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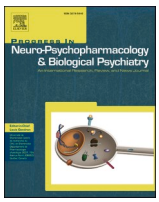

Functional network properties in schizophrenia and bipolar disorder assessed with high-density electroencephalography

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ABSTRACT

Background: The study of the cortical functional network properties in schizophrenia (SZ) may benefit from the use of graph theory parameters applied to high-density electroencephalography (EEG). Connectivity Strength (CS) assesses global synchrony of the network, and Shannon Graph Complexity (SGC) summarizes the network distribution of link weights and allows distinguishing between primary and secondary pathways. Their joint use may help in understanding the underpinnings of the functional network hyperactivation and task-related hypomodulation previously described in psychoses.

Methods: We used 64-sensor EEG recordings during a P300 oddball task in 128 SZ patients (96 chronic, CR, and 32 first episodes, FE), as well as 46 bipolar disorder (BD) patients, and 92 healthy controls (HC). Pre-stimulus and modulation (task-response minus pre-stimulus windows values) of CS and SGC were assessed in the theta band (4–8 Hz) and the broadband (4–70 Hz).

Results: Compared to HC, SZ patients (CR and FE) showed significantly higher pre-stimulus CS values in the broadband, and both SZ and BD patients showed lower theta-band CS modulation. SGC modulation values, both theta-band and broadband, were also abnormally reduced in CR patients. Statistically significant relationships were found in the theta band between SGC modulation and both CS pre-stimulus and modulation values in patients. CS altered measures in patients were additionally related to their cognitive outcome and negative symptoms. A primary role of antipsychotics in these results was ruled out.

Conclusions: Our results linking SGC and CS alterations in psychotic patients supported a hyperactive and hypomodulatory network mainly involving connections in secondary pathways.

1. Introduction

The biological substrates of mental functions are still largely unknown. However, we can reasonably assume that they involve the coordinated activity of most of the cerebral cortex, changing over the course of milliseconds and propagating swiftly along nearby and distant regions. Therefore, the study of the underpinnings of the pathological alterations of these functions would benefit from assessing the global properties and rapid changes of brain activity. In this context, global network parameters derived from graph theory applied to high temporal resolution electroencephalography (EEG) data may be particularly useful.

Our group has previously used this combination of techniques during an oddball task to elicit the P300 potential in schizophrenia (SZ) and

Abbreviations: SZ, schizophrenia; CR, chronic patients; FE, First episodes; BD, bipolar disorder; HC, healthy controls; CS, Connectivity Strength; SGC, Shannon Graph Complexity; H, Shannon Graph Entropy..

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bipolar disorder (BD) patients to assess EEG pre-stimulus (or baseline) activity and network modulation. To date, we have reported an increased clustering coefficient (CLC) in SZ, suggesting higher network segregation in the pre-stimulus window during task performance, compared to healthy controls (HC) (Gomez-Pilar et al., 2017). We also described abnormally higher baseline global network connectivity in patients, indexed by Connectivity Strength (CS), in the broadband and the theta band (Cea-Cañas et al., 2020). Together, these findings support a baseline hypersynchrony of the functional network specific to SZ prior to the stimulus onset (Gomez-Pilar et al., 2018a). Remarkably, that increase in pre-stimulus CS was associated with a lower modulation of the Spectral Entropy (SE) of the EEG data (Gomez-Pilar et al., 2018b), which is a replicated finding in SZ patients (Bachiller et al., 2014; Molina et al., 2018, 2020). This is additionally supported by the deficit in CS modulation in the theta band found in a later study, associated with a reduced cognitive performance (Cea-Cañas et al., 2020). Finally, these results in SZ were found to be inconsistent in BD patients and unrelated to antipsychotic (AP) treatment (Cea-Cañas et al., 2020).

Our previous reports were based on low-density EEG recordings: 17 (Gomez-Pilar et al., 2017) or 29 electrodes (Cea-Cañas et al., 2020; Gomez-Pilar et al., 2018a); and relatively small sample sizes: 57 SZ, and 59 HC (Gomez-Pilar et al., 2017) or 79 SZ, 29 BD, and 63 HC (Cea-Cañas et al., 2020). The former is a potential limitation, since some network parameters are strongly dependent on the number of nodes (EEG sensors in our analyses). This issue is especially relevant for new parameters, such as Shannon Graph Complexity (SGC) (Gomez-Pilar et al., 2018c), that may help to understand the underpinnings of the above-mentioned network hypersynchrony, since it allows to identify its underlying functional structure. This point may be relevant to understand the biological underpinnings of psychotic disorders, since such hypersynchrony may be secondary to the replicated deficit in inhibitory activity in the cortex in schizophrenia (Gonzalez-Burgos and Lewis, 2012). In this context, the SGC measure could help to understand the functional structure underlying the baseline hyperactivation and its modulation

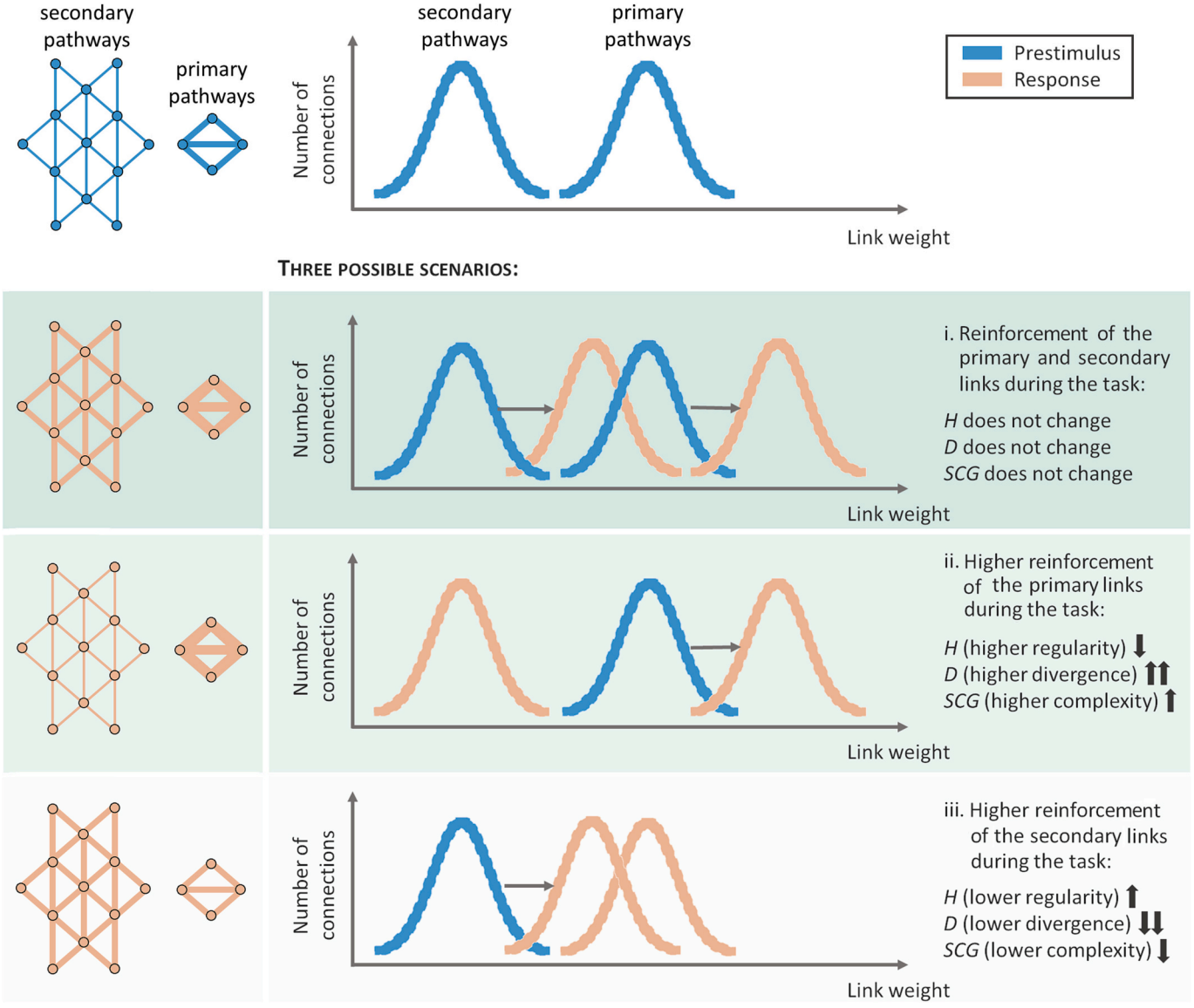

Fig. 1. Description of the three possible scenarios of the Shannon Graph Complexity (SGC) modulation due to an increase in Connectivity Strength (CS) with task performance: (i) an increase of both the primary and secondary pathways are reinforced, which results in similar SGC, regularity and divergence values; (ii) primary connections increase significantly, resulting in an increase in regularity and SGC values; and (iii) secondary connections increase significantly, resulting in less regularity and SGC values. The latter option is the most likely interpretation of SGC decrease, in line with our current and previous results (Gomez-Pilar et al., 2018c). Initially, it is characterized by a small number of strong connections (primary pathways or backbone network), and a much larger number of weak connections (secondary pathways), Thus, the activation of secondary connections would result in a less balanced/more variable network, increasing the H value.

deficits that characterize these patients.

