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ORIGINAL PAPER

Noise power associated with decreased task-induced variability of brain electrical activity in schizophrenia

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Abstract In schizophrenia, both increased baseline metabolic and electroencephalographic (EEG) activities as well as decreased task-related modulation of neural dynamics have been reported. Noise power (NP) can measure the background EEG activity during task performance, and Shannon entropy (SE) is useful for quantifying the global modulation of EEG activity with a high temporal resolution. In this study, we have assessed the possible relationship between increased NP in theta and gamma bands and decreased SE modulation in 24 patients with schizophrenia and 26 controls over the parietal and central regions during a P300 task. SE modulation was calculated as the change from baseline to the active epoch (i.e., 150–550 ms following the target stimulus onset). Patients with schizophrenia displayed statistically significant higher NP values and lower SE modulation than healthy controls. We found a significant association between gamma NP and SE in all of the participants. Specifically, a NP increase in the gamma band was followed by a decrease in SE change. These results support the notion that an excess of gamma activity, unlocked to the task being performed, is accompanied by a decreased modulation of EEG activity in schizophrenia.

Keywords Schizophrenia · Noise power · Shannon entropy · Inhibition · Gamma · Theta

Introduction

Noise power (NP) is a static measurement of the background electroencephalographic (EEG) activity. It represents the amount of power unrelated to the task being performed [13, 23]. This parameter may be quantified globally or for each EEG frequency band as the difference between the power of the averaged signal (which is related to the task being performed) and the total power of the signal (which includes both the background EEG activity—unrelated to task processing—and the task-related signal).

A significant NP excess in patients with schizophrenia has been reported both in the gamma band [7, 19, 22] and considering the whole EEG spectrum [22]. According to our previously reported data, the gamma NP excess was statistically significant at parietal (P3 and P4) and central (Fz and Pz) electrodes. Although this excess was associated with a hampered performance in several cognitive domains and negative symptoms [7, 19, 22], the pathophysiological significance of the NP excess is still unclear, since NP may be subject to a number of confounding factors (e.g., ocular microsaccades in the gamma band) [24]. Other non-brain contributors to scalp-recorded activity (e.g., muscular

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tone) and medication-related effects may also play a role in determining the higher amount of NP in patients with schizophrenia when compared to controls.

A relationship has been postulated between an increased basal activity and a hampered task-related modulation of regional perfusion using functional magnetic resonance imaging (fMRI) [12]. Hence, the possibility of an association between NP and the dynamic changes of EEG during a task might be assessed to ascertain the pathophysiological relevance of NP in schizophrenia. It could be hypothesized that if the reported NP increase in this syndrome has a functional significance, it might be associated with a hampered modulation of EEG spectral activity during the performance of a task.

Several measurements of task-related modulation of neural dynamics are available. Among these, Shannon entropy (SE) quantifies the regularity of the signal, based on the peaks of the power spectral density (PSD) of EEG activity [10]. Thus, a high SE value implies a flat, uniform spectrum with a broad spectral content (i.e., a more regular signal), whereas a low SE indicates a spectrum with few dominant spectral peaks. As a consequence, SE change during a given task may be used to assess EEG modulation. In a previous study that aimed to assess the EEG correlates of response to relevance in a P300 task, SE change was significantly lower in patients than in controls for the relevant tone, mainly in the parieto-central region [3], a similar location to the reported for gamma NP increase [7, 19]. The frequency correlates of SE decrease (i.e., modulation) in healthy controls included a significant decrease in power of high-frequency bands (i.e., beta and gamma) along with a significant increase in theta band power. These changes were significantly smaller in patients than in controls (i.e., SE modulation was lower in patients than in controls during the processing of the relevant tone) [3]. Furthermore, a decrease in SE modulation was associated with higher symptoms scores [3].

