C, Torres EM, Dunnett SB (2006) Comparison of incremental and accelerating protocols of the rotarod test for the assessment of motor deficits in the 6-ohda model. J Neurosci Methods 158:219–223
29. Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, Someya Y, Sassa T, Sudo Y, Matsushima E, Iyo M, Tateno Y, Toru M (1997) Decreased prefrontal dopamine d1 receptors in schizophrenia revealed by pet. Nature 385:634–636
30. Olsson M, Nikkhah G, Bentlage C, Bjorklund A (1995) Forelimb akinesia in the rat parkinson model: differential effects of dopamine agonists and nigral transplants as assessed by a new stepping test. J Neurosci 15:3863–3875
31. Polich J (2007) Updating p300: an integrative theory of p3a and p3b. Clin Neurophysiol 118:2128–2148

32. Poza J, Hornero R, Abasolo D, Fernandez A, Garcia M (2007) Extraction of spectral based measures from meg background oscillations in alzheimer's disease. Med Eng Phys 29:1073–1083
33. Poza J, Hornero R, Escudero J, Fernandez A, Sanchez CI (2008) Regional analysis of spontaneous meg rhythms in patients with alzheimer's disease using spectral entropies. Ann Biomed Eng 36:141–152
34. Rangel-Gomez M, Hickey C, van Amelsvoort T, Bet P, Meeter M (2013) The detection of novelty relies on dopaminergic signaling: evidence from apomorphine's impact on the novelty n2. PLoS One 8:e66469
35. Redgrave P, Gurney K (2006) The short-latency dopamine signal: a role in discovering novel actions? Nat Rev Neurosci 7:967–975
36. Rissling AJ, Park SH, Young JW, Rissling MB, Sugar CA, Sprock J, Mathias DJ, Pela M, Sharp RF, Braff DL, Light GA (2013) Demand and modality of directed attention modulate "pre-attentive" sensory processes in schizophrenia patients and nonpsychiatric controls. Schizophr Res 146:326–335
37. Roach BJ, Mathalon DH (2008) Event-related eeg time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia. Schizophr Bull 34:907–926
38. Rozas G, Labandeira Garcia JL (1997) Drug-free evaluation of rat models of parkinsonism and nigral grafts using a new automated rotarod test. Brain Res 749:188–199
39. Sabeti M, Katebi S, Boostani R (2009) Entropy and complexity measures for eeg signal classification of schizophrenic and control participants. Artif Intell Med 47:263–274
40. Schoen W, Chang JS, Lee U, Bob P, Mashour GA (2011) The temporal organization of functional brain connectivity is abnormal in schizophrenia but does not correlate with symptomatology. Conscious Cogn 20:1050–1054
41. Shannon CE (1948) A mathematical theory of communication. Bell Syst Tech 27:379–423, 623–656
42. TEA Ediciones SA (1999) Escala wechsler de inteligencia para adultos. TEA Ediciones, S.A, Madrid, España
43. Uhlhaas PJ, Singer W (2010) Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci 11:100–113
44. von Stein A, Chiang C, Konig P (2000) Top-down processing mediated by interareal synchronization. Proc Natl Acad Sci USA 97:14748–14753