The SGC summarizes the distribution of link weights in the network. Particularly, low complexity values –close to zero– correspond to a complete random link weight distribution of the network (*i.e.*, high entropy). This would also be the case in a very regular distribution of the network link values (*i.e.*, low entropy). On the contrary, a network that neither shows a completely random nor completely regular distribution shows high complexity values –close to one (Tononi et al., 1998). Complex networks are characterized by the simultaneous coexistence of: (i) a backbone made of a low number of connections with high-value link weights, and (ii) a high number of connections with low-value link weights (*i.e.*, secondary pathways); the latter being more widely and variably distributed than the former (Gomez-Pilar et al., 2018c). Therefore, the SGC may help to understand whether the network hyperactivation described in SZ is related to local changes of network connections or whether, on the contrary, it is associated with widespread and delocalized brain changes. We previously used SGC to assess functional network reconfiguration in SZ patients and HC, revealing a lower task-related modulatory capacity in the pathological group (Gomez-Pilar et al., 2018c). To illustrate more clearly the contribution of this measure, Fig. 1 depicts different possibilities of change in SGC (and its subcomponents) due to the modulatory increase in CS during the performance of a cognitive task, involving primary and secondary pathways as previously described.

Accordingly, in the present work we sought to: (i) replicate previous results on CS in SZ using high-density EEG recordings in a larger –and mostly new– sample; and (ii) assess their relations with network complexity using the SGC measure. According to our previous report (*i.e.,* higher pre-stimulus broadband CS and decreased theta-band CS modulation in patients (Cea-Cañas et al., 2020), here we study SGC and CS parameters in two frequency ranges (theta [4–8 Hz] and broadband [4–70 Hz]), and two task-related conditions (baseline and modulation). Finally, we also aimed to assess: (iii) the clinical relevance of our results by studying their relationship to symptoms and cognitive outcome, and (iv) the possible role of AP treatment.

We considered of interest to evaluate these parameters in both SZ and BD groups given the different CS baseline and modulation values previously found between them (Cea-Cañas et al., 2020), as well as their well-known clinical and neurobiological similarities. Moreover, using data from the BD group would be helpful in isolating the effects of antipsychotic treatment and diagnostic specificity. The theta band was selected for study based on our previous results of altered CS, as mentioned above, and the literature supporting its related alterations from early stages and in first episodes under different ERP paradigms (*e.g.*, Hua et al., 2023; Solís-Vivanco et al., 2021).

Our hypotheses were (i) that we could replicate the increased baseline CS and lower CS modulation values in the theta band in the Sz group, and (ii) that the analysis of SGC values and its modulation would help in identifying the functional patterns underlying network modulation in normal subjects and their alterations in patients.

2. Materials and methods

2.1. Participants

This study included 128 SZ patients (96 chronic, CR, and 32 first episodes, FE), 46 BD patients, and 92 HC, slightly overlapping with previous samples (*i.e.,* 58 patients and 18 HC in (Cea-Cañas et al., 2020)).

The exclusion criteria were: (i) a total Intelligence Quotient (IQ) below 70; (ii) a history of neurological disorders; (iii) past or present substance abuse, except for nicotine or caffeine; (iv) the presence of any other psychiatric process for patients; and (v) any history of psychiatric diagnosis or treatment for controls.

2.2. Clinical and cognitive assessment

Patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association, 2013). Positive symptoms were scored using the Spanish version of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987; Peralta and Cuesta, 1994) and negative symptoms using the Brief Assessment of Negative Symptoms (BNSS) (Kirkpatrick et al., 2011; Mané et al., 2014). All SZ and 28 BD patients were receiving stable doses of atypical AP.

Sociodemographic data were screened through personal interviews. IQ and cognitive performance were respectively assessed using the Spanish versions of the Wechsler Adult Intelligence Scale – 3rd Edition (WAIS-III) (Seisdedos Cubero, 1999; Wechsler, 1997) and the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004; Segarra et al., 2011).

2.3. EEG recordings and pre-processing

About 13 min of eyes-closed EEG activity were recorded in each subject while performing a three-stimulus auditory oddball paradigm (*i.e.,* P300 task). Six hundred sequences of target (500 Hz-tone, probability 0.2), distractor (1000 Hz-tone, probability 0.2), and standard tones (2000 Hz-tone, probability 0.6) were randomly presented. Each tone lasted 50 milliseconds (ms), with an inter-stimulus interval randomly jittering between 1.16 and 1.44 s (s) and comprised a rise and fall time of 5 ms with a presentation intensity of 90 dB. Participants were asked to press a button whenever they detected a target tone. Only 'attended' targets (*i.e.,* tones followed by a behavioral response) were considered for further analysis.

EEG data were recorded in all subjects using a 64-channel system (Brain Vision, Brain Products GmbH). Active electrodes were placed at FP1, FP2, F7, F8, F3, F4, Fz, FC5, FC6, FC1, FC2, T7, T8, C3, Cz, C4, CP5, CP6, CP1, CP2, TP9, TP10, P7, P8, P3, P4, Pz, O1, O2, Oz, AF7, AF3, AFz, F1, F5, FT7, FC3, FCz, C1, C5, TP7, CP3, P1, P5, PO7, PO3, POz, PO4, PO8, P6, P2, CPz, CP4, TP8, C6, C2, FC4, FT8, F6, F2, AF4, and AF8, following the international 10–10 system, as well as two electrooculography (EOG) channels. EEG channels were referenced over Cz during acquisition and re-referenced offline to the averaged activity of all the sensors (Bledowski et al., 2004; Gomez-Pilar et al., 2018d). The impedance was maintained under 5 kΩ and a sampling rate frequency of 500 Hz was used.

Data were pre-processed using EEGLAB v13.6.5b (Delorme and Makeig, 2004) and Matlab R2020b (MathWorks Inc., MA, USA), as well as custom scripts. First, the signals were band-pass filtered (finite impulse response filters with a Hamming window) between 1 and 70 Hz, and a 50 Hz notch filter was utilized to remove the power line artifact. EOG recordings and Independent Component Analysis (ICA) were used to minimize electromyographic (EMG) contamination (Bachiller et al., 2015; Delorme et al., 2007).

2.4. CS and SGC network parameters

The interaction between neural activity in different cerebral regions can be used to represent the brain as a graph. Each electrode would correspond to a node, and the neural coupling between electrodes would set the network edges (Stam and van Straaten, 2012). In this study, the Phase Locking Value (PLV) between electrodes was used to estimate the neural coupling (Lachaux et al., 1999). PLV is sensitive to low-amplitude oscillatory EEG components (Spencer et al., 2003) in addition to non-linearities (van Diessen et al., 2015). The Continuous Wavelet Transform (CWT) was used to compute the PLV. To this end, phase information from each trial was extracted from the CWT (Bob et al., 2008) and cones of influence were considered to remove edge effects (Torrence et al., 1998). The PLV between two EEG channels was obtained by evaluating the variability of phase differences across trials (Gomez-Pilar et al.,

2018b):

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

where Nt is the number of trials, $\Delta\varphi xy$ is the instantaneous phase difference between the signals x and y, k is the time interval, and s is the scaling factor of the mother wavelet. Functional connectivity matrices, with values ranging between 0 and 1, were generated using the PLV values, in which 0 means that the two signals had no synchronization and 1 that they were perfectly synchronized.