Our findings suggest that SE change may be a reliable quantifier of EEG modulation, which summarizes EEG signal organization. Therefore, in this study we wanted to analyze the association between this measure and the amount of NP in the gamma band. Our working hypothesis was that increased NP values would be associated with a decreased SE modulation during the same task. In addition, we focused on the region where a significant deficit of SE modulation was reported in our patients (i.e., parieto-central region) [3].

Subjects and methods

Participants

The dataset analyzed in this study included 24 patients with paranoid schizophrenia and 26 healthy controls. Patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition criteria. This group included 11 chronic stably treated (CP) and 13 minimally treated patients (MTP). The chronic stably treated patients were previously treated with atypical antipsychotics: risperidone (6 cases, 2–6 mg/day), olanzapine (2 cases, 5–20 mg/day), aripiprazole (1 case, 10–15 mg/day) and clozapine (2 cases, 100–350 mg/day). Doses and drugs were unchanged during the 3 months preceding EEG recordings. 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 for 48–72 h 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. As we previously reported, this administration did not change NP [19] or SE [3] values in a small group of healthy controls ($n = 5$).

The control group was recruited through newspaper advertisements and remunerated for their cooperation. To discard major psychiatric antecedents (personal or family relatives) and treatments, they were previously assessed by a semi-structured psychiatric interview by one investigator (V. Molina).

The exclusion criteria can be summarized as: (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 urine analysis.

Written informed consent was obtained from the patients, as well as from 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 Brain Vision® (Brain Products GmbH; Munich, Germany) equipment. Electrodes were mounted in an 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 sitting down

with their eyes closed in order to avoid muscle and eye movements. Thirteen minute length of event-related potentials (ERP) was acquired at a sampling rate of 250 Hz, while participants underwent an auditory odd-ball task. To elicit P3a and P3b components, an odd-ball 3-stimulus paradigm was employed. 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. Only correctly identified target epochs were included in the analyses.

Artifact rejection was conducted following a two-step approach. Firstly, data were imported into EEGLAB and an independent component analysis (ICA) was carried out to decompose ERPs in a total of 17 components [6]. After 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 an amplitude exceeding a statistical-based local threshold. Thereafter, an off-line 1- to 70-Hz filter was applied. EEG recordings were then segmented into 800-ms-length epochs from −250 to 550 ms with respect to the stimulus onset (200 samples per epoch).

Noise power (NP)

As described in previous articles [7, 19], we calculated noise magnitude, which is subsequently denoted as "noise power," following the recommendations of Möcks et al. [13] and Winterer et al. [22]. The calculation of noise power was based on signal-to-noise ratio (SNR), a measure of the quality of the EEG signal applied to each frequency band. It is computed by the Brain Vision® software (Brain Products GmbH, Munich, Germany) [5] for the time window from −50 to 600 ms for the target stimuli and after the specific band filtering.

For every individual participant, band and electrode, the averaged noise power (ANP) was computed. Its definition is based on the balance between the averaged total power (ATP), which includes the contribution of both signal and noise power, and SNR, which is obtained by dividing the average signal power between the average noise power. The following formula summarizes the computation of the ANP:

$$\mathrm{ANP} = \frac{\mathrm{ATP}}{\mathrm{SNR} + 1}. \tag{1}$$

It is noteworthy that the ANP quantifies the noisy part of the EEG activity related to the event. In this framework, "noise" is equivalent to activity not time-locked to the stimuli (see Supplementary Materials for details).

Spectral entropy (SE)

Entropy is a thermodynamic property, useful to quantify the disorder of a system. In information theory, entropy is a measure of uncertainty [4]. Previous studies used SE to estimate the irregularity in the EEG in terms of the flatness of PSD [1]. A uniform spectrum with a broad spectral content (e.g., white noise) gives a high SE value. On the contrary, a narrow power spectrum with only few spectral dominant components (e.g., a sum of sinusoids) yields a low SE value [10]. Hence, SE can be considered as a disorder quantifier. To calculate SE, we applied the definition of Shannon's entropy computed over the normalized PSD (PSD_n).

