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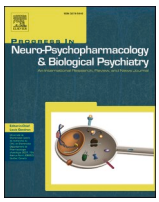

Relation between EEG resting-state power and modulation of P300 task-related activity in theta band in schizophrenia

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ABSTRACT

There is some consistency in previous EEG findings that patients with schizophrenia have increased resting-state cortical activity. Furthermore, in previous work, we have provided evidence that there is a deficit in the modulation of bioelectrical activity during the performance of a P300 task in schizophrenia. Our hypothesis here is that a basal hyperactivation would be related with altered ability to change or modulate cortical activity during a cognitive task. However, no study so far, to the best of our knowledge, has studied the association between resting-state activity and task-related modulation. With this aim, we used a dual EEG paradigm (resting state and oddball task for elicitation of the P300 evoked potential) in a sample of patients with schizophrenia ($n = 100$), which included a subgroup of patients with first episode psychosis ($n = 30$), as well as a group of healthy controls ($n = 93$). The study measures were absolute power for resting-state; and spectral entropy (SE) and connectivity strength (CS) for P300-task data, whose modulation had been previously found to be altered in schizophrenia. Following the literature on P300, we focused our study on the theta frequency band. As expected, our results showed an increase in resting state activity and altered task-related modulation. Moreover, we found an inverse relationship between the amount of resting-state activity and modulation of task-related activity. Our results confirm our hypothesis and support the idea that a greater amount of resting theta-band synchrony could hamper the modulation of signal regularity (quantified by SE) and activity density (measured by CS) during the P300 task performance. This association was found in both patients and controls, suggesting the existence of a common mechanism and a possible ceiling effect in schizophrenia patients in relation to a decreased inhibitory function that limits their cortical reactivity to the task.

1. Introduction

A replicated finding in schizophrenia is the reduced modulation of brain bioelectrical activity during the performance of a task, mainly studied by EEG recordings during task-induced cognitive performance (Northoff and Gomez-Pilar, 2021). This reduction has been proposed as a biomarker of psychotic syndrome (Molina et al., 2020), as it seems to be present in first episode patients, independently of antipsychotic and other biological treatments, and it has been associated to negative symptoms and cognitive impairment (Molina et al., 2018, 2020). This

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alteration is observed consistently and independently of the sensory modality or domain (Northoff and Gomez-Pilar, 2021). These findings suggest a supramodal and domain-general impairment in the capacity to modulate activity, which could be related to alterations in temporo-spatial dynamics in resting periods (Northoff and Huang, 2017).

The parameters that summarize the spectral EEG information are useful for assessing the modulation of brain activity. Among these, spectral entropy (SE) quantifies the degree of disorder or uncertainty associated with a signal. High SE values correspond to a relatively uniform activity spectrum with a broad spectral content (i.e., a random signal), whereas low SE values are obtained when only a few spectral components are involved (i.e., a more regular signal), and SE modulation can be assessed as the change in the regularity of the signal spectral components, e.g. during the performance of a cognitive task. Differences in spectral EEG modulation between patients and healthy controls can be analyzed by assessing the corresponding differences in SE between the temporal windows immediately preceding and following a task-related stimulus. Thus, in previous reports, we showed deficits of EEG modulation during a P300 task, using the SE measure, where patients with schizophrenia showed higher SE modulation values (i.e., less change) compared to healthy controls (Bachiller et al., 2014a, 2014b), and replicated this finding in two new and different samples (Molina et al., 2018, 2020).

The underpinnings of decreased SE modulation in schizophrenia are poorly understood. One possibility is that, similarly to the resting and activation patterns studied with fMRI, increased baseline activity may hamper task-related modulation (Manoach, 2003). Indeed, our group has reported that pre-stimulus (or baseline) activity, measured as connectivity strength (CS) during the performance of a P300 task, is negatively associated with SE modulation (Gomez-Pilar et al., 2018). CS is an extension of the activity density measurement in binary networks, which summarizes the average edge values of all combinations of nodes in the network. This measure represents a quantitative index of the amount of synchrony between neural assemblies. In relation to this, we also reported higher pre-stimulus CS values in the global (broadband) and theta bands during the performance of a P300 task in patients with schizophrenia (Cea-Cañas et al., 2020).

Consistent with a possible excess of basal activity, we also reported higher EEG noise power values associated with lower SE modulation in schizophrenia (Molina et al., 2016). Noise power is the amount of non-evoked activity during the performance of a task (Winterer et al., 2000). Moreover, we also found that increased noise power values in schizophrenia were associated with negative symptoms and worse performance on cognitive tests (Díez et al., 2013; Suazo et al., 2012).

Taken together, these data suggest that higher non-specific values of EEG activity may hamper task-related modulation. However, as previously stated, the baseline CS assessments were made using the pre-stimulus activity (i.e., the phase-locking values during the pre-stimulus window in a P300 task), and thus under conditions of cognitive expectation of a task-related stimulus. Similarly, noise power assessments were also obtained during task performance. In order to understand the possible substrates of deficits in task-related EEG modulation, we believe it is of interest to assess their relations to true resting state activity, that is, when the participant is not performing any specific task or mental exercise. There are consistent data supporting higher spectral EEG power in the resting state. Studies measuring resting state activity showed consistent and reliable increases in absolute theta power in patients with schizophrenia (Newson and Thiagarajan, 2019). In this line, some authors studied the predictive value of resting-state EEG activity on the modulation of brain connectivity during a task in healthy subjects (Li et al., 2015; Rogala et al., 2020), finding that resting activity was associated with task-related connectivity, and that the group with higher resting power values showed lower capacity for EEG activity modifications and poorer behavioral performance (Rogala et al., 2020). However, to our knowledge, there are no studies analyzing the association between resting-state activity and task-related activity modulation using EEG in patients with schizophrenia. This association is of potential interest in the context of a possible cortical inhibition deficit in schizophrenia (Gonzalez-Burgos et al., 2011), which could increase basal activity and thus alter its modulation during task performance. Therefore, in the present study, we further explored the possibility of predicting task-related modulation of EEG activity in patients with schizophrenia from their resting-state EEG power values. Given that we used a P300 task and that this task is known to increase the amount of theta-band activity (Başar-Eroglu et al., 1992; Spencer and Polich, 1999), we selected activity in this frequency band to assess possible relations between EEG resting-state activity and task-related activity modulation.

