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ORIGINAL PAPER

Decreased spectral entropy modulation in patients with schizophrenia during a P300 task

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Abstract Spectral entropy (SE), also known as Shannon entropy, is a useful parameter for quantifying the global regularity of the electroencephalographic (EEG) signal. Hence, it is of interest in the assessment of the electrophysiological correlates of cognitive processing in schizophrenia. However, to date, SE has been barely used in studies comparing resting EEG recordings between patients and controls. In this work, we compared SE between resting baseline [−250 0] ms and active task [150 550] ms windows of a P300 task in 31 patients with schizophrenia and 38 controls. Moreover, we also calculated the median frequency (MF) and relative power in each frequency band for these windows to assess the correlates of the possible SE differences. Controls showed a significant ($p < 0.0029$) SE decrease (i.e., meaning higher signal regularity) from baseline to the active task window at parietal and central electrode sites. This SE decrease from baseline to active conditions was significantly lower in patients. In controls, this SE decrease was accompanied by a statistically significant decrease in MF (i.e., a significant slowing of the EEG activity), not observed in patients. In this latter group, the difference in SE between resting baseline and active task windows was inversely correlated to positive and total symptoms scores, as measured with the positive and negative symptoms scale. Our data support the relevance of SE in the study of cerebral processing in schizophrenia.

Keywords Schizophrenia · Spectral entropy · Theta · Gamma · Median frequency

Introduction

The analysis of the fast bioelectrical changes from baseline to the processing stages of a cognitive task may be useful to better understand the dynamic abnormalities of information

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processing in schizophrenia (i.e., alterations that may appear at some but not all stages of this processing). Several attempts have been made to investigate neural dynamics associated with schizophrenia by the use of complexity measurements of the electroencephalogram (EEG). However, to date, this approach has yielded contradictory results [1].

Among the potentially relevant complexity parameters for the study of schizophrenia, spectral entropy (SE) allows for quantifying the degree of disorder contained in a signal. SE is a measure derived from the original definition suggested by Shannon [2], who defined entropy as the average amount of information of a probability distribution. The concept was extended to EEG power spectral density (PSD) by Inouye et al. [3]. A high SE value implies a flat, uniform spectrum with a broad spectral content (i.e., a more irregular signal), whereas a low SE indicates a spectrum with a narrower frequency range (i.e., a more regular signal). In this framework, SE allows for the assessment of differences in information content and signal variability average across time. Moreover, SE enables to compare the signal dispersion between groups, [4] thus holding potential for the study of cognitive processing substrates. Likewise, SE may allow for a novel approach to improve our understanding of the altered cortical processing mechanism in mental illness, especially when considering task-related differences between baseline and active conditions.

SE values indirectly reflect spectral EEG composition (lower values imply a more regular signal). The EEG frequency bands likely have different functions for the coordination of activity across cortical regions [5–7]. Therefore, tasks involved in the activation of diverse cerebral regions are advisable to assess SE differences in patients. The odd-ball paradigm may be useful in this respect, since it is involved in the activation of several different brain areas [8, 9], and it has the additional advantage of its relative simplicity, which reduces possible performance-related problems. Patients with schizophrenia have shown reduced delta and theta activity 200–500 ms post-stimulus during a P300 task, along with reduced event-related potentials (ERP) amplitudes [10], suggesting smaller SE differences in relation to task performance. The altered inter-regional connectivity reported in schizophrenia [11] also suggests that the modulations of oscillations may be abnormal during a cognitive task in patients with this syndrome.

To date, SE has been scarcely used in schizophrenia research. In this regard, its discriminatory ability in comparison with other parameters has been assessed by Sabeti et al. [12]. They did not find any differences between groups in SE values during resting-state activity. However, using a SE-based method, an increased connection entropy was described in patients with schizophrenia in the gamma band [13].

In the present study, we have further explored the ability of SE to characterize abnormal cognitive processing during a P300 task elicited in patients with schizophrenia. Two additional parameters were used to clarify the basis of possible differences in SE: median frequency (i.e., the frequency value that divides the signal power in half) and relative power (i.e., the proportion of total spectral power attributable to a given band). These parameters have been used to quantify the contribution of different frequency bands to spectral power in patients with schizophrenia and healthy controls during the baseline and the task-processing stages of an auditory odd-ball test. Finally, the relation between significant changes in SE and clinical scores was also explored.

Methods and materials

Participants

Thirty-one patients with paranoid schizophrenia, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders 4th revised edition criteria, and 38 controls were included in the study. Patients group was formed by 20 chronic, stably treated (CP) and 11 minimally treated patients (MTP). These patients were labeled as MTP because prior to their inclusion they had not received 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 these patients, 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. In order to rule out the acute effects of haloperidol on power, five controls (included in the 38 controls of the study) 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 MTP.