Two temporal windows from the EEG signal were analyzed: (i) the pre-stimulus window, which corresponds to a period of expectation from −300 ms to the stimulus onset; and (ii) the response window, which corresponds to the period between 150 and 450 ms after the stimulus onset as it is related to the P3b response. This procedure was applied for both the theta band (4–8 Hz) and the broadband (4–70 Hz) (Gomez-Pilar et al., 2018a; Gomez-Pilar et al., 2018b).

Adjacency matrices were computed for the pre-stimulus and the response windows. From these matrices, the Connectivity Strength (CS) was computed as follows:

$$CS = \frac{\sum_{i=1}^{N}\sum_{j>i} W_{ij}}{N\,(N-1)/2} \quad (2)$$

where N refers to the total number of nodes of the network, and W_{ij} refers to PLV between nodes i and j (Gomez-Pilar et al., 2018b).

The Shannon Graph Complexity (SGC) indexes the weight distribution balance of the network (Gomez-Pilar et al., 2018d). Based on the hypothesis that a well-designed brain network –with complexity values closer to one– exhibits an optimal balance between functional integration and segregation (Deco et al., 2015; Tononi et al., 1998), this parameter considers that both a completely random weight distribution and a completely ordered distribution show a low degree of complexity –values closer to zero. To capture the interaction between higher and lower link-weight value connections –which may be arbitrarily separated into primary and secondary pathways (see Fig. 1)–, SGC is defined as the product of the Shannon Graph Entropy (H) and the Statistical Disequilibrium (D) (Gomez-Pilar et al., 2018c):

$$SGC = H{\cdot}D, \quad (3)$$

where H and D are given by the following formulas:

$$H = \frac{-1}{log_2 T}\sum_{i=1}^{N}\sum_{j>i}\frac{w_{ij}}{W} log_2 \frac{w_{ij}}{W}, \quad (4)$$

$$D = \sqrt{\frac{1}{T-1}}\cdot\frac{\sigma}{\bar{w}}. \quad (5)$$

where T is the total number of connections in a fully connected graph, W is the sum of all weights of the graph, $\bar{w}$ is the average of all edge values of the graph, and σ is the standard deviation of those values (Gomez-Pilar et al., 2018c).

Task-related CS and SGC modulations were obtained as the response minus baseline windows values. These measures allow us to assess the intra-individual change associated with the cognitive task.

2.5. Statistical analyses

ANOVA and Bonferroni *post hoc* analyses were used to study differences in sociodemographic, clinical, and cognitive variables. Categorical measures were assessed using the chi-square test.

Preliminarily, we studied the differences between groups for the SGC and H parameters, with the aim of characterizing their values in healthy subjects and patients (*i.e.*, theta band and broadband, pre-stimulus window and modulation). The H parameter allowed us to elucidate the direction of change towards a more or less complex system (*i.e.,* a more or less regular distribution of the network link weights). As for our main objective, we studied CS values to replicate our previous results. Only those CS variables that showed significant differences in both CR and FE patients *versus* HC were stated as 'effect of the illness' and considered for subsequent analyses. These contrasts were performed using a multivariate general linear model (GLM) Bonferroni corrected. The variable 'group' (CR, FE, BD, and HC) was set as independent factor, graph parameters were the dependent factors, and age and sex were covariates.

Then, we analyzed the relation between CS and SGC in the same frequency range to assess the complexity underpinnings of CS alterations in patients. To this end, we performed regression models including CS values as dependent variables, and SGC values as independent variables. Next, to assess the clinical relevance of CS alterations, we applied further regression models using symptoms and cognitive performance as dependent variables. Since we collected seven cognitive scores per subject, to avoid an inflated risk of type I errors, we reduced these scores to a smaller number using a principal components analysis (PCA) without rotation.

Finally, to evaluate the treatment role on the results, we: (i) compared BD patients with and without AP treatment on CS and SGC values using the Mann-Whitney U test, and (ii) assessed its correlation with AP dose (CPZ equivalents) in all patients using Pearson's coefficient. Similarly, using Mann-Whitney tests we compared CS and SGC values between patients receiving or not anticonvulsants, lithium of benzodiazepines. The p-value was Bonferroni-corrected considering the final number of correlations performed.

3. Results

3.1. Between-group comparisons

The groups did not differ in sex distribution ($\chi^2 = 7.414$, df = 3, $p = 0.060$), but did differ in age ($F(3,262) = 10.156$, $p < 0.001$), with CR and BD patients being older than FE (*post hoc* $p = 0.006$ and $p = 0.003$, respectively) and HC (*post hoc* $p < 0.001$ in both cases). CR patients had significantly less education than HC ($F(3,226) = 13.967$, $p < 0.001$). Illness duration was significantly longer in CR and BP than in FE ($F(3,146) = 11{,}176$, $p < 0.001$ in both comparisons). SZ patients received higher CPZ equivalent doses than BD patients ($F(3,131) = 12.431$, $p < 0.001$). CR patients obtained higher BNSS scores than BD patients ($F(3,142) = 3.615$, $p = 0.022$). Cognitive performance was significantly lower in all subgroups of patients than in HC (*post hoc* $p < 0.001$ in most cases, as seen in Table 1).

The SGC, H, and CS values by group, frequency range, and task condition, as well as their significant differences are shown also in Table 1 and in Fig. 2.

3.1.1. Shannon graph complexity (SGC) and entropy (H)

HC showed an overall decrease in network complexity (SGC) with task performance (*i.e.,* negative modulation values). The GLM showed a significant group effect on this measure (Wilks' lambda = 0.877, $F(12.000, 674.958) = 2.867$, $p = 0.001$; eta squared = 0.043, medium effect size). The non-pathological effect of the P300 task on H was a positive modulation in HC, that is, towards a more irregular or diverse network distribution. In this case, the GLM showed a significant group effect on this measure (Wilks' lambda = 0.869, $F(12.000, 674.958) = 2.978$, $p < 0.001$; eta squared = 0.046, medium effect size). Sex and age had no significant effect on H values in both GLM (Wilks' lambda>0.960). There were no significant pre-stimulus between-groups differences for SGC and H parameters.

Between-subjects tests revealed significant group differences for SGC and H modulation both in the theta band (respectively: Type III sum of squares = 1.074×10^{-5}, $F = 6.818$, df = 3, $p < 0.001$; Type III sum of squares = 9.188×10^{-5}, $F = 6.178$, df = 3, $p < 0.001$) and in the

Table 1
Demographic, cognitive, and clinical characteristics, as well as baseline and modulation network values in Connectivity Strength (CS), Shannon Graph Complexity (SGC), and Shannon Graph Entropy (H) with P300 task in the broadband and theta band.