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

where L is the number of spectral components in the [1 70] Hz frequency range.

Parameter baseline correction

In order to achieve a stimulus-independent characterization, a baseline correction process was carried out. The time–frequency analysis provides a value for each parameter into each temporal segment. The baseline and the stimulus response windows 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" [16]. For that purpose, a pre-stimulus parameter mean (i.e., $\langle \mathrm{SE}|_{\mathrm{baseline}} \rangle$) was firstly obtained as the average of baseline values. Secondly, the pre-stimulus parameter mean was subtracted from the stimulus response values (i.e., $\mathrm{SE}|_{\mathrm{response}}$) and then the result was divided by the pre-stimulus parameter mean. Finally, corrected values were averaged in order to obtain a baseline correction parameter value for each subject.

$$\mathrm{SE} = \left\langle \frac{\mathrm{SE}|_{\mathrm{response}} - \langle \mathrm{SE}|_{\mathrm{baseline}} \rangle}{\langle \mathrm{SE}|_{\mathrm{baseline}} \rangle} \right\rangle, \tag{3}$$

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

Frequency and spatial analyses

We analyzed SE changes at Pz, Fz, P3 and P4 electrodes, since SE modulation changes were significantly different between patients (both CP and MTP) and controls at these sensors. Given the relevance of theta and gamma

oscillations in human cognition and the significant modulation of these bands during a P300 task [3], we decided to assess the contribution of NP in these bands to the modulation of EEG activity in schizophrenia.

In order to estimate SE modulation, we calculated the target ([150 450] ms post-stimulus) minus baseline ([−250 0] ms). The proportion of change with respect to baseline SE, normalized to the unit, was used as an estimation of SE modulation (i.e., 0.05 means a 5 % decrease of SE).

Statistical analyses

Age and IQ were compared between patients and controls using *t* tests. Sex distribution was compared using a Chi-squared test. NP in theta and gamma bands as well as SE modulation values was compared between patients and controls using *t* tests.

In order to assess the statistical significance of the relationship between NP and SE modulation, we used repeated stepwise multivariate lineal regressions. We focused on the parietal and central regions, since a decreased SE modulation and an increased NP were found at these regions in previous studies [3, 7]. Therefore, dependent variables in each regression were percent of changes of SE from baseline to active epochs at P3, P4, Pz ad Fz electrodes, whereas independent variables were theta and gamma NP in all electrodes. Percent of changes of SE were expressed as the difference between target and baseline divided by baseline SE values. Thereby, a SE decrease would be negative.

A Bonferroni correction was applied (4 regression analyses). Hence, the significance level was accordingly set at $\alpha = 0.0125$. Separate regressions were calculated for controls and patients, with an exploratory analysis that was necessary to ascertain whether significant relationships in the patient sample could be found in both patient groups.

In case an association was found between NP and SE modulation, further analysis was carried out to test whether similar data were found in the MTP group. The purpose of this analysis was to confirm that treatment did not play a major role in these associations. Moreover, the significance of the association between NP and SE modulation after distractor and standard tones was assessed using a similar regression model in order to analyze the specificity of these relationships.

Results

Demographic, clinical, EEG parameters and between-group comparisons are summarized in Table 1. Nonsignificant differences were found in age or sex distribution between patients and controls ($p > 0.46$). Total IQ was significantly lower in patients than in controls.