The clinical status of the patients was scored using the positive and negative syndrome scale (PANSS) [14]. We used the Spanish version of the Wechsler Adult Intelligence Scale third edition (WAIS-III) to assess IQ. Cognitive assessment was acquired by the Spanish version of the brief assessment of cognition in schizophrenia (BACS) scale [15]. Employment status was stratified as: employed (currently studying or working) or unemployed (looking for a job or retired); and educational level as completed academic courses.

Controls were recruited through newspaper advertisements and remunerated for 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.

Demographic and clinical characteristics are shown in Table 1.

The exclusion criteria included: (1) total intelligence quotient (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 urinalysis.

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

Table 1 Demographic, clinical, cognitive and EEG parameters

	Patients		Controls
	CP	MTP	
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 general	34.92 (17.56)	33.63 (7.24)	NA
PANSS total	76.26 (15.63)	76.27 (11.37)	NA
Total IQ** (WAIS-III)	86.308 (14.942)	82.185 (16.761)	101.935 (12.439)
P3a artifact-free epochs	88.30 (9.76)	80.09 (17.37)	82.42 (18.52)
P3b artifact-free epochs	78.65 (19.78)	69.90 (18.16)	84.47 (9.32)
P3a amplitude (Cz) in μV	1.18 (1.14)	0.68 (1.43)	1.27 (1.16)
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

CP chronic stable patients, *MTP* minimally treated patients, *NA* not applicable

Significance of between-groups comparisons is shown in the first column (Kruskal–Wallis test, * $p < 0.01$; ** $p < 0.005$; *** $p < 0.001$)

Electroencephalographic recording

EEG recordings were performed while the participants underwent an auditory odd-ball task. To elicit P3a and P3b components, an odd-ball 3-stimulus paradigm was employed with a 500 Hz-tone target, a 1,000 Hz-tone distracter and a 2,000 Hz-tone standard stimulus.

Accordingly, participants heard binaural tone bursts (duration 50 ms, rise and fall time 5 ms and intensity 90 dB) presented with random stimulus onset asynchrony of 1,000 and 1,500 ms. 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 the mouse button whenever they detected the target tones, to close their eyes and avoid eye movements and muscle artifacts. Non-attended target tones were discarded. Nevertheless, for distractor and standard tones non-attended trials were included, whereas attended tones were discarded.

The EEG was recorded using a BrainVision® (Brain Products GmbH; Munich, Germany) equipment from 17 tin sensors mounted in an electrode cap (Electro-Cap International, Inc.; Eaton, Ohio, USA), according to the revised 10/20 International System. Electrode impedance was always kept under 5 kΩ. Figure 1 shows an example of two raw EEG trials, from a patient with schizophrenia and a control. The stimulus onset was represented by the red line. Baseline and active task responses were obtained in the (−250,0) ms and (150,550) ms interval, respectively.

Recordings were referenced over Cz electrode, the sampling rate was 250 Hz, and the signal was recorded continuously. Data were re-referenced to the average activity of all active sensors [16], because common average reference is less sensitive to microsaccadic artifacts in high frequency recordings [17]. P3a and P3b components were, respectively, calculated from distractor and target stimuli. Firstly, ERP grand-averages were automatically performed using BrainVision Analyzer® (Brain Products GmbH; Munich, Germany). Secondly, P3a and P3b were defined as the mean of ERP grand-average amplitude in the 300–400 ms interval.

Artifact rejection was conducted, following a two-steps approach. Firstly, data were imported into EEGLAB, and an independent component analysis was carried out to decompose ERPs in a total of 17 components [18]. 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 discard EEG segments that displayed an amplitude exceeding a statistical-based local threshold. Thereafter, an off-line 1–70 Hz filter was applied. EEG recordings were then segmented into 800 ms-length epochs from −250 to 550 ms with respect to the onset of the stimulus (200 samples per