2. Methods

2.1. Subjects

The sample of participants included 93 healthy controls (42 males; 45.16%); 100 patients with schizophrenia (58 males; 58%), of which 30 were first episodes (17 males; 56.67%); and 70 chronic (41 males; 58.57%).

Healthy controls were recruited through newspaper advertisements. Patients were diagnosed by one of the psychiatrists in the group through clinical interviews according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V). All participants reported no hearing problems. The demographic and clinical characteristics of the sample are shown in Table 1.

The clinical status of the patients was assessed using the Spanish version of the Positive and Negative Syndrome Scale (PANSS). The type of current drug treatment was recorded after consultation with the patients' psychiatrist or recent medical history. The dose of antipsychotic treatment was transformed into equivalents of chlorpromazine mg per day. Drugs and doses were stable during the 3 months prior to the EEG recordings. At the time of inclusion, schizophrenia patients were all receiving atypical antipsychotics (16 with clozapine), 18 received antidepressants, 4 anticholinergics and 37 benzodiazepines (see Table 1).

Our exclusion criteria were: (i) any neurological illness; (ii) history of cranial trauma with loss of consciousness longer than one minute; (iii) past or present substance abuse, except nicotine or caffeine; (iv) total intelligence quotient (IQ) under 70; (iv) for patients, any other psychiatric process; and (v) for controls, any current psychiatric or neurological diagnosis and/or treatment with drugs known to act on the central nervous system.

We obtained written informed consent from all participants after providing full printed and verbal information. The local ethical committee approved the study according to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. EEG recordings

The EEG was acquired using a Brain Vision® equipment (Brain Products GmbH; Munich, Germany) and two different cap sets (64 and 32 electrodes, both Electro-Cap International, Inc.; Eaton, Ohio, USA). Before data analysis, the EEG montage was reduced to the common 29-channel according to the modified 10/10 International System at electrodes Fp1, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FCz, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, O1, Oz, and O2 placements. Fpz was used as the ground channel. Two additional electrooculography (EOG) electrodes were placed for monitoring eye blinks and both vertical and lateral eye movements. EEG signals were referenced online to the Cz electrode and recorded continuously at a sampling rate of 500 Hz. Electrode impedance was kept below 5 kΩ during the recordings.

All participants underwent two EEG recording paradigms. First, a 5-min-long resting EEG session was recorded while participants were comfortably seated in a quiet room and instructed to keep their eyes closed and body relaxed. Secondly, to elicit P3a and P3b components (by

Table 1
Description of demographic, clinical and EEG scores in patients and control subjects.

	Schizophrenia ($N = 100$)	First-episode ($N = 30$)	Healthy controls (N = 93)
Demographic and clinical			
Male:Female ratio	58:42	17:13	42:51
Age – in years	36.570 (10.393)	30.167 (9.962)	34.022 (10.350)
Education – in years	**13.667 (3.706)** ***	**15.080 (3.840)** *	17.079 (2.889)
Total IQ	**91.529 (13.856)** ***	**87.038 (15.465)** ***	115.000 (11.254)
Illness duration – in months	107.921 (121.701)	9.150 (17.548)	N/A
CPZ equivalents – in mg/d	402.494 (335.651)	350.833 (228.641)	N/A
Pharmacology – number of patients having a specific drug:			
Antipsychotics	100	30	N/A
Clozapine	16	0	N/A
Antidepressants	18	4	N/A
Anticholinergics	4	0	N/A
Benzodiazepines	37	6	N/A
Symptoms (PANSS scores)			
Positive scale	11.628 (4.243)	11.357 (3.803)	N/A
Negative scale	16.500 (7.236)	14.357 (4.112)	N/A
Total scale	53.205 (18.765)	48.786 (12.902)	N/A
EEG measurement scores			
Reaction time – in ms	**273.859 (45.139)** ***	265.323 (47.755)	251.150 (39.031)
Percentage of correct responses	**89.558 (14.481)** ***	**90.886 (13.573)** ***	97.185 (5.604)
Percentage of false alarms	**10.942 (15.128)** ***	**8.358 (14.973)** **	2.686 (4.581)
P3b amplitude (Pz)	**1.695 (2.050)** ***	2.070 (2.069)	2.707 (1.666)
Resting-state power – theta band	**0.214 (0.965)** ***	−0.103 (0.974)	−0.231 (0.990)
SE-baseline	**−0.132 (1.056)**	−0.171 (0.997)	0.142 (0.921)
SE-response	**−0.065 (1.118)**	−0.155 (1.045)	0.070 (0.856)
SE-modulation	**0.163 (0.682)** *	0.068 (0.719)	−0.175 (1.236)
CS baseline – theta band	**0.365 (0.035)** **	0.362 (0.031)	0.352 (0.034)
CS response – theta band	**0.383 (0.032)** ***	0.388 (0.036)	0.406 (0.047)
CS modulation – theta band	**0.017 (0.028)** ***	**0.027 (0.030)** ***	0.054 (0.041)

Differences between patients and controls are marked with asterisks. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.005$ (Student's t or χ^2 test, when corresponding). (SE: Spectral entropy, CS: Connectivity strength).

distractor and target stimuli respectively), a 3-stimulus oddball (P300) paradigm was employed with a 500 Hz target tone, a 1000 Hz distractor tone, and a 2000 Hz standard stimulus tone. Accordingly, participants heard binaural tone bursts (duration 50 ms, rise and fall time 5 ms and intensity 90 dB) presented with a random stimulus onset asynchrony of 1000 and 1500 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 other muscles activity. The P3b amplitude was calculated at the Pz electrode as its average over the window of interest 150–450 ms. Only the target/P3b potential trials were analyzed following the methodology of our previous work. Only attended target stimuli (i.e., followed by a response) were studied in the present work, that is, for the calculation of the SE and CS measures. Reaction times for target detection, as well as detection and false alarm error rates were collected.

2.3. EEG resting-state power

Once recorded, resting-state EEG signals were first off-line re-referenced to the average activity of all sensors (Bledowski et al., 2004) and 1 to 70 Hz bandpass and 50 Hz notch filtered. Next, to improve signal artifact correction, an independent component analysis (ICA) including EEG and EOG data was applied. All components clearly corresponding to eye movement were subtracted.

Recordings were then divided into 1-s epochs. Those exceeding a range of ±70 μV in any of the 29 EEG channels were automatically rejected. Additionally, a visual inspection was carried out to manually reject remaining epochs still presenting clear artifacts. Pre-processing was performed using Fieldtrip toolbox for Matlab. Subject data were included in the analysis only if 20 or more useful epochs were still available after data pre-processing. The average number of valid segments per participant was 87 (SD = 17.65).