	CR (n = 96)	FE (n = 32)	BD (n = 46)	HC (n = 92)
Sociodemographic				
Sex (M/F)	62/34	15/17	21/25	45/47
Age (years)	39.31 (11.26) **#	31.47 (11.49) ¥	40.89 (11.82) **#	32.23 (11.76)
Education (years)	12.57 (3.62) **¥	14.38 (4.05)	14.51 (3.19)	16.06 (3.11)
Clinical measures				
CPZ equivalents (mg/d)	415.06 (334.82) ¥¥	294.67 (116.78)	207.44 (193.98)	–
Illness duration (months)	150.19 (127.98) ##	23.92 (71.92) ¥¥	158.41 (116.20) ##	–
Positive symptoms (PANSS)	12.72 (5.28)	13.47 (5.24)	9.85 (6.24)	–
Negative symptoms (BNSS)	24.89 (16.29) ¥	25.87 (18.89)	14.91 (13.45)	–
Pharmacology (% treated)				
Antipsychotics	100.00%	100.00%	60.87%	0.00%
Anticonvulsants	11.46%	0.00%	32.61%	0.00%
Lithium	5.21%	0.00%	43.47%	0.00%
Benzodiazepines	34.38%	31.25%	19.56%	1.09%
Cognition				
IQ (WAIS Total)	88.96 (15.82) **	90.17 (16.02) **	92.64 (11.55) **	112.06 (13.01)
BACS - Verbal memory	35.80 (11.17) **#	43.00 (9.75) **	38.59 (9.19) **	51.22 (9.89)
BACS - Working memory	16.18 (5.08) **	18.16 (4.48) **	17.08 (4.02) **	21.67 (3.47)
BACS - Motor speed	56.36 (19.67) **	60.84 (18.39) **	56.77 (15.88) **	74.27 (13.53)
BACS - Verbal fluency	19.26 (5.66) **	20.88 (4.96) **	21.96 (5.58) **	26.86 (5.18)
BACS - Processing speed	40.31 (13.16) **	46.42 (13.35) **	45.31 (10.31) **	66.63 (10.99)
BACS - Problem solving	15.14 (5.05) **	16.42 (3.77)	15.67 (3.00) *	18.04 (2.74)
Cognitive Factor (PCA)	−0.62 (0.95) **#	−0.13 (0.77) **	−0.31 (0.57) **	0.88 (0.62)
Connectivity Strength (CS)				
CS baseline – Theta band	0.3734 (0.0368)	0.3829 (0.0335)	0.3739 (0.0340)	0.3679 (0.0303)
CS modulation – Theta band	***0.0231 (0.0259)*** **	***0.0134 (0.0318)*** *	***0.0137 (0.0268)*** **	***0.0362 (0.0341)***
CS baseline – Broadband	***0.3236 (0.0334)*** *	***0.3311 (0.0336)*** *	***0.3185 (0.0290)***	***0.3065 (0.0263)***
CS modulation – Broadband	−0.0006 (0.0093)	−0.0010 (0.0084)	−0.0022 (0.0068)	−0.0002 (0.0077)
Shannon Graph Complexity (SGC)				
SGC baseline – Theta band	0.0118 (0.0007)	0.0121 (0.0005)	0.0119 (0.0007)	0.0120 (0.0006)
SGC modulation – Theta band	−0.0002 (0.0006) **	−0.0003 (0.0007)	−0.0003 (0.0007)	−0.0007 (0.0008)
SGC baseline – Broadband	0.0106 (0.0009)	0.0111 (0.0006)	0.0108 (0.0009)	0.0109 (0.0009)
SGC modulation – Broadband	0.0000 (0.0003) *	0.0000 (0.0003)	0.0000 (0.0002)	−0.0001 (0.0003)
Shannon Graph Entropy (H)				
H baseline – Theta band	0.9817 (0.0023)	0.9805 (0.0014)	0.9812 (0.0022)	0.9807 (0.0019)
H modulation – Theta band	0.0005 (0.0020) **	0.0008 (0.0021)	0.0008 (0.0022)	0.0019 (0.0025)
H baseline – Broadband	0.9864 (0.0022)	0.9849 (0.0017)	0.9862 (0.0023)	0.9857 (0.0026)
H modulation – Broadband	0.0000 (0.0007) *	0.0001 (0.0007)	0.0001 (0.0006)	0.0004 (0.0008)

Data are given as mean (standard deviation), except sex, given as total number of subjects.
CR: Chronic Schizophrenia; FE: First Episodes; BD: Bipolar Disorder; HC: Healthy Controls.
M/F: Male/Female; CPZ: Chlorpromazine; IQ: Intelligence Quotient.
Broadband baseline CS and theta CS modulation (in bold italics) are the scores considered to be effect of the illness (significant differences CR *vs* HC and EF *vs* HC).
* $p < 0.05$, ** $p < 0.001$ in comparison to HC; ¥ $p < 0.05$, ¥¥ $p < 0.001$ in comparison to BD; # $p < 0.05$, ## $p < 0.001$ in comparison to FE (Chi-squared test, ANOVA, or Multivariate GLM – Bonferroni-corrected, when corresponding).

broadband (respectively: Type III sum of squares = 9.365×10^{-7}, F = 4.485, df = 3, $p = 0.004$; Type III sum of squares = 7.767×10^{-6}, F = 5.020, df = 3, $p = 0.002$; Bonferroni-corrected in all cases). Pairwise comparisons showed that SGC and H modulation values in the theta band ($p < 0.001$ in both cases) and in the broadband ($p = 0.004$ and $p = 0.002$, respectively) were significantly lower in CR patients, indicating less change with the task compared to HC. These significant differences were not found for FE and BD patients (see Table 1 and Fig. 2).

The relative probability of connectivity weights (shown as PLV measures) in the baseline and response windows underlying the SGC baseline and modulation is shown in Fig. 3.

3.1.2. Connectivity strength (CS)

HC showed positive values for the theta CS modulation, indicating that –in normal conditions– task response increased baseline global synchrony. The GLM showed a significant group effect for this measure (Wilks' lambda = 0.800, F(12.000, 674.958) = 4.937, $p < 0.001$; eta squared = 0.072, medium effect size), with non-significant sex and age effects (Wilks' lambda>0.980 in both cases). There were no significant between-groups differences for pre-stimulus CS in the theta band.

Between-subjects tests showed significant group differences for pre-stimulus broadband CS (Type III sum of squares = 0.019, F = 6.875, df = 3, $p < 0.001$) and theta CS modulation (Type III sum of squares = 0.032, F = 12.165, df = 3, $p < 0.001$). Pairwise comparisons revealed that, compared to HC, pre-stimulus broadband CS was significantly higher and theta CS modulation was significantly lower in CR ($p = 0.003$ and $p < 0.001$, respectively) and FE ($p = 0.001$ and $p = 0.002$, respectively). Additionally, BD patients also showed an abnormally lower CS modulation in the theta band ($p < 0.001$) (see Table 1 and Fig. 2). Thus, subsequent regression analyses were conducted using these two specific CS measures, comprising a total of 2 (CS measures) by 8 (SGC and H measures) regression analyses ($p = 0.05/16 = 0.003$ required after Bonferroni correction).

3.2. Regression analyses

3.2.1. Relationship between CS and SGC

CS modulation was inversely predicted in patients by SGC modulation in the theta band ($R^2 = 0.388$, F(1,172) = 110.511, $\beta = -0.625$, $p < 0.001$) (Fig. 4, top-right). This relation was also significant for SZ ($R^2 = 0.390$, F(1,126) = 82.297, $\beta = -0.629$, $p < 0.001$) and FE patients ($R^2 = 0.589$, F(1,30) = 45.458, $\beta = -0.776$, $p < 0.001$) considered alone. Thus, as the distribution of network links weight becomes less balanced in the response window (SGC decrease, which is the normal response), global synchrony increases. Moreover, pre-stimulus SGC and CS modulation in patients, showed a direct relationship in the theta band ($R^2 =$