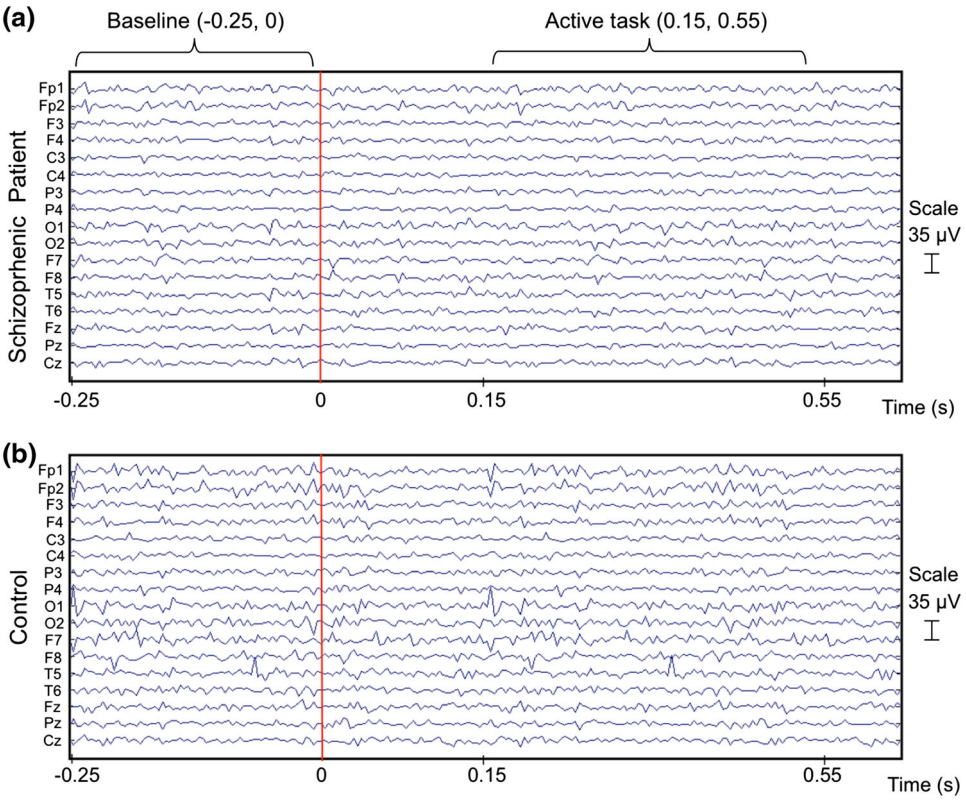

Fig. 1 Raw EEG trials from 17 acquisition electrodes (channels *Fp1*, *Fp2*, *F3*, *F4*, *C3*, *C4*, *P3*, *P4*, *O1*, *O2*, *F7*, *F8*, *T5*, *T6*, *Fz*, *Pz* and *Cz*) for: **a** a patient with schizophrenia; and **b** a control participant

epoch). The average number of selected epochs for target condition is shown in Table 1.

Spectral analysis and definition of parameters

A typical approach for characterizing electromagnetic brain recordings is based on the analysis of their spectral content. In order to describe the power spectrum properties, the power spectral density (PSD) function was estimated. PSD represents how the power is distributed in the frequency domain. EEG recordings are non-stationary signals, whose characteristics may change over time [19]. Therefore, non-stationary signal analysis techniques, such as time–frequency distributions, may be appropriate to accurately describe their properties [20, 21]. In the present study, a sliding temporal window technique was applied to obtain the time-evolution of PSD segments. Each EEG epoch of 800 ms ($M = 200$ samples) was divided into temporal segments of 168 ms ($L = 41$ samples) with a 90 % overlapping. Then, 32 time intervals identified by i ($i = 1,\ldots,32$) were obtained, and PSD was calculated for each temporal window. Finally, the spectral content between 1 and 70 Hz was selected, and PSD was normalized ($\mathrm{PSD_n}$).

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

After the normalization, it follows that $\sum_{f=1\mathrm{Hz}}^{70\mathrm{Hz}} \mathrm{PSD}^{(i)}(f) = 1$ for each i. Then, in the band of interest [1 70] Hz, $\mathrm{PSD_n}$ can be considered as a probability distribution. This representation provides a suitable tool to apply several spectral parameters.

Spectral entropy (SE)

Entropy is a thermodynamic function, which was adapted to the context of information theory. Its original meaning involves uncertainty of information in terms of disorder, discrepancy and diversity [22]. Previous studies used SE to estimate the irregularity in the EEG in terms of the flatness of PSD [23]. 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 [3]. Thus, SE can be considered as a disorder quantifier. To calculate SE, we applied the definition of Shannon's entropy computed over $\mathrm{PSD_n}$.

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

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

Median frequency (MF)

An alternative way to summarize the changes in the spectral content of EEG recordings is the MF. It is defined as the frequency that comprises 50 % of the power [20]. MF is calculated from PSD_n between 1 and 70 Hz. MF offers a simple way of quantifying the spectral content of PSD.

$$\sum_{f=1\mathrm{Hz}}^{\mathrm{MF}^{(i)}} \mathrm{PSD}_n^{(i)}(f) = 0.5, \quad i = 1, \ldots, 32. \tag{3}$$

Relative power (RP)

The RP represents the relative contribution of several oscillatory components to the global power spectrum. It is useful to analyze the changes in the spectral content of EEG recordings. It is noteworthy that several advantages can be found when comparing RP to absolute power (AP). Hence, RP is independent from the thresholds of the measurement equipment. Likewise, RP obtains lower inter-subject variability than AP [24]. RP was calculated by summing the contribution of the spectral components included in the conventional EEG frequency bands: delta (δ, 1–4 Hz), theta (θ, 4–8 Hz), alpha (α, 8–13 Hz), beta 1 (β_1, 13–19 Hz), beta 2 (β_2, 19–30 Hz) and gamma (γ, 30–70 Hz).

$$\mathrm{RP}_{f_p}^{(i)} = \sum_{f \in f_p} \mathrm{PSD}_n^{(i)}(f), \quad f_p = \{\delta, \theta, \alpha, \beta_1, \beta_2, \gamma\}, \quad i = 1, \ldots, 32. \tag{4}$$

Parameter baseline correction

We used a baseline correction process in order to achieve a stimulus-independent characterization. The time–frequency analysis provides a value for each temporal segment. The baseline was defined as the available 250 ms pre-stimulus recording. Thus, the values of the previous parameters in the [−250 0] ms interval were averaged to obtain a "pre-stimulus parameter mean." The baseline correction was then carried out using the "percent change from baseline method" [25]. For that purpose, firstly, the pre-stimulus parameter mean is subtracted from the response value for each participant (mean of the values in the [250 550] ms interval), and then the result is divided by the pre-stimulus parameter mean.