A spectrum analysis based on Fourier transform was applied on the segmented data to estimate the absolute power (expressed in μV^2). We used a fixed window length method based on Hanning taping (Fieldtrip toolbox for Matlab). Time window length was set to 1 s (1 Hz frequency resolution). The average absolute power value was then calculated for the theta frequency band (4 to 8 Hz).

2.4. EEG spectral entropy (SE) during P300 task

EEG recordings obtained during the P300 task were also re-referenced to the average activity of all active sensors. Signals were band pass filtered between 1 and 70 Hz and a 50 Hz notch filter was used to remove power line interference (zero-phase finite impulse response filters). Next, a 3-step procedure was conducted in which artifacts were rejected (Alejandro Bachiller et al., 2015): (i) an independent component analysis to remove eye-blinks and muscle artifacts (Delorme and Makeig, 2004); (ii) a trial segmentation into 1 s windows, ranging from 300 ms before to 700 ms after the stimulus onset; and (iii) an adaptive trial rejection using statistical thresholding to discard the remaining noisy trials.

The concept of entropy originally comes from the field of thermodynamics and involves the uncertainty of information in terms of disorder, diversity and discrepancy (Scheeringa et al., 2011). In this context, SE is a measure of the entropy applied over the EEG power spectrum, that is, an estimation of the flatness of the spectral content (von Stein et al., 2000). Thus, SE can be considered an index of signal regularity, since it measures how the spectral components are distributed (Gomez-Pilar et al., 2018). For example, a signal with a large range of spectral components (e.g., white noise) has a flat power spectral density and, therefore, high values of SE (close to 1). On the contrary, a signal with few spectral components (e.g., a pure sinusoidal wave) yields minimum SE values (close to 0).

SE was computed from the normalized continuous wavelet transform (CWT) in the frequency range of 1–70 Hz. The CWT is a form of time-frequency representation of a signal that is conceptually related to the short-term Fourier transform, which makes it appropriate for the detection of dynamic ERP components, due to its balance between frequency and time resolution (Núñez et al., 2017). The time-dependent wavelet-based SE can be defined as follows:

$$SE(k) = -\frac{1}{log(M)} \bullet \sum_{s} WS_n(k,s) \bullet \log[WS_n(k,s)],$$

where SE is the spectral entropy (as a function of time); WS_n is the normalized wavelet scalogram across the spectrum, which summarizes

the distribution of the signal energy; *k* is the time interval; *s* is the frequency component; and *M* Is the number of spectral components in the wavelet scalogram.

The SE was computed only for trials of correct target response in two windows: baseline (300 ms before stimulus-to-stimulus onset) and response (150 ms to 450 ms from the stimulus onset, centered around the P3b peak). Afterwards, it was averaged in each of the two windows. Further details can be found in our previous studies (Gomez-Pilar et al., 2018; Molina et al., 2018).

The measure 'SE modulation' was computed as the SE difference between response and pre-stimulus windows (Gomez-Pilar et al., 2018), providing a measure of the degree of change in signal regularity across time. Since a decrease of SE in the response window has been robustly observed as normal behavior in controls, negative SE modulation values are expected in patients as well (Gomez-Pilar et al., 2018; Molina et al., 2018). Therefore, it is important to clarify here –relevant to the interpretation of results in the discussion– that more negative SE modulation results (i.e., with higher absolute values) imply a greater change (or modulation) of the signal. This is because of the direction of the subtraction: smaller SE values during the task response (a higher order state) minus larger SE values during the pre-stimulus baseline (a lower order state).

2.5. EEG connectivity strength (CS) during P300 task

Connectivity strength was computed as described in our previous works (Gomez-Pilar et al., 2018; Molina et al., 2020) and its application to functional connectivity analyses is based on phase locking values (PLV) of the signals between EEG sensors.

After the preprocessing of the EEG signal described above, and using a CWT approach to perform filtering and phase extraction in one operation (Bob et al., 2008), the PLV between two signals *x(t)* and *y(t)* was obtained evaluating the variability of the phase difference across successive trials:

$$PLV_{xy}(k,s) = \frac{1}{Nt}\left|\sum_{n=1}^{n} e^{\Delta\varphi xy(k,s,n)}\right|,$$

where *Nt* is the number of trials, $\Delta\varphi_{xy}$ is the instantaneous phase difference between *x* and *y* signals, *k* is the time interval, and *s* the frequency component.

Finally, the CS was computed in the above-defined baseline and response windows using the network density as:

$$D = \frac{\sum_{i=1}^{N}\sum_{j>i} w_{ij}}{T},$$

where *wij* refers to PLV values between nodes *i* and *j*; *N* is the total number of nodes of the network; and $T = N(N-1)/2$ is the total number of connections in the undirected graph.

Finally, 'CS modulation' was computed as the CS difference between response and pre-stimulus windows. Our previous publications can be consulted for further details (Gomez-Pilar et al., 2018; Molina et al., 2020).

2.6. Statistical analysis

Age, years of education and IQ were contrasted between the schizophrenia and control groups using Student's *t*-test. Sex distribution was compared between groups using a chi-square (χ^2) test.

In order to reduce the number of scores on resting-state theta power and task-related SE modulation (one for each electrode), we performed a principal component analysis (PCA) for each measurement and saved each of the participants' factorial scores (Regression Method) for further analysis. The CS measurement is unique for the entire scalp recording and no variable reduction was necessary.

EEG measurement scores were contrasted between the schizophrenia and control groups using Student's *t*-test. Simple linear regression analyses between EEG measures were performed assuming the resting-state theta power factor score as the predictor measure and the task-related modulation scores (SE and CS) as the dependent variables. Regression analyses were performed for each study group and for the SE and CS predicted measures independently. In order to closer study the relations between resting-state and task-related baseline measurements, regression analyses between resting-state power and baseline CS, and between resting-state power and baseline SE were additionally performed independently for each group.

When significant results were obtained for the group of patients with schizophrenia (which includes both chronic and first-episodes), we were interested in replicating the corresponding result in the first-episode subgroup, to discard a primary role for chronicity of the illness (i.e., a Student's t-test for first episodes only vs. healthy controls and/or regression analyses for first episodes only).

All statistical analyses were performed using IBM SPSS Amos 24 for Windows.