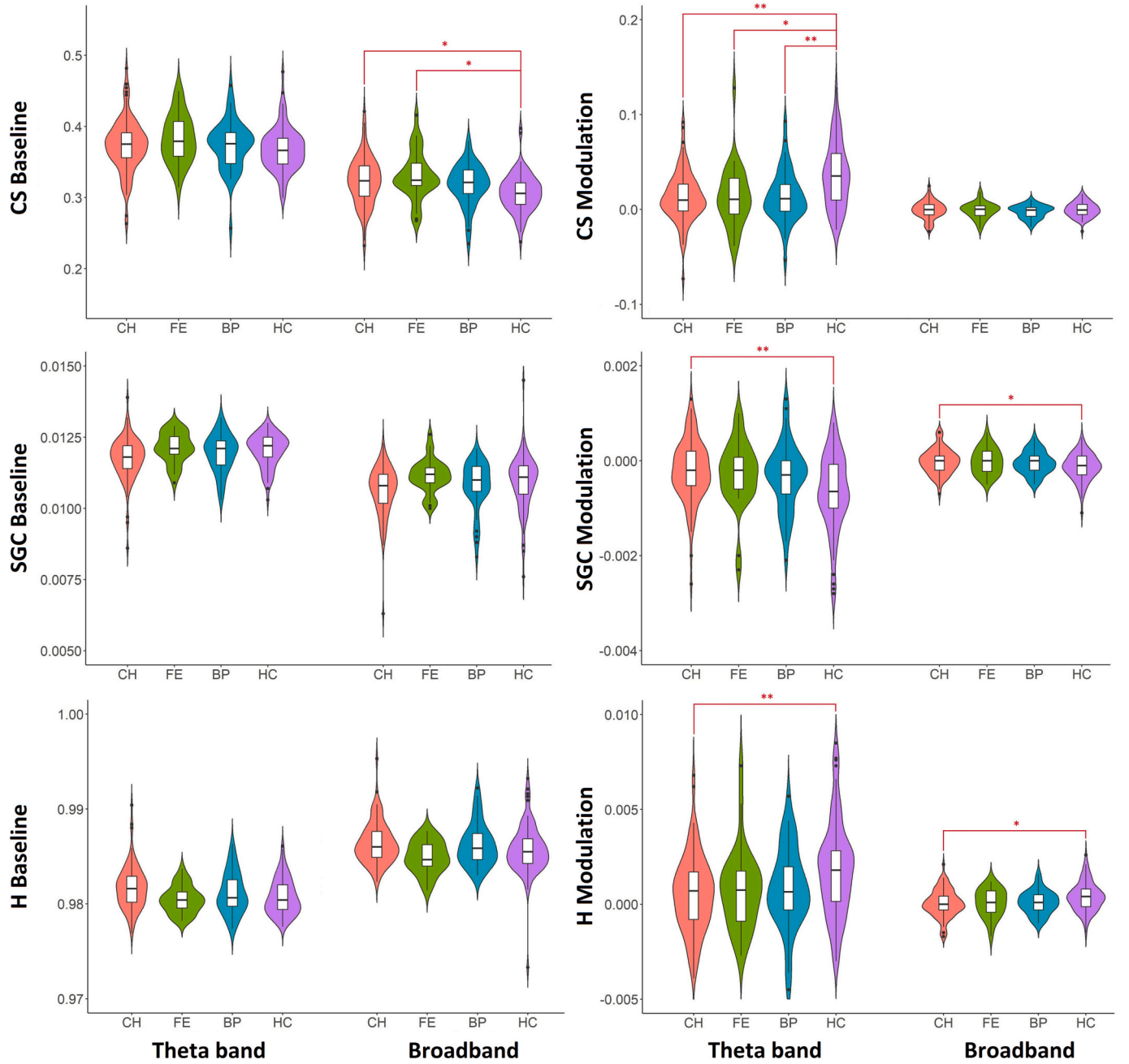

Fig. 2. Violin plots showing the differences in Connectivity Strength (CS), Shannon Graph Complexity (SGC), and Shannon Graph Entropy (H) values for the theta band and the broadband. Between-group significant differences are joined by red lines. CR: chronic schizophrenia, FE: first episodes, BD: bipolar disorder, HC: healthy controls. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

0.054, F(1,172) = 10.934, β = −0.244, p < 0.001) (Fig. 4, top-left), also significant for SZ patients alone (R^2 = 0.054, F(1,126) = 8.185, β = 0.247, p = 0.005), suggesting that a lower CS modulation is related to a less balanced/more random baseline distribution (*i.e.,* lower SGC and higher H values) of link weights. The first, but not the second, relationship was also found in HC (R^2 = 0.374, F(1,90) = 27.876, β = −0.623, p < 0.001) (Fig. 4, middle row), suggesting a normal relationship between both modulatory parameters.

3.2.2. Relationship to cognitive and clinical measures

The PCA resolved a single cognitive factor (all scores loading positively; 61% of the variance). Two (CS measures) by 3 (PANSS-positive, BNSS, and cognitive global scores) comparisons were performed (Bonferroni-corrected p = 0.008 required).

Cognitive performance was inversely predicted in patients by pre-stimulus broadband CS (R^2 = 0.051, F(1,152) = 9.276, β = −0.240, p = 0.003), also found as a trend for SZ patients when studied separately (R^2 = 0.039, F(1,113) = 5.568, β = −0.217, p = 0.020). Negative symptoms were inversely predicted by CS theta modulation (R^2 = 0.048, F(1,141) = 8.188, β = −0.234, p = 0.005), also found as a trend for SZ patients alone (R^2 = 0.050, F(1,109) = 6.849, β = −0.243, p = 0.010). Hence, lower increase in CS modulation were related to poorer cognition and increased negative symptoms (Fig. 4, bottom row).

3.3. Medication effects

No significant differences were found between BD patients receiving (n = 28) or not (n = 18) AP medication for pre-stimulus broadband CS

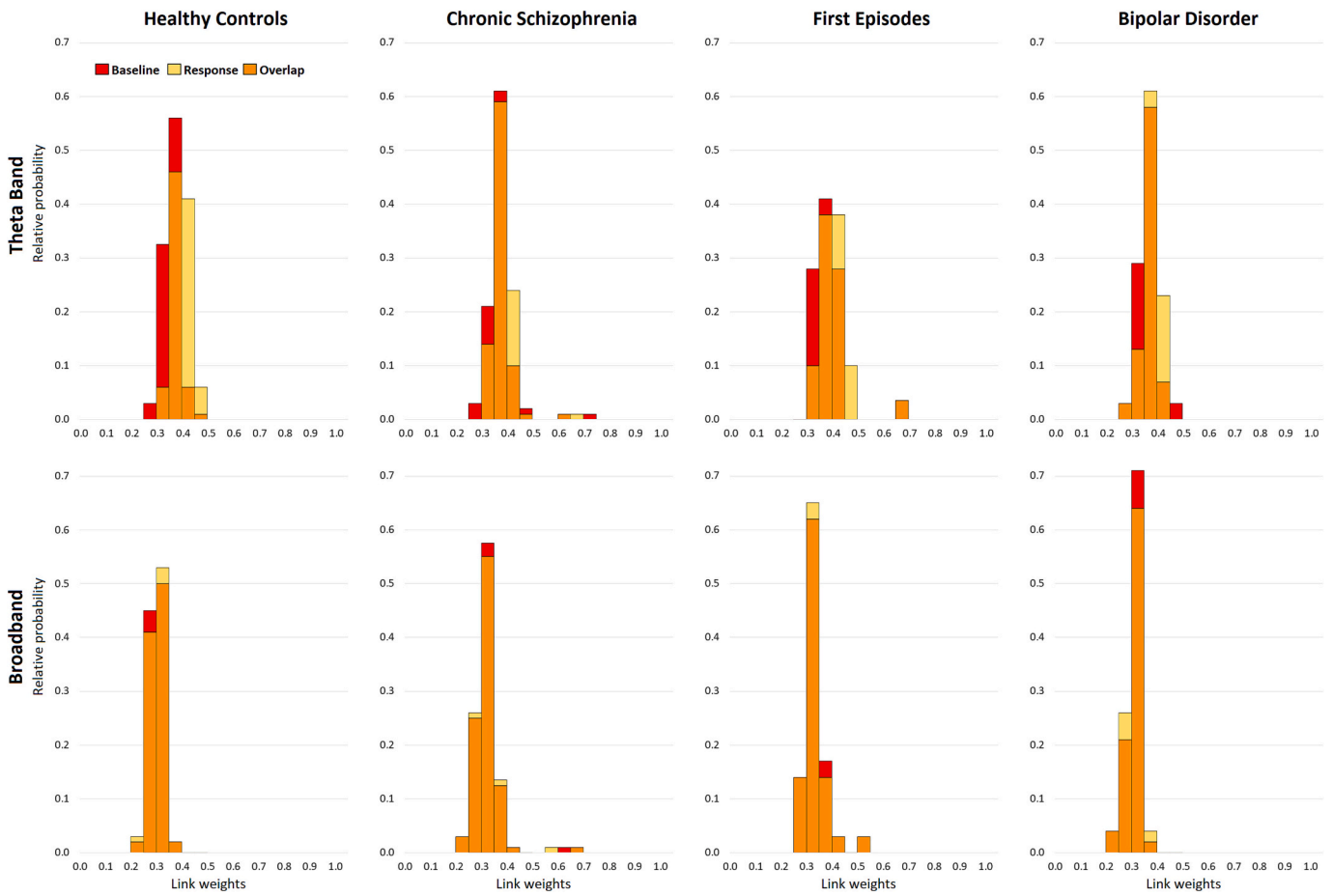

Fig. 3. Histograms of the relative probability of connectivity weights (PLV measures) at baseline and response windows. Especially in the theta band, they outline task-related transition from a higher number of connections of lower link weight (baseline) to a lower number of connections of higher link weight (response). This modulation is shown to be reduced in patients compared to controls.