Statistical analyses

Sex distribution, age, completed courses, IQ, cognitive performance (BACS) and P3a and P3b amplitudes were compared between patients and controls using non-parametric tests.

As a general rule, to minimize the possible influence of chronicity and treatment upon the study parameters, we planned to compare those parameters between patients and controls (p level corrected for multiple comparisons) and then testing whether: (a) the same pattern appeared in the comparison between MTP and controls; and (b) no differences were found between both patients groups.

To explore differences in *SE* between patients and controls, the significance maps of both within- and between groups were assessed (Figs. 1, 2).

In a first step, the significance of SE difference within each group was assessed, comparing the mean SE values from baseline [−250 0] ms and active [150 550] ms windows, with Wilcoxon signed-rank tests (Bonferroni corrected, $\alpha = 0.05/17$ electrodes $= 0.0029$).

Then, between-groups differences were assessed in: (1) baseline SE values; and (2) SE difference from baseline to active windows, which were expressed as the SE percent of change (calculated as $\left\langle \frac{\mathrm{SE}-\mathrm{SE}^{BL}}{\mathrm{SE}^{BL}} \right\rangle$, where SE represents the spectral entropy in the active condition and SE^{BL} its value

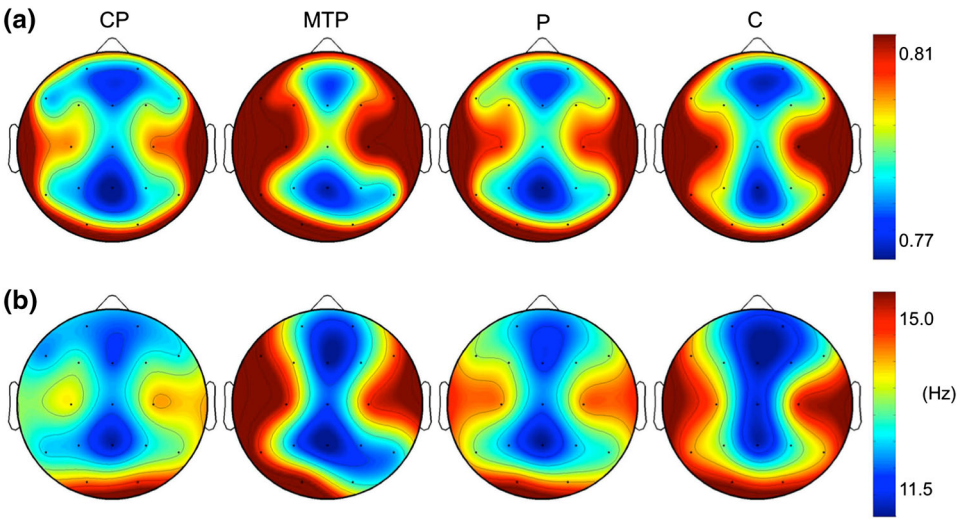

Fig. 2 Baseline SE (**a**) and MF (**b**) maps in the three groups. There were no significant differences at $p < 0.05$ level between patients and controls, between any group of patients and controls, or between patient subgroups. *CP* chronic stable patients, *MTP* minimally treated patients, *P* patients; *C* controls

at baseline; negative values indicates a SE decrease in the active condition). These differences were tested with Mann–Whitney *U* tests (Bonferroni corrected, $\alpha = 0.05/17 = 0.0029$; trend $\alpha = 0.0058$). The analyses were supplemented by comparing SE values between both groups of patients, and between MTP and controls, again using Mann–Whitney *U* tests (uncorrected in this case, given the confirmatory purpose of this subtest).

Classification performance of SE between patients and controls was evaluated by a receiver operating characteristics (ROC) analysis. For that purpose, a linear discriminant analysis (LDA) and a LDA with a leave-one-out cross-validation (LOO-CV) procedure were assessed. LOO-CV procedure provides a nearly unbiased estimate of the true error rate of the classification procedure [26]. Average value of all the electrodes was used in the classification analyses. Classification statistics were shown in terms of the area under ROC curve (AUC), sensitivity (percentage of patients with a correct classification), specificity (proportion of controls properly recognized) and accuracy (total fraction of well-classified patients and healthy participants). Similar analyses were repeated for the comparisons between MTP versus controls, and MTP versus CP.