Table 1 Demographic, clinical, cognitive and parameters extracted from EEG activity

	Controls	Patients
Sex distribution (M:F)	16:9	16:8
Age (years)	32.7 (13.0)	36.0 (9.7)
Total IQ**	101.8 (12.2)	85.1 (15.5)
PANSS-positive	NA	19.2 (5.1)
PANSS-negative	NA	19.7 (5.9)
PANSS-total	NA	73.4 (16.7)
Correct target detection (%)	90.4 (21.4)	82.5 (18.29)
SE change Fz**(target)	−0.029 (0.033)	−0.011 (0.014)
SE change Pz**(target)	−0.014 (0.017)	0.002 (0.019)
SE change P3*(target)	−0.006 (0.020)	0.004 (0.016)
SE change P4 (target)	−0.003 (0.019)	0.005 (0.015)
SE change Fz (distractor)	−0.017 (0.024)	−0.008 (0.012)
SE change Pz (distractor)	−0.019 (0.020)	−0.002 (0.012)
SE change P3 (distractor)	−0.006 (0.019)	−0.001 (0.012)
SE change P4 (distractor)	−0.009 (0.015)	−0.001 (0.011)
SE change Fz (standard)	−0.009 (0.010)	−0.002 (0.005)
SE change Pz (standard)	−0.003 (0.009)	−0.001 (0.009)
SE change P3 (standard)	−0.001 (0.005)	−0.002 (0.005)
SE change P4 (standard)	−0.002 (0.007)	−0.001 (0.005)
Gamma NP Fz	0.005 (0.003)	0.008 (0.003)
Gamma NP Pz	0.005 (0.003)	0.008 (0.005)
Gamma NP P3**	0.006 (0.004)	0.011 (0.007)
Gamma NP P4**	0.007 (0.004)	0.012 (0.007)
Theta NP Fz	0.110 (0.058)	0.100 (0.046)
Theta NP Pz	0.079 (0.055)	0.079 (0.052)
Theta NP P3	0.075 (0.049)	0.095 (0.053)
Theta NP P4*	0.069 (0.031)	0.099 (0.065)

Values are shown as mean (standard deviation, SD). Spectral entropy (SE) values are indicated as percent of change (normalized to the unit). As compared to minimally treated patients, the chronic patients showed more negative symptoms (22.2 ± 5.4 vs 15.2 ± 3.6, $t = 3.21$, $p = 0.005$) and more noise power (NP) in the theta band at Fp1 (0.15 ± 0.06 vs 0.08 ± 0.03, $t = 3.15$, $p = 0.005$), without significant differences between groups of patients in positive or total PANSS scores, IQ, number of correct target responses, NP values or SE modulation values

NP values are expressed in squared microvolts (μV^2)

NA not applicable, *M* male, *F* female

Significance of between-group comparisons is shown in the first column (*t* test, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$)

Patients showed significantly lower SE modulation than controls (P3, Pz and Fz). Moreover, NP values were significantly higher for patients in the gamma band (Fz, P3 and P4) and in the theta band (P4).

SE change between target and baseline at P3 (i.e., SE modulation) was predicted by gamma NP at the same electrode for patients ($R^2 = 0.314$, $df = 1.23$; $F = 10.49$, $\beta = 0.560$, $p = 0.004$). SE modulation at P4 was similarly

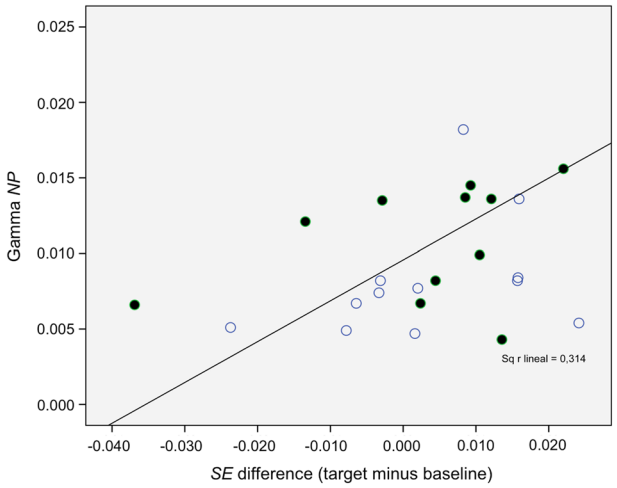

Fig. 1 Association between gamma NP at P3 and SE modulation at P3 in patients. *Open circles* chronic stable patients; *Solid circles* minimally treated patients