3. Results

There were no significant differences in age and sex between the group of all patients with schizophrenia and the control group ($t(191) = 1.706$, $p = 0.090$ and $\chi^2(1) = 3.181$, $p = 0.074$, respectively). First-episode patients also did not differ significantly from controls in these two variables ($t(121) = -1.790$, $p = 0.076$ and $\chi^2(1) = 1.203$, $p = 0.273$, respectively). Patients with schizophrenia were shown to have fewer years of education ($t(102) = -4.883$; $p < 0.001$) and lower IQ ($t(169) = -12.165$; $p < 0.001$) than healthy controls. These findings remained significant when only first-episode patients were studied ($t(61) = -2.355$, $p = 0.022$ and $t(110) = -10.126$, $p < 0.001$, respectively) (Table 1).

Schizophrenia patients showed a significant decrease in their P3b amplitude ($t(191) = -3.607$, $p < 0.001$) compared to healthy controls (Fig. 1). In addition, patients showed worse behavioral performances on the task than controls on measures of reaction time ($t(191) = 3.587$, $p < 0.001$) and percentages of correct responses ($t(191) = -4.577$, $p < 0.001$) and false alarm errors ($t(191) = 4.858$, $p < 0.001$) (Table 1). As for EEG scores, compared to healthy controls, patients with schizophrenia showed significantly higher resting-state activity in the theta

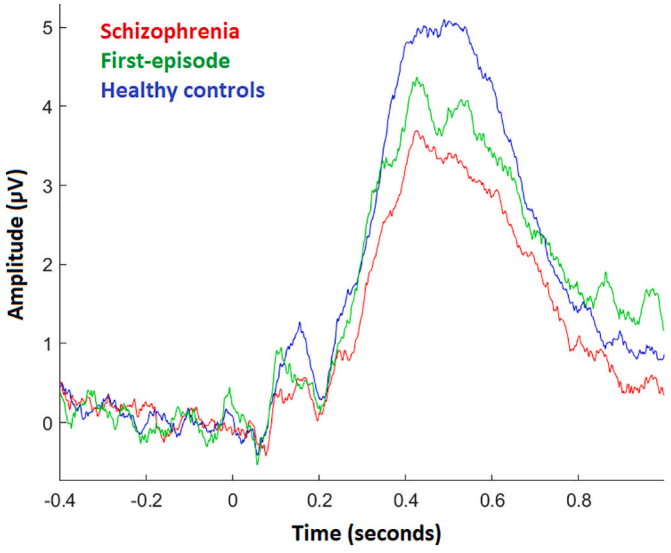

Fig. 1. Comparison of P3b response between all schizophrenia patients (red), the subgroup of first-episode patients (green) and healthy controls. (blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

band (t(191) = 3.163; $p = 0.002$), as well as significantly higher values of task-related SE modulation (t(191) = 2.377, $p = 0.018$). Patients with schizophrenia showed a positive average SE modulation value (in factor scores), meaning that, on average, SE baseline scores were lower than SE response scores (changed from a state of higher to lower overall signal regularity). On the contrary, healthy controls showed a negative average value (in factor scores) in SE modulation (changed from a state of lower to higher signal regularity) (Table 1). Fig. 2 shows topographically on the scalp the values of these EEG measurements for the different groups and their contrasts patients vs. controls.

On CS measures, patients with schizophrenia showed significantly higher CS baseline (t(191) = 2.741, $p = 0.007$), as well as significantly lower CS response (t(191) = −4.066, $p < 0.001$) and CS modulation (t(191) = −7.277, $p < 0.001$) values than healthy controls. When only first-episode patients were analyzed, only the significantly lower CS modulation scores compared to controls remained (t(121) = −3.380, $p = 0.001$) (Table 1).

3.1. Regression analyses

Fig. 3 shows the results of the simple linear regression analyses and their best-fitting lines for each of the study groups and EEG measures analyzed.

In patients with schizophrenia, resting-state theta-band power was positively and significantly associated with SE modulation (corresponding to their factor scores; $R^2 = 0.055$, F(1) = 5.710; β = 0.235, $p = 0.019$). This relation was equally significant in the control group ($R^2 = 0.347$, F(1) = 48.408; β = 0.589, $p < 0.001$), but not in the subgroup of first-episode patients ($R^2 = 0.071$, F(1) = 2.132; β = 0.266, $p = 0.155$).

As for the relation between resting-state power and CS modulation, both in the theta band, the former score was able to significantly predict the latter in patients with schizophrenia ($R^2 = 0.053$, F(1) = 5.514; β = −0.231, $p = 0.021$) and healthy controls ($R^2 = 0.104$, F(1) = 10.542; β = −0.322, $p = 0.002$), but this time with a negative sign correlation. These two scores were not significantly related for the first episode subgroup ($R^2 = 0.090$, F(1) = 2.776; β = −0.300, $p = 0.107$).

On the other hand, the study of the relation between resting-state power and baseline CS scores, also both in the theta band, found a positive association for the schizophrenia group ($R^2 = 0.063$, F(1) = 6.603; β = 0.251, $p = 0.012$), but not for the control group ($R^2 = 0.000$, F(1) = 0.003; β = −0.006, $p = 0.957$) or the first-episode subgroup ($R^2 = 0.010$, F(1) = 0.285; β = 0.100, $p = 0.597$).

Finally, the study of the relation between resting-state power and baseline SE scores found a negative association for both the control ($R^2 = 0.546$, F(1) = 109.286; β = −0.739, $p < 0.001$) and the schizophrenia groups ($R^2 = 0.472$, F(1) = 87.776; β = −0.687, $p < 0.001$), and also for the first-episode subgroup ($R^2 = 0.562$, F(1) = 35.883; β = −0.749, $p < 0.001$).