The corresponding SE values at each sensor were calculated to be subsequently used in statistical analysis (see below) and to depict the magnitude of the differences in SE changes between groups.

To explore the basis of possible SE differences, we planned to assess the statistical significance of the between-groups differences in the variation of MF (significance maps, Bonferroni corrected, $\alpha = 0.05/17 = 0.0029$; Fig. 4) and the relation between SE and MF differences (using pair-wise Pearson's *r* correlations between SE and MF differences at each electrode location; Suppl. Tables 1 and 2). We also assessed between-groups differences in baseline MF values. This analysis was completed by comparing RP differences between baseline and active condition in each band, using Wilcoxon signed-rank tests ($\alpha = 0.00049$; 0.05/102; 17 electrodes and 6 bands).

Finally, to assess the clinical relevance of possible differences in SE, stepwise multivariate linear regression was used. PANSS positive, negative and total scores were used as dependent variables, and SE values at each sensor were introduced as predictive variables.

Results

Patients and controls did not differ in age or sex distribution, but they differed in completed courses and total IQ (Table 1). P3b, but not P3a amplitudes, were reduced in the patients (Table 1).

Spectral entropy

Baseline values

Figure 2 shows the mean SE topographic distribution in the baseline window for each group. SE at baseline did not differ between the groups.

Spectral entropy differences

From baseline to active windows, SE showed a statistically significant and widespread decrease in the control group. The SE decrease was almost absent in MTP and was more spatially restricted in the stable patients (Fig. 3a).

The comparison of *SE* differences (baseline to active windows) between patients and controls revealed a significantly lower difference in the former over parietal and central regions, predominantly left-sided and extending to the left frontal electrodes. This pattern was similar in chronic and MT patients as separately compared with controls, without statistically significant differences between patients groups (Fig. 3c).

Additionally, ROC curves were used to assess the ability of SE values to discriminate patients from control participants. Two methods were applied: LDA with and without LOO-CV. The highest accuracy was achieved by LDA (76.8 %, accuracy; 71.1 %, sensitivity; 83.9 %, specificity; 0.789, AUC). Lower classification statistics were reached by LDA with LOO-CV (72.4 %, accuracy; 74.2 %, sensitivity; 71.0 %, specificity; 0.789, AUC). Fig. S1 shows ROC curves, for both classification methodologies, to discriminate between: patients and controls, MTP and controls, and CP and MTP.

The magnitude of *SE* values per sensor is shown in Suppl. Table 1.

Equivalent analyses have been carried out for distractor non-attended trials. SE showed a statistically significant decrease in the control group, whereas SE changes were absent in MTP and CP. The comparison of SE differences between patients and controls did not show significant differences.

Association with clinical scores

In the patients, the difference in SE between active and baseline segments at C3 was significantly and directly associated with positive ($R^2 = 0.279$; $p = 0.013$; $\beta = 0.545$, $t = 2.75$), and total ($R^2 = 0.223$; $p = 0.035$; $\beta = 0.472$, $t = 2.27$) PANSS scores. Given that the more positive SE values represent less SE decrease, the smaller this decrease was from baseline to active epochs, the higher clinical scores. This association was confirmed in MTP for