(U = 209.00, z = −0.366, p = 0.714) or theta CS modulation (U = 198.00, z = −0.634, p = 0.526). Similarly, BD patients with or without AP showed no differences in SGC measures (U = 185.00, z = −0.952, p = 0.575).

For the correlation analysis, the four network parameters that showed significant results in the previous analyses were considered, so a p = 0.0125 was required after Bonferroni correction. The relation between AP dose (CPZ equivalents) and CS values, considering all patients having AP treatment, fell short of statistical significance: pre-stimulus broadband CS: r(172) = 0.191, uncorrected p = 0.015; theta CS modulation: r(172) = −0.114, uncorrected p = 0.150). Regarding complexity parameters, the relation between pre-stimulus broadband SGC and AP dose was significant and inverse (r(172) = −0.251, uncorrected p = 0.001), remaining significant in CR (r(94) = −0.330, uncorrected p = 0.002) but not in FE or BD patients. SGC modulation in the theta band did not show significant correlations with AP dose (r(172) = −0.080, uncorrected p = 0.309).

There were no significant differences between patients receiving or not anticonvulsants, lithium or benzodiazepines (Supplementary Figs. 1 and 2).

4. Discussion

Using 64-electrode EEG recordings during a cognitive task, we confirmed an increased broadband pre-stimulus CS in SZ patients, both CR and FE, and a decreased theta-band CS modulation in SZ and BD patients, related to cognitive dysfunction and negative symptoms.

The increased broadband pre-stimulus CS may suggest widespread hyperactivation of the brain under the baseline condition in SZ. CS is a network parameter based on the PLV, which reflects the synchrony of EEG signals across sensors and the joint activation of neural groups results in phase synchronization of their signals. Thus, higher pre-stimulus CS values would reflect increased global synchrony of baseline cortical activity, which might hamper the modulatory response to the P300 task. The abnormally higher pre-stimulus CS in patients and its inverse relationship with cognitive performance, in the context of evidence supporting decreased inhibitory activity in SZ (Gonzalez-Burgos et al., 2011), is also consistent with a state of cortical hypersynchrony, which might hinder adaptation to cognitive demands.

In turn, the CS hypomodulation in the theta band in both SZ and BD patients could reflect an impairment to increase power in this band, as previously described in healthy subjects during a P300 task (Başar-Eroglu and Demiralp, 2001; Yordanova and Kolev, 1998), so our patients would not show such expected task-induced increase in theta synchrony. The reduced P300 amplitude, along with decreased evoked and induced slow-band activity previously found in SZ patients (Doege et al., 2009), is also consistent with a hypomodulation of theta oscillations in this illness. Our group, in a completely different SZ sample, consistently reported a smaller increase in relative theta power during the same task (Bachiller et al., 2014).

Although previous studies have linked alterations in the theta band with cognitive deficits in schizophrenia (Cao et al., 2022), our results only achieved this relationship for the broadband CS baseline. This may be due, first, to the fact that our cognitive measure was global, whereas other works related the theta band to specific measures of working memory, executive control, or short-term memory load, probably

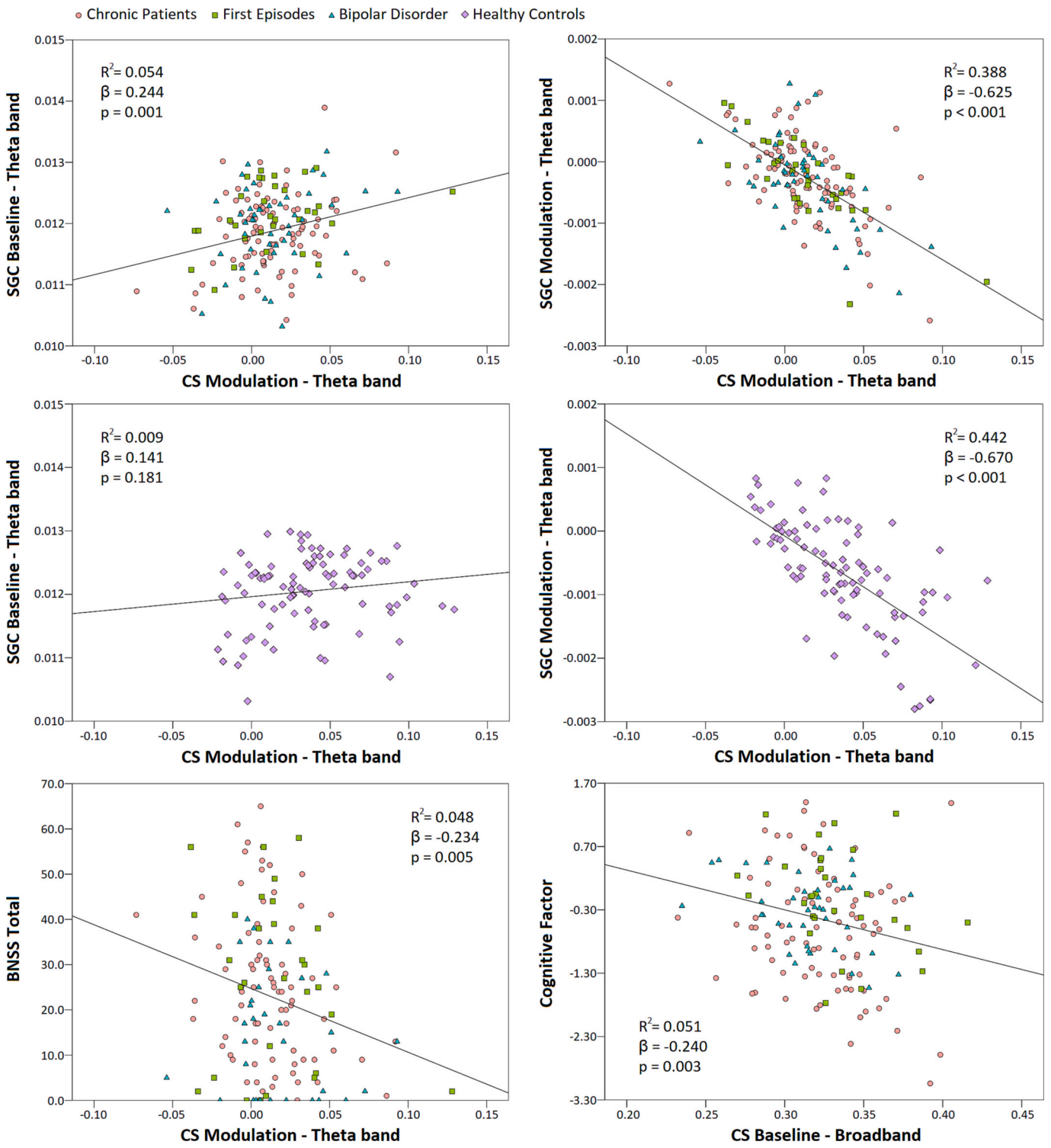

Fig. 4. Relationships (regression analysis) between CS values considered illness effect (*i.e.*, altered both in chronic and first episode patients *versus* healthy controls) and other network, clinical, and cognitive measures. Statistically significant associations were found between CS modulation and SGC baseline (top-left) and modulation (top-right). In controls only the latter significant relationship was found (middle row). Finally significant relationships were found between negative symptoms and theta-band CS modulation (bottom-left), and between cognitive performance and pre-stimulus broadband CS (bottom-right).

mediated by hippocampal-prefrontal binding process of widely distributed cortical assemblies through fast-frequency coupling (Barr et al., 2017; Bygrave et al., 2019). Secondly, our broadband measures incorporate activity in the fast-frequency bands such as gamma, which has been linked to altered inhibitory activity in schizophrenia through parvalbumin-positive interneurons (Gonzalez-Burgos and Lewis, 2012), which may underlie the increased CS baseline values.