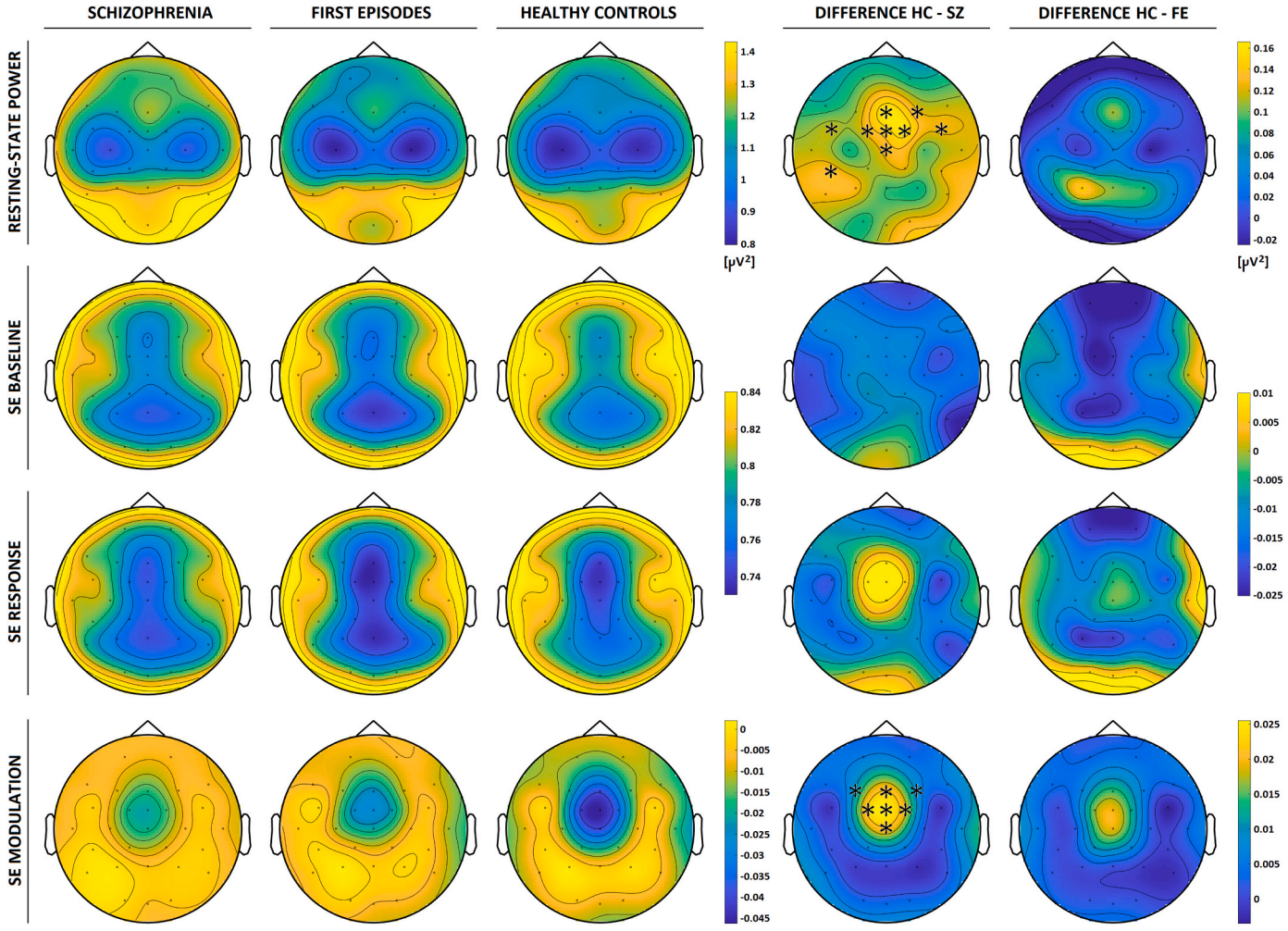

Fig. 2. Spatial scalp distribution for each group of the resting-state power and spectral entropy (SE) values related to the P300 task (baseline, response and response minus baseline modulation). Differences between patients and controls are shown on the right. Those electrodes where they differ significantly are marked with an asterisk (Bonferroni correction, $p \leq 0.05/29 = 0.002$). (SZ: Schizophrenia patients, FE: First Episode patients, HC: Healthy Controls).