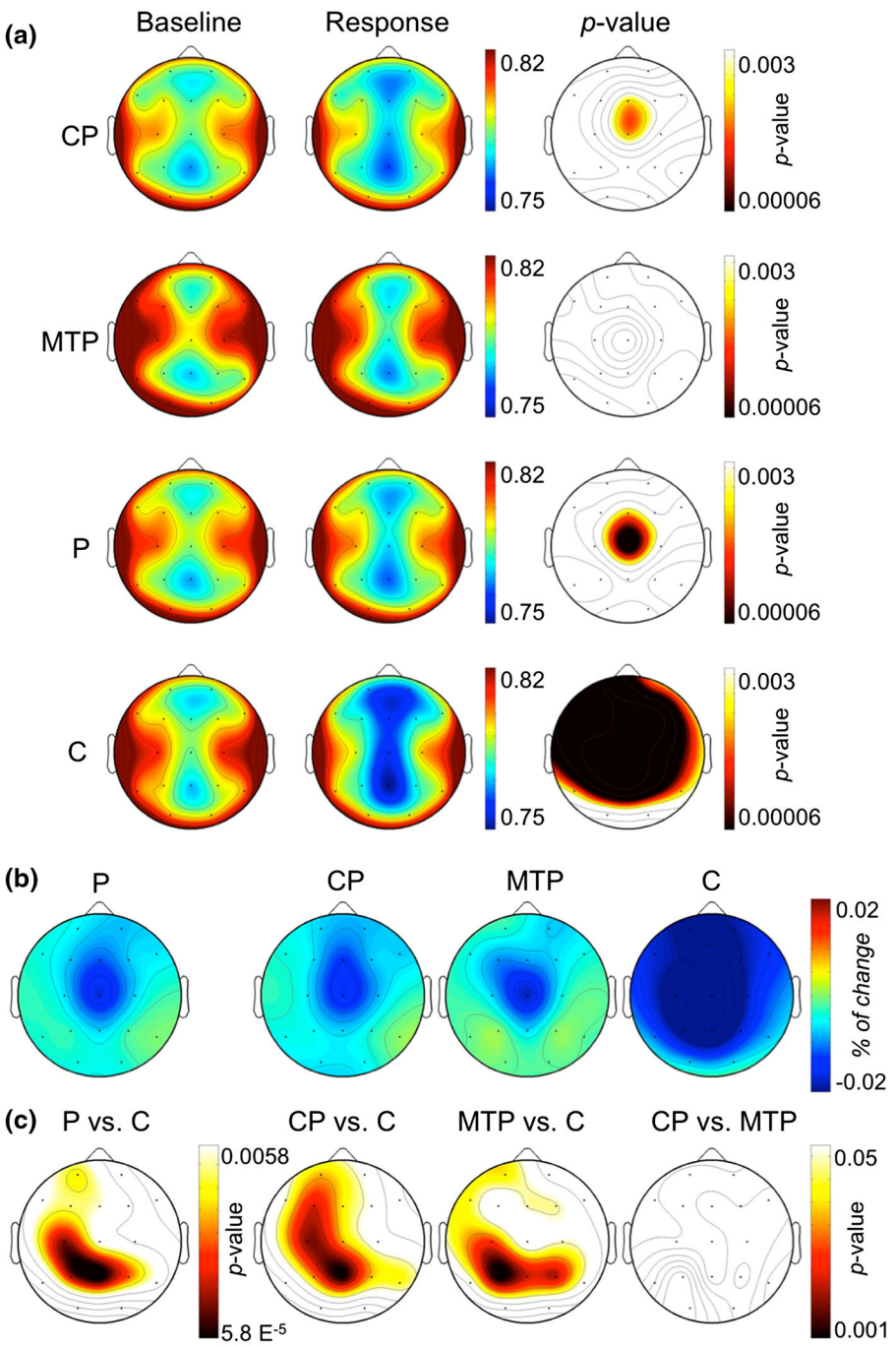

Fig. 3 **a** SE maps at baseline and active window in the three groups (*p* values of the within-groups differences are shown in the *right* column); **b** maps depicting the difference between active and baseline SE values; **c** topographic maps depicting the statistical results of the between-groups differences between active and baseline variation of SE values

total PANSS scores ($R^2 = 0.673$; $p = 0.01$; $\beta = 0.575$, $t = 3.01$) (Fig. S2).

SE differences after haloperidol in healthy participants

An equivalent analysis was performed to the signal recorded in five healthy participants, before and 24 h after a 2 mg single dose of haloperidol. We did not detect any significant effect of haloperidol in the healthy participants. Fig. S3 shows the mean SE values obtained pre- and post-treatment.

Median frequency

Baseline values

MF at baseline did not differ between any group of patients and controls (Fig. 2).