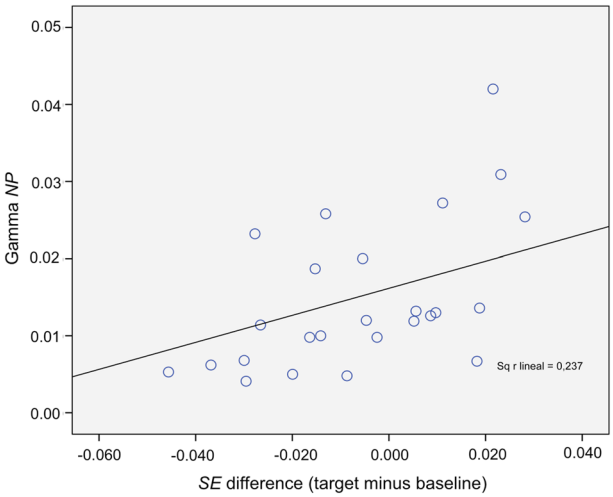

Fig. 2 Association between gamma NP at T5 and SE modulation at P3 in controls

predicted by NP at P3 ($R^2 = 0.314$, $df = 1.23$; $F = 9.03$, $\beta = 0.540$, $p = 0.007$). The positive β values in both cases indicate a direct relationship between an increase in SE change (i.e., less SE decrease from baseline to target) and higher NP values over parietal electrodes. This result is shown in Fig. 1.

SE change at P3 was directly predicted by gamma NP at P3 for the MTP group ($R^2 = 0.419$, $df = 1.11$; $F = 7.21$, $\beta = 0.647$, $p = 0.023$). In this subgroup, SE change at P4 was also predicted by gamma NP at C4 ($R^2 = 0.468$, $df = 1.11$; $F = 8.80$, $\beta = 0.684$, $p = 0.014$). In addition, a positive association was found between SE modulation at Pz and gamma NP at P4, though it was not statistically significant ($R^2 = 0.170$, $df = 1.23$; $F = 5.23$, $\beta = 0.438$, $p = 0.032$).

SE modulation at P3 was also associated with gamma NP at T5 for healthy controls ($R^2 = 0.292$, $df = 1.25$; $F = 9.47$, $\beta = 0.540$, $p = 0.005$). Moreover, SE modulation at Pz was predicted by gamma NP at O1 ($R^2 = 0.253$, $df = 1.25$; $F = 7.80$, $\beta = 0.540$, $p = 0.005$). Finally, SE modulation at Fz was predicted by gamma NP at Pz ($R^2 = 0.273$, $df = 1.25$; $F = 8.62$, $\beta = 0.522$, $p = 0.007$). As Fig. 2 shows, the direction of the association between NP and SE modulation was the same in patients and controls.

Given the fact that common variance between gamma and theta NP could have obscured any existing association in the regression between theta NP and SE modulation, post hoc we computed a new regression only including theta NP as the independent variable. In this case, nonsignificant associations were found between theta NP and SE modulation at the required level.

Nonsignificant associations were found between NP and SE modulation at P3, P4, Fz or Pz after distractor and standard tones.

Finally, separate regressions were computed for patients and controls in order to explore the topographic specificity of the described association between NP and SE modulation. Hence, the possible prediction of SE modulation at occipital electrodes can be assessed based on NP values. No associations were detected at O1 between NP and SE. However, SE modulation at O2 was predicted for patients by gamma NP at C3 ($R^2 = 0.266$, $F = 7.97$, $\beta = 0.493$, $p = 0.01$) and for controls by gamma NP at P4 ($R^2 = 0.319$, $F = 12.63$, $\beta = 0.587$, $p = 0.003$).