Negative symptoms were related to theta CS modulation in our patients. Considering the role of low-frequency bands in the synchronization between distant brain regions (von Stein et al., 2000), theta baseline hypersynchrony and –in particular– the subsequent hypomodulation might hamper the integration of distinct aspects of mental

life and thus contribute to the severity of these symptoms. In this context, smaller theta modulation seems coherent with decreased interactions between brain areas with a larger role in emotion and planning, which could likely result in negative symptoms such as anhedonia or apathy, with an inverse relation between modulation (*i.e.*, regional interactions) and clinical severity.

Regarding the possible interaction between connectivity and complexity parameters, our results revealed a relationship between their modulatory measures, that is: (i) an abnormally lower broadband and theta-band SGC decrease (*i.e.,* less negative modulation) in CR patients, (ii) an abnormally lower CS increase (*i.e.,* less positive modulation) in all patients in the theta band, and (iii) a clearly significant negative relationship between SGC and CS theta-band modulation in patients. These data suggest that lower CS modulation in patients would relate to a less complex or balanced network in terms of the distribution of connection weights (*i.e.,* patients with lower –or more abnormal– changes in CS are those with more 'normal' –or similar to HC– changes in SGC values). Due to lower SGC values, the relevant question would then be: *What kind of more unbalanced (i.e., more or less regular) network scenario do patients present?* Since, as expected from previous works (Gomez-Pilar et al., 2018c), patients showed lower SGC values and higher H values (*i.e.,* less ordered/more random weight distribution network) than HC, their abnormally lower CS modulation would be consistent with a higher number of active connections (*i.e.,* larger and more variable link weights) at baseline, also consistent with the significant positive relationship between CS modulation and SGC baseline in the theta band (Fig. 4, top-left) and the higher pre-stimulus CS values found in patients in the broadband compared to HC.

Interestingly, as shown by our significant regression analyses (Fig. 4, middle row), HC show the same negative relationship between CS and SGC modulation values in theta band, providing evidence of a normal but diminished mechanism in patients with schizophrenia. These results also support a mechanism that would be significantly attenuated in patients *versus* HC, in which specific connections with the lowest link weight values at baseline (*i.e.,* secondary pathways in the network) increase their weights with task performance. This would lead to a lower network balance and higher diversity/lower regularity in their connection weights (*i.e.,* lower SGC and higher H values, respectively), since the initial situation is characterized by a small number of strong primary connections –a network backbone–, and a much larger number of weak connections –secondary pathways. In other words, the activation of some of the secondary pathways would result in a less balanced network, and the H value would increase as a result of a more diverse or irregular distribution of the network link weights. Fig. 1 summarizes the three possible scenarios of complexity change due to a task-related increase in CS, including the one that our data support.

Fig. 3 plots the change in the relative probability of different link weights and summarizes this rationale since: (i) CS modulation in HC would involve an increase in the connection weights of the pathways with low PLV (*i.e.,* secondary pathways) at baseline; and (ii) such connections are likely to be more active in patients at baseline and change less with task performance (*i.e.,* higher relative probability and lower PLV values). This is likely due to their lower SGC and higher CS and H values at baseline, which would lead to impaired modulatory capacity. Indeed, the direct relation in patients –but not in HC– between baseline SGC and CS modulation in the theta band supports a basal hyperactivation in schizophrenia that would hamper connectivity modulation due to a lesser activation of secondary pathways during task performance, which would make the network less diverse/more regular than HC due to the higher proportion of link weights of these at baseline *versus* the primary connections, as discussed before (see Fig. 1).

The absence of significant differences in SGC parameters in FE patients *versus* HC suggests a chronicity and/or treatment effect in CR patients. However, the latter possibility is less likely due to the absence of significant relationships between graph measures and AP doses, and the lack of differences between BD cases receiving or not AP. However, despite our efforts to disentangle medication and illness effects, these effects cannot be completely ruled out except with treatment-naïve patients. Another limitation in our work is that there is an increasing acknowledgement of the coexistence of several pathological processes within what we now denominate as SZ or BD, but here we have treated our samples as belonging to unitary illnesses by clinical diagnosis. In our current study, BD and SZ patients shared a decreased theta-band CS modulation, but their results differed for other network parameters. This may indicate that different pathways may lead to network hypomodulation in both diagnostic entities. Moreover, within psychosis, different biotypes may have distinct network properties, according to our previous work where we found a subgroup of patients with more severe cognitive deficits and characterized by increased pre-stimulus CS values (Fernández-Linsenbarth et al., 2021). Finally, EEG has limitations for spatial resolution and reliable graph analysis. However, the replication of previous findings, the increased sample size, and the combined use of high-density EEG and network analyses can be accounted as strengths of the present study.

5. Conclusions

Our data support: (i) a global pre-stimulus hyperactivity during a P300 task in SZ associated with increased cognitive impairment; and (ii) a reduced modulation of theta activity in both SZ and BD patients, related to greater negative symptoms. The joint analysis of the CS and SGC parameters support that higher pre-stimulus CS values in patients are associated with a lower network adaptive capacity to cognitive demands, that is, a more dissimilar global functional network, likely based on differences in link weight distributions of secondary pathways. Such neurophysiological dysfunctions possibly underlie (at least) part of the symptomatological expression of schizophrenia and/or bipolar disorder, and may help advance the study and development of alternative pharmacological intervention targets, such as those based on GABA-mediated inhibitory neurotransmitter mechanisms.

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Ethical statement

The study was approved by the Research Board of the Clinical University Hospital of Valladolid and was conducted in compliance with the Declaration of Helsinki of 1975, as revised in 2008. Each participant signed a written informed consent after being fully informed about the details of the experiment.

CRediT authorship contribution statement

Álvaro Díez: Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft. **Javier Gomez-Pilar:** Formal analysis, Software, Visualization, Writing – review & editing. **Jesús Poza:** Formal analysis, Software, Writing – review & editing. **Rosa Beño-Ruiz-de-la-Sierra:** Data curation, Investigation, Writing – review & editing. **Inés Fernández-Linsenbarth:** Data curation, Investigation, Writing – review & editing. **María Recio-Barbero:** Investigation, Writing – review & editing. **Pablo Núñez:** Formal analysis, Software, Visualization, Writing – review & editing. **Pedro Holgado-Madera:** Investigation, Writing – review & editing. **Vicente Molina:** Conceptualization, Funding acquisition, Methodology, Project administration,

Supervision, Writing – original draft.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2023.110902.

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders (DSM–5).

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

Bachiller, A., Romero, S., Molina, V., Alonso, J.F., Mañanas, M.A., Poza, J., Hornero, R., 2015. Auditory P3a and P3b neural generators in schizophrenia: an adaptive sLORETA P300 localization approach. Schizophr. Res. 169 (1–3), 318–325. https://doi.org/10.1016/j.schres.2015.09.028.

Barr, M.S., Rajji, T.K., Zomorrodi, R., Radhu, N., George, T.P., Blumberger, D.M., Daskalakis, Z.J., 2017. Impaired theta-gamma coupling during working memory performance in schizophrenia. Schizophr. Res. 189, 104–110. https://doi.org/10.1016/J.SCHRES.2017.01.044.

Başar-Eroglu, C., Demiralp, T., 2001. Event-related theta oscillations: an integrative and comparative approach in the human and animal brain. Int. J. Psychophysiol. 39 (2–3), 167–195. https://doi.org/10.1016/S0167-8760(00)00140-9.

Bledowski, C., Prvulovic, D., Goebel, R., Zanella, F.E., Linden, D.E., 2004. Attentional systems in target and distractor processing: a combined ERP and fMRI study. Neuroimage 22 (2), 530–540. https://doi.org/10.1016/j.neuroimage.2003.12.034.

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.