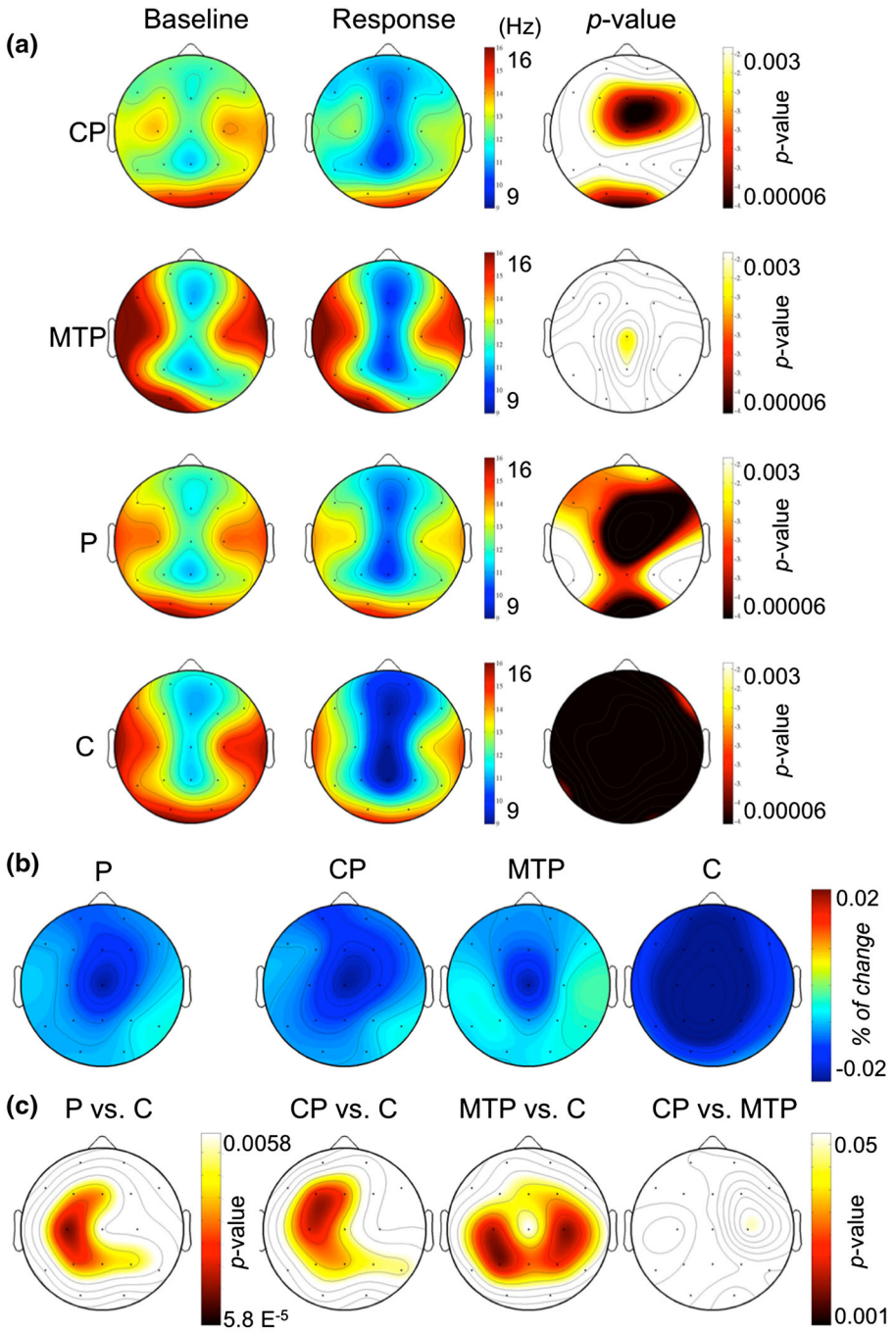

Fig. 4 **a** MF topographic maps at baseline and active window in the three groups (values shown in Hz; *p* values of the within-groups differences are shown in the *right column*); **b** maps depicting the difference between active and baseline MF values; **c** *p* values topographic maps depicting the significance of the between-groups differences between active and baseline variation of MF values

Differences in median frequency

In controls, there was a decrease in MF values across the entire cortex (−1 Hz approximately), while patients showed a smaller or no difference in MF (Fig. 4a).

The comparison of MF differences between patients and controls revealed a significantly lower decrease in the patients in approximately the same area that showed a lower SE difference in this group (Fig. 4c). Again, the pattern of differences as compared with controls was similar in both groups of patients, and no differences were detected between them. Values of MF at each sensor are shown in Suppl. Table 2.

In patients as well as in controls, MF and SE differences were highly correlated at each electrode (in all cases, $r > 0.6$, $p < 0.001$; Fig. S4).

Relative power

Delta and theta band RP increased in patients and controls ($p < 0.00049$) from baseline to active conditions, but this

increase was lower in the patients group than controls. There was a widespread *RP* decrease for the high frequency bands in controls during the active condition, again smaller in the patients (Fig. S5).

Discussion

Healthy controls showed statistically significant and widespread SE and MF decreases from baseline to active window during an odd-ball task. The same differences were significantly smaller in patients, and they correlated with clinical scores in this group. Secondary analyses revealed that the power increase observed in theta and delta bands was smaller in the patients in the active window as compared with baseline. A smaller decrease in high frequency oscillations was also observed in the patients in the active window.

To the best of our knowledge, the few SE studies published so far in schizophrenia have not explored changes with cognitive processing. The reported absence of significant SE differences in the resting state between medicated patients and controls [12] is consistent with the lack of baseline differences in our sample. Likewise, in resting conditions, increased entropy specific to the gamma band has been reported in schizophrenia [13]. Our data demonstrate that significantly altered SE may be found in schizophrenia in the difference in EEG signal distribution in relation to cognitive processing. In this regard, SE may be a valuable parameter for this kind of analysis, since it was less altered in patients than in controls with the processing of target stimuli. According to our data, this approach may be more sensitive to differences between patients with schizophrenia and controls than the comparison of resting SE values. Indeed, classification analyses revealed a significant discrimination between our patients and controls based on SE change that also held when only MTP patients were considered.

Two classification methodologies have been evaluated, LDA with and without LOO-CV. In the case of LDA with LOO-CV, the data of one participant are excluded from the training set one at a time and then classified on the basis of the threshold calculated from the data of all other participants [27]. Despite the fact that the classification statistics decrease with this procedure, it provides a nearly unbiased estimate of the true error rate of the classification method [26].