Discussion

According to the present results, an increased amount of gamma NP was associated with a decrease of SE change during the processing of the relevant target in a P300 task. Gamma, but not theta, NP was selected as a predictor of SE modulation. This result suggests that patients with schizophrenia showed greater interference in the normal processes of spectral modulation due to the gamma instead of the theta power excess. SE change was predicted by NP at the same (P3) or nearby sensors, which can be related to the rather poor spatial resolution of EEG and the low density of sensors used in the study. Gamma NP at parietal and central electrodes also contributed to predict SE modulation at O2, suggesting a widespread interference of gamma NP on SE modulation.

SE modulation has been previously reported to be associated with positive and total PANSS scores (i.e., the less

SE change the more severe clinical scores) in a sample mostly overlapping with the present one [2].

The described association between NP and SE change is coherent with data showing an excess of resting perfusion in schizophrenia [12]. In that study, the excess perfusion was associated with hampered task-related modulation [12], in particular in the default-mode network (DMN) [21], whose components include parieto-central regions (i.e., those found to show increased NP values along with a decreased task-related SE modulation). The association between gamma band oscillations and cerebral blood flow (CBF) modulation seems stronger than the corresponding association of CBF with oscillations in other bands [14, 17]. Therefore, gamma NP excess and the decreased modulation of DMN may share a similar substrate in schizophrenia. A lack of deactivation of regions involving this network [15] may thus have a similar underpinning, as is the case of the smaller SE change that we found in our patients [2]. Interestingly, the present results suggest that this slight SE change is related to background hyperactivation in the gamma band.

Owing to the likely involvement of extra-cerebral sources in the scalp-recorded oscillations in the gamma band, the role of these oscillations in human cognition and pathology are controversial [24]. However, the present results would be difficult to interpret if gamma NP had a primarily artifactual origin. Previous data suggest that an increase in NP is associated with cognitive deficits in schizophrenia [7, 19, 22]. In turn, these data are coherent with our findings of significant gamma NP interference in the modulation of EEG activity during a task. Certainly, this modulation is conceivably necessary for cognitive performance: Slow oscillations may reflect long-range synchronization, reflecting the recruitment of distant regions during task performance. In our previous study [3], SE decrease in controls was parallel to a slowing of the median frequency of the spectrum and to an increase in theta power, significantly smaller in controls than in patients with schizophrenia. Therefore, according to the present results we may hypothesize that an increase in gamma NP may be associated with a hampered recruitment of distant cortical regions in schizophrenia.

A similar pattern of association was found in controls between gamma NP and SE modulation, although the sensors selected as predictors were different. This result suggests that the underlying mechanism may be quantitatively rather than qualitatively abnormal and supports the interest of considering this relationship as a single construct in future studies. A possible explanation underpinning such an association may be related with inhibitory transmission, due to its recognized role in genesis and maintenance of gamma oscillations [9, 20] and its relevance for schizophrenia [8]. In other words, increased cortical inhibition deficits might contribute to the NP excess in patients and, therefore, to the decreased task-related EEG modulations. This issue represents a quantitative difference when compared to controls. Parvalbumin (PV) neurons may be more relevant for the generation of gamma oscillations [18], while theta rhythms may be more coupled to the cholecystokinin subtype of interneurons [11]. In the context of the data supporting an involvement of PV+ neurons dysfunction in schizophrenia [9], our results may point to a greater involvement of PV+ neurons in the cortical dysfunction of our patients.

Among the study limitations, the post-stimulus epoch differs between the SE modulation (550 ms) and the NP (600 ms) assessments. Nevertheless, the differences in the post-stimulus epochs are unlikely to contribute to the observed associations. SE modulation was assessed in the 150–450 ms interval and NP is an averaged static measurement (i.e., invariant during the selected epoch).

In conclusion, an excess of gamma background oscillatory activity may interfere with the normal modulation of EEG activity in patients with schizophrenia, perhaps reflecting a dimensional mechanism also present in healthy controls.

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Conflict of interest The authors have no conflicts of interest to declare.

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