Bygrave, A.M., Jahans-Price, T., Wolff, A.R., Sprengel, R., Kullmann, D.M., Bannerman, D.M., Kätzel, D., 2019. Hippocampal–prefrontal coherence mediates working memory and selective attention at distinct frequency bands and provides a causal link between schizophrenia and its risk gene GRIA1. Translational Psychiatry 2019 9:1 9 (1), 1–16. https://doi.org/10.1038/s41398-019-0471-0.

Cao, Y., Han, C., Peng, X., Su, Z., Liu, G., Xie, Y., Zhang, Y., Liu, J., Zhang, P., Dong, W., Gao, M., Sha, S., Zhao, X., 2022. Correlation between resting Theta power and cognitive performance in patients with schizophrenia. Front. Hum. Neurosci. 16 https://doi.org/10.3389/FNHUM.2022.853994.

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. https://doi.org/10.1016/j.pnpbp.2019.109801.

Deco, G., Tononi, G., Boly, M., Kringelbach, M.L., 2015. Rethinking segregation and integration: contributions of whole-brain modelling. Nat. Rev. Neurosci. 16 (7), 430–439. https://doi.org/10.1038/NRN3963.

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.

Delorme, A., Sejnowski, T., Makeig, S., 2007. Enhanced detection of artifacts in EEG data using higher-order statistics and independent component analysis. NeuroImage 34 (4), 1443–1449. https://doi.org/10.1016/J.NEUROIMAGE.2006.11.004.

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.

Fernández-Linsenbarth, I., Planchuelo-Gómez, Á., Díez, Á., Arjona-Valladares, A., de Luis, R., Martín-Santiago, Ó., Benito-Sánchez, J.A., Pérez-Laureano, Á., González-Parra, D., Montes-Gonzalo, C., Melero-Lerma, R., Morante, S.F., Sanz-Fuentenebro, J., Gómez-Pilar, J., Núñez-Novo, P., Molina, V., 2021. Neurobiological underpinnings of cognitive subtypes in psychoses: a cross-diagnostic cluster analysis. Schizophr. Res. 229, 102–111. https://doi.org/10.1016/J.SCHRES.2020.11.013.

Gomez-Pilar, J., Lubeiro, A., Poza, J., Hornero, R., Ayuso, M., Valcárcel, C., Haidar, K., Blanco, J.A., Molina, V., 2017. Functional EEG network analysis in schizophrenia: evidence of larger segregation and deficit of modulation. Prog. Neuropsychopharmacol. Biol. Psychiatry 76, 116–123. https://doi.org/10.1016/j.pnpbp.2017.03.004.

Gomez-Pilar, J., de Luis-García, R., Lubeiro, A., de la Red, H., Poza, J., Núñez, P., Hornero, R., Molina, V., 2018a. Relations between structural and EEG-based graph metrics in healthy controls and schizophrenia patients. Hum. Brain Mapp. 39 (8), 3152–3165. https://doi.org/10.1002/hbm.24066.

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

Gomez-Pilar, J., Poza, J., Bachiller, A., Gómez, C., Núñez, P., Lubeiro, A., Molina, V., Hornero, R., 2018c. Quantification of graph complexity based on the edge weight distribution balance: application to brain networks. Int. J. Neural Syst. 28 (1) https://doi.org/10.1142/S0129065717500320.

Gomez-Pilar, J., Poza, J., Gómez, C., Northoff, G., Lubeiro, A., Cea-Cañas, B.B., Molina, V., Hornero, R., 2018d. Altered predictive capability of the brain network EEG model in schizophrenia during cognition. Schizophr. Res. 201, 120–129. https://doi.org/10.1016/J.SCHRES.2018.04.043.

Gonzalez-Burgos, G., Lewis, D.A., 2012. NMDA receptor hypofunction, parvalbumin-positive neurons, and cortical gamma oscillations in schizophrenia. Schizophr. Bull. 38 (5), 950–957. https://doi.org/10.1093/schbul/sbs010.

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

Hua, J.P.Y., Roach, B.J., Ford, J.M., Mathalon, D.H., 2023. Mismatch negativity and theta oscillations evoked by auditory deviance in early schizophrenia. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. https://doi.org/10.1016/J.BPSC.2023.03.004.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3616518.

Keefe, R.S.E., Goldberg, T.E., Harvey, P.D., Gold, J.M., Poe, M.P., Coughenour, L., 2004. The brief assessment of cognition in schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr. Res. 68 (2–3), 283–297. https://doi.org/10.1016/j.schres.2003.09.011.

Kirkpatrick, B., Strauss, G.P., Nguyen, L., Fischer, B.A., Daniel, D.G., Cienfuegos, A., Marder, S.R., 2011. The brief negative symptom scale: psychometric properties. Schizophr. Bull. 37 (2), 300. https://doi.org/10.1093/SCHBUL/SBQ059.

Lachaux, J.P., Rodriguez, E., Martinerie, J., Varela, F.J., 1999. Measuring phase synchrony in brain signals. Hum. Brain Mapp. 8 (4), 194–208. https://doi.org/10.1002/(SICI)1097-0193(1999)8:4<194::AID-HBM4>3.0.CO;2-C.

Mané, A., García-Rizo, C., Garcia-Portilla, M.P., Bergé, D., Sugranyes, G., Garcia-Alvarez, L., Bernardo, M., Bobes, J., Fernandez-Egea, E., 2014. Spanish adaptation and validation of the brief negative symptoms scale. Compr. Psychiatry 55 (7), 1726–1729. https://doi.org/10.1016/J.COMPPSYCH.2014.05.024.

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. Schizophrenia Research 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? Journal of Psychiatry & Neuroscience : JPN 45 (5), 322–333. https://doi.org/10.1503/JPN.190032.

Peralta, V., Cuesta, M.J., 1994. Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. Psychiatry Res. 53 (1), 31–40.

Segarra, N., Bernardo, M., Gutiérrez, F., Justicia, A., Fernández-Egea, E., Allas, M., Salfont, G., Contreras, F., Gascón, J., Soler-Insa, P.A., Menchon, J.M., Junque, C., Keefe, R.S., 2011. Spanish validation of the brief assessment in cognition in schizophrenia (BACS) in patients with schizophrenia and healthy controls. Eur. Psychiatry 26, 69–79.

Seisdedos Cubero, N., 1999. Escala de inteligencia de Wechsler para adultos-III: adaptación española. TEA.

Solís-Vivanco, R., Mondragón-Maya, A., Reyes-Madrigal, F., de la Fuente-Sandoval, C., 2021. Impairment of novelty-related theta oscillations and P3a in never medicated first-episode psychosis patients. Npj Schizophrenia 7 (1), 1–9. https://doi.org/10.1038/s41537-021-00146-3.

Spencer, K.M., Nestor, P.G., Niznikiewicz, M.A., Salisbury, D.F., Shenton, M.E., McCarley, R.W., 2003. Abnormal neural synchrony in schizophrenia. J. Neurosci. 23 (19), 7407–7411.

Stam, C.J., van Straaten, E.C.W., 2012. The organization of physiological brain networks. Clinical Neurophysiology 123 (6), 1067–1087. https://doi.org/10.1016/J.CLINPH.2012.01.011.

Tononi, G., Edelman, G.M., Sporns, O., 1998. Complexity and coherency: integrating information in the brain. Trends Cogn. Sci. 2 (12), 474–484. https://doi.org/10.1016/S1364-6613(98)01259-5.

Torrence, C., Compo, G.P., Torrence, C., Compo, G.P., 1998. A practical guide to wavelet analysis. BAMS 79 (1), 61–78. https://doi.org/10.1175/1520-0477(1998)079.

van Diessen, E., Senders, J., Jansen, F.E., Boersma, M., Bruining, H., 2015. Increased power of resting-state gamma oscillations in autism spectrum disorder detected by routine electroencephalography. Eur. Arch. Psychiatry Clin. Neurosci. 265 (6), 537–540. https://doi.org/10.1007/S00406-014-0527-3.

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 [pii].

Wechsler, D., 1997. Wechsler Adult Intelligence Scale - Third Edition (WAIS-III). The Psychological Corporation.

Yordanova, J., Kolev, V., 1998. Single-sweep analysis of the theta frequency band during an auditory oddball task. Psychophysiology 35 (1), 116–126. https://doi.org/10.1111/1469-8986.3510116.