MF and SE differences were highly correlated in all groups, suggesting that the SE decrease in controls was contributed by a slowing of the EEG signal during the active part of the test. In our controls, the RP comparisons indicate a decrease in high frequency bands, which was lower in the patients and likely underlie their smaller MF difference. This result is coherent with the lower reduction in gamma power observed during a P300 test in patients with schizophrenia [28], as well as with previous reports of higher gamma noise power in schizophrenia during a P300 task [29–31]. Noise power represents the amount of gamma activity not related to task performance (i.e., the power difference in this band between the total and the averaged signals). It is likely that such a smaller modulation of fast oscillations is reflected on a lower entropy decrease in our patients. Taken together with this, the lower SE and MF difference in our patients suggest a relatively rigid and disorganized cortico-cortical transmission during task performance in schizophrenia, which may in part relate to a hyper-active baseline state.

The lower decrease in SE observed in our patients is probably also influenced by a lower increase of theta and delta oscillations during the active window as compared with controls. Previous results revealed higher theta amplitudes in healthy participants during target processing in a similar odd-ball task (as compared to non-target) [10]. Similarly, delta and theta event-related spectral perturbation (the amount of power change from baseline) was lower in patients with schizophrenia but not schizotypal personality disorder as compared to controls during a P300 test [32]. In this context, our data give further support to a reduced response in these bands during cognitive activation in the schizophrenic brain. Slow theta [5] and beta [7] oscillations have a role in the synchronization between relatively distant regions, while gamma band may be more involved in the short-range communication [6, 7]. Besides, the dominant frequency of a neuronal assembly is dependent on its size (i.e., on the number of participating neurons), the lower frequencies involving larger assembly sizes [33]. Slow bands oscillations have been proposed to subtend cortico-cortical interactions [34]. Recent researches using functional [35, 36] and diffusion magnetic [37] resonance suggest a shift from functional segregation (i.e., more local functioning) to integration across development. In this framework, the lower change (i.e., the lesser increase in slow bands RP) in our patients during the active window suggests a cortical functioning similar to that expected in earlier developmental stages.

The direction of the association between SE percent of change (active minus baseline divided by baseline SE) and clinical scores was positive in patients, suggesting that the lower changes in SE during the P300 task were associated with a higher clinical severity (i.e., patients with smaller SE decrease in the active condition would have larger PANSS scores). Our patients did not show an impaired behavioral performance in the test, suggesting that the decreased SE difference did not influence the performance of a simple task. However, more complicated tasks, such as those running in real life (understanding others intentions,

integrating information sources and so on) might be hampered in the patients as a consequence of the more rigid cerebral function revealed by their lower SE decrease. Speculatively, in this context, the direct association between SE and positive symptoms may arise as a consequence of an impaired capacity for processing real-life stimuli. Such a problem may in turn have a relation with the aberrant salience proposed in schizophrenia [38], in whose framework the discrimination of target (i.e., relevant) stimuli from background activity may be impaired. Therefore, this may be expressed as a reduced difference in the spectral composition between baseline and active conditions of an odd-ball paradigm, as well as in higher positive symptoms such as delusions and hallucinations. In a previous study, resting gamma entropy was unrelated to symptoms [13], suggesting that the smaller capacity for SE difference may correlate to the clinical profile, rather than its baseline increase.

The possibility exists that smaller SE differences in our patients were contributed by the treatment received. However, this possibility is unlikely the main reason for that altered SE, since there was no SE difference between MT and chronic patients. In addition, pre- and post-haloperidol SE differences between baseline and active condition in healthy controls did not show significant results. Moreover, a comparison of resting EEG entropy values in patients with schizophrenia between pre- and post-treatment states revealed that antipsychotics reduced entropy in frontal regions and did not affect its values in temporal regions [39]. Hence, the small entropy reduction from baseline to active conditions found in our study is unlikely secondary to the treatment received. Although multi-scale entropy was used in that study [39], instead of *SE*, a high degree of correlation between both measurements can be assumed. In the same direction, it seems likely that neuroleptic-naïve patients show higher EEG complexity values than healthy controls and their chronic treated counterpart one. In any case, similar studies in neuroleptic-naïve cases are needed to adequately address this point. Moreover, although our cases showed the usual P3b amplitude reduction in schizophrenia, they did not show the P3a reduction also found in this syndrome [40–42]. This issue could be related to the relatively small sample size, in particular of MTP.

Some limitations in our study merit further consideration. Firstly, the sample size is small especially in patients' subtypes. Thus, a larger database including recordings from both patients' subtypes is needed to confirm the performance of the methods used in the current research. Secondly, all patients have been diagnosed as paranoid schizophrenia; due to the fact that it is the most prevalent schizophrenia subtype. Finally, SE has certain limitations; the spectral-based method is sensitive to spike or artifacts. Nevertheless, it should be taken into account that a two-step artifact rejection approach was applied, minimizing their impact.

As a conclusion, SE may be a useful parameter for the study of cognitive processing abnormalities in schizophrenia. The reduced SE difference during the processing of a target stimulus in patients was correlated with clinical severity and may be informative of the underlying altered cortical functions in this syndrome.

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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 standards 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.

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