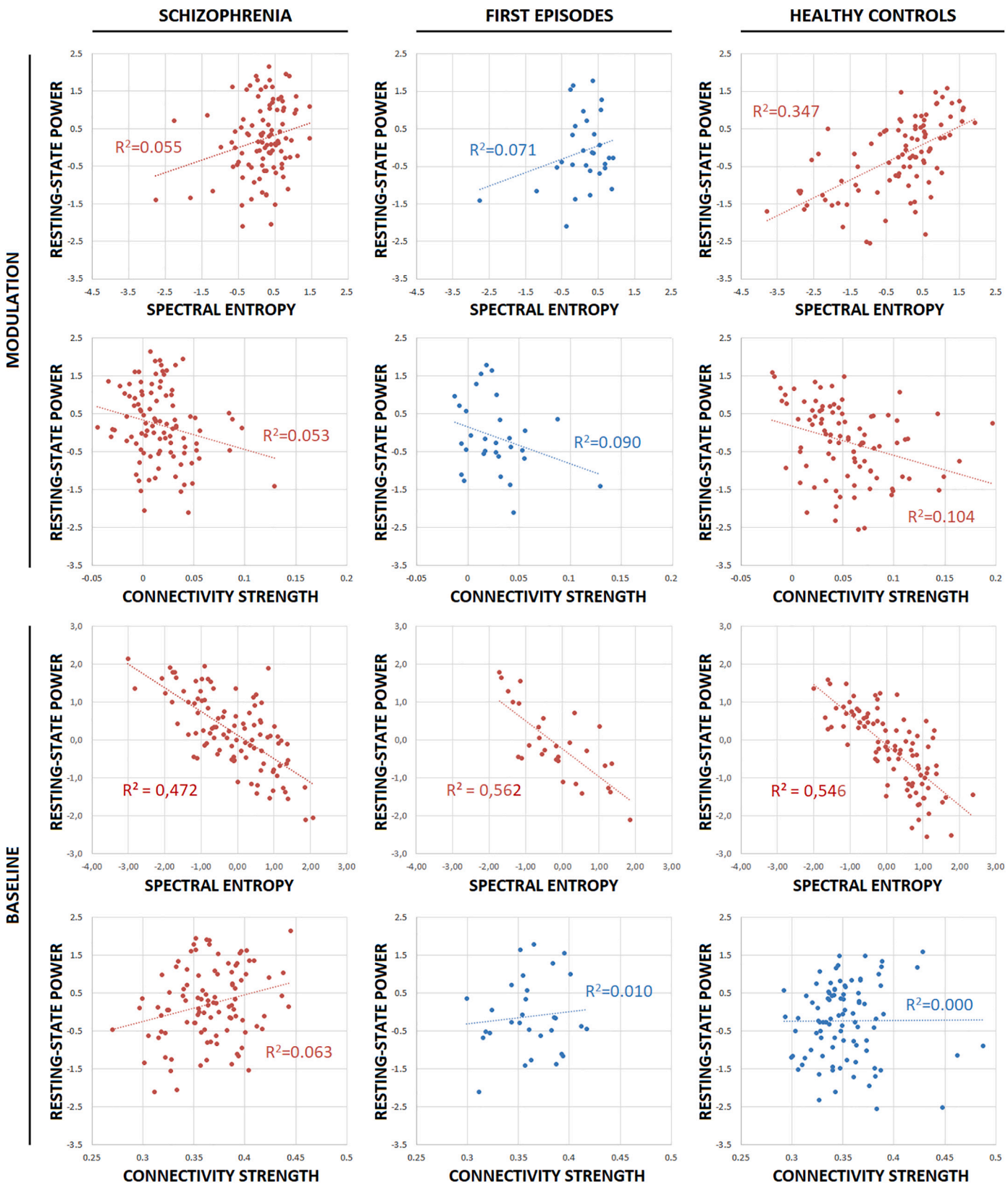

Fig. 3. Results of simple linear regression analyses and their best-fitting lines. Respectively predictor and dependent variables: resting-state theta-band power and task-related SE modulation (top row); resting-state power and task-related CS modulation, both in the theta band (second row); resting-state theta-band power and task-related SE baseline (third row); and resting-state power and task-related CS baseline, both in the theta band (bottom row). As noted in the corresponding methods section, and contrary to the CS modulation scores, lower SE modulation values imply a greater change or modulation of signal regularity. Significant and non-significant associations are shown in red and blue, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

According to the present results, the amount of resting state activity in the theta band was inversely associated, in our subjects, with modulation of task-related EEG activity (for both SE and CS scores) during a P300 paradigm. Following our previous works, we studied target/P3b potential trials. This relation was in both patients and controls.

Our group has previously reported, in three completely different samples, a deficit in SE modulation in subjects with schizophrenia during the performance of a P300 task (Bachiller et al., 2014a; Molina et al., 2018, 2020). However, the pre-stimulus (also called baseline) condition may not be the same as the resting state, since the former is embeded in the performance of the P300 task, that is, possibly including cognitive activity of stimulus expectation. Therefore, to test the hypothesis that a basal hyperactive state is related to hampered modulation of EEG activity, we calculated the relations between resting-state activity and task-related SE modulation. In previous EEG literature, pre-stimulus and resting states have been analyzed together in terms of their relation to task-related modulation (Northoff and Gomez-Pilar, 2021), which underlies the relevance of a separate assessment of the resting state.

The relation found here between resting-state theta power and task-related EEG modulation appears consistent with data supporting the role of this band in the performance of the oddball task. In healthy subjects, performance of a P300 task was associated with an increase in the theta density of the EEG activity (Başar-Eroglu et al., 1992; Spencer and Polich, 1999). In the same line, in one of our previous report that included most of the current sample, healthy controls showed a decrease in median frequency (MF) from the pre-stimulus to the response window (i.e., a global slowing of the mean EEG rhythm) (Molina et al., 2018).

We have reported elsewhere the relation between pre-stimulus theta activity and reduced SE modulation during a P300 task in schizophrenia, considering SE as a summary of global activity. First, patients in the above-mentioned report showed less MF modulation during that task (from the pre-stimulus to the response windows), implying a lower increase in slow band density with task performance (Molina et al., 2018). Notably, MF modulation correlated in patients with lower SE modulation, suggesting that theta modulation underlies the change in global EEG activity during a P300 task and, consequently, lower SE change in schizophrenia. This finding is also consistent with the previous report in schizophrenia of a reduction in induced and evoked theta activity during an oddball paradigm (Doege et al., 2009). Second, the graph parameter "connectivity strength" (CS) in the theta band (which reflects the amount of global functional connectivity in this frequency band, based on the phase locking of the signal from different sensors) was found to be inversely associated with SE modulation in schizophrenia patients (Gomez-Pilar et al., 2018). In the same report, we described that increases in global connectivity (CS in the theta band) were related to SE modulation, consistent with a more strongly connected system being more ordered in its spectral components.

The CS score is a measure of synchrony and can therefore be considered related to power, which is also derived from the synchronous firing of neuronal groups. Thus, the association found here between resting-state theta power and SE modulation during a P300 task seems consistent with the relation between higher CS and lower SE modulation in schizophrenia (Gomez-Pilar et al., 2018). This finding would mean that similar relations could be found between pre-stimulus and resting-state hyperactivities, on the one hand, and task-related modulation of EEG activity, on the other. Accordingly, both SE and theta-band CS values at baseline correlated significantly (with positive and negative sign, respectively) with resting-state theta power in patients. This seems consistent with the higher theta-band power in the resting state and its lower increase during a cognitive task in schizophrenia patients when compared to controls (Garakh et al., 2015). On the other hand, we could ask which component, baseline or response, mainly contributes to the alterations in SE and/or CS modulation. Firstly, we found no significant differences between groups for SE baseline and SE response values. Secondly, patients show significantly higher CS baseline values and lower SE response values. Thus, our results support a contribution of greater pre-stimulus connectivity to task-related alterations in neural activity modulation, but we cannot rule out an additional contribution of a worse response to task demands once the target stimulus has appeared.

Considering all these data together, some support is given to the possibility that during both the resting state and the pre-stimulus baseline, a greater amount of theta-band synchrony hampers the modulation of EEG activity during task performance, with this modulation being translated into an increase in the density of theta-band EEG activity from the pre-stimulus to the response window. A similar decrease in the theta band modulation with cognitive activity was reported (Hanslmayr et al., 2013).

Given that the P300 task likely activates a broad neural network (Bledowski et al., 2004; Soltani et al., 2000) and that slow bands have been implicated in long-range synchronization (von Stein et al., 2000; Womelsdorf et al., 2007), our data appear consistent with a ceiling effect for theta activity in such synchronization. In other words, an excess of theta activity in patients at baseline may hamper the possibility of adequately synchronizing the regions expected to be involved in cognitive performance.

A possible underpinning of the high basal activity may be related to the decreased inhibitory function described in schizophrenia patients (Gonzalez-Burgos et al., 2011). Functional coupling of diverse brain regions and synaptic assemblies may be subtended by neural oscillations (Buzsáki, 2006). Therefore, if a hyperactive basal state exerts a ceiling effect that hampers task-related modulation of such oscillations, then cognition may ultimately be impaired. The finding that this same association was found in controls may suggest that the relation between inhibition and modulation is quantitative rather than qualitative, that is, that patients would differ from controls in the amount of inhibitory activity, rather than in the presence of any qualitatively abnormal inhibitory function. This would lead to the possibility that inhibition is not necessarily affected in all patients.

Functional magnetic resonance imaging (fMRI) assessment of baseline and task-related activity patterns reveals data consistent with the possibility of reduced inhibition in schizophrenia. However, the important differences between fMRI and EEG lead us to be cautious in comparing results. Using fMRI, a relation between an increase in basal activity and a decrease in task-related modulation was postulated (Manoach, 2003), a pattern similar to that reported in the present study. Also based mainly on fMRI findings, it has been proposed that an intrinsic brain network architecture present during resting state may primarily shape the functional network architecture during task performance (Cole et al., 2014). In other words, and consistent with our EEG findings, the properties of resting activity may determine the ability to modulate, and thus the ability to adapt to environmental demands.

A limitation is the use of absolute power rather than EEG measurements based on phase. However, in order to test the hypothesis of an inhibition deficit in the resting state, we believe that a simple measure of cortical activity, not phase-locked with any kind of cognitive stimulation or processing, is sufficiently informative. Moreover, as already mentioned, previous results from our group using CS (including phase information) support the same relation between pre-stimulus activity and its modulation. Another limitation of our study is that we have only calculated relations between resting activity and modulation for the theta band, since increases in power have been consistently observed during the P300 task. Assessments for other frequency bands could also yield relevant results, but also increase the number of comparisons leading to type I errors.

In conclusion, we have described here a similar relation between resting-state activity, measured as theta power, and SE modulation as we have previously reported between theta-band CS and SE modulation in a sample that mostly overlaps with the present one.

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CRediT authorship contribution statement

María Iglesias-Tejedor: Methodology, Formal analysis, Writing – original draft. **Álvaro Díez:** Methodology, Formal analysis, Writing – original draft. **Vicent Llorca-Bofí:** Data curation. **Pablo Núñez:** Data curation. **Carolina Castaño-Díaz:** Data curation. **Berta Bote:** Data curation. **Rafael Segarra:** Data curation. **Javier Sanz-Fuentenebro:** Data curation. **Vicente Molina:** Conceptualization, Writing – review & editing, Project administration, Supervision.

Data availability

Data will be made available on request.

References

Bachiller, A., Díez, Á., Suazo, V., Domínguez, C., Ayuso, M., Hornero, R., Poza, J., Molina, V., Díez, A., Suazo, V., Domínguez, C., Ayuso, M., Hornero, R., Poza, J., Molina, V., 2014a. Decreased spectral entropy modulation in patients with schizophrenia during a P300 task. Eur. Arch. Psychiatry Clin. Neurosci. 264 (6), 1–11. https://doi.org/10.1007/s00406-014-0488-6.

Bachiller, A., Lubeiro, A., Díez, Á., Suazo, V., Dominguez, C., Blanco, J.A.A., Ayuso, M., Hornero, R., Poza, J., Molina, V., Domínguez, C., Blanco, J.A.A., Ayuso, M., Hornero, R., Poza, J., Molina, V., 2014b. Decreased entropy modulation of EEG response to novelty and relevance in schizophrenia during a P300 task. Eur. Arch. Psychiatry Clin. Neurosci. 265 (6) https://doi.org/10.1007/s00406-014-0525-5.

Bachiller, Alejandro, Poza, J., Gomez, C., Molina, V., Suazo, V., Hornero, R., Gómez, C., Molina, V., Suazo, V., Hornero, R., 2015. A comparative study of event-related coupling patterns during an auditory oddball task in schizophrenia. J. Neural Eng. 12 (1), 16007. https://doi.org/10.1088/1741-2560/12/1/016007.

Başar-Eroglu, C., Başar, E., Demiralp, T., Schürmann, M., 1992. P300-response: possible psychophysiological correlates in delta and theta frequency channels. A review. Int. J. Psychophysiol. 13 (2) https://doi.org/10.1016/0167-8760(92)90055-G.

Bledowski, C., Prvulovic, D., Hoechstetter, K., Scherg, M., Wibral, M., Goebel, R., Linden, D.E., 2004. Localizing P300 generators in visual target and distractor processing: a combined event-related potential and functional magnetic resonance imaging study. J. Neurosci. 24 (42), 9353–9360, 24/42/9353 [pii]. https://doi.org/10.1523/JNEUROSCI.1897-04.2004.

Bob, P., Palus, M., Susta, M., Glaslova, K., 2008. EEG phase synchronization in patients with paranoid schizophrenia. Neurosci. Lett. 447 (1) https://doi.org/10.1016/j.neulet.2008.09.055.

Buzsáki, G., 2006. Diversity of cortical functions: inhibition. In: Rythms of the Brain. Oxford University Press, pp. 61–79.

Cea-Cañas, B., Gomez-Pilar, J., Núñez, P., Rodríguez-Vázquez, E., de Uribe, N., Díez, Á., Pérez-Escudero, A., Molina, V., 2020. Connectivity strength of the EEG functional network in schizophrenia and bipolar disorder. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 98, 109801. https://doi.org/10.1016/j.pnpbp.2019.109801.

Cole, M.W., Bassett, D.S., Power, J.D., Braver, T.S., Petersen, S.E., 2014. Intrinsic and task-evoked network architectures of the human brain. Neuron 83 (1). https://doi.org/10.1016/j.neuron.2014.05.014.

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 (1). https://doi.org/10.1016/j.jneumeth.2003.10.009.

Díez, Á., Suazo, V., Casado, P., Martín-Loeches, M., Molina, V., Martin-Loeches, M., Molina, V., Díez, A., Suazo, V., Casado, P., Martín-Loeches, M., Molina, V., 2013. Spatial distribution and cognitive correlates of gamma noise power in schizophrenia. Psychol. Med. 43 (September), 1–11. https://doi.org/10.1017/S0033291712002103.

Doege, K., Bates, A.T., White, T.P., Das, D., Boks, M.P., Liddle, P.F., 2009. Reduced event-related low frequency EEG activity in schizophrenia during an auditory oddball task. Psychophysiology 46 (3), 566–577. https://doi.org/10.1111/j.1469-8986.2009.00785.x.

Garakh, Z., Zaytseva, Y., Kapranova, A., Fiala, O., Horacek, J., Shmukler, A., Gurovich, I. Y., Strelets, V.B., 2015. EEG correlates of a mental arithmetic task in patients with first episode schizophrenia and schizoaffective disorder. Clin. Neurophysiol. 126 (11), 2090–2098. https://doi.org/10.1016/j.clinph.2014.12.031.

Gomez-Pilar, J., de Luis-García, R., Lubeiro, A., de Uribe, N., Poza, J., Núñez, P., Ayuso, M., Hornero, R., Molina, V., 2018. Deficits of entropy modulation in schizophrenia are predicted by functional connectivity strength in the theta band and structural clustering. NeuroImage. Clin. 18, 382–389. https://doi.org/10.1016/j.nicl.2018.02.005.

Gonzalez-Burgos, G., Fish, K.N., Lewis, D.A., 2011. GABA neuron alterations, cortical circuit dysfunction and cognitive deficits in schizophrenia. Neural Plast. 2011 https://doi.org/10.1155/2011/723184.

Hanslmayr, S., Backes, H., Straub, S., Popov, T., Langguth, B., Hajak, G., Bäuml, K.H.T., Landgrebe, M., 2013. Enhanced resting-state oscillations in schizophrenia are associated with decreased synchronization during inattentional blindness. Hum. Brain Mapp. 34 (9), 2266–2275. https://doi.org/10.1002/hbm.22064.

Li, F., Liu, T., Wang, F., Li, H., Gong, D., Zhang, R., Jiang, Y., Tian, Y., Guo, D., Yao, D., Xu, P., 2015. Relationships between the resting-state network and the P3: evidence from a scalp EEG study. Sci. Rep. 5 https://doi.org/10.1038/srep15129.

Manoach, D.S., 2003. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. Schizophr. Res. 60 (2–3), 285–298. S0920996402002943 [pii].

Molina, V., Bachiller, A., Suazo, V., Lubeiro, A., Poza, J.J., Hornero, R., 2016. Noise power associated with decreased task-induced variability of brain electrical activity in schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 266 (1), 55–61. https://doi.org/10.1007/s00406-014-0569-6.

Molina, V., Bachiller, A., Gomez-Pilar, J., Lubeiro, A., Hornero, R., Cea-Cañas, B., Valcárcel, C., Haidar, M.K., Poza, J., 2018. Deficit of entropy modulation of the EEG in schizophrenia associated to cognitive performance and symptoms. A replication study. Schizophr. Res. 195, 334–342. https://doi.org/10.1016/j.schres.2017.08.057.

Molina, V., Lubeiro, A., de Luis Garcia, R., Gomez-Pilar, J., Martín-Santiago, O., Iglesias-Tejedor, M., Holgado-Madera, P., Segarra-Echeverría, R., Recio-Barbero, M., Núñez, P., Haidar, M.K., Fernández-Sevillano, J., Sanz-Fuentenebro, J., 2020. Deficits of entropy modulation of the EEG: a biomarker for altered function in schizophrenia and bipolar disorder? J. Psychiatry Neurosci. 45 (5) https://doi.org/10.1503/jpn.190032.

Newson, J.J., Thiagarajan, T.C., 2019. EEG frequency bands in psychiatric disorders: a review of resting state studies. Front. Hum. Neurosci. 12 (January), 1–24. https://doi.org/10.3389/fnhum.2018.00521.

Northoff, G., Gomez-Pilar, J., 2021. Overcoming rest-task divide-abnormal Temporospatial dynamics and its cognition in schizophrenia. Schizophr. Bull. 47 (3), 751–765. https://doi.org/10.1093/schbul/sbaa178.

Northoff, G., Huang, Z., 2017. How do the brain's time and space mediate consciousness and its different dimensions? Temporo-spatial theory of consciousness (TTC). In. Neurosci. Biobehav. Rev. 80 https://doi.org/10.1016/j.neubiorev.2017.07.013.

Núñez, P., Poza, J., Bachiller, A., Gomez-Pilar, J., Lubeiro, A., Molina, V., Hornero, R., 2017. Exploring non-stationarity patterns in schizophrenia: neural reorganization abnormalities in the alpha band. J. Neural Eng. 14 (4), 46001. https://doi.org/10.1088/1741-2552/aa6e05.

Rogala, J., Kublik, E., Krauz, R., Wróbel, A., 2020. Resting-state EEG activity predicts frontoparietal network reconfiguration and improved attentional performance. Sci. Rep. 10 (1) https://doi.org/10.1038/s41598-020-61866-7.

Scheeringa, R., Fries, P., Petersson, K.M., Oostenveld, R., Grothe, I., Norris, D.G., Hagoort, P., Bastiaansen, M.C., 2011. Neuronal dynamics underlying high- and low-frequency EEG oscillations contribute independently to the human BOLD signal. Neuron 69 (3), 572–583. S0896-6273(10)01081-0 [pii]. https://doi.org/10.1016/j.neuron.2010.11.044.

Soltani, M., Knight, R.T., Yamaguchi, S., Chao, L.L., Nielsen-Bohlman, L., 2000. Neural origins of the P300. Crit. Rev. Neurobiol. 14 (3–4), 199–224.

Spencer, K.M., Polich, J., 1999. Poststimulus EEG spectral analysis and P300: attention, task, and probability. Psychophysiology 36 (2). https://doi.org/10.1017/S0048577299971615.

Suazo, V., Díez, T., Martín, C., Ballesteros, A., Casado, P., Martín-Loeches, M., Molina, V., Díez, Á., Martín, C., Ballesteros, A., Casado, P., Martín-Loeches, M., Molina, V., 2012. Elevated noise power in gamma band related to negative symptoms and memory deficit in schizophrenia. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 38 (2), 270–275. https://doi.org/10.1016/j.pnpbp.2012.04.010.

von Stein, A., Chiang, C., Konig, P., 2000. Top-down processing mediated by interareal synchronization. Proc. Natl. Acad. Sci. U. S. A. 97 (26), 14748–14753. https://doi.org/10.1073/pnas.97.26.14748 97/26/14748.

Winterer, G., Ziller, M., Dorn, H., Frick, K., Mulert, C., Wuebben, Y., Herrmann, W.M., Coppola, R., 2000. Schizophrenia: reduced signal-to-noise ratio and impaired phase-locking during information processing. Clin. Neurophysiol. 111 (5), 837–849. S1388-2457(99)00322-3 [pii].

Womelsdorf, T., Schoffelen, J.M., Oostenveld, R., Singer, W., Desimone, R., Engel, A.K., Fries, P., 2007. Modulation of neuronal interactions through neuronal synchronization. Science 316 (5831), 1609–1612. https://doi.org/10.1126/science.1139597, 316/5831/1609 